Comorbid Substance Use Disorders Among Youth With Bipolar Disorder: Opportunities for Early Identification and Prevention

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Objective: The burden of substance use disorders (SUDs) among adults with bipolar disorder is well documented. Comparatively less is known regarding comorbid SUD among youth with bipolar disorder. This article aims to integrate the extant literature on this topic and to suggest strategies for delaying or preventing SUD among youth with bipolar disorder.

Data Sources and Study Selection: Relevant studies in English were identified using PubMed and MEDLINE (1950–February 2009). Search terms were *bipolar disorder* cross-referenced with *child*, *adolescent*, or *youth*, and *alcohol*, *drug*, or *substance*, and *abuse*, *dependence*, or *disorder*. Articles were selected on the basis of containing data regarding both bipolar disorder and SUD. The search was supplemented by manually reviewing reference lists from the identified publications.

Data Synthesis: Epidemiologic and clinical studies demonstrate that youth-onset bipolar disorder confers even greater risk of SUD in comparison with adult-onset bipolar disorder. Recent studies of youth with bipolar disorder have not identified childhood SUD (0%); however, the prevalence of SUD escalates during adolescence (16%–39%). Substance use disorder among bipolar youth is associated with legal and academic difficulties, pregnancy, and suicidality. Few studies have addressed interventions for this population, although studies are underway. Because bipolar disorder onset most commonly precedes SUD among youth (55%–83%), there is a window of opportunity for prevention.

Conclusions: Pending the results of ongoing treatment studies, several strategies are suggested for curtailing the burden of SUD in youth with bipolar disorder. These include screening for substance use among bipolar youth beginning at age 10 irrespective of other risk factors, education and intervention at the family level, and implementation of preventive interventions that have been successful in other populations.

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Both clinical[1] and epidemiologic[2] studies of adults with bipolar disorder indicate that the majority suffer from a comorbid substance use disorder (SUD)—ie, abuse of or dependence on alcohol or drugs—during their lifetime. Although not uniquely associated with an increased risk of SUD, bipolar disorder is arguably the Axis I diagnosis most strongly associated with SUD among adults.[3] Even the presence of subthreshold manic symptoms may confer increased risk of SUD compared to major depressive disorder (MDD).[4] When SUD occurs in bipolar disorder, recovery is delayed, relapse is hastened, symptoms are greater in number and persist between episodes, and disability and mortality are increased.[5] Bipolar patients with versus without SUD demonstrate increased impulsivity,[6] suicidality,[7] polarity "switching" into mania,[8] and forensic difficulties,[9] and they demonstrate decreased medication compliance[10] and quality of life.[11] Even those who manage to recover from SUD exhibit impaired role functioning compared to patients with no history of SUD.[12] Taken together, findings from adults indicate that SUD confers a marked increase in the burden of bipolar disorder regardless of how this burden is defined.

Unfortunately, youth-onset bipolar disorder (the term *youth* refers to children and/or adolescents) may confer an elevated risk of SUD even in comparison to adult-onset bipolar disorder. Data from the largest clinical study[13] of bipolar disorder to date indicate that the lifetime prevalence of alcohol use disorders and drug use disorders among childhood-onset and adolescent-onset subjects was significantly greater than among adult-onset subjects.[13] This finding has been replicated in a representative population sample of the United States.[14] The question may not be who among bipolar youth is at risk for SUD, but, rather, who among them is not at risk?

In contrast to the evolving body of literature regarding the epidemiology, burden, and treatment of comorbid SUD among adults with bipolar disorder, relatively little is known regarding SUD among youth with bipolar disorder. There are several possible explanations for the relative paucity of research on this topic among youth with bipolar disorder. First, unlike studies of adults, many youth in studies of bipolar disorder have not passed through the full period of greatest risk for SUD onset. In fact, large-scale studies[15–18]

from independent research laboratories have found no preadolescent cases of SUD. Studies to date have therefore relied on relatively small samples of adolescents in examining this topic. Second, most treatment studies examining pharmacologic and psycho-social interventions for bipolar disorder have excluded youth with SUD. Therefore, the efficacy of those interventions for youth with bipolar disorder and SUD is unknown. Third, nascent research on bipolar disorder among children and adolescents to date has focused on phenomenology, nosology, treatment, and differential diagnosis. Although debate continues, many gains have been made in the validation of pediatric bipolar disorder. Just as the field as a whole is moving into its next developmental stage, so too are many children and adolescents with bipolar disorder entering new developmental stages. For youth with bipolar disorder, these developments comprise, among other things, a period of risk during which crucial decisions will be made regarding use of cigarettes, alcohol, and illicit drugs. The first section of this article aims to integrate the extant literature on this topic, and the discussion section offers strategies for delaying or preventing SUD among youth with bipolar disorder.

METHOD

Relevant studies in English were identified using PubMed and MEDLINE (1950–February 2009). Search terms were *bipolar disorder* cross-referenced with *child*, *adolescent*, or *youth*, and *alcohol*, *drug*, or *substance*, and *abuse*, *dependence*, or *disorder*. Articles were included if they contained data relevant to this article's focus on comorbid bipolar disorder and SUD among youth. The search was supplemented by manually reviewing reference lists from the identified publications.

RESULTS

Community Prevalence

A representative community study[19] in the United States enrolled 1,709 adolescents, including 18 subjects with full bipolar disorder and an additional 97 subjects with significant subsyndromal bipolar symptoms. Despite a high prevalence of psychiatric conditions in the nonbipolar group, the prevalence of SUD was significantly higher among subjects with full bipolar disorder (22.2%) and subsyndromal bipolar disorder (23.7%) as compared to the rest of the sample (10.4%). The prevalence of drug use disorders was 16.7% in the full bipolar group and 18.6% in the subsyndromal bipolar group. Alcohol use disorders were present in 11.1% of the full bipolar group and 12.4% of the subsyndromal bipolar group, both significantly higher than among nonbipolar subjects.[19]

A German community study[20] enrolled 1,395 adolescents, including 36 with bipolar spectrum disorders. Of these, 67% (24 of 36) reported a history of cannabis use and 22% (8 of 36) reported a history of cannabis use disorders. The prevalence of cannabis use and cannabis use disorders among subjects with no mental disorder (n = 738 controls) was 22% and 1%, respectively. Whereas 33% of bipolar-spectrum subjects with a history of cannabis use (8 of 24) met criteria for cannabis use disorder, this finding was true of only 6% of controls (10 of 164). Moreover, bipolar-spectrum subjects had nearly 3-fold greater incidence (ie, development of new cases) of cannabis use disorder during prospective follow-up into young adulthood as compared to controls, even after controlling for externalizing disorders, age, and gender.[20]

Clinical Prevalence

Prevalence of SUD in clinical samples depends on whether the sample is composed of inpatients, outpatients, or both. A study of 34 adolescent inpatients admitted for acute mania found that 39% met criteria for SUD,[21] although rates as low as 15% have been reported.[22] Studies of mainly outpatients report a broad range of prevalence estimates varying from 32%[23] to 0%.[17] However, most large-scale studies of pediatric bipolar disorder suggest an SUD prevalence of roughly 20% among adolescents (≥ 13 years old),[15,16,24] and all report a 0% prevalence among children (< 13 years old) with bipolar disorder.[15–17,24] Prospective follow-up of children with bipolar I disorder indicates that the incidence of SUD during 8 years of follow-up is a staggering 32%.[25]

Several studies suggest that SUDs are more common among youth with bipolar disorder than among healthy controls and psychiatric clinical controls. Wilens and colleagues[26] found that the prevalence of SUD was significantly higher among subjects with bipolar disorder (n = 86) compared to those without bipolar disorder (n = 247; OR = 2.8), even after controlling for variables such as age, gender, and psychiatric comorbidity. In a subsequent study, Wilens and colleagues[23] compared youth with bipolar disorder (n = 57) to clinical control youth (n = 46) without bipolar disorder. Again, despite the fact that the control group had high rates of psychopathology (eg, 22% with multiple anxiety disorders, 20% with oppositional defiant disorder, 17% with attention-deficit/hyperactivity disorder), subjects with bipolar disorder demonstrated significantly greater prevalence of SUD compared to controls (32% vs 7%). Conduct disorder conferred a 5-fold increased risk of SUD. Nonetheless, the increased prevalence of SUD among youth with bipolar disorder remained significant after controlling for conduct disorder.[23] These findings were replicated in the most recent and largest study from this group,[27] including 105 adolescents with bipolar disorder and 98 controls.

Dilsaver and colleagues[28] examined the prevalence of alcohol abuse and drug abuse among Latino adolescent outpatients with bipolar disorder (n = 115) as compared to those with MDD (n = 140). The prevalence of alcohol abuse was not significantly higher among bipolar subjects (20%)

versus subjects with MDD (11%). However, the prevalence of drug abuse was significantly higher among bipolar subjects (37%) compared to subjects with MDD (19%).

Few studies have reported the prevalence of bipolar disorder among youth with SUD. Estimates range from 3%–9%.[29–31] Although higher than the population rate, these prevalences were not directly compared to those of controls.

Childhood Versus Adolescent Onset of Bipolar Disorder in Clinical Samples

Wilens and colleagues[26] found that prevalence of SUD among adolescent subjects with adolescent-onset bipolar disorder was significantly greater than among adolescents with childhood-onset bipolar disorder (< 13 years old; 39% vs 8%). After correction for factors that could potentially confound this association, including current age, gender, attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, and multiple anxiety disorders, youth with adolescent-onset bipolar disorder were 8.8 times more likely to have comorbid SUD compared to youth with childhood-onset bipolar disorder. Although this finding was replicated in a subsequent study by Wilens and colleagues,[23] it was not replicated when this topic was examined in the Course and Outcome of Bipolar Youth (COBY) sample.[18] The discrepancy may relate to differences in referral patterns, the extent of early treatment, or other unknown factors. Further study is needed to clarify whether or not onset of bipolar disorder in adolescence confers a markedly greater risk of SUD as compared to childhood-onset bipolar disorder.

Order of Onset of Bipolar Disorder and Substance Use Disorder in Clinical Samples

The relative order of onset of bipolar disorder and SUD has been the focus of several adult studies.[32,33] Among the majority of adults, SUD is more likely to be antecedent (ie, with onset prior) to bipolar disorder.[34] In contrast, Wilens and colleagues[23] found that bipolar disorder onset was antecedent to SUD onset in 83% of the 18 subjects with comorbid bipolar disorder and SUD. In a previous study for which SUD was an inclusion criterion, Wilens and colleagues[35] found that among 11 subjects with comorbid bipolar disorder and SUD, bipolar disorder antedated SUD in 55%, onset concurrently in 9%, and onset following SUD in 36%. In the COBY sample,[18] bipolar disorder was antecedent to SUD in 60% of cases, onset concurrently in 10%, and onset following SUD in 30%. Overall, it appears that bipolar disorder precedes SUD among the majority of adolescents with comorbid bipolar disorder and SUD.

Burden of Substance Use Disorders Among Youth With Bipolar Disorder

Limited findings have been reported regarding the burden of comorbid SUD among adolescents with bipolar disorder. Geller and colleagues[36] conducted a study of lithium for comorbid bipolar disorder and SUD among adolescents (n = 18 with bipolar disorder and n = 7 at risk for bipolar disorder). The majority of subjects (52%) reported being arrested during their lifetime, and 46% of those arrested reported convictions. Nearly one-third had repeated a grade, and one-fifth was not in school at the time of study enrollment.

Adolescents with SUD in the COBY study[18] (n = 40) were significantly less likely to be living with both parents and had significantly greater lifetime prevalence of physical abuse, sexual abuse, suicide attempts, conduct disorder, and posttraumatic stress disorder (PTSD), compared to adolescents without SUD. In addition, 42% of those with SUD reported past-year trouble with police in comparison to 17% of those without SUD. Similarly, 12-month prevalence of pregnancy and abortion were significantly higher among females with (20% and 12%, respectively) versus without (1% and 0%, respectively) comorbid SUD. In logistic regression analyses, the findings regarding living with both parents, conduct disorder, suicide attempts, and trouble with police remained significant, and the association of SUD with pregnancy and abortion was reduced to a statistical trend.[18]

Recent findings[37] from COBY indicate that children and adolescents with bipolar disorder who are overweight or obese are significantly more likely to have SUD compared to those who are not overweight or obese (15% vs 6%). Moreover, SUD was associated with the largest odds ratio for overweight or obese (2.79) in a logistic regression analysis controlling for demographic and clinical variables. In contrast, recent epidemiologic findings[38] from adults with bipolar disorder indicate that SUD may be inversely related to being overweight or obese. Further studies are needed to determine whether this discrepancy is related to developmental differences, methodological differences, or an unknown confound.

Wilens and colleagues[39,40] reported that both conduct disorder and PTSD are associated with SUD among adolescents with bipolar disorder. Subjects with full-threshold PTSD had higher rates than subjects with subthreshold PTSD or no PTSD, and the most common order of onset of these conditions was bipolar disorder, PTSD, then SUD.[39] Similar to the COBY study, subjects with conduct disorder were significantly more likely to also have SUD than were subjects without conduct disorder (47% vs 15%). Subjects with conduct disorder were far more likely to manifest a combined alcohol-use plus drug-use disorder than were subjects without conduct disorder (40% vs 6%).[40] Attention-deficit/hyperactivity disorder was not significantly associated with SUD in either this sample or the COBY sample.

Two studies have reported on the impact of SUD on the course of adolescent bipolar disorder. Strober and colleagues[41] conducted a 5-year follow-up study of 54 adolescents with bipolar I disorder consecutively admitted to an inpatient service. In that study, albeit underpowered, SUD

was not a significant predictor of bipolar disorder relapse at 5 years. A recent study by DelBello and colleagues[42] examined the prospective course of bipolar disorder among 71 adolescents recruited during their first hospitalization for a manic or mixed episode. At intake, 8% had an alcohol use disorder and 7% had a cannabis use disorder. Thirty-eight percent of the adolescents without an alcohol use disorder were medication adherent, as compared to 0% of adolescents with an alcohol use disorder ($P = .06$). Despite the modest number of subjects with an alcohol use disorder (n = 6), alcohol use disorder was the strongest predictor of syndromic recurrence in this study, and time to recurrence was significantly shorter among subjects with an alcohol use disorder.

To date, no studies have examined risk and/or protective factors for SUD among youth with bipolar disorder. Some of the clinical correlates discussed above may be protective factors (eg, living with both biologic parents), whereas others may be risk factors (eg, history of physical or sexual abuse, conduct disorder). However, longitudinal studies regarding the timing of these correlates with respect to SUD are needed before the concepts of risk and protection can be invoked.

Cigarette Smoking

Studies focusing on SUD frequently do not examine cigarette smoking or include nicotine dependence within the category of SUD. However, cigarette smoking (with or without the diagnosis of nicotine dependence) is important to consider because its onset frequently precedes that of other forms of substance use and because it is one of the central putative factors associated with the increased medical burden of bipolar disorder.[43] Unfortunately, the quit rate among adult smokers with bipolar disorder is approximately one-third that of adults with no mental illness.[44]

Wilens and colleagues[45] found that adolescent boys with bipolar disorder and attention-deficit/hyperactivity disorder were significantly more likely to smoke than were adolescents boys with attention-deficit/hyperactivity disorder but not bipolar disorder (35% vs 12%), although this difference was largely accounted for by comorbid conduct disorder. The prevalence of smoking among bipolar youth was 50% among those with no history of psychiatric treatment, 30% among those who had received counseling only, 50% among those who had received medication only, and 0% among those who had received both counseling and medication. Despite the fact that the study could not control for severity of illness and duration or intensity of treatment, it nonetheless provides a signal that multimodal treatment of bipolar disorder among adolescents may have a salutary effect on cigarette smoking.[45] In a later study[27] of adolescent males and females, bipolar disorder conferred a 12-fold increased risk of smoking versus controls, even accounting for demographic and clinical factors.

Twenty-five percent of COBY subjects, across the age range of 7–17 years, reported a history of smoking (11% daily, 14% ever).[46] Smoking was associated with increased lifetime prevalence of suicide attempts, physical abuse, and conduct disorder. The prevalence of SUD was significantly higher among daily smokers (43%) and ever smokers (26%) compared to never smokers (1%). Parental smoking history was associated with a 2-fold increased risk of smoking. In comparison to light daily smokers (< 10 cigarettes/d), heavy daily smokers (≥ 10 cigarettes/d) had greater prevalence of SUD and suicide attempts and worse depression severity. Consistent with findings from adults with bipolar disorder, smoking among youth with bipolar disorder was independently associated with suicide attempts and SUD.[46]

Finally, a study of adults and adolescents with bipolar disorder found that cannabis abuse or dependence was prevalent among 40.6% of adolescent smokers versus 0% of nonsmokers and that alcohol abuse or dependence was prevalent among 21.9% of smokers versus 2.1% of nonsmokers.[47] Taken together with the COBY findings, these data suggest that absence of smoking history virtually rules out SUD among youth with bipolar disorder. Future prospective studies are needed to examine the question of whether cigarette smoking increases the risk for progression to other substances of abuse among bipolar youth. Unfortunately, studies to date have not clarified the order of onset of smoking with respect to other substance use among bipolar youth.

Family History

A recent study[48] addressed the question of what aspects of bipolar disorder are familial (ie, phenotypes that are disproportionately prevalent within family pedigrees). The familiality of 40 diverse phenotypic features was examined in a large sample of 1,246 adults from 172 multiplex families participating in genetic linkage studies of bipolar disorder. Only 5 features remained significant after conservative statistical correction: social relations, substance abuse, alcoholism, psychosis, and suicide attempt. Moreover, substance abuse and alcoholism were among the 3 most robust familial factors.

Some clinical data from bipolar youth support this finding. For example, Todd and colleagues[49] examined the prevalence of alcoholism among the nonaffectively ill relatives of children with bipolar disorder, children with MDD, and controls. Alcoholism was prevalent among 20.3% of relatives of bipolar disorder probands, 12.3% of relatives of MDD probands, and 6.4% of relatives of control probands. This increased prevalence was observed in both sexes.

Biederman and colleagues[50] examined the familial association between conduct disorder, SUD, and bipolar disorder among bipolar youth, stratified on the presence or absence of conduct disorder. These 2 groups were compared to (1) youth with conduct disorder but not bipolar disorder and (2) control subjects. Both bipolar disorder and conduct disorder were independently associated with increased prevalence of alcohol dependence in family members, but the nonsignificant interaction implies an additive rather

than synergistic effect. There was a significant independent effect of proband bipolar disorder on familial drug dependence; however, the effect of proband conduct disorder on familial drug dependence was no longer significant after accounting for proband bipolar disorder.

Wilens and colleagues[51] examined family history of bipolar disorder and SUD in a study of 108 adolescents with bipolar disorder, of whom 34 had comorbid SUD, and 96 adolescent controls. The prevalence of bipolar disorder and of SUD was higher among parents of both groups of adolescents with bipolar disorder (with and without comorbid SUD) in comparison to the parents of adolescent controls. Neither parental bipolar disorder nor parental SUD among parents of bipolar youth was significantly associated with comorbid SUD in the adolescent. The authors concluded that the findings provide evidence for cosegregation (ie, the tendency for closely linked traits to be inherited together) of bipolar disorder and SUD in parents of youth with bipolar disorder and that assortative mating (ie, mating of individuals having more traits in common than likely in random mating) cannot explain the comorbidity of bipolar disorder and SUD in parents of bipolar disorder–SUD probands.

Finally, findings from the COBY study[18] suggest that familiality of bipolar disorder and SUD may vary to some degree across the bipolar spectrum. When subjects with bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified were analyzed together, there were no significant differences in first-degree or second-degree family psychiatric history among bipolar adolescents with versus without comorbid SUD. However, when adolescents with bipolar I disorder were analyzed separately, subjects with comorbid SUD were found to have significantly greater prevalence of mania among first-degree relatives versus adolescents without SUD (57% versus 31%), and a trend was observed among second-degree relatives (48% versus 28%, $P = .08$). Moreover, adolescents with bipolar I disorder and comorbid SUD had significantly greater prevalence of comorbid mania and SUD among first-degree relatives compared to adolescents with bipolar I disorder but no SUD (35% versus 13%).[18]

Taken together, family studies indicate the following: youth with bipolar disorder—with or without comorbid SUD—have exceedingly high rates of SUD among family members; the prevalence of SUD among families of bipolar youth is even greater than among families of youth with MDD and cannot be explained by comorbid conduct disorder; and the bipolar disorder–SUD phenotype appears to run in families of youth with bipolar I disorder, similar to findings in adults.

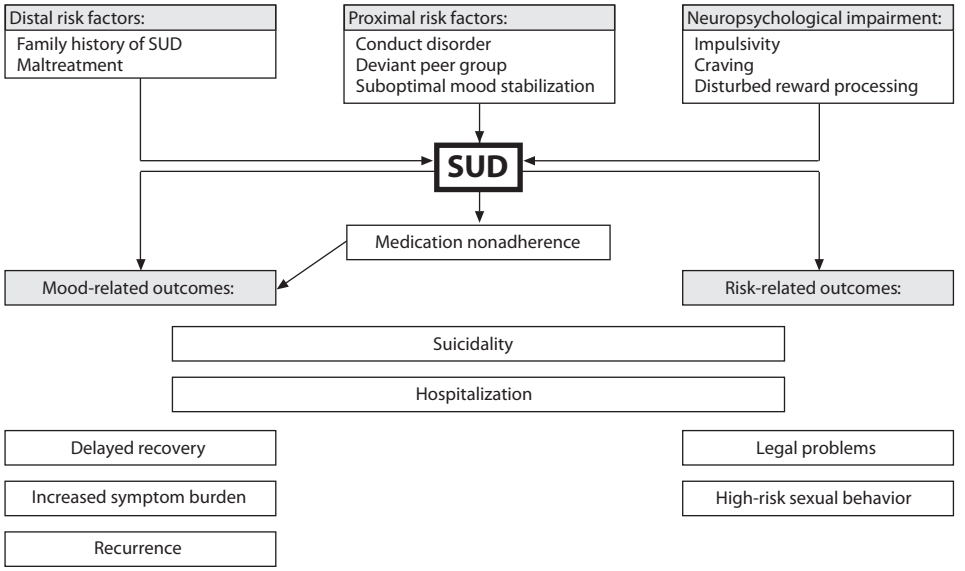
Neurobiologic Differences

Most research on mood-SUD comorbidity is based on adults with long durations of illness for each disorder, making it difficult to parse antecedents from consequences of comorbid SUD.[52] Research with adolescents provides an opportunity to examine whether neurobiologic differences (those related to brain anatomy, physiology, and biology) exist that can be used as vulnerability markers for SUD. A small study[53] using structural magnetic resonance imaging compared adolescents with bipolar disorder with (n = 7) and without (n = 7) comorbid cannabis abuse or dependence. Subjects with versus without cannabis abuse or dependence demonstrated greater structural abnormalities in frontal, temporal, and subcortical regions linked with emotion and motivational regulation. Although 3 of 7 subjects with cannabis abuse or dependence had ≥ 1 year of prescan cannabis exposure, this exposure is far less than that observed in studies of adults. This short exposure increases confidence that the findings may reflect underlying differences as opposed to differences caused by substance use. Future longitudinal studies of bipolar youth will help clarify whether these neurobiologic correlates of SUD are in fact antecedents or consequences of SUD. In addition to examining structural and functional neuroanatomy, future longitudinal studies should examine whether interactions between stressful life events and hypothalamic-pituitary-adrenal activity predict SUD. A recent study by Rao and colleagues[54] elegantly demonstrated that elevated baseline cortisol is associated with subsequent onset of SUD among youth with MDD, particularly among subjects with preceding stressful life experiences. Figure 1 provides a framework that integrates the contribution of neuropsychological factors and other risk factors for SUD in bipolar disorder with the consequences of SUD in this population.

Treatment of Comorbid Bipolar Disorder and Substance Use Disorder

Few studies have directly addressed the treatment of comorbid bipolar disorder and SUD. Geller and colleagues[55] examined the efficacy of lithium for adolescents with bipolar disorder and temporally secondary substance dependence. Twenty-five adolescent outpatients with either bipolar disorder (n = 17) or MDD with predictors of future bipolarity (n = 8) were assigned to 6 weeks of treatment with lithium or placebo. Duration of comorbid bipolar disorder and SUD for at least 2 months was necessary, and bipolar disorder must have either preceded SUD by at least 2 weeks or have been present for at least 2 weeks in the absence of substance use. Subjects needed to be free of psychotropic medications for the previous 4 weeks. Most subjects were living with both parents (84%), approximately two-thirds were male, and additional psychiatric comorbidity was common (16% for anxiety, 20% for conduct disorder, 32% for attention-deficit/hyperactivity disorder). After 6 weeks, subjects in the lithium group were significantly less likely to have positive urine drug assays (approximately 10%) compared to subjects receiving placebo (approximately 35%) and had significantly greater improvement on the Children's Global Assessment Scale. In intent-to-treat analyses, there was no significant difference in lithium serum levels

Figure 1. Schematic Model of Substance Use Disorders (SUDs) in Bipolar Disorder



between responders (mean ± SD, 0.88 ± 0.27 mEq/L) and nonresponders (mean ± SD, 0.79 ± 0.34 mEq/L).[55] Since this study was conducted, there have been several large-scale positive studies for youth manic/mixed episodes, leading to US Food and Drug Administration approval of several atypical antipsychotic medications. Unfortunately, those studies excluded bipolar disorder subjects with SUD. Given the substantial prevalence of SUD in both clinical and epidemiologic studies, representative studies including youth with comorbid bipolar disorder and SUD are needed to determine whether these and other medications (eg, valproate sodium, lamotrigine) are efficacious for bipolar youth with comorbid SUD.

Selected findings from trials of adults with comorbid bipolar disorder and SUD may be informative, although replication is needed in samples of adolescents. Salloum and colleagues[56] conducted a 24-week placebo-controlled study of adjunctive valproate for 59 subjects with bipolar disorder; subjects treated with valproate reported fewer drinking days, consumed fewer drinks on heavy drinking days, had longer time to relapse of heavy drinking, and had lower γ-glutamyl transpeptidase levels compared to subjects randomly assigned to placebo. Another placebo-controlled study (N = 102) of 12 weeks of adjunctive quetiapine for outpatients with bipolar disorder and alcohol use disorder found no significant effect of quetiapine on alcohol use.[57] Open-label data suggest that lamotrigine and aripiprazole may also show promise, but findings are constrained by modest sample sizes and absence of control groups.[58,59] Finally, Weiss and colleagues[60] demonstrated that integrated group therapy (n = 32) targeting bipolar disorder and SUD simultaneously is superior to standard drug counseling (n = 32), resulting in fewer days of substance use and greater therapy attendance, but also more mood symptoms.

Little is known about the risks and benefits of using anticraving (eg, naltrexone) or aversive (eg, disulfiram) medications for adults with bipolar disorder and SUD or for youth with SUD in general. There have been no studies of these medications in youth with bipolar disorder and SUD. According to American Academy of Child and Adolescent Psychiatry practice parameters for SUD,[61] use of these medications is optional and should be approached with caution, particularly among youth with psychiatric comorbidity.

Findings from studies of nonbipolar adolescents with SUD may also be informative. There is a sizeable body of literature regarding psychosocial treatment of youth with SUD—and a nascent body of literature regarding psychosocial treatment of youth with SUD and psychiatric comorbidity such as depression. However, no study to date has examined the effect of psychosocial treatment on youth with comorbid bipolar disorder and SUD. The 600-subject Cannabis Youth Treatment study[62] found that the manualized psychosocial interventions tested, including family therapy and a combination of cognitive-behavioral therapy and motivational enhancement therapy among others, were of comparable efficacy. However, previous studies[63–65] suggested that family therapy may be superior to other psychosocial interventions. Indeed, either family therapy or significant family involvement is part of the minimal standard of care for youth with SUD.[61]

Treatment studies specifically targeting comorbid bipolar disorder and SUD among adolescents are underway, including a placebo-controlled study of adjunctive topiramate added to quetiapine and a manualized psychosocial

intervention (Melissa P. DelBello, MD, principal investigator). Although topiramate has not proven to be an efficacious mood stabilizer among adults, preliminary evidence from youth suggest potential benefits in this population,[66] and this agent appears to be highly efficacious in the treatment of alcohol dependence among adults.[67] Given the promising findings of adjunctive valproate among adults with bipolar disorder and comorbid alcohol dependence, replication among adolescents with bipolar disorder is indicated to determine whether there are similar benefits with respect to alcohol and substance use. Another pilot study is underway examining an integrated adaptation of family-focused treatment[68] that targets both bipolar disorder and SUD.[69] Additional studies are needed to examine whether manualized interventions such as motivational enhancement therapy and cognitive-behavioral therapy are also effective interventions in this population.

Given the limitations of the extant literature, the question arises as to the standard of care for youth with bipolar disorder and comorbid SUD. Current treatment guidelines[70] for bipolar disorder recommend that both conditions should be treated simultaneously, and, citing Wilens et al,[26] state that optimal treatment "involves an integration of treatment modalities rather than merely consecutive treatments with a specific focus on either substance abuse or BPD."[70(p228)] Specific consideration should be given to medications that, in addition to having mood-stabilizing properties, relieve withdrawal and/or craving, have low liability for abuse or diversion, and are well tolerated and conveniently dosed in order to maximize adherence.[71] American Academy of Child and Adolescent Psychiatry practice parameters[61] identify elements of the minimal standard of care for SUD, including appropriate confidentiality, screening, establishing the diagnosis, collecting toxicology, providing specific treatment for SUD, involving the family, and identifying psychiatric comorbidity. An additional consideration among youth with bipolar disorder relates to medication adherence, which is particularly poor among bipolar youth with SUD.[42] Given the centrality of pharmacotherapy to the treatment of bipolar disorder, it is important to incorporate specific strategies to maximize and maintain adherence. Potential strategies include brief motivational interviewing delivered by the pharmacotherapist, a separate structured intervention, and prioritization of medication adherence as a family problem in family-focused treatment and other interventions.

DISCUSSION

The current literature suggests that the majority of youth with bipolar disorder will suffer from SUD during their lifetime. There is an urgent need and great opportunity for early identification and prevention of SUD and for attenuation of the deleterious impact of SUD on the course of bipolar disorder. Large-scale controlled studies of pharmacologic and psychosocial interventions are needed. The largest positive pharmacologic[36] and psychosocial[60] studies on this topic have sample sizes of 59 and 62, respectively. In comparison, the only pharmacologic study among youth included 18 subjects with bipolar disorder and SUD,[36] and no studies of psychosocial interventions among youth with bipolar disorder and SUD have been published. Even in short-term clinical trials of adults with comorbid bipolar disorder and SUD, attrition rates may exceed 60%.[72] Given the known waxing and waning longitudinal course of both bipolar disorder and SUD, longer-term maintenance treatment studies of this population are needed. Specialized multisite clinical trial networks may offer the best chance of recruiting and retaining sufficient sample sizes to test pharmacologic and psychosocial treatments, and this methodological approach applies equally to studies of longitudinal course, genetics, and neurobiology. The emphasis of our suggestions for future directions, however, relates to clinical and research strategies that could potentially improve early identification and prevention of SUD comorbidity among youth with bipolar disorder. The epidemiologic findings reviewed above suggest that—as with adults—the significant association between bipolar disorder and SUD among youth cannot be explained by biases inherent in treatment-seeking samples.[73] Therefore, even bipolar youth not seeking treatment may benefit from preventive interventions focusing on SUD.

Early Identification

Early identification in this context extends beyond SUD and includes early identification and treatment of bipolar disorder. From an epidemiologic and temporal perspective, youth-onset bipolar disorder may be considered a risk factor for developing SUD. Given the growing body of evidence for pharmacologic and psychosocial treatments among bipolar youth, it is reasonable to hypothesize that bipolar disorder is a *modifiable* risk factor, insofar as treated bipolar disorder may confer lesser propensity for later SUD as compared to untreated bipolar disorder. Data from adults indicate prolonged time from bipolar disorder onset to diagnosis and treatment, and this latency is most prolonged among those with early onset of bipolar disorder.[74,75]

Bipolar disorder precedes SUD among the majority of youth with both conditions, and the latency from bipolar disorder onset to SUD onset among youth is greater than 2 years on average.[18] What can be done to identify SUD in its budding stages? Many youth whom we see clinically with SUD report preadolescent substance use; however, their substance use is rarely detected at the reported onset age. One possible explanation for this is that substance-using preadolescents are more likely to answer falsely when asked directly about substance use. Another possibility is that psychiatrists and other mental health professionals may be less likely to ask children about substance use without their caregivers present; for adolescents, asking about substance use without a parent present is part of the standard of care.

We therefore suggest that screening should commence at 10 years of age (or earlier, as clinically indicated), regardless of the presence of other risk factors. At a minimum, screening should comprise asking the youth (without the parent present) and a parent about use of nicotine, alcohol, and drugs. Ideally, the youth should also be provided with the opportunity to disclose substance use on a self-report questionnaire. In addition, we suggest that truly random urine drug screening be employed starting at 13 years of age to maximize the sensitivity and minimize time-to-recognition of substance use. We use the term *truly random* because, in our experience, random urine drug screening is generally undertaken when treating youth with known or suspected substance use problems. However, truly random screening would be undertaken for all youth aged 13 or above with bipolar disorder. Given the profound risks associated with bipolar disorder and SUD comorbidity, we believe that such vigilance is justifiable. When patients are maintained on psychotropic medications, we screen for endocrine-metabolic abnormalities regularly, independent of risk factors, family history, or symptoms. We advocate that the development of SUD should similarly be viewed as a clandestine process that requires truly random screening independent of family history or suspected or known use.

Prevention

Opportunities for SUD prevention exist for any child or adolescent with bipolar disorder. *Selective* prevention strategies, those designed to target youth with a significant risk factor (in this case, bipolar disorder is the risk factor for SUD),[76] targeting bipolar youth who have never used substances have not yet been examined. Similar *universal* strategies (ie, for youth in general) used in nonbipolar community samples carry minimal risk and have been shown to be cost-effective.[77] Relatively brief universal family-focused preventive interventions for 11-year-old children have demonstrated reduced initiation and reduced frequency of substance use.[78,79] For example, the 7-session Iowa Strengthening Families Program conferred a relative reduction versus a control condition of 45.1% for ever using alcohol and 55.6% for ever being drunk at 2-year follow-up.[78] Taken together with favorable evidence for family-focused treatment among adolescents with bipolar disorder,[80] these findings suggest that preventive family-focused interventions may yield benefits in terms of both improved mood stability and delayed or attenuated substance use. Modifications to address the specific personal and familial needs of bipolar youth would enhance the current preventive intervention manuals.

Another strategy for selective prevention of SUD among bipolar youth is to advocate for substance-free homes. Data from pediatric settings indicate that parents are accepting of questions regarding their own smoking, and even of advice to decrease their smoking.[81] However, only half of all parents who attend their children's primary care visits report being asked about household member smoking status, and less than one-third are counseled about the risks of modeling smoking behavior.[82] Given that concerns about parental response to such an approach are common among clinicians, it will be important for future studies to collect similar information regarding acceptance of substance-related questions and advice among parents of bipolar youth, among whom SUDs are common.[51] In the absence of such data, we advocate for clinical strategies to promote substance-free homes, such as educating parents about the high risk of SUD in bipolar disorder and the specific consequences that may result from SUD in this population. Ideally, specific parent-targeted questions and advice regarding substance use would be incorporated. This strategy is particularly important for youth with bipolar disorder in the light of the family history findings reviewed above. Those findings indicate that bipolar youth are far more likely than healthy youth or youth with other forms of psychopathology to have relatives who use substances excessively.

Indicated prevention strategies, targeting youth with subthreshold manifestations of a disorder,[76] are needed in order to target bipolar youth who have initiated substance use but have not manifested SUD. A growing body of literature supports the benefits of brief interventions, usually based on motivational interviewing principles, for reducing substance use. Even two 15-minute sessions of brief physician advice in the context of primary care appointments is superior to a control condition in reducing hazardous drinking among young adults.[83] In fact, a single-session motivational interviewing intervention for 16–20-year-olds rendered benefits versus a control condition in terms of use of cigarettes, alcohol, and cannabis (effect sizes: 0.37, 0.34, and 0.75, respectively).[84] The effect of this intervention was greater among heavier users and among those with more concomitant risk factors. Interventions to reduce substance use that has not evolved into SUD may be particularly beneficial in bipolar disorder. Preliminary evidence indicates that even moderate alcohol use is associated with increased burden of illness among adults with bipolar disorder,[85] and that even weekly use of cannabis is associated with a nearly 4-fold risk of subsequent mania.[86] No study has tested a pharmacologic or psychosocial treatment for reducing the frequency of substance use among bipolar disorder subjects without SUD, and such studies are needed. In the interim, detailed instructions regarding how to incorporate motivational interviewing approaches to reduce substance use among adolescents can be gleaned from publicly available manuals and articles.[87]

Treatment interventions target people who already manifest SUD.[76] The term *tertiary prevention* has been used to describe treatment interventions that seek to reduce the morbidity associated with SUD. Given the complexity of managing pediatric bipolar disorder, let alone the added challenges of comorbid SUD, there is a risk of overlooking

opportunities to prevent "collateral damage." Again, there is evidence that even brief focused interventions may be effective. Dedicating a single therapy session to the topic of human immunodeficiency virus (HIV) within a 16-week course of cognitive-behavioral therapy for youth with MDD, conduct disorder, and SUD was associated with significantly enhanced knowledge regarding HIV and improved beliefs regarding condom use.[88] Moreover, there was nonsignificant improvement in actual behavior such as obtaining condoms. Previous findings suggest that the salience of acquired immunodeficiency syndrome (AIDS) prevention and pregnancy prevention predict condom use, even when sexual activity occurs during an episode of substance use.[89] Another study[90] examined the impact of a brief intervention for harm reduction with alcohol-positive adolescents in a hospital emergency department. Alcohol consumption during follow-up did not differ significantly between subjects randomly assigned to standard care versus the brief intervention (a single motivational interviewing session). However, subjects in the brief intervention group demonstrated significantly lower incidence of drinking and driving (62% vs 85%), traffic violations (3% vs 23%), alcohol-related injuries (21% vs 50%), and other alcohol-related problems in comparison to subjects who received standard care. These findings suggest that brief interventions may also attenuate risky behaviors among youth with bipolar disorder and SUD, whether or not there is a reduction in substance use.

CONCLUSION

To date, findings from adolescents with bipolar disorder mirror those from adults: youth with bipolar disorder are at increased risk for SUD, and comorbid SUD among youth with bipolar disorder is associated with mood recurrence, medication nonadherence, suicidality, legal problems, and adolescent pregnancy. However, the prevalence of SUD is approximately half of the rate observed among adults with bipolar disorder. Therefore, in addition to a great need for empirical evaluation of pharmacologic and psychosocial treatments, there is a great opportunity for prevention. This opportunity exists at all levels of care, for all types of providers, and regardless of the degree of substance use.

Drug names: aripiprazole (Abilify), disulfiram (Antabuse), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), naltrexone (Vivitrol, ReVia, and others), quetiapine (Seroquel), topiramate (Topamax and others), valproate sodium (Depacon and others).

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REFERENCES

1. Chengappa KN, Levine J, Gershon S, et al. Lifetime prevalence of substance or alcohol abuse and dependence among subjects with bipolar I and II disorders in a voluntary registry. *Bipolar Disord.* 2000; 2(3, pt 1):191–195.
2. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry.* 2004;61(8):807–816.
3. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. *JAMA.* 1990;264(19):2511–2518.
4. Merikangas KR, Herrell R, Swendsen J, et al. Specificity of bipolar spectrum conditions in the comorbidity of mood and substance use disorders: results from the Zurich cohort study. *Arch Gen Psychiatry.* 2008;65(1):47–52.
5. Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. *Bipolar Disord.* 2001;3(4):181–188.
6. Swann AC, Dougherty DM, Pazzaglia PJ, et al. Impulsivity: a link between bipolar disorder and substance abuse. *Bipolar Disord.* 2004;6(3):204–212.
7. Dalton EJ, Cate-Carter TD, Mundo E, et al. Suicide risk in bipolar patients: the role of co-morbid substance use disorders. *Bipolar Disord.* 2003;5(1):58–61.
8. Goldberg JF, Whiteside JE. The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. *J Clin Psychiatry.* 2002;63(9):791–795.
9. Quanbeck CD, Stone DC, Scott CL, et al. Clinical and legal correlates of inmates with bipolar disorder at time of criminal arrest. *J Clin Psychiatry.* 2004;65(2):198–203.
10. Weiss RD, Greenfield SF, Najavits LM, et al. Medication compliance among patients with bipolar disorder and substance use disorder. *J Clin Psychiatry.* 1998;59(4):172–174.
11. Singh J, Mattoo SK, Sharan P, et al. Quality of life and its correlates in patients with dual diagnosis of bipolar affective disorder and substance dependence. *Bipolar Disord.* 2005;7(2):187–191.
12. Weiss RD, Ostacher MJ, Otto MW, et al; for STEP-BD Investigators. Does recovery from substance use disorder matter in patients with bipolar disorder? *J Clin Psychiatry*. 2005;66(6):730–735, quiz 808–809.
13. Perlis RH, Miyahara S, Marangell LB, et al; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry.* 2004;55(9): 875–881.
14. Goldstein BI, Levitt AJ. Further evidence for a developmental subtype of bipolar disorder defined by age at onset: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Am J Psychiatry.* 2006;163(9):1633–1636.
15. Biederman J, Faraone SV, Wozniak J, et al. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. *J Psychiatr Res.* 2005;39(6):611–622.
16. Findling RL, Gracious BL, McNamara NK, et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord.* 2001;3(4):202–210.
17. Geller B, Tillman R, Craney JL, et al. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Arch Gen Psychiatry.* 2004;61(5):459–467.
18. Goldstein BI, Strober MA, Birmaher B, et al. Substance use disorders among adolescents with bipolar spectrum disorders. *Bipolar Disord.* 2008;10(4):469–478.
19. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry.* 1995;34(4):454–463.
20. Wittchen HU, Fröhlich C, Behrendt S, et al. Cannabis use and cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal community study in adolescents. *Drug Alcohol Depend.* 2007;88(suppl 1):S60–S70.
21. West SA, Strakowski SM, Sax KW, et al. Phenomenology and comorbidity of adolescents hospitalized for the treatment of acute mania. *Biol Psychiatry.* 1996;39(6):458–460.
22. McElroy SL, Strakowski SM, West SA, et al. Phenomenology of

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adolescent and adult mania in hospitalized patients with bipolar disorder. *Am J Psychiatry.* 1997;154(1):44–49.
23. Wilens TE, Biederman J, Kwon A, et al. Risk of substance use disorders in adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2004;43(11):1380–1386.
24. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry.* 2006;63(10):1139–1148.
25. Geller B, Tillman R, Bolhofner K, et al. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. *Arch Gen Psychiatry.* 2008;65(10):1125–1133.
26. Wilens TE, Biederman J, Millstein RB, et al. Risk for substance use disorders in youths with child- and adolescent-onset bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 1999;38(6):680–685.
27. Wilens TE, Biederman J, Adamson JJ, et al. Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: a controlled study. *Drug Alcohol Depend.* 2008;95(3): 188–198.
28. Dilsaver SC, Akiskal HS, Akiskal KK, et al. Dose-response relationship between number of comorbid anxiety disorders in adolescent bipolar/unipolar disorders, and psychosis, suicidality, substance abuse and familiality. *J Affect Disord.* 2006;96(3):249–258.
29. Bukstein OG, Brent DA, Kaminer Y. Comorbidity of substance abuse and other psychiatric disorders in adolescents. *Am J Psychiatry.* 1989; 146(9):1131–1141.
30. Stowell RJ, Estroff TW, Stowell RJ, et al. Psychiatric disorders in substance-abusing adolescent inpatients: a pilot study. *J Am Acad Child Adolesc Psychiatry.* 1992;31(6):1036–1040.
31. Latimer WW, Stone AL, Voight A, et al. Gender differences in psychiatric comorbidity among adolescents with substance use disorders. *Exp Clin Psychopharmacol.* 2002;10(3):310–315.
32. Strakowski SM, DelBello MP, Fleck DE, et al. Effects of co-occurring alcohol abuse on the course of bipolar disorder following a first hospitalization for mania. *Arch Gen Psychiatry.* 2005;62(8):851–858.
33. Goldstein BI, Levitt AJ. Factors associated with temporal priority in comorbid bipolar I disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry.* 2006;67(4):643–649.
34. Strakowski SM, DelBello MP, Fleck DE, et al. The impact of substance abuse on the course of bipolar disorder. *Biol Psychiatry.* 2000;48(6): 477–485.
35. Wilens TE, Biederman J, Abrantes AM, et al. Clinical characteristics of psychiatrically referred adolescent outpatients with substance use disorder. *J Am Acad Child Adolesc Psychiatry.* 1997;36(7):941–947.
36. Geller B, Cooper TB, Sun K, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry.* 1998;37(2):171–178.
37. Goldstein BI, Birmaher B, Axelson DA, et al. Preliminary findings regarding overweight and obesity in pediatric bipolar disorder. *J Clin Psychiatry.* 2008;69(12):1953–1959.
38. McIntyre RS, McElroy SL, Konarski JZ, et al. Substance use disorders and overweight/obesity in bipolar I disorder: preliminary evidence for competing addictions. *J Clin Psychiatry.* 2007;68(9):1352–1357.
39. Steinbuchel PH, Wilens TE, Adamson JJ, et al. Posttraumatic stress disorder and substance use disorder in adolescent bipolar disorder. *Bipolar Disord.* 2009;11(2):198–204.
40. Wilens TE, Martelon M, Kruesi MJ, et al. Does conduct disorder mediate the development of substance use disorders in adolescents with bipolar disorder? a case-control family study. *J Clin Psychiatry.* 2009;70(2):259–265.
41. Strober M, Schmidt-Lackner S, Freeman R, et al. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry.* 1995;34(6):724–731.
42. DelBello MP, Hanseman D, Adler CM, et al. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry.* 2007;164(4):582–590.
43. Kupfer DJ. The increasing medical burden in bipolar disorder. *JAMA.* 2005;293(20):2528–2530.
44. Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness: a population-based prevalence study. *JAMA.* 2000;284(20):2606–2610.
45. Wilens TE, Biederman J, Milberger S, et al. Is bipolar disorder a risk for cigarette smoking in ADHD youth? *Am J Addict.* 2000;9(3):187–195.
46. Goldstein BI, Birmaher B, Axelson DA, et al. Significance of cigarette smoking among youths with bipolar disorder. *Am J Addict.* 2008;17(5):364–371.
47. Heffner JL, DelBello MP, Fleck DE, et al. Cigarette smoking in the early course of bipolar disorder: association with ages-at-onset of alcohol and marijuana use. *Bipolar Disord.* 2008;10(7):838–845.
48. Schulze TG, Hedeker D, Zandi P, et al. What is familial about familial bipolar disorder? resemblance among relatives across a broad spectrum of phenotypic characteristics. *Arch Gen Psychiatry.* 2006;63(12): 1368–1376.
49. Todd RD, Geller B, Neuman R, et al. Increased prevalence of alcoholism in relatives of depressed and bipolar children. *J Am Acad Child Adolesc Psychiatry.* 1996;35(6):716–724.
50. Biederman J, Faraone SV, Wozniak J, et al. Parsing the association between bipolar, conduct, and substance use disorders: a familial risk analysis. *Biol Psychiatry.* 2000;48(11):1037–1044.
51. Wilens TE, Biederman J, Adamson J, et al. Association of bipolar and substance use disorders in parents of adolescents with bipolar disorder. *Biol Psychiatry.* 2007;62(2):129–134.
52. Rao U. Links between depression and substance abuse in adolescents: neurobiological mechanisms. *Am J Prev Med.* 2006;31(suppl 1): S161–S174.
53. Jarvis K, DelBello MP, Mills N, et al. Neuroanatomic comparison of bipolar adolescents with and without cannabis use disorders. *J Child Adolesc Psychopharmacol.* 2008;18(6):557–563.
54. Rao U, Hammen CL, Poland RE. Mechanisms underlying the comorbidity between depressive and addictive disorders in adolescents: interactions between stress and HPA activity. *Am J Psychiatry.* 2009;166(3):361–369.
55. Geller B, Williams M, Zimerman B, et al. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord.* 1998;51(2):81–91.
56. Salloum IM, Cornelius JR, Daley DC, 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.
57. Brown ES, Garza M, Carmody TJ. A randomized, double-blind, placebo-controlled add-on trial of quetiapine in outpatients with bipolar disorder and alcohol use disorders. *J Clin Psychiatry.* 2008;69(5):701–705.
58. Brown ES, Perantie DC, Dhanani N, et al. Lamotrigine for bipolar disorder and comorbid cocaine dependence: a replication and extension study. *J Affect Disord.* 2006;93(1–3):219–222.
59. Brown ES, Jeffress J, Liggin JD, et al. Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. *J Clin Psychiatry.* 2005;66(6):756–760.
60. Weiss RD, Griffin ML, Kolodziej ME, et al. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. *Am J Psychiatry.* 2007;164(1):100–107.
61. Bukstein OG, Bernet W, Arnold V, et al; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with substance use disorders. *J Am Acad Child Adolesc Psychiatry.* 2005;44(6):609–621.
62. Dennis M, Godley SH, Diamond G, et al. The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials. *J Subst Abuse Treat.* 2004;27(3):197–213.
63. Liddle HA. Family-based therapies for adolescent alcohol and drug use: research contributions and future research needs. *Addiction.* 2004;99(suppl 2):76–92.
64. Waldron HB, Slesnick N, Brody JL, et al. Treatment outcomes for adolescent substance abuse at 4- and 7-month assessments. *J Consult Clin Psychol.* 2001;69(5):802–813.
65. Latimer WW, Winters KC, D'Zurilla T, et al. Integrated family and cognitive-behavioral therapy for adolescent substance abusers: a stage I efficacy study. *Drug Alcohol Depend.* 2003;71(3):303–317.
66. Delbello MP, Findling RL, Kushner S, et al. A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44(6):539–547.
67. Johnson BA, Rosenthal N, Capece JA, et al; Topiramate for Alcoholism Advisory Board; Topiramate for Alcoholism Study Group. Topiramate for treating alcohol dependence: a randomized controlled trial.

JAMA. 2007;298(14):1641–1651.
68. Miklowitz DJ, George EL, Axelson DA, et al. Family-focused treatment for adolescents with bipolar disorder. *J Affect Disord.* 2004;82(suppl 1): S113–S128.
69. Goldstein BI, Goldstein TR, Miklowitz DJ, et al. Development of integrated family-focused treatment (FFT) for adolescents with bipolar disorder and comorbid substance use disorders [presented at the 48th Annual NCDEU Meeting: New Research Approaches for Mental Health Interventions]. In: *Poster Abstracts of the 48th Annual NCDEU Meeting: The Art and Science of Personalizing Treatments for Mental Disorders*; May 27–30, 2008; Phoenix, AZ. Session II-9:91.
70. Kowatch RA, Fristad M, Birmaher B, et al; Child Psychiatric Workgroup on Bipolar Disorder. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44(3):213–235.
71. Kosten TR, Kosten TA. New medication strategies for comorbid substance use and bipolar affective disorders. *Biol Psychiatry.* 2004; 56(10):771–777.
72. Nomamiukor N, Brown ES. Attrition factors in clinical trials of comorbid bipolar and substance-related disorders. *J Affect Disord.* 2009; 112(1–3):284–288.
73. Feinstein AR, Walter SD, Horwitz RI. An analysis of Berkson's bias in case-control studies. *J Chronic Dis.* 1986;39(7):495–504.
74. Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. *J Affect Disord.* 1994;31(4):281–294.
75. Suominen K, Mantere O, Valtonen H, et al. Early age at onset of bipolar disorder is associated with more severe clinical features but delayed treatment seeking. *Bipolar Disord.* 2007;9(7):698–705.
76. Weisz JR, Sandler IN, Durlak JA, et al. Promoting and protecting youth mental health through evidence-based prevention and treatment. *Am Psychol.* 2005;60(6):628–648.
77. Spoth RL, Guyll M, Day SX. Universal family-focused interventions in alcohol-use disorder prevention: cost-effectiveness and cost-benefit analyses of two interventions. *J Stud Alcohol.* 2002;63(2):219–228.
78. Spoth R, Redmond C, Lepper H. Alcohol initiation outcomes of universal family-focused preventive interventions: one- and two-year follow-ups of a controlled study. *J Stud Alcohol Suppl.* 1999;13:103–111.
79. Spoth RL, Redmond C, Shin C. Randomized trial of brief family interventions for general populations: adolescent substance use outcomes 4 years following baseline. *J Consult Clin Psychol.* 2001;69(4):627–642.
80. Miklowitz DJ, Axelson DA, Birmaher B, et al. Family-focused treatment for adolescents with bipolar disorder: results of a 2-year randomized trial. *Arch Gen Psychiatry.* 2008;65(9):1053–1061.
81. Moss D, Cluss PA, Mesiano M, et al. Accessing adult smokers in the pediatric setting: what do parents think? *Nicotine Tob Res.* 2006;8(1): 67–75.
82. Winickoff JP, McMillen RC, Carroll BC, et al. Addressing parental smoking in pediatrics and family practice: a national survey of parents. *Pediatrics.* 2003;112(5):1146–1151.
83. Grossberg PM, Brown DD, Fleming MF. Brief physician advice for high-risk drinking among young adults. *Ann Fam Med.* 2004;2(5):474–480.
84. Strang J, McCambridge J. Can the practitioner correctly predict outcome in motivational interviewing? *J Subst Abuse Treat.* 2004;27(1):83–88.
85. Goldstein BI, Velyvis VP, Parikh SV. The association between moderate alcohol use and illness severity in bipolar disorder: a preliminary report. *J Clin Psychiatry.* 2006;67(1):102–106.
86. Henquet C, Krabbendam L, de Graaf R, et al. Cannabis use and expression of mania in the general population. *J Affect Disord.* 2006;95(1-3):103–110.
87. McCambridge J, Strang J. Development of a structured generic drug intervention model for public health purposes: a brief application of motivational interviewing with young people. *Drug Alcohol Rev.* 2003;22(4):391–399.
88. Thurstone C, Riggs PD, Klein C, et al. A one-session human immunodeficiency virus risk-reduction intervention in adolescents with psychiatric and substance use disorders. *J Am Acad Child Adolesc Psychiatry.* 2007;46(9):1179–1186.
89. Bailey SL, Gao W, Clark DB. Diary study of substance use and unsafe sex among adolescents with substance use disorders. *J Adolesc Health.* 2006;38(3):297–20, e13–e20.
90. Monti PM, Colby SM, Barnett NP, et al. Brief intervention for harm reduction with alcohol-positive older adolescents in a hospital emergency department. *J Consult Clin Psychol.* 1999;67(6):989–994.

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