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New Medication Strategies for Comorbid Substance Use and Bipolar Affective Disorders

Comorbidity of substance abuse disorders (SUD) with bipolar disorders (BPD) is a serious treatment problem. Childhood BPD can be further complicated by comorbidity with attention-deficit/hyperactivity disorder (ADHD) and later SUD during adolescence. The aim of this article is to review the literature on pharmacotherapies for these patients. Developing the ideal pharmacotherapy for BPD and SUD can be informed by the role of γ-aminobutyric acid (GABA) in the neurobiology of SUD. This ideal pharmacotherapy would have several key characteristics. These characteristics include treating the BPD, relieving withdrawal symptoms, and preventing relapse to SUD. The ideal medication should have low abuse liability, require infrequent dosing, be well tolerated, and have few side effects. A medication approaching this ideal is the GABA enhancer valproate. Adding atypical antipsychotic agents might not improve valproate's efficacy, but combining GABA medications with selective serotonin reuptake inhibitors holds promise for SUD with depression. Pemoline might be the best option for minimizing the risk of SUD complicating comorbid ADHD with BPD.

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Substance use disorders (SUD) have substantial comorbidity with affective disorders, particularly bipolar disorder (BPD) (Frye et al 2003; Merikangas et al 1998). In the most often cited community survey, persons with bipolar I disorder had a 46% lifetime prevalence of alcohol-related disorders, compared with only 14% in the population as a whole (Regier et al 1990). Bipolar disorder is also much more common in people with alcohol dependence than in the general population, with a 6% prevalence in men (odds ratio 12) and 7% in women (odds ratio 5). Comorbidity of SUD with an affective disorder, particularly bipolar disorder, is associated with poorer treatment outcome than BPD alone (Rounsaville et al 1986, 1987; Salloum and Thase 2000). The challenge is to discover medications that treat both the SUD and comorbid BPD simultaneously. Many pharmacotherapies are effective for BPD; however, of the SUDs, only three—alcohol, opiates, and nicotine—have specific approved pharmacotherapies. The other classes of drugs, including stimulants and marihuana, have no approved pharmacotherapies, although active medication development programs are under way. Because there are few SUD pharmacotherapies, several medications that have been effective for BPD have also been examined for SUD with comorbid BPD; however, controlled trials in bipolar patients with comorbid SUD are lacking, despite severe complications from this comorbidity.

Substance abuse disorders are associated with such problems as poor medication compliance, more medication side effects, money needed for daily living being spent on drugs, and involvement in illegal activities. Furthermore, the drug use itself can cause effects that interfere with treatment of both the SUD and the comorbid disorder. For example, alcohol use can lead to amnesia, withdrawal hallucinations, seizures, and organic brain syndromes that might result from metabolic complications of liver dysfunction (Batey 2000). Stimulant use can cause paranoia, suicidality, strokes, and seizures (Kosten and Singha 2001). These effects

might impair judgment and contribute to drug abuse in these populations. In addition, drug abuse might be promoted because it improves secondary effects of treatment medications, such as relief from the side effects of neuroleptics; however, complications of conventional neuroleptic medications might be less common in drug-abusing psychotic patients, who seem to have fewer negative symptoms of psychosis and less parkinsonism (Kosten and Ziedonis 1997; Krystal et al 1999). Yet, patients might also self-medicate with abused drugs to relieve dysphoria and social isolation related to psychosis (Green et al 1999). Medications might prevent aversive effects of abused drugs (such as post-stimulant abuse crashes) or enhance the "high" from abused drugs, leading to continued drug use (Buckley 1998). Clearly, there are various reasons that drug abuse is sustained in these comorbid populations.

The purpose of this article is to review medication strategies for SUD and BPD. First, we will review the basic neurobiology of reinforcement in SUD and its modulation by other neurotransmitter systems. Next, we will present the characteristics of acceptable medications for use in treating comorbid BPD and SUD. Finally, we will examine various agents for BPD that have been tested in SUD populations.

NEUROBIOLOGY OF REINFORCEMENT

The selection of medications for patients with BPD and comorbid SUD requires consideration of the underlying neurobiology of drug reinforcement and dependence. Most drugs of abuse activate the mesolimbic dopamine (DA) system (Di Chiara and Imperato 1988; Koob and Bloom 1988). This system includes DA projections from the ventral tegmental area to the nucleus accumbens, as well as other forebrain structures (Fuxe et al 1985). The mesolimbic DA system is linked to cocaine reinforcement (Ritz et al 1987) and it is also activated, either directly or indirectly, by substances other than cocaine, including opiates, nicotine, and alcohol (Di Chiara and Imperato 1988). Thus, one approach to developing effective medications is to antagonize the reinforcing effects of drugs through antidopaminergic activity; however, blocking this reinforcement system might be particularly problematic in BPD patients (Kosten 2002; Platt et al 2002).

The neurobiology of affective disorders overlaps with substance dependence, as previously reviewed (Markou et al 1998). Abnormalities in the dopaminergic and serotonergic neurotransmitter systems are critical to both types of disorders. Medications for patients with BPD and comorbid SUD might need to address a "reward-deficiency syndrome" secondary to dysfunctional dopamine-mediated mesocorticolimbic neurons in individuals with BPD and psychotic features (Green et al 1999; Markou et al 1998). Such a syndrome is likely made worse by medications that directly antagonize the reinforcing effects of abused drugs by blocking dopaminergic activity (Buckley 1999; Kosten 1997, 2002; Platt et al 2002); however, modulating DA neurons to decrease DA release might be effective (Dewey et al 1997).

The inhibitory neurotransmitter system—γ-aminobutyric acid (GABA)—modulates DA neurons to decrease DA release when release is stimulated by abused drugs (Dewey et al 1997). The GABAergic neurons projecting from the nucleus accumbens and substantia nigra DA neurons inhibit neurons in the mesolimbic and nigrostriatal DA systems, respectively (Gerasimov and Dewey 1999; Kushner et al 1997; Morgan and Dewey 1998). Because the mesolimbic pathway is thought to mediate the rewarding actions of most abused drugs, inhibition of this system by increasing GABA input might decrease the rewarding effects of abused drugs. The neurotransmitter GABA is synthesized in GABAergic nerve terminals from glutamate by the enzyme glutamate decarboxylase (GAD) (Watanabe et al 2002). The breakdown of GABA to succinic semialdehyde is mediated by GABA transaminase (GABA-T). These two enzymes control the concentration of GABA in the brain and are modulated by potential treatment agents for SUD and BPD. With regard to SUD, the irreversible inhibitor of GABA transaminase, γ-vinyl-GABA (vigabatrin), attenuates cocaine-induced DA release, conditioned place preferences, and locomotor activity in rats (Dewey et al 1997, 1998). With regard to BPD, the activities of the GAD and GABA-T enzymes are modulated by valproate, a mainstay of bipolar treatment (Loscher 2002). Thus, medications that target the GABA system hold promise for the treatment of comorbid BPD and SUD.

CHARACTERISTICS OF AN IDEAL MEDICATION

The ideal medication for treating both BPD and SUD has not been developed, but several available agents for treating BPD might also benefit SUD. The current options include agents for bipolar and major depressive disorders. We will review valproate for treating comorbid SUD and bipolar mania and the atypical antipsychotics for treating comorbid SUD with psychotic disorders. Detailed

review of antidepressants for comorbid SUD and major depression can be found elsewhere in this issue of *Biological Psychiatry.*

The ideal medication would include several key characteristics. First, it needs to relieve symptoms of the BPD. Second, it needs to relieve withdrawal symptoms or drug craving so as to reduce drug use. Third, it should prevent relapse to abuse after the withdrawal treatment is successfully completed. Fourth, it needs to have low abuse liability and preferably be available in a formulation, such as an oral, transdermal, or depot formulation, that cannot be diverted to other routes of administration (e.g., intravenous). Fifth, it should require infrequent dosing to enhance medication adherence. Sixth, it should be well tolerated and have no or few side effects. Despite this seemingly difficult task, several medications currently available approach this ideal, as discussed in the next sections.

BIPOLAR MANIC PHASE

Recently, Salloum and Thase (2000) reviewed the treatment literature for SUD and BPD and emphasized the use of mood stabilizers, such as valproate and carbamazepine. Carbamazepine has had particular efficacy in relieving alcohol withdrawal, and both it and valproate might be helpful to prevent relapse (Malcolm et al 1989, 2001, 2002). In these patients, mood stabilizers alone are usually not sufficient, and many patients are given benzodiazepines or atypical antipsychotic agents, such as risperidone or olanzapine. Benzodiazepines might be problematic additions to the pharmacotherapy of patients with comorbid SUD, but other GABA agents might be useful. These GABA agents can improve response to the mood stabilizers, as well as provide pharmacotherapy for the SUD.

A prominent treatment for BPD is valproate because it holds promise for treating both SUD and BPD. Preliminary studies with valproate suggest a role in relapse prevention for alcoholism and stimulant dependence (Malcolm et al 2001). In an open-label trial, cocaine abusers with serum valproate levels of >50 μg/mL had fewer cocaine-positive urine samples than those with serum levels of <50 μg/mL (Halikas et al 2001). In another open-label study with cocaine users, the safety and tolerability of a loading dose of divalproex, a better-tolerated formulation of valproate, was examined (Myrick et al 2001). Divalproex (20 mg/kg/day in three divided daily doses) was well tolerated during this 8-week study, and cocaine use decreased. These pilot studies suggest that valproate is well tolerated in cocaine and alcohol users, and it might address both the mania and substance use in bipolar patients with cocaine or alcohol use disorders. Divalproex might also be useful in adolescents with BPD and SUD, although only lithium has been tested and shown efficacy for BPD and SUD, in a small study of 21 adolescents (Geller et al 1998). Because divalproex was effective in adolescents with explosive tempers, who frequently have comorbid SUD (Donovan et al 2000), and divalproex is associated with significantly better compliance than lithium, future studies should examine divalproex in adolescents with BPD and SUD (Weiss et al 1998). Clearly, the utility of any medication for these patients depends on their willingness to continue taking it, and divalproex is better accepted.

Antipsychotic agents are added to mood stabilizers in approximately two thirds of bipolar patients, and these agents might have some utility for comorbid SUD (Keck et al 1996; Sernyak et al 1997). This utility of atypical antipsychotics for SUD in BPD is based on an extension of their efficacy in patients with schizophrenic psychoses and SUD (Brown et al 2002; Buckley 1998, 1999; Green et al 1999; Volavka 1999). Clinical studies in patients with primary schizophrenia or schizoaffective disorder indicate that typical antipsychotics might increase substance use, whereas atypical antipsychotics reduce substance abuse (McEvoy et al 1995; Wilkins 1997). Several small, single-site, chart review studies of clozapine, olanzapine, and risperidone support a reduction in substance abuse with these agents (Brown et al 2002; Buckley 1998, 1999; Green et al 1999; Volavka 1999). Small prospective studies have also been done. For example, a 12-month open-label trial of olanzapine showed that all 30 schizophrenic patients achieved full or partial substance abuse remission (Littrell et al 2001); however, a national administrative database study in a Department of Veterans Affairs sample of 1900 schizophrenic veterans found no improved efficacy after a switch from typical antipsychotics to olanzapine (Sernyak et al 2003). Rather than improvement, those patients with SUD who were switched from typical antipsychotics to olanzapine showed a 2% deterioration in global assessment of functioning.

Another important caveat in the utility of atypical antipsychotics for SUD in BPD is that these agents target different symptoms in bipolar and schizophrenic psychoses. The negative symptoms of schizophrenia usually are considered the motivation for abusing drugs, and the atypical antipsychotics might reduce these symptoms better than conventional neuroleptics (Buckley 1998, 1999; Green et al 1999; Volavka 1999); however, atypical antipsychotics target the positive symptoms, such as agitation and hallucinations, in mania, and the

motivation for abusing drugs in bipolar patients might be the desire for euphoria. This motivation for euphoria is more typical of primary SUD patients. Thus, direct examinations of efficacy for atypical antipsychotics in primary SUD patients might be more relevant to bipolar than to schizophrenic patients.

Studies of the efficacy of atypical antipsychotics for primary SUD have been contradictory. Human laboratory studies support the potential efficacy of risperidone and olanzapine in treating primary substance abusers. Clozapine pretreatment significantly diminished the subjective responses to cocaine, including "high" and "rush," in a cocaine administration study (Farren et al 2000). Risperidone treatment decreased cocaine craving during withdrawal in cocaine-dependent patients (Newton et al 2001; Roy et al 1998); however, in outpatient studies, risperidone did not reduce cocaine use compared with placebo, and its dose could not be increased to more than 4 mg owing to side effects (e.g., Grabowski et al 2000). Furthermore, a 12-week, double-blind, placebo-controlled, pilot trial involving 30 cocaine-dependent subjects treated with olanzapine (10 mg/day) showed that treatment retention and abstinence from cocaine were slightly but significantly better in the placebo-treated subjects (Kampman et al 2003). Thus, controlled studies do not support the efficacy of either risperidone or olanzapine in primary SUD and suggest that they produce significant side effects; however, more recently developed atypical antipsychotics, like the partial DA agonist aripiprazole, have not been studied in SUD (Yokoi et al 2002). Overall, these data suggest limited promise for atypical antipsychotics to reduce SUD in bipolar patients.

Depressive phase

Current guidelines recommend the use of antidepressants in bipolar depression only after treatment with a mood stabilizer, and antidepressants alone have no role (Salloum and Thase 2000). The use of selective serotonin reuptake inhibitors (SSRIs) with mood stabilizers is common for treating depression in BPD. Advances in the next few years are likely to support the use of augmentation agents with SSRIs to enhance their efficacy in comorbid SUD patients. One of the most common augmentation agents for SSRI in the treatment of primary depression is bupropion. Bupropion is also an important agent for SUD because it has U.S. Food and Drug Administration approval for the treatment of nicotine dependence (Hughes et al 1999; Hurt et al 1997). Bupropion's dual action as a DA and noradrenergic reuptake blocker has suggested that other agents with this mechanistic profile might be useful. A similar blocker of noradrenergic reuptake is venlafaxine. Venlafaxine improves depression, decreases cocaine use, is well tolerated, and has rapid action, as shown in a study of 13 depressed cocaine abusers (McDowell et al 2000). A larger controlled study is now under way.

Although no specific studies address the use of antidepressants for adolescents with bipolar depression and SUD, the SSRI fluoxetine has been recommended for depressed adolescents with SUD (Deas and Thomas 2001; Lohman et al, unpublished data; Riggs et al 1997). Preliminary data from an ongoing, randomized, controlled trial of fluoxetine for depression in 120 adolescents with conduct disorder and SUD indicates that fluoxetine has a very good safety profile, even in nonabstinent adolescents with polydrug abuse (Lohman et al, unpublished data); however, another SSRI, paroxetine, is now relatively contraindicated owing to its association with increased suicidality in adolescents (Emslie et al 1997; Waechter 2003). Suicidality remains rare and might be prevented by careful monitoring and dosage reduction if early SSRI doses lead to agitation or akathisia. No antidepressant medication has yet demonstrated safety and efficacy in a conclusive, controlled clinical trial in adolescents with SUD.

Other agents might be combined with antidepressant medications for the treatment of SUD and BPD, but many common strategies, such as combinations of antidepressants with thyroid or serotonergic enhancers, have not been studied in this population of SUD patients. In one study, Sokolski et al (1999) used a nonabused GABA agonist, gabapentin, in bipolar patients who were only partially responsive to their former treatment medication. The patients showed significant improvement in mania and depression ratings after the addition of gabapentin to the antidepressant medication. These patients did not have SUD, but gabapentin has been suggested for SUD on the basis of its neuropharmacologic profile. The excitatory amino acid antagonists, such as lamotrigine, might be helpful for BPD or psychotic depression with stimulant dependence (Brown et al 2003). Brown et al (2003) conducted an open-label trial of lamotrigine in 30 outpatients with DSM-IV BPD and cocaine dependence and found significant improvement in depression, psychosis, and cocaine cravings, although not in cocaine use.

More generally, GABA enhancers might be useful augmentation agents for depression and comorbid SUD because they reduce substance abuse (Gonzalez et al 2003; Smith et al 1998, 2002). Benzodiazepines are GABA modulators used for bipo-

lar and affective disorders, but they are not ideal medications for patients with SUD because of their potential for abuse. Indeed, benzodiazepines are relatively contraindicated in SUD patients because these patients commonly use much more than prescribed (Sellers et al 1993; Weiss et al 1998). Current GABA medications with low abuse liability that are being investigated for the treatment of SUD include gabapentin, baclofen, tiagabine, gabapentin, and topiramate (Gonzalez et al 2003; Kampman et al 2004; Ling et al 1998). Gabapentin was presented earlier as a treatment of BPD and might also improve SUD in depressed patients (Sokolski et al 1999). Tiagabine is a GABA reuptake blocker, and the other medications seem to have more direct GABA receptor interactions. Topiramate is particularly promising for alcoholism. In a recent double-blind, randomized, placebo-controlled, 12-week trial in 150 alcoholics, topiramate-treated patients had fewer drinks per day, more days abstinent, and 28% fewer heavy drinking days (Johnson et al 2003). Each of these agents has the potential to augment the efficacy of SSRIs in patients with depression and SUD. The ideal medication combination for patients with BPD and SUD might include other GABA agents.

Another approach is to augment antidepressants with agents that primarily target SUD. For example, naltrexone is approved for alcohol and opiate dependence. Although naltrexone has not improved psychotic symptoms more than typical neuroleptics alone for schizophrenia, it could be considered for the alcohol or opiate dependence of BPD patients (Marchesi et al 1995; O'Malley 1996; Sernyak et al 1998). Naltrexone also might have some efficacy for comorbid alcoholism and depression (Salloum and Thase 2000; Salloum et al 1998). A pilot study of 14 patients found that naltrexone decreased alcohol use and reduced depressive symptoms among depressed alcoholics who failed to abstain from alcohol use despite treatment with an SSRI alone (Salloum et al 1998). Similarly, the partial opiate agonist buprenorphine has clear efficacy for the treatment of opiate dependence, with efficacy comparable to that of methadone maintenance (Johnson et al 2000; Ling et al 1996). It also relieves depressive symptoms, but this awaits more careful tests and should probably be limited to patients who already have opiate dependence (Emrich et al 1982; Kosten et al 1990).

Finally, pharmacotherapy might target the stress that leads to relapse in comorbid SUD and possibly precipitates BPD recurrence. Lofexidine, an $\alpha 2$ noradrenergic agonist, reduces adrenergic activity and attenuates stress-induced reinstatement of drug seeking in laboratory animals (Shaham et al 2000; Stewart 2000). In 18 abstinent opiate-dependent patients taking naltrexone, lofexidine was significantly better than placebo for retaining patients in treatment and reducing their opiate craving and use (Sinha et al, unpublished data). Thus, this approach might be a useful adjunct in BPD patients with comorbid SUD.

The bipolar patients with comorbid SUD who decrease drug abuse often show improved mood symptoms. Reduction in symptoms might also lead to decreased drug abuse. Pharmacotherapy can help with both problems, but the potential risks of pharmacotherapy need to be considered when one is selecting the best treatment of mood symptoms, in terms of efficacy, safety, and compliance, in this population. Noncompliance with lithium could pose a risk if it is taken improperly and without frequent monitoring of serum levels. Elevated liver enzymes secondary to viral or alcoholic hepatitis can require dose reductions of valproic acid or carbamazepine. Thus, even the best medications for BPD are problematic with comorbid SUD.

Adolescent bipolar and attention-deficit/hyperactivity disorders

Adolescents with BPD might be treated for attention-deficit/ hyperactivity disorder (ADHD) before BPD is diagnosed (Geller and Luby 1997). When patients are seen initially because of bipolar symptoms, approximately 90% of prepubertal and 30% of adolescent bipolar subjects have had ADHD (Geller et al 1995). Furthermore, adolescents with BPD might initially seem to have ADHD owing to overlapping symptoms and the more common occurrence of ADHD in this age group (Faraone et al 1997; Geller et al 2000). Psychostimulants are a common pharmacotherapy for ADHD but might be contraindicated in most patients with BPD (Dunn and Kronenberger 2003; Geller and Luby 1997; Max et al 1995). Thus, the implications of stimulant treatment in these patients need consideration.

An important issue is whether stimulant treatment during adolescence might exacerbate comorbid SUD or increase the risk for developing SUD in these vulnerable patients. To minimize the risk of exacerbating comorbid SUD, a medication should have low abuse potential. Pemoline is the only available psychostimulant with low abuse potential, compared with the relatively high abuse potential of the schedule II psychostimulants (e.g., methylphenidate, dextroamphetamine) (Klein-Schwartz and McGrath 2003). Only one controlled medication trial of pemoline has been conducted in adolescents with ADHD and SUD (Riggs et al 1996,

2004). The results from this controlled study were consistent with those from a previous open study (Riggs et al 1996). In that study, the safety and efficacy of pemoline for ADHD were equivalent in nonabstinent adolescents to those reported in adolescents without SUD; however, pemoline did not reduce substance use in the absence of specific treatment for SUD. Recent concerns about the rare but serious potential for liver toxicity with pemoline and the recommendations for frequent monitoring of liver enzymes has diminished the clinical feasibility of using pemoline in outpatient settings (Safer et al 2001; Willy et al 2002). Nonetheless, because pemoline allows once-per-day dosing and has low abuse potential, it is still considered an important treatment option for ADHD in substance abuse treatment programs. Medications with low abuse liability, such as bupropion and atomoxetine, have shown efficacy for ADHD in adults and adolescents without SUD (Barrickman et al 1995; Kratochvil et al 2002; Michelson et al 2002; Riggs et al 1998; Spencer et al 2002; Wilens et al 2001). Bupropion seems to be most helpful in adolescents who have SUD, ADHD, and depression (Riggs et al 1998). The safety profiles of these medications suggest that they would be treatment options for ADHD in adolescents with comorbid SUD (Daviss et al 2001).

Perhaps more important is the fact that 90% of prepubertal children have ADHD before manifesting BPD. Although there are no long-term data on treating childhood BPD with stimulants, effective treatment for ADHD in other patients without comorbid BPD reduces the risk for subsequent SUD (Wilens et al 2003). Across six studies (two with follow-up in adolescence and four in young adulthood) comprising 674 medicated subjects and 360 unmedicated subjects who were followed at least 4 years, pharmacotherapy for ADHD produced a twofold reduction in risk for SUD in youths. The two studies that reported follow-up during adolescence showed a sixfold reduction in the development of SUD, which strongly argues for the protective effect of these medications in preventing early-onset SUD during the period of active pharmacotherapy.

Conclusion

In summary, some progress has been made with the use of existing medications to treat dually diagnosed patients with SUD and BPD. Many agents examined for these comorbid patients enhance GABA activity, which can reduce DA-mediated reinforcement from abused drugs. Several of these GABA agents also relieve withdrawal symptoms and prevent relapse in SUD. Other key medication characteristics for treatments of comorbid BPD and SUD include low abuse liability, infrequent dosing, and being well tolerated. The mood stabilizer valproate is a promising treatment agent for SUD with BPD because it has many of these characteristics. It relieves symptoms of BPD and alcohol withdrawal and likely helps prevent relapse to drinking. Valproate also has low abuse liability and comes in a once-daily, oral formulation that is well tolerated. Improving valproate's efficacy by adding atypical antipsychotic agents might not be useful for the SUD, however, because neither olanzapine nor risperidone have been effective for primary SUD. In contrast, combining various GABA medications with SSRIs holds promise for SUD with depression because this augmentation can improve BPD treatment and might reduce drug use. Several GABA agents have low abuse liability, but except for valproate they require frequent dosing and gradual induction over several weeks to minimize side effects. The mood stabilizers with GABA activity might need to be combined with nonabused stimulants, such as pemoline, to treat ADHD in adolescents with BPD. Pemoline might also prevent the onset of complicating SUD in this population. Although pemoline has low abuse liability and requires infrequent dosing, the possibility of liver toxicity makes this treatment approach less than ideal. Thus, new treatment strategies for comorbid SUD with BPD might focus on GABA agents that appear to reduce SUD and address the key characteristics listed above.

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