

Bipolar Disorder

& IMPULSIVE SPECTRUM LETTER

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Bipolar Disorder With Comorbid Alcohol or Substance Abuse

by Joseph F. Goldberg, MD

Epidemiologic studies in the past two decades show that lifetime drug and alcohol abuse or dependence arises in half or more of individuals with bipolar disorder (BD).^{1,2} Among adults with drug or alcohol use disorders, BD is more likely to co-occur than any other Axis I psychiatric disorder.³ More recent findings from the National Institute on Alcohol Abuse and Alcoholism's National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) reveal nearly a 14-fold increased risk for any drug dependence in those with mania,⁴ citing a 58.0% lifetime prevalence of alcohol abuse or dependence and a 37.5% lifetime prevalence of any drug use disorder among individuals with BD.⁵

Some observers speculate that drug and alcohol use disorders may be more prevalent in the general population today than was the case in past generations. Others have suggested that the relatively high prevalence rates of these disorders in the modern era reflect better awareness of the deleterious effects of drugs and alcohol, coupled with more rigorous screening and surveillance monitoring. Regardless of the possible causes, dual-diagnosis BD with alcohol or drug misuse remains a significant challenge for diagnosis and treatment and a substantial source of morbidity and mortality among individuals with complex

forms of affective disorder.

Despite the frequent co-occurrence of drug or alcohol abuse or dependence with BD, as described in **Figure 1**, remarkably little systematic research has examined this distinct patient subgroup. Most clinical pharmacotherapy trials in patients with BD exclude those with current or recent alcohol or substance abuse/dependence, since in clinical practice it is difficult to clarify when behavioral or mood symptoms are the cause or the result of psychoactive substance misuse. In some instances, psychoactive substance use could arise as a maladaptive effort to modulate dysphoric affective states, anxiety or mood instability; in others, substance misuse may derive from recklessness or sensation-seeking behaviors associated with mania; in still other settings, BD and substance misuse may coexist as two distinct illnesses that exert mutually antagonistic effects. No single model appears to explain the basis for coincident substance use disorders and BD, requiring clinicians to adopt a systematic approach to understanding symptoms and providing appropriate pharmacotherapy and/or psychosocial interventions.

Diagnostic Uncertainties

Because alcohol and drug abuse or dependence often coincide with mood

instability and impulsive behaviors, clinicians often struggle to discriminate between so-called primary mood disorders and the iatrogenic effects of psychoactive substances. The *DSM-IV-TR* identifies the construct of a substance-induced mood disorder as a "prominent and persistent disturbance in mood that is judged to be due to the direct physiological effects of a substance," such as a drug of abuse. Some authors have reported that structured interviews, such as the Psychiatric Research Interview for Substance and Mental Disorders (PRISM),⁶ can help improve the reliability and confidence with which some psychiatric diagnoses can be made among individuals with active substance abuse.⁷ However, formal rater agreement of lifetime primary mood disorder diagnoses in patients with current substance abuse appears to be lower for BD ($\kappa=0.40$) than for major depressive disorder ($\kappa=0.70$).⁷

While some clinicians (and the *DSM-IV-TR*) attach substantial importance to the chronology of substance abuse and affective symptoms, epidemiologic studies suggest that over 90% of individuals with mood symptoms during periods of active substance abuse meet lifetime *DSM-IV* criteria for an independent mood disorder.⁴ In the absence of a reliable formula by which to discern substance-induced mood

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Educational Objectives

Upon completion of this activity, the learner will be able to:

- Discuss the prevalence and epidemiology of bipolar disorder with comorbid alcohol/substance abuse.
- Explain the complex relationship between bipolar disorder and alcohol/substance abuse.
- Review current psychosocial and pharmacologic treatments for bipolar disorder with comorbid alcohol/substance abuse.

Who Will Benefit

This activity was designed to meet the continuing education needs of psychiatrists and other physicians, physician assistants, registered nurses and advanced practice psychiatric nurses. Other mental health care professionals may find this activity informative and should check with their state licensing and certification boards to determine if it meets their continuing education requirements.

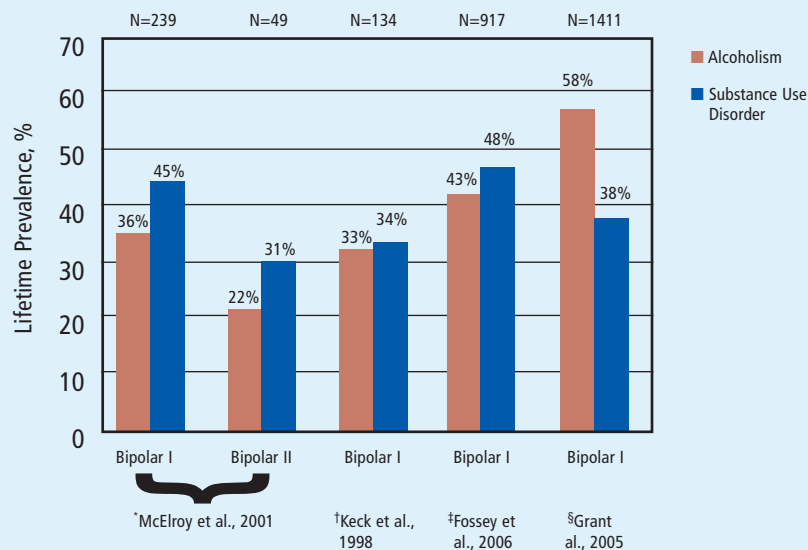
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Figure 1

Lifetime Prevalence Rates of Alcohol and Substance Abuse or Dependence in Contemporary Studies of Bipolar Disorder (Sample Sizes >100)



*McElroy et al. *Am J Psychiatry*. 2001;158(3):420-426; †Keck et al. *Am J Psychiatry*. 1998;155(5):646-652; ‡Fossey et al. *Am J Addict*. 2006;15(2):138-143; §Grant et al. *J Clin Psychiatry*. 2005;66(10):1205-1215.

Source: Goldberg JF (2006)

disorders from separable dual diagnoses, clinical strategies may be guided by basic principles as summarized in the **Table**.

Research efforts to untangle the chronology of substance misuse and mood disorders have been further hampered by a scarcity of prospective long-term investigations. Few follow-up studies account for the impact of illness duration, other comorbidities and the effects of past treatment nonresponse when considering the effect of alcohol or substance misuse on the course of BD. Such potential confounding factors are at least partly minimized in studies that focus on patients identified during a first affective episode, before later-stage disease complications arise. Notably, while prevalence rates of alcohol or substance abuse/dependence in first-episode mania patients (~30%)⁸ are higher than rates seen in the general population (about 15% to 20%), they remain considerably lower than the 60% to 70% prevalence rates reported in large-scale epidemiologic studies that include multi-episode patients,

as reported in the National Comorbidity Survey,² the Epidemiologic Catchment Area Survey¹ or NESARC samples.⁵ A key clinical implication from these observations is the potential for early diagnosis and treatment to forestall the progression, and the near-doubling of prevalence rates, of substance misuse as a later complication of multiple episodes in BD.

Strakowski and colleagues⁹ conducted a five-year follow-up study of 144 first-episode mania patients, of whom 27 had prior alcohol abuse/dependence and 33 developed alcohol abuse/dependence subsequent to a first mania. When mania preceded alcoholism, recovery from the index manic episode was slower and less frequent, and time spent with both alcohol and affective symptoms was more extensive during the follow-up period. Rather than conclude that antecedent alcoholism “protects” against poor outcome in BD, other analysis suggested that the age at onset of BD may occur later when alcoholism precedes rather than follows a first manic episode.¹⁰

Further support for this distinction comes from recent data from the National Institute of Mental Health’s Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), comparing outcomes for patients with BD that preceded substance abuse (primary) or followed it (secondary).¹¹ From among the first 1,000 patients entering the STEP-BD program, those with a comorbid substance use disorder were substantially more likely to have the onset of their BD precede their onset of substance misuse (62%), while 26% had their onset of a substance use disorder before their onset of bipolar illness; an additional 11% had coincident onset of both disorders. As compared to patients in whom substance use disorder preceded the onset of BD, those in whom BD preceded a substance use disorder had fewer days of euthymia, more episodes of mania and depression, and a more extensive history of suicide attempts. However, these differences in outcome were no longer seen when controlling for the age at onset of BD.

In further studies tracking the course of alcohol and affective symptoms, Fleck and colleagues¹² recently found no direct temporal correlation between alcohol use symptoms and symptoms related to mania or depression, although age at onset of BD again emerged as a significant mediator of illness course. Patients whose alcoholism preceded their BD had a substantially later age at onset of BD (mean age=24) than was seen in patients for whom BD preceded the onset of alcoholism (mean age=16). Alcoholism preceding BD appears associated with a lower risk for alcohol abuse to progress to dependence.

Family-Genetic Correlates

Winokur and colleagues¹³ were among the first to describe differences in the familial risk for BD in patients with versus without comorbid alcoholism or drug abuse. In a series of investigations, familial risk for BD appeared greater in bipolar probands with (rather than without) drug abuse.¹⁴ However, a family history of alcoholism was not increased among alcoholic versus nonalcoholic patients with BD,¹⁵ nor was a family history of BD greater in dual-diagnosis versus bipolar-only probands.¹³ These findings argue against an additive



model of genetic risks for two separate disorders. Subsequent work has further suggested that among alcoholic patients with BD, familial risk for bipolar illness appears greater when alcohol abuse follows, rather than precedes, the onset of BD.¹⁶

Epidemiologic Considerations

While alcoholism in general appears more frequently among men than women, women with BD have a substantially higher risk for alcoholism as compared to women in the general population (about sevenfold); by contrast, there appears a comparatively much lower risk for alcoholism among men with BD as compared to men in the general population (about threefold).¹⁷ Possible racial differences have not been identified for the prevalence of alcohol or other drug abuse specifically in patients with BD, although higher risks for substance use disorders among ethnic minorities have previously been well-documented in the general population. Barriers to treatment for substance use disorders in the United States are also more extensive for African Americans or Hispanics than for whites.¹⁸

Neurobiology and Neurocognition

Structural as well as possible functional neuroanatomic deficits have been associated with alcohol abuse or dependence co-occurring with BD. Frye and colleagues (personal communication) examined changes in white matter density in bipolar patients with or without comorbid alcoholism and found greater ratios of n-acetylaspartate (a marker of neuronal viability) to choline (an index of white matter density) in hippocampal regions among participants with alcoholism, suggesting a greater loss of white matter in the presence of alcoholism, above and beyond the extent of white matter disease otherwise associated with BD itself.¹⁹

In studies of neurocognitive function, as compared to normal control participants, patients with BD plus alcohol dependence demonstrated poorer executive function (verbal memory) and frontal lobe deficits (e.g., set shifting and categorization) above and beyond the neurocognitive deficits typically seen in BD without comorbid alcoholism.²⁰ The duration of affective illness and early age at onset both appear

Table

Clinical Considerations in the Differentiation of Substance-Induced Versus Primary Affective Disorders

- Longitudinal history, focusing on historical presence of prolonged mood symptoms (or formal syndromic criteria, per *DSM-IV*) prior to the onset of substance abuse (per *DSM-IV*) or else in the established absence of intoxication or withdrawal states
- Persistence of affective symptoms beyond a reasonable period of time (e.g., 4 weeks, per *DSM-IV*) following intoxication or withdrawal states
- Role for collateral history from third-party historians
- Family history of affective disorder
- Early age at onset of mood disorder

Source: Goldberg JF (2006)

to contribute to neurocognitive deficits in patients with BD, although the adverse effects of alcohol on frontal lobe function appear to occur independent of these features related to the illness burden of BD.

Impact on Course of Illness

Comorbid alcohol or substance use disorders are frequently cited contributors to poor treatment outcome, illness complexity and functional impairment. Even among first-episode patients, the time until recovery from an index manic episode lags significantly in the presence of comorbid substance abuse/dependence.²¹ In the STEP-BD study, bipolar patients with either past or current substance abuse had poorer psychosocial functioning and quality of life as compared to bipolar patients with no substance abuse; however, outcomes were less impaired after sustained remission from substance use disorders.¹¹

It remains an issue whether (and when) BD and alcohol or substance use disorders may follow a similar or divergent longitudinal course. Winokur and colleagues¹³ found the course and prognosis of alcoholism to be more favorable in the presence rather than absence of BD. In outcome studies of first-episode mania, affective relapse occurred in the absence of recurrent alcohol symptoms about half the time (54%), while alcohol relapse occurred independent of mood symptoms in the remainder (46%).¹⁰

Drug and alcohol misuse in BD have been recognized as contributors to poor

clinical or functional outcome in a number of domains. An elevated risk for suicidal behaviors has notably been a key area related to comorbid substance use. Even when affective symptoms may be substance-induced rather than primary, a threefold risk for suicidal behaviors has been demonstrated in patients with known prior diagnoses of BD.²²

Psychosocial Treatments

The confluence of alcohol or drug abuse with BD can involve unique cognitive, emotional, interpersonal and behavioral difficulties for which structured psychotherapies can provide useful augmentation to pharmacotherapy. Approaches that have been empirically studied include variants of cognitive therapy, particularly an integrative group therapy (IGT) developed by Weiss and colleagues²³ that incorporates elements of substance abuse relapse prevention in conjunction with a cognitive-behavioral approach focusing on issues related to mood, medication adherence, managing high-risk situations and the use of coping skills. Weiss et al.²⁴ found that about two-thirds of dual-diagnosis patients with BD and substance abuse perceived their drug use as a means to self-regulate one or more affective symptoms. After six months, IGT was associated with significantly fewer days of drug use among the patient subgroup that linked their substance use with self-regulation. This suggests that screening for such associations may be a useful parameter

for estimating the potential utility and efficacy of prescribed psychotherapy.

Other forms of psychotherapy that have begun to demonstrate antidepressant or thymoleptic efficacy in conjunction with pharmacotherapy for BD include interpersonal/social rhythm therapy and family-focused therapy. While these modalities have not yet been adapted or studied for individuals with comorbid alcohol or drug use disorders, they offer promising strategies for targeting symptoms and functional impairment in dual-diagnosis patients with BD. Particular issues related to depression, interpersonal loss and risk for suicide may also be especially relevant for cognitively oriented psychotherapies adapted to dual-diagnosis patients with BD and alcoholism.²⁵

Finally, the role of 12 Step and related support groups has not received formal study among substance-abusing patients with BD. In general, participation in such programs as an adjunct to formal treatment has been associated with a doubling of the likelihood to maintain recovery from alcoholism as compared to outcomes for individuals in treatment without involvement in a 12 Step program.²⁶

Pharmacotherapy Implications

A number of general principles bear on the management of BD with comorbid substance misuse. A first consideration is when to intervene pharmacologically for affective symptoms that arise in the context of extensive drug or alcohol use. Because dysphoria and disinhibition are common and often self-limited phenomena during acute intoxication states, some experts advise caution in assuming a need to introduce psychotropic medications beyond those needed to manage acute withdrawal states. Most authorities point to the importance of a longitudinal history in determining the role for mood-stabilizing or other long-term agents. In other words, the historical presence of a lifetime manic or hypomanic episode in the absence of active alcohol or drug abuse would support the utility of starting, restarting or optimizing an antimanic agent. The persistence of affective symptoms beyond several weeks' duration after resolution of a detoxification or withdrawal state also may favor the use

of thymoleptic agents. In practice, clinicians sometimes initiate mood-stabilizing and/or antidepressant medications when affective symptoms prominently arise during periods of drug or alcohol abuse despite the absence of empirical evidence for the necessity or efficacy of antimanic or antidepressant medications for substance-induced mood disorders, based largely on concepts related to harm avoidance in the absence of clear diagnoses of an independent affective disorder.

Delayed time until the initiation of mood stabilizers also bears on the longitudinal course of illness, and the potential for a more complex course of illness. Goldberg and Ernst²⁷ found that in patients with BD plus comorbid alcoholism, the average time until first treatment with a mood stabilizer was longer (average=13.3 years) than that seen in bipolar patients without comorbid alcoholism (average=8.2 years).

At the same time, some data preliminarily question the safety of certain psychotropic agents in the presence of substance abuse. In one retrospective study, a lifetime history of drug or alcohol abuse/dependence was associated with an approximate sevenfold increased likelihood for the development of antidepressant-induced mania.²⁸ Safety issues also arise when using hepatically metabolized agents without first assuring adequate liver function. For example, the use of divalproex (Depakote) is generally considered safe provided that liver enzyme levels do not exceed more than three times the upper limit of a laboratory normal reference range. There exists only a limited controlled trial literature on the pharmacotherapy of BD with comorbid substance abuse, which may be summarized as follows.

Lithium. Despite initial enthusiasm about the possible benefits of lithium (Eskalith, Lithobid) to reduce symptoms of alcohol abuse,²⁹ naturalistic studies have suggested that lithium may be less effective for BD when complicated by alcohol or drug abuse.^{30,31} (Indeed, alcohol and substance use comorbidity have come to represent a common form of illness complexity that appears to diminish the optimal benefits of lithium, prompting interest in alternative mood-stabilizing agents during the past two decades.) One small retrospective chart review found higher rates of recovery

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from acute mania with comorbid substance abuse/dependence during treatment with divalproex or carbamazepine (Tegretol) (either alone or with lithium) as compared to lithium pharmacotherapy with neither anticonvulsant.³²

Interestingly, by contrast, a small, randomized, controlled trial of lithium in adolescent outpatients with BD and comorbid substance abuse/dependence found significantly greater reductions in both substance use and overall outcome with lithium than placebo (46.2% versus 8.3%, respectively, in the intent-to-treat sample).³³ These observations raise the hypothesis that comorbid substance abuse might attenuate lithium responsivity in adult patients with BD, but potentially to a lesser degree in pediatric BD where neuronal plasticity may be more robust.

Divalproex. Despite the wide prevalence of BD with comorbid alcohol or drug use disorders, divalproex at present stands as the only psychotropic compound with efficacy in adult patients with BD and current alcoholism. After initial open-label trials suggested the mood benefits of divalproex to be robust despite the presence of alcohol or substance abuse/dependence,^{32,34} Salloum and colleagues³⁵ published a large, randomized, double-blind trial comparing divalproex to treatment as usual, consisting of lithium carbonate and psychosocial interventions. While reductions in manic or depressive symptoms were similar between both treatment arms, a significantly greater reduction in drinking behavior was observed among participants taking divalproex (**Figure 2**). Specifically, patients taking divalproex had significantly fewer drinks per day, fewer drinks per heavy drinking day and a lower proportion of heavy drinking days. Those taking divalproex or placebo were similar at baseline in key illness parameters (such as years of alcoholism or BD, extent of alcohol use, or current affective symptoms). This observation suggests a potential advantage for divalproex to reduce symptoms of alcoholism, independent of its efficacy for affective symptoms, in dually diagnosed patients with BD.

In a separate investigation of adults with BD and substance abuse, Weiss and colleagues³⁶ observed significantly higher

rates of medication adherence during pharmacotherapy with divalproex than lithium. Because poor treatment adherence arises in half or more of individuals with BD,³⁷ particularly those with comorbid drug or alcohol abuse/dependence,³⁸ attention to differences in adherence patterns across mood-stabilizing agents becomes a useful dimension when anticipating long-term outcomes.

Topiramate. Among anticonvulsant agents, topiramate (Topamax) incorporates several mechanisms of action thought to contribute to thymoleptic effects: It exerts an anti-glutamatergic (i.e., antiexcitatory) effect by blocking the post-synaptic α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/Type II kainic acid receptor; it blocks sodium and calcium channels; and it is an inhibitor of carbonic anhydrase. Despite these properties, several controlled trials have found no advantage for topiramate over placebo in the treatment of bipolar mania.³⁹ Possible antidepressant properties were suggested in one small randomized study comparing topiramate to bupropion (Wellbutrin),⁴⁰ although reports exist elsewhere in the epilepsy literature suggesting the potential for topiramate to destabilize mood by inducing depression.⁴¹ While its thymoleptic effects remain unproven, topiramate has shown robust efficacy for reducing alcohol use in adults with alcohol dependence. Johnson and colleagues⁴² published a randomized, double-blind, placebo-controlled trial of topiramate (target dose of 300 mg/day) in adults with alcohol dependence and observed fewer drinks per day, fewer drinks per drinking day, longer days of abstinence and less craving with topiramate than placebo.

Other anticonvulsants. Apart from divalproex, extended-release carbamazepine (Equetro) and lamotrigine (Lamictal) remain the sole other anticonvulsant agents with demonstrated efficacy from placebo-controlled trials in at least one phase of BD. One small open trial with lamotrigine for outpatients with BD and cocaine dependence found significant improvement in affective symptoms as well as dollars spent on cocaine,⁴³ although the small sample size and lack of a placebo or comparison group make these findings preliminary in nature.

Limited controlled data exist to support the utility of other anticonvulsant agents for acute episodes of mania or depression in patients with BD. However, recent findings involving links between anxiety and alcoholism suggest a potential ancillary role for at least some anticonvulsants, regardless of their thymoleptic efficacy per se. For example, Perugi and colleagues⁴⁴ evaluated the effectiveness of open-label gabapentin (Neurontin) (mean dose=1270 mg/day) in treatment-resistant BD and found the presence of panic disorder and alcohol abuse to be predictive of a favorable overall response. This suggests the possibility that gabapentin may be useful for targeting comorbid features of anxiety and alcoholism in patients with BD.

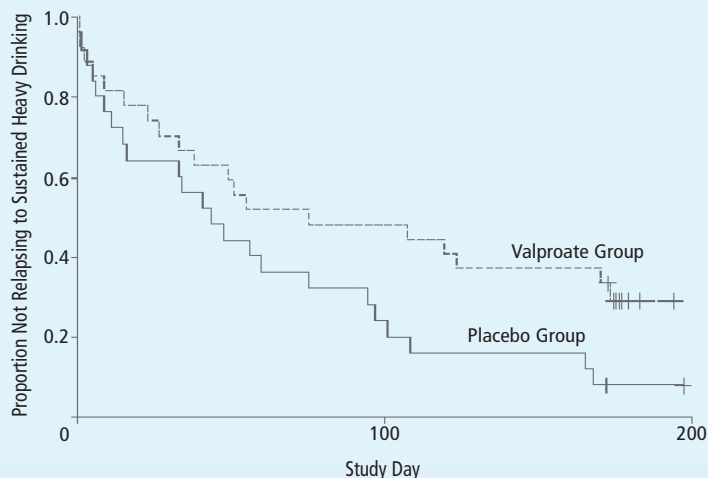
Other anticonvulsant agents with possible anxiolytic effects include tiagabine (Gabitril)⁴⁵ and pregabalin (Lyrica).⁴⁶ However, the former agent has been associated with pro-convulsant effects as well as the worsening of affective symptoms in patients with BD,⁴⁷ while reports of the induction of mania have been reported in premarketing studies in connection with the latter agent.

Naltrexone. Naltrexone (ReVia) remains among the best-studied and most efficacious pharmacotherapies for alcohol dependence,⁴⁸ and its new long-acting injectable formulation (Vivitol) represents a potentially helpful addition to existing medication options. Neither naltrexone nor the injectable formulation have been systematically studied in individuals with alcohol dependence comorbid with BD. Sonne and Brady⁴⁹ reported two cases of apparent opiate withdrawal induced by naltrexone, raising the interesting hypothesis that blockade of endogenous opiates in patients with BD could adversely affect mood and physiologic homeostasis. Further studies are needed to evaluate both the safety and efficacy of naltrexone for alcoholism in individuals with BD.

Disulfiram. Little information exists regarding the safety and efficacy of disulfiram (Antabuse) for individuals with BD. As an inhibitor of dopamine- β -hydroxylase, there exists at least theoretical concern for the potential induction of psychosis,⁵⁰ although such adverse outcomes have not been extensively reported in the clinical

Figure 2

Divalproex Versus Placebo for Alcohol Relapse Prevention in Bipolar Disorder



Kaplan-Meier survival curve for time to relapse to sustained heavy drinking (3 consecutive heavy drinking days [≥ 5 drinks per day for men and ≥ 4 drinks per day for women]), by treatment group (log-rank test, $P = .048$).

Source: Salloum et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Arch Gen Psychiatry*. 2005;62(1):37-45. Reprinted with permission.

literature.

Acamprosate. Acamprosate (Campral), the most recently approved pharmacotherapy for alcohol dependence, is thought to modulate alcohol craving via its blockade of the metabotropic glutamate subtype 5 receptor,⁵¹ which may in turn regulate mesolimbic dopamine function.⁵² Studies have not been reported on the use of acamprosate in individuals with BD, although given its putative ability to reduce glutamatergic transmission, it holds theoretical interest for possible mood regulatory effects. The recent multicenter Combined Pharmacotherapies and Behavioral Interventions (COMBINE) trial⁴⁸ found a surprisingly poor outcome with acamprosate in reducing alcohol relapse symptoms relative to other treatments, including naltrexone.

Modafinil. Modafinil (Provigil) is a nondopaminergic stimulant with minimal abuse liability approved by the U.S. Food and Drug Administration for improving wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea and shift work sleep disorder.

The rationale for its use in cocaine dependence stems from its potential to reduce anergia, anhedonia and craving and from an effect on cognitive processes to reduce impulsive responding.⁵³ A recent preliminary randomized, controlled trial in adult patients with cocaine dependence suggested an advantage for modafinil over placebo.⁵⁴ Elsewhere, modafinil has shown greater antidepressant efficacy than placebo when added to mood stabilizers for patients with bipolar depression.⁵⁵ Together, these observations raise the possibility that the off-label use of modafinil could yield some benefit for depressed patients with BD.

Atypical antipsychotics. Limited data suggest a potential role for quetiapine (Seroquel) for the improvement of mood symptoms, as well as prolongation of abstinence, in patients with substance dependence,⁵⁶ including cocaine dependence.⁵⁷ The potential anxiolytic and antidepressant effects of quetiapine, as observed in studies of bipolar depression without active alcohol or drug abuse,⁵⁸ suggest a further role for this agent to target anxiety or depressive features in BD, in themselves common when alcohol or

substance abuse comorbidity is evident.

Another small, open trial found significant improvement from baseline in affective symptoms as well as alcohol craving when substance-abusing patients with BD or schizoaffective BD were switched from other antipsychotics to aripiprazole (Abilify).⁵⁹ This agent may be of particular interest to problems related to craving and substance abuse by virtue of aripiprazole's partial agonism of the D₂ dopamine receptor, which could at least theoretically help to regulate abnormal dopaminergic tone in the reward pathway. Other atypical antipsychotics have not, as yet, been the specific focus of study in bipolar patients with comorbid alcohol or substance abuse.

Combined Interventions

Clinicians and patients often presume that integrative treatments merging pharmacotherapy with structured psychosocial interventions likely yield better outcomes than those seen with either modality alone. While such conceptualizations make clinical sense, there has been little research specifically examining this issue. Among individuals with alcoholism, there exists a small literature to suggest an advantage for combining naltrexone with a specific behavioral intervention;⁶⁰ but it is noteworthy that the recent multisite COMBINE randomized, controlled study⁴⁸ found that patterns of recovery seen with naltrexone plus medical management were no greater with the addition of a cognitive-behavioral intervention. Those investigators speculated that the structure, format and consistency of medical management may have provided a meaningful additional benefit to naltrexone alone, making it difficult to discern the optimal specific content of an effective psychosocial intervention added to naltrexone. Whether or not such psychotherapy-augmentation strategies would yield different findings in the presence of alcoholism with an active mood disorder remains to be demonstrated.

Summary

Bipolar disorder and alcohol or substance use disorders frequently co-occur. Accurate diagnosis involves a systematic assessment of longitudinal symptoms and their relationship to periods of abstinence. Prognosis and



outcome generally appear better when the onset of BD occurs later in life, and when it follows rather than precedes the emergence of substance misuse. Despite a limited database from randomized trials with dual-diagnosis patients, pharmacotherapies can be utilized that target specific symptom domains related to mood, anxiety, craving and impulsivity. Self-help recovery programs may provide a useful adjunct to formal treatment. Psychotherapies integrated with pharmacotherapies should aim to address relapse-prevention skills, recognition of prodromal symptoms, medication adherence, and the cognitive and interpersonal factors that may jeopardize sobriety or sensitize patients to mood destabilization and relapse.

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Posttest

1. Epidemiologic studies suggest that over ____ of individuals with mood symptoms during periods of active substance abuse meet lifetime *DSM-IV* criteria for an independent mood disorder.
 - a. 65%
 - b. 70%
 - c. 85%
 - d. 90%
2. From among the first 1,000 patients entering the STEP-BD program, which statement below is TRUE?
 - a. Patients with comorbid substance use disorder were more likely to have the onset of their BD precede their onset of substance misuse.
 - b. Patients with comorbid substance use disorder were more likely to have the onset of a substance use disorder before their onset of bipolar illness.
 - c. Patients with comorbid substance use disorder were more likely to have coincident onset of both disorders.
 - d. None of the above.
3. Which of the following statements are TRUE?
 - a. Women with BD have a substantially higher risk for alcoholism as compared to women in the general population.
 - b. Men with BD have a much lower risk for alcoholism compared to men in the general population.
 - c. a and b
 - d. None of the above.
4. Which of the following psychosocial treatments may be useful in treating patients with BD and substance use disorders?
 - a. Family-focused therapy
 - b. Integrative group therapy
 - c. Interpersonal/social rhythm therapy
 - d. All of the above
5. A lifetime history of drug or alcohol dependence may be associated with a _____ increased likelihood of antidepressant-induced mania.
 - a. Threefold
 - b. Sevenfold
 - c. Twofold
 - d. 12-fold
6. The COMBINE study found that medication plus a cognitive-behavioral intervention resulted in which of the following outcomes?
 - a. Better than medication and medication management.
 - b. Worse than medication and medication management.
 - c. No different than medication and medication management.
 - d. None of the above.