INTRODUCTION

Charlene E. Le Fauve and Raye Z. Litten

Alcohol-dependent individuals have exceptionally high rates of co-occurring psychiatric disorders compared to nonalcoholics (Regier et al., 1990). Comparable odds to have a diagnosis of antisocial personality disorder than noncomorbid alcoholics, the prognosis for treatment is often poor, particularly among patients with more severe psychiatric illnesses. Development of effective interventions to treat this population is in the early stages of research. Although the interaction between the psychiatric condition and alcoholism is complex, progress has been made. The NIAAA has supported a number of state-of-the-art pharmacological and behavioral trials in a variety of comorbid psychiatric disorders. Some of these trials have been completed and are presented here. The symposium presented some new research findings from clinical studies with the aim of facilitating the development of treatments that improve alcohol and psychiatric outcomes among individuals with alcohol-use disorders and co-occurring psychiatric disorders. The panel focused on social anxiety disorder, depression, bipolar disorder, and schizophrenia.

Key Words: Pharmacotherapy, Alcoholism Treatment, Psychiatric Comorbidity.
stratified a variation of outcomes to different treatment interventions, and those with high psychiatric severity showed no improvement with any treatment.

Progress has recently been made in conducting state-of-the-art studies of pharmacological and behavioral interventions in a number of comorbid psychiatric disorders. For example, several NIAAA-supported trials have been completed in depressed alcoholics. Results have been mixed. Mason et al. (1996) demonstrated that although the tricyclic antidepressant desipramine reduced symptoms of depression in alcoholic patients with major depression, it had limited success in reducing drinking. Similarly, McGrath et al. (1996) found that the tricyclic antidepressant imipramine was effective in reducing depressive symptoms in alcoholics with mild to moderate depression, but no differences were evident in alcohol intake between the imipramine and placebo groups.

The effects of selective serotonin reuptake inhibitors (SSRIs) are less clear. Cornelius et al. (1997) showed that fluoxetine diminished both depression and drinking in severely depressed alcoholics. In contrast, Pettinati et al. (2001), McGrath (1998), and Moak et al. (2003) reported that the SSRI sertraline or fluoxetine was no more effective than placebo in reducing the severity of depression or drinking in a population of less severely depressed alcoholics. Thus, it seems that although antidepressants, in at least certain conditions, can improve depression and, at least to a limited extent, reduce drinking, their effects may vary and may also be a function of the subtype of depression. Investigations are currently under way to determine whether the pharmacological treatment of both disorders (naltrexone for alcoholism and sertraline or fluoxetine for depression) is more effective than monotherapy. Dr. Moak offers a summary of double-blind, placebo-controlled pharmacological treatment studies of comorbid alcohol dependence and depression and presents implications for future research.

Few studies have been conducted to test the efficacy of behavioral therapies in depressed alcoholics (Brown and Ramsey, 2000). Brown et al. (1997) found that cognitive-behavioral therapy (CBT) for depression was effective not only in improving depression, but also in decreasing the frequency of drinking in alcoholics with increased depressive symptoms. However, future studies on depressed alcoholics need to develop and test behavioral therapies that address both depression and alcohol disorders and also need to determine their optimal integration with pharmacological agents.

Research has just begun to identify and evaluate effective treatments for alcohol-abusing and -dependent patients with generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, and panic disorder. Buspirone, a partial 5-hydroxytryptamine \(5-\text{HT}_{1A}\) agonist, has been evaluated in several trials using alcoholic patients with a collateral generalized anxiety disorder. Tollefson et al. (1992) and Kranzler et al. (1994) found it effective in reducing the symptoms of anxiety in anxious alcoholics. Moreover, Kranzler et al. showed that concurrent with improvement of anxiety, patients treated with buspirone were more likely to stay in treatment and to delay a return to heavy drinking. However, Malcolm et al. (1992) did not demonstrate differences in improvement of anxiety or a reduction in drinking outcome in buspirone-treated versus placebo-treated anxious alcoholics.

In alcoholic patients with a comorbid social anxiety disorder, Randall et al. (2001a) found unexpectedly that a CBT specific for alcohol dependence was more effective in reducing drinking than one designed to simultaneously address both alcoholism and social anxiety. Further, the improvement in social anxiety was equivalent for both therapies. A new trial has been initiated and is included in this symposium panel to determine the efficacy of paroxetine in individuals with a dual diagnosis of alcohol-use disorder and social anxiety disorder.

Finally, even less is known about the treatment of alcoholics with a more severe mental illness. The NIAAA is currently supporting a trial of valproate in alcohol-dependent patients with bipolar disorder and of clozapine in schizophrenic alcoholics. Results of these investigations were presented in our panel by Drs. Ihsan Salloum and Alan Green.

In summary, research to evaluate effective pharmacological and behavioral treatments for patients diagnosed with alcohol-use disorder and psychiatric comorbidity is still in early stages. The NIAAA has supported a number of state-of-the-art pharmacological and behavioral trials with a variety of comorbid psychiatric disorders. Several of these trials have been completed and are presented here. These trials begin to address several fundamental clinical issues surrounding the treatment of psychiatric comorbidity. These include the following: (1) Are medications approved for treating the psychiatric disorder effective in patients who also have alcoholism [in obtaining Food and Drug Administration (FDA) approval for psychotropic medications, pharmaceutical companies usually exclude alcoholics from their studies]? (2) Should the pharmacological and behavioral treatment of alcoholics with psychiatric comorbidity differ from that offered to noncomorbid alcoholics? (3) Does treatment of either alcoholism or the psychiatric condition improve the outcome for the other disorder? (4) Should treatments for alcohol problems and psychiatric conditions be conducted simultaneously or sequentially? (5) Does the treatment strategy differ for each type of psychiatric comorbidity, as well as for subpopulations within a comorbidity (e.g., primary versus secondary, severity, or sex)?

The presentations in this symposium will begin to address these issues relative to alcohol comorbidity in four major psychiatric disorders: depression, anxiety, bipolar disorder, and schizophrenia. The speakers present their recent findings and discuss the relationship to the current literature. The eventual goal of the NIAAA’s developing
portfolio of studies in this area is to develop guidelines for the treatment of each comorbid psychiatric condition.

TREATMENT OF CO-OCCURRING ALCOHOL USE AND ANXIETY DISORDERS

Carrie L. Randall and Sarah W. Book

Lifetime co-occurrence of an alcohol-use disorder and an anxiety disorder ranges from 6 to 20% depending on the specific type of anxiety disorder (Kessler et al., 1997). Social anxiety disorder (formerly referred to as social phobia) is the anxiety disorder at the high end of the range and is the anxiety disorder that this presentation will focus on, although the issues raised relate to other types of co-occurring anxiety disorders, as well.

The relationship between alcohol and anxiety is complex, and making an accurate diagnosis is often difficult because of overlapping symptoms or because of alcohol-induced anxiety. It is important to note that for social anxiety disorder, the typical age of onset in early adolescence, which makes a differential diagnosis in alcohol-dependent individuals less complicated. Social anxiety disorder comes in two forms: a generalized or a specific type (DSM-IV, 1994). Individuals with the generalized type of social anxiety disorder fear public scrutiny, embarrassment, and negative evaluation in a broad range of social situations. Examples include meeting new people, speaking up in a group, talking to someone in authority, or being the focus of attention. Individuals with social anxiety disorder of the generalized type are typically more impaired than those with a specific social fear and also have more psychiatric comorbidities, such as alcoholism. Social anxiety disorder is more than shyness. Unfortunately, most individuals with social anxiety disorder never seek treatment for their problem.

Given the early onset of social anxiety disorder—often nearly a decade before the onset of a serious drinking problem—one can ask whether social anxiety disorder increases the risk of developing alcoholism. Individuals cope with their distorted perception of negative evaluation in social situations by manipulating their lives such that feared situations occur infrequently, by totally avoiding the feared situations or, commonly, with alcohol. Whether drinking actually reduces stress is not clear (Carrigan and Randall, 2003), but, regardless, as long as some individuals have the expectancy or belief that it will, they will continue to use it to self-medicate. Our working theoretical model is based on a similar one initially proposed by Kushner et al. (2001). In this self-medication model, social anxiety initiates drinking in the search for stress relief; drinking to reduce stress maintains drinking behavior, and alcohol becomes a negative reinforcer. Finally, social anxiety plays a role in alcohol relapse if it is left untreated, especially because socially anxious individuals might not benefit as much from traditional group therapy and self-help approaches as non-socially anxious individuals. Our model implies that successful treatment of social anxiety in the course of alcohol treatment should improve drinking outcome.

Our group has conducted two randomized clinical trials to address this scientific issue: one with CBT (Randall et al., 2001a) and one with the SSRI paroxetine (Randall et al., 2001b). Both CBT (Hambrick et al., 2003; Heimberg, 2002) and paroxetine (Stein et al., 1998) have been shown to be effective interventions for social anxiety disorder in non-alcohol-dependent samples.

Treatment of Comorbid Alcoholism and Social Anxiety Disorder: A CBT Trial. In this study (Randall et al., 2001a), 93 alcoholics with co-occurring social anxiety disorder who were seeking treatment for alcoholism were divided randomly into 2 groups. It will be recalled that the onset of social anxiety disorder is typically in the teen years, so this particular anxiety disorder is more accurately diagnosed without a prolonged abstinence period than other types of anxiety disorders that have overlapping psychiatric symptoms with alcohol withdrawal. One group (the alcohol-only group) received 12 weekly individual sessions of manualized CBT for their alcohol problem in an outpatient setting (Kadden et al., 1995). The experimental group (dual group) received the same 12 weekly individual sessions of manualized CBT for alcoholism but also received simultaneous manualized treatment for social anxiety disorder, modified from that successfully used in a group setting (Hope and Heimberg, 1993). The social anxiety treatment included identifying hierarchies of feared situations, attending to cognitive restructuring, and assigning exposure therapy as homework. The primary hypotheses were that the experimental group (dual treatment) would show a greater reduction in social anxiety and would have better alcohol outcomes than the alcohol-only group.

Contrary to our hypothesis, there were few differences between the groups on most dependent variables. When differences emerged, they were in a direction opposite to the prediction. That is, the dual-treated group had slightly, but significantly, more heavy drinking days and less abstinence than the alcohol-only group. One reason that a reduction in drinking was not observed in this study might be because the first hypothesis was not supported. That is, our hypothesized causal chain predicted between-group differences in reductions in social anxiety. Why the dual-treatment group did not show more of a reduction in social anxiety is not clear. The effect on social anxiety symptoms from baseline was a modest 20% decrease, and this occurred in both groups. Thus, the working model was not tested adequately.

Treatment of Comorbid Alcohol Dependence and Social Anxiety Disorder: A Pharmacotherapy Trial. A pharmacotherapy for social anxiety that was both effective for social anxiety and safe to use in an alcoholic population was not available when our first clinical trial for comorbid alcoholism and social anxiety disorder was initiated in 1994. At that time, the only medication shown in placebo-controlled trials to decrease social anxiety was phenelzine, a mono-
amine oxidase inhibitor (Liebowitz et al., 1986), which may interact adversely with some types of alcohol. In 1998, paroxetine, an SSRI, was shown in a multisite clinical trial to reduce social anxiety symptoms markedly over a 12-week period, with group differences emerging by week 4 (Stein et al., 1998). Paroxetine was approved by the FDA for the treatment of social anxiety disorder and, until recently, was the only approved medication for treatment of this disorder. However, as in most clinical trials, individuals with comorbid alcohol dependence were excluded from the studies used to support FDA approval. Thus, before we could embark on a large-scale pharmacotherapy study with paroxetine in socially anxious alcoholics, safety and efficacy in the treatment of social anxiety had to be established.

In a small, double-blind, 8-week placebo-controlled clinical trial, our research group conducted such a study (Randall et al., 2001b). All subjects met diagnostic criteria for both an alcohol-use disorder and social anxiety disorder. The pilot study results were encouraging. They demonstrated that, despite the small sample size, both clinician ratings of improvement in social anxiety and self-reports of social anxiety fears and avoidance were more marked in the paroxetine group (target dose of 60 mg/day) than the placebo group. Improvement appeared by week 6, and the reduction from baseline in social anxiety levels was greater than we had observed in the CBT study described previously (Randall et al., 2001a). Also, important to our working hypothesis was that alcohol outcome variables started to show group differences in the final 2 weeks of the trial. Improvement in alcohol outcome variables, such as the percentage of heavy drinking days, seemed to lag approximately a week behind improvement in social anxiety levels. Clinician-rated improvement in alcohol severity favored the paroxetine group. Taken together, these results with the pharmacotherapeutic agent paroxetine supported its safety and efficacy for the treatment of social anxiety in alcohol-dependent subjects.

It also emphasized the need for a longer clinical trial to test the hypothesis that alcohol outcomes will improve in the group treated with paroxetine, secondary to an improvement in social anxiety. Such a trial with individuals with comorbid social anxiety disorder and alcohol dependence seeking alcohol treatment is planned. A trial of individuals with comorbid social anxiety disorder and alcohol-use disorder seeking treatment for social anxiety disorder and not alcoholism is under way. Both studies will track changes in levels of social anxiety, as well as alcohol consumption frequency and quantity. The first study will test our working model as it relates to drinking, social anxiety, and relapse. The ongoing study, which is more preventive in nature because it seeks individuals early in their drinking careers, will determine whether drinking to cope with social anxiety can be reduced if social anxiety levels are reduced in an attempt to prevent the need for alcohol treatment.

Research Opportunities. Clinical trials have shown that alcoholism and anxiety disorder comorbidity is high and has been associated with worse alcohol treatment outcome (Driessen et al., 2001). Despite this, there are few controlled clinical trials related to treatment of this comorbidity, and this line of research is in its infancy. Each study poses as many questions as it answers, and the field is developing and being refined with each published well-controlled clinical trial. Research opportunities are similar to those in other comorbid conditions. That is, it is important to identify the best approach to treatment both in terms of treatment modality (e.g., pharmacotherapy or behavioral therapy) and in terms of the timing of the treatments (e.g., simultaneous, sequential, or parallel) and to use evidence-based treatments. Given that alcoholics are frequently excluded from controlled clinical trials, it may be important to establish that the treatment of choice for the anxiety disorder is actually effective and safe in alcohol-dependent individuals. Manualized treatments will permit replication and standardization. Advances in the treatment of both alcoholism and anxiety disorders (new medications and new behavioral therapies) will afford more opportunities to mix and match treatments to determine optimal combinations. Depending on the type of presenting anxiety disorder (e.g., social anxiety disorder, generalized anxiety disorder, obsessive compulsive disorder, or posttraumatic stress disorder), different treatments and different staging of treatments may be required. Relapse prevention is only one goal. Prevention of the development of alcoholism and the necessity for alcohol treatment is also an important goal.

PHARMACOLOGICAL TREATMENT OF ALCOHOL DEPENDENT PATIENTS WITH COMORBID DEPRESSION
Darlene H. Moak

Prevalence and Significance of Comorbid Alcohol Dependence and Depression. Alcohol dependence and depression are common disorders that frequently occur together in the same individual. In the United States, the lifetime prevalence of alcohol dependence is 13%, whereas major depression occurs in 17% of all individuals (Kessler et al., 1997). In general, alcohol-use disorders are associated with a 2- to 4-fold increase in the prevalence of depression (Grant and Harford, 1995; Kessler et al., 1997). The consequences of this comorbidity are significant. Individuals with depression are more likely to relapse to alcohol use (Greenfield et al., 1998). In turn, alcohol dependence decreases the likelihood of remission from major depression (Mueller et al., 1994). Individuals with comorbid alcohol dependence and depression have greater utilization of health resources, greater functional impairment, and an increased risk of suicide compared with noncomorbid individuals (Grant and Hasin, 1999; Olfson et al., 2000).

Diagnostic Issues in Comorbid Individuals. The distinction between primary depression, that is, depression that predates the onset of alcohol dependence or persists during...
sustained complete abstinence from alcohol, and depression that is secondary to alcohol use is believed by many researchers and clinicians to be important. Secondary depression is believed in most cases to resolve with abstinence, whereas primary depression is believed to necessitate specific treatment. It is important to establish a timeline of onset for both disorders and to define any periods of complete abstinence and any mood symptoms during these periods of abstinence. The assistance of family members and other collateral sources of information can be very valuable in this process. The commonly used Structured Clinical Interview for DSM has been shown to be problematic in regard to its ability to reliably diagnose these comorbid conditions (Kranzler et al., 1996a). A newer instrument, the Psychiatric Instrument for Substance Use and Mental Disorders (PRISM), can assist in increasing the accuracy of diagnoses in these individuals (Hasin et al., 1996). Because it has been shown that an earlier onset of major depression is associated with an increased risk of alcohol dependence, determining the age of onset of these comorbid disorders seems to be of clinical importance (Hanna and Grant, 1997).

Treatment Studies to Date. A summary of double-blind, placebo-controlled pharmacological treatment studies of comorbid alcohol dependence and depression is shown in Table 1. The SSRIs were of particular interest as potential therapeutic agents in this population, given evidence of central nervous system serotonergic dysfunction in alcohol-dependent individuals (Ballenger et al., 1979) and decreased alcohol intake in animal models of alcohol dependence (McBride et al., 1990). SSRIs were subsequently shown to decrease drinking in non–treatment-seeking problem drinkers (Naranjo and Knoke, 2001). Additional benefits of SSRIs compared with older antidepressants such as the tricyclics are a favorable side-effect profile and a minimal risk of lethality when taken in overdose. The SSRI fluoxetine was effective in decreasing both depression and alcohol use in an inpatient sample of severely depressed alcohol-dependent individuals, many of whom had attempted suicide before hospitalization (Cornelius et al., 1997). A subsequent study of the SSRI sertraline in inpatient alcohol-dependent men with secondary depression also showed a positive effect for depression outcome (Roy, 1998). In this study, alcohol outcome was not reported because only one subject drank during the study. Two studies of sertraline in less severely depressed outpatients, however, showed no effect of sertraline on either alcohol or depression outcome (Pettinati et al., 2001). It should be noted that the results of the multisite industry-sponsored study of sertraline are as yet preliminary and that data from this study are still being analyzed. A recently completed study of sertraline in outpatients found a positive effect of active treatment on depression in women only and found a clinically modest but significant decrease in drinks per drinking day in subjects who received sertraline (Moak et al., 2003). Study characteristics that support the high internal validity of this study include use of the PRISM to confirm the diagnosis of primary depression, a high study completion rate of 70%, and rigorous attention to medication compliance. The tricyclic antidepressants imipramine and desipramine were shown to be effective in decreasing depression in outpatients (Mason et al., 1996; McGrath et al., 1996). Although there was no effect on alcohol intake in the study by McGrath et al., depressed subjects who received desipramine in the study by Mason et al. did have a longer time to relapse than depressed subjects who received placebo. Finally, nefazodone, a newer serotonergic antidepressant that acts mainly as an antagonist at the

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>No. of Patients</th>
<th>Depression outcome</th>
<th>Alcohol outcome</th>
<th>Other treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGrath et al. (1996)</td>
<td>Imipramine</td>
<td>69</td>
<td>+</td>
<td>0</td>
<td>Relapse prevention</td>
<td>Outpatients, primary depression</td>
</tr>
<tr>
<td>Mason et al. (1996)</td>
<td>Desipramine</td>
<td>71</td>
<td>+</td>
<td>+</td>
<td>No standard therapy</td>
<td>Outpatients, decrease in relapse seen only in 28 patients with secondary depression (other patients not depressed)</td>
</tr>
<tr>
<td>Cornelius et al. (1997)</td>
<td>Fluoxetine</td>
<td>51</td>
<td>+</td>
<td>+</td>
<td>Supportive</td>
<td>Inpatients; severe depression was the primary focus of hospitalization</td>
</tr>
<tr>
<td>Roy (1998)</td>
<td>Sertraline</td>
<td>36</td>
<td>+</td>
<td>NA</td>
<td>No standard therapy</td>
<td>Inpatients for 2 weeks initially; alcohol outcome not reported as only one subject drank during study</td>
</tr>
<tr>
<td>Roy-Byrne et al. (2000)</td>
<td>Nefazodone</td>
<td>64</td>
<td>+</td>
<td>0</td>
<td>Skills training</td>
<td>Outpatients, primary depression</td>
</tr>
<tr>
<td>Pettinati et al. (2001)</td>
<td>Sertraline</td>
<td>100</td>
<td>0</td>
<td>+</td>
<td>12-step</td>
<td>Outpatients, drinking outcome positive only in patients without depression</td>
</tr>
<tr>
<td>Moak et al. (2003)</td>
<td>Sertraline</td>
<td>82</td>
<td>+</td>
<td>+</td>
<td>Project MATCH CBT</td>
<td>Outpatients, 70 patients with primary depression and 12 patients with family history of mood disorder; Positive depression outcome in women only; improved alcohol outcome limited to 1 outcome measure</td>
</tr>
<tr>
<td>Kranzler (personal communication)</td>
<td>Sertraline</td>
<td>390</td>
<td>0</td>
<td>0</td>
<td>Medical management</td>
<td>Outpatients, 189 patients in group A, 120 patients in group B (HAM-D ≤17 after 7-day single-blind placebo)</td>
</tr>
</tbody>
</table>

+, active drug significantly better than placebo; 0, no difference between active drug and placebo; NA, not applicable; HAM-D, Hamilton Rating Scale for Depression.
5-hydroxytryptamine-2 receptor, decreased depression but not drinking in outpatient subjects (Roy-Byrne et al., 2000).

**Conflicting Results and Future Directions.** There are probably several explanations for the somewhat varied results from these well-designed studies. Subject characteristics are likely of great importance. Studies that focused on more severely depressed, inpatient individuals had more favorable results for SSRIs than studies that recruited less severely depressed outpatients. As noted in Table 1, studies also varied in whether they recruited individuals with primary or secondary depression; several studies included individuals who were not depressed. The study by Pettinati et al. (2001), in fact, found that sertraline decreased drinking only in individuals without any lifetime history of depression. There may also be an interactive effect of alcoholic typology with pharmacological treatments, in particular with the SSRIs. In two studies, alcoholics with an earlier onset of alcohol dependence, a greater family history of alcohol-use disorders, and more sociopathy (Babor type B alcoholics) who received either fluoxetine or sertraline had worse alcohol-use outcomes than type A alcoholics (Babor et al., 1992; Kranzler et al., 1996b; Pettinati et al., 2000). The possible influence of alcoholic typology on outcome in depressed alcoholics has not been well studied to date. Gender may play a role in response to antidepressants. In the study by Moak et al. (2003), only female subjects had improved depression with sertraline compared with placebo. Some studies in nonalcoholic depressed samples have suggested that women, particularly those who are premenopausal, respond better to SSRIs than men, but other studies have not found a gender effect on outcome. Nonetheless, given that alcohol-dependent women are more likely than alcohol-dependent men to have primary depression, the possibility that gender may be a mediating factor on outcome in pharmacological treatment studies in this population merits further exploration. Finally, the interaction between antidepressants and concomitant psychosocial treatment may have influenced the results that were obtained in the studies discussed previously. As can be seen in Table 1, a variety of psychosocial treatments were used, ranging from minimal medication-management treatment to weekly individual CBT. In one study of depressed alcoholics, CBT resulted in greater improvement in depression than a relaxation therapy control, suggesting that CBT may be of particular benefit in this population (Brown et al., 1997). The combination of SSRIs and pharmacological treatments to decrease alcohol use, in particular the opiate antagonist naltrexone, is being studied in this population in several ongoing trials. There are as yet no published studies regarding the possible effectiveness of combining antidepressants and acamprosate, a medication that is still experimental in the United States but that has been widely used in Europe and has been shown to decrease alcohol intake. Also of interest would be studies of antidepressants with mechanisms of action that differ from those of the SSRIs. For instance, venlafaxine, a newer antidepressant that blocks reuptake of both serotonin and norepinephrine, has not been studied in individuals with comorbid alcohol dependence and depression. Finally, very little is known about the interaction of medication and psychosocial treatment in this population.

**Efficacy of Valproate in Bipolar Alcoholics: A Double Blind, Placebo-Controlled Study**

Ihsan M. Salloum, Jack R. Cornelius, Dennis C. Daley, Levent Kirisci, Johnathan Himmelhoch, and Michael E. Thase

Bipolar disorder has the highest rate of co-occurring alcohol dependence compared with any other severe psychiatric disorder (Kessler et al., 1997). More than half of individuals with bipolar disorder have an additional lifetime diagnosis of alcohol- or substance-use disorder. Comorbidity of alcoholism and bipolar disorder represents a serious clinical challenge and is associated with severe disabilities, morbidity, and a heightened risk for suicide (Salloum and Thase, 2000).

Significant unmet treatment needs remain for comorbid alcoholism with bipolar disorder. Little research has been conducted on effective treatment interventions aiming at maintaining abstinence and preventing relapse in this high-risk population. There is a serious lack of evidence-based effective pharmacological treatment approaches for comorbid patients because they have been systematically excluded from clinical trials in an attempt to reduce sources of bias.

The anticonvulsant, which is also used as a mood stabilizer, may be particularly suitable for the treatment of concurrent alcoholism and bipolar disorder. Sodium valproate has been found effective in bipolar disorder (Bowden et al., 1994). Its antikindling/GABAergic properties may have a beneficial effect on reducing alcohol consumption through improving alcohol-withdrawal symptoms (Rosenthal et al., 1998) and reducing craving states (Brady et al., 1995).

We tested the hypothesis that sodium valproate may be beneficial in decreasing alcohol use and also stabilizing mood symptoms in a sample of treatment-seeking, acutely ill subjects who met DSM-IV diagnostic criteria for current alcohol dependence with a co-occurring acute episode of bipolar I disorder. We conducted a double-blind, placebo-controlled, randomized parallel-group trial of 6 months' duration that compared two treatment groups: sodium valproate plus treatment as usual (TAU; lithium carbonate and supportive psychosocial treatment) versus placebo plus TAU.

Subjects were randomized to treatment groups after a 1-week washout period and a baseline assessment to confirm study eligibility. The baseline assessment battery included the Structured Clinical Interview for DSM-IV (First et al., 1994), the Addiction Severity Index (McLellan et al., 1980), the Alcohol Use Inventory (Horn et al., 1983), the Bech-Rafaelsen Mania Scale (BRMS), the Hamilton Rat-
ing Scale for Depression (Thase et al., 1983), the timeline follow-back method for assessing recent drinking (Sobell et al., 1988), and assessment of medication side effects and self-report of medication compliance. Postrandomization evaluations were conducted at 2-week intervals up to 24 weeks and included the BRMS, the Hamilton Rating Scale for Depression, the timeline follow-back, and assessment of medication side effects and self-report of medication compliance. Liver function tests (γ-glutamyl transpeptidase [GGTP], alanine aminotransferase, and aspartate aminotransferase) and measurements of trough valproate and lithium serum concentrations were performed at weeks 2, 4, 8, 12, 16, 20, and 24. All study participants were provided with weekly individual dual-diagnosis recovery counseling.

The mixed model with restricted maximum likelihood estimation method and unrestricted covariance matrix was used to analyze longitudinal data. First we used the mixed model with the following covariates: time of assessment, bipolar subtype (mixed, manic, or depressed), and treatment group (placebo or valproate). The second nested model included an additional covariate of compliance.

The sample included 72 adult male and female subjects who enrolled in the study by signing a written, informed consent. Fifty-nine subjects were randomized to the treatment groups. Of these, 52 subjects (valproate, \( n = 27 \); placebo, \( n = 25 \)) had an assessment after randomization and were entered into the intent-to-treat analysis. The sample mean age was approximately 38 years (SD, 9.3 years), 29% were women, and 25% were African American. The two treatment groups were similar on pretreatment demographic and clinical variables at baseline. On average, the valproate group stayed 67% of the study duration (mean, 112 days; SD, 69 days), whereas placebo subjects stayed for 61% of the study duration (mean, 102 days; SD, 67 days). The two groups were similar on the number of counseling sessions received and on adjunctive pharmacological treatments received, with the only exception of medication to enhance sleep, which was higher for the placebo group [\( n = 8 \) (38%) versus \( n = 2 \) (9%); Fisher’s exact test; \( p = 0.031 \)]. The two groups were also similar on the average lithium serum concentration throughout the study [mean, 0.68 mEq/liter (SD, 0.33 mEq/liter) versus 0.66 mEq/liter (SD, 0.30 mEq/liter) for the valproate and the placebo groups, respectively]. The average valproate serum concentration was 51.5 μg/ml (SD, 29). Self-report of medication compliance significantly correlated with the serum lithium concentration (\( p = 0.010 \)) and the serum valproate concentration (\( p = 0.053 \)).

Pharmacotherapy was well tolerated by both treatment groups, and no serious drug-related adverse events were recorded during the study period. The valproate group had a trend toward reporting a higher incidence of nausea than the placebo group [39% (\( n = 9 \)) versus 9.5% (\( n = 2 \)); Fisher’s exact test; \( p = 0.073 \)]. After controlling for time of assessment, age, gender, ethnicity, bipolar subtype, weekly alcohol use, any additional medication, and medical problems, the two groups were similar on changes in liver injury enzymes, alanine aminotransferase, and aspartate aminotransferase. However, the placebo group had significantly higher levels of GGTP than the valproate group (\( p = 0.045 \)). Further, GGTP positively correlated with weekly alcohol use in the same model (\( p = 0.015 \)).

The results of the efficacy analysis with the mixed effects model showed a significant advantage for the valproate group [12 (44.4%) of 27] over placebo [17 (68%) of 25] on the proportion of heavy drinking days (\( p = 0.021 \)) and showed an advantage for the valproate group on the reduction in the number of standard drinks per heavy drinking day [mean, 5.59 (SD, 8.89) vs. 10.21 (SD, 10.78; \( p = 0.055 \)]; this became statistically significant when the compliance variable was added to the model (\( p = 0.018 \)).

The valproate group also had a significant advantage on the time to relapse to sustained heavy drinking [mean, 93 days (SD, 74 days) for the valproate group versus 62 days (SD, 61 days) for the placebo group; Kaplan-Meier survival analysis; \( p = 0.048 \)]. Further, the valproate group had an advantage on the number of drinks per drinking day when the compliance variable was added to the model [mean, 5.14 (SD, 8.52) versus placebo: mean, 8.87 (SD, 10.11; \( p = 0.022 \)].

The two groups were similar on overall changes in mood symptoms. On the average, manic symptoms decreased substantially during the study period; by contrast, depressive symptoms remained at moderate levels for both groups. Although there was no advantage to either group on changes in manic or depressive symptoms, there was a trend for the valproate group to achieve earlier remission (a score of <7 on the BRMS) from mania (Kaplan-Meier survival analysis; \( p = 0.073 \)).

The results of this study confirmed in part our hypothesis that valproate may be useful, not only in stabilizing mood states, but also in decreasing alcohol use among bipolar alcoholics. To our knowledge, this is the first double-blind placebo-controlled study conducted in this population of alcohol dependence and comorbid bipolar disorder. Geller et al. (1998) reported an advantage of lithium over placebo in improving mood symptoms and substance use in a small, 6-week, double-blind, placebo-controlled study of adolescent bipolar disorder with secondary substance use. In that study, however, the placebo group did not receive pharmacotherapy to stabilize their mood state. In our study, valproate seems to have decreased heavy drinking beyond its effect on mood state, because both treatment groups were similar in terms of manic and depressive symptoms. Our findings of decreased heavy alcohol use are concordant with a recent pilot double-blind, placebo-controlled study of valproate in alcohol-dependent patients without comorbid psychiatric conditions (Brady et al., 2002). In that study, valproate had an advantage over placebo on relapse to heavy drinking.

Manic and depressive symptom responses in our study were also concordant with reports in nonalcoholic bipolar
disorder samples of a good response of manic symptoms but a less optimal response of depressive symptoms. The results of our study may have limited generalizability because of the small sample size and setting. However, these results also suggest that valproate may be the preferred medication for patients with alcoholism and bipolar disorder comorbidity.

ALCOHOLISM AND SCHIZOPHRENIA: EFFECTS OF ANTIPSYCHOTICS

Alan I. Green, Robert E. Drake, Suzannah V. Zimmet, Rael D. Strous, Melinda Salomon, and Mark Brenner

Schizophrenia is a chronic, relapsing disorder, with symptoms beginning in late adolescence or early adulthood. Although the disorder is thought to occur nearly equally in men and women, the onset in women tends to be approximately 5 years later than in men. The disorder is characterized by hallucinations and delusions (so-called positive symptoms); by apathy, avolition, and anhedonia (negative symptoms); and by disorganized thinking or behavior. Cognitive deficits also occur, particularly in the domains of attention and memory; such deficits occur early in the course of the disorder and persist, leading to decreases in functioning and to social and occupational disability. Current treatment strategies for the disorder involve the use of antipsychotic medication, especially the atypical (or novel) antipsychotic medications introduced in the past decade. In recent years, there has been an attempt to identify the symptoms of schizophrenia early in the course of the disorder, in the hope that early intervention with atypical antipsychotics may improve the natural trajectory of the disorder.

Alcohol- and substance-use disorders are very common in patients with schizophrenia. The Epidemiologic Catchment Area study (Regier et al., 1990) suggested that 47% of patients with schizophrenia have a lifetime history of a substance-use disorder and that 34% of such patients have a lifetime diagnosis of an alcohol-use disorder. Even studies of patients early in the course of a schizophrenic disorder indicate a high frequency of a comorbid substance-use disorder: cannabis-use disorder, in particular, has been frequently identified in patients within the first episode of schizophrenia.

Alcohol- and substance-use disorders have negative consequences for patients with schizophrenia. They are associated with an earlier age of onset, increased relapses, treatment noncompliance, a poorer overall response to antipsychotic medication, more hospitalizations, increased violence and suicide, and increased medical costs (Green et al., 2002). Decreasing alcohol or substance use in patients with schizophrenia is a major goal of treatment programs.

Given that alcohol and substance abuse is so common in patients with schizophrenia but is associated with such a negative outcome, an important issue relates to the basis of the alcohol/substance abuse in this population. Some have suggested that patients with schizophrenia may use alcohol and other substances to self-medicate negative symptoms of the disorder (e.g., Khantzian, 1997). Our group has proposed a neurobiological theory that suggests that dysfunction in the dopamine-mediated mesocorticolimbic brain reward circuits underlies alcohol and substance abuse in these patients (Green et al., 1999). According to this theory, alcohol and other substances, through their effects on dopamine systems, may transiently ameliorate these reward circuit deficits, but they also worsen the course of schizophrenia. Another neurobiological model, one consistent with ours, has also been proposed by Chambers et al. (2001).

Treatment of patients with schizophrenia involves the use of the antipsychotic medications, introduced into clinical practice in the 1950s. The first of these antipsychotic drugs, now often referred to as typical antipsychotics, are potent blockers of the dopamine D2 receptor. Although these typical antipsychotics are effective in the treatment of positive symptoms of schizophrenia, they tend to have little beneficial effect on negative symptoms or cognitive deficits, and they do not seem to limit the tendency of these patients to use and abuse alcohol and other substances. Beginning with the reintroduction of clozapine in the early 1990s, however, a group of atypical, or novel, antipsychotic medications—medications with a broader spectrum of clinical actions—were introduced into clinical use. Clozapine, the prototype novel antipsychotic, is more effective than other agents in the treatment of patients unresponsive to typical agents (Kane et al., 1988). It is interesting to note that clozapine, unlike the typical antipsychotics, is a relatively weak D2 receptor blocker, but it has potent antagonistic effects at other dopamine receptors, as well as at adrenergic and serotonergic receptor sites. This broad-spectrum pharmacological profile of clozapine is thought to be related to its unusual panoply of clinical effects.

The potential value of the novel antipsychotic agents in patients with schizophrenia and co-occurring alcohol-use and other substance-use disorders has been investigated in recent years. Most of the available evidence involves clozapine. Preliminary studies from our group and others suggest that clozapine treatment is associated with a decrease in alcohol and other substance use in patients with schizophrenia. In a naturalistic, clinical services survey by our group, we reported that among 151 patients who had a co-occurring alcohol-/substance-use disorder, remission of alcohol-use disorder occurred in 79% of patients treated with clozapine versus 34% of patients treated with a typical agent (Drake et al., 2000). A second retrospective study by our group reported consistent findings (Zimmet et al., 2000). Moreover, these data regarding the effects of clozapine in this population are supported by similar data developed by two other groups of investigators (Buckley et al., 1999; Lee et al., 1998).

Data regarding the potential effects of the other novel antipsychotics are quite limited. We have reported that
risperidone may not be as effective as clozapine in limiting alcohol or cannabis use in these patients (Green et al., 2003), although a report by Smelson et al. (2002) suggests that patients with schizophrenia and comorbid cocaine dependence have a better outcome when treated with risperidone than do patients treated with the typical antipsychotic haloperidol. Others have suggested that olanzapine may have some effectiveness in this population, although a study by Noordsy et al. (2001) suggests that the rate of improvement in patients treated with olanzapine is similar to that achieved by patients treated with typical antipsychotics. Finally, limited data developed by Brown et al. (2002) suggest that the novel antipsychotic quetiapine may decrease stimulant cravings in comorbid patients. Clearly, further studies on clozapine and other novel antipsychotics need to be performed in this population. Our group is engaged in a study of clozapine versus other antipsychotics in patients with schizophrenia and co-occurring alcohol-use disorder that may contribute new data to this issue.

Our group has suggested that the effects of clozapine in patients with co-occurring alcohol-use and other substance-use disorders may relate to the broad-spectrum pharmacological effects of clozapine—including its weak D2-blocking ability linked to its blocking ability at noradrenergic α2 receptors and its ability to increase norepinephrine in the brain and periphery—that tend to ameliorate the dysfunction in the dopamine-mediated brain reward circuits that underlie substance abuse in comorbid patients (Green et al., 1999). Studies are under way in animals and in humans to assess whether this theoretical formulation can be supported by experimental investigation.

CONCLUSIONS
Charlene E. Le Fauve and Raye Z. Litten

Drs. Carrie Randall and Sarah Book examined the hypothesis that successful treatment of social anxiety in the course of alcohol treatment will improve drinking outcome, by using two randomized clinical trials (CBT and paroxetine). Results of the CBT trial showed no differences in drinking outcome between treatment-seeking alcoholics treated for alcoholism only and those treated for both alcoholism and social anxiety disorder. However, a small, double-blind, 8-week placebo-controlled clinical trial showed differences in alcohol outcome variables toward the end of the trial such that, in addition to improvements in social anxiety levels, clinician-rated improvement in alcohol severity was better in the paroxetine group.

Dr. Darlene Moak provided an excellent review of medication trials to treat depression and alcoholism. The literature reveals mixed results depending on how the diagnosis of depression is derived (Structured Clinical Interview for DSM versus PRISM), the type of depression (lifetime, current, moderate, severe, primary, or secondary), the type of medication (SSRIs or tricyclics), and other variables such as gender and the type of alcoholism (type A versus type B). She concludes with a discussion of the use of combinations of SSRIs and other medications (e.g., naltrexone or acamprosate) or the use of other antidepressants with different mechanisms of action from those of the SSRIs (e.g., venlafaxine).

Dr. Ihsan Salloum and colleagues tested the hypothesis that sodium valproate, an anticonvulsant mood stabilizer, may be useful in decreasing alcohol-use outcomes and also stabilizing mood symptoms among treatment-seeking alcoholics with a comorbid diagnosis of an acute episode of bipolar I disorder. The essential feature of bipolar I disorder is a clinical course that is characterized by the occurrence of one or more manic episodes or mixed episodes (i.e., meeting criteria for both manic episode and major depressive episode nearly every day for at least a week). Often individuals have had one or more major depressive episodes (DSM-IV). In the only study of its kind, Dr. Salloum and colleagues conducted a double-blind, placebo-controlled, randomized parallel-group trial comparing medication plus TAU with placebo plus TAU. The results confirmed that in addition to stabilizing mood, sodium valproate also decreased alcohol use in bipolar alcoholics.

Dr. Alan Green and colleagues offered a brief summary of the comorbidity literature with respect to alcohol and substance-use disorders among schizophrenic populations. The group presents a distinction between the use of typical and atypical (or novel) antipsychotics with respect to alcohol- and substance-use disorder outcomes. Clozapine, an antipsychotic with a broad spectrum of antagonistic effects at some dopaminergic, adrenergic, and serotonergic receptor sites, has shown the most promise in the treatment of alcoholics who also have severe mental illness. A theoretical model is offered that might explain the improvements seen in alcohol outcomes; this warrants further study.

Findings presented here are encouraging and support the need for more pharmacotherapy trials that target psychiatric comorbidity. The data show very preliminary evidence that to best serve persons who meet criteria for more than one disorder in combination with alcoholism, the alcohol treatment research field must make this area a priority. Several promising avenues have been identified here for continued work on establishing the efficacy of specific pharmacotherapies for the treatment of alcohol abuse and alcoholism as they occur juxtaposed with anxiety, depression, bipolar disorder, and schizophrenia. Trials are still needed to explore combinations of medications and to effectively integrate pharmacotherapies with psychosocial therapies. Matching specific pharmacological/psychosocial interventions to different aspects of alcoholism and comorbid psychopathology and devising techniques to enhance compliance are other areas that require further exploration.

Those who are both alcoholic and anxious, depressed, bipolar, schizophrenic, or otherwise psychiatrically compromised require unique expertise for effective treatment from providers. Often seen in primary care settings, emergency
rooms, homeless shelters, or community service entities, individuals with these comorbid disorders rarely obtain proper diagnoses and treatment during their initial contact with health-care systems. Research is sorely needed to improve the cadre of medication and behavioral treatment options that might be provided. Until we are able to treat all aspects of comorbid psychiatric conditions along with alcohol dependence, we will unsuccessfully treat the individual as a whole.

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