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# Bipolar Disorder and Alcohol Use Disorder: A review

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## Abstract

Bipolar disorder and alcohol use disorder represent a significant comorbid population, which is significantly worse than either diagnosis alone in presentation, duration, co-morbidity, cost, suicide rate, and poor response to treatment. They share some common characteristics in relation to genetic background, neuroimaging findings, and some biochemical findings. They can be treated with separate care, or ideally some form of integrated care. There are a number of pharmacotherapy trials, and psychotherapy trials that can aid programme development. Post-treatment prognosis can be influenced by a number of factors including early abstinence, baseline low anxiety, engagement with an aftercare programme and female gender. The future development of novel therapies relies upon increased psychiatric and medical awareness of the co-morbidity, and further research into novel therapies for the comorbid group.

### Keywords

Alcohol Use Disorder; Bipolar Disorder; treatment; integrated; psychotherapy; pharmacotherapy; genetic; neuroimaging; comorbidity; treatment programme; FIRESIDE; integrated group therapy

## Introduction

Bipolar disorder (BD) and alcohol use disorder (AUD) are independently a common cause of significant psychopathology in the general population. BD can affect up to 3% of the population in some countries; with the increasing awareness of the bipolar spectrum of disorders, this figure could increase over time. AUD, incorporating alcohol abuse and dependence, which can affect up to 13% of the general adult population in some surveys (Regier et al., 1990), and can have a lifetime incidence of up to 18% (Hasin et al., 2007), is a major cause of psychopathology in the general population. The co-morbidity of AUD in BD can reach 45% (Kessler et al., 1997; Cardoso et al., 2008), and the odds ratio for AUD in bipolar I disorder is higher than for bipolar II disorder, ( 3.5 and 2.6 respectively) (Hasin et al., 2007). The co-morbidity of BD in AUD is also high (Kessler et al., 1997; Frye and Salloum, 2006).

Thus together, the co-morbidity of AUD and BD represents a large segment of the population, although probably significantly hidden. AUD with BD produces a significant increased risk of associated psychopathology including longer duration of withdrawal from alcohol, increased severity of manic and depressive symptoms (Feinman and Dunner, 1996; Salloum et al., 2002) , increased associated psychopathology, increased suicide risk, poorer prognosis, higher cost, increased morbidity and overall decreased degree of function

(Cardoso et al., 2008; Strakowski et al., 2005a; Van Zaane et al., 2010). This increase in associated problems is also compounded by the traditional separation of psychiatry and addiction treatment services in many countries. This division leads to comorbid patients falling between two stools, and not getting adequate intervention from either services. This has been compounded by a paucity of research in the area of comorbidity, in particular by a lack of research about successful treatment intervention for co-morbidity. Thus standard treatment interventions and standardised treatment protocols do not exist, and each treating practitioner and treatment service determines individually how to deal with the problem. There have been few academic or international collegiate bodies that have investigated the area of comorbidity, and thus no NICE guidelines (National Institute of Clinical Excellence, UK), or equivalent to help determine best practice. This absence of guidelines, or even consensus, leads in general to poor or inadequate practice.

## How do comorbid BD and AUD develop?

If the AUD commences before the BD, then one hypothesis for the comorbidity would be that the AUD activates a predisposition towards BD in that subgroup; although there is no genetic or familial evidence for this (Maier and Merikangas, 1996). The other hypothesis, namely that patients with BD use alcohol to self-medicate their mood symptoms, or drink a result of their tendency towards impulsive behaviours, may also apply (Swann et al., 2003). It is likely, however, that within the spectrum of comorbid AUD and BD, there lies a variety of orders and associations, and that no one hypothesis explains the full spectrum of presentations. Consistent with this is the fact that when comorbid groups are studied, some patients present with BD first, some with AUD first, and some patients present with both simultaneously (Strakowski et al., 2005a). Those with AUD first tend to be older and tend to recover more quickly, whereas those with BD first tend to spend more time with affective disorder, and have more symptoms of AUD (Strakowski et al., 2005a). There are some gender differences also in that more men than women with BD tend to be alcoholic (Frye et al., 2003).

## Genetics

BD is a highly genetic disorder, with a family history in about 80% of patients. Recent research confirms the importance of the genetics of the disorder; although there has not been to date a specific chromosome region or gene specifically confirmed as involved, several regions are of interest (Craddock and Sklar 2009; Farmer et al., 2007; Serrettit and Mandelli, 2008).

Alcohol dependence is also highly genetic (Mayfield et al., 2008), and a wide range of studies confirm that association (Kendler et al., 2009). In early to mid-adolescence, initiation of alcohol use may be an environmental effect (with social and peer influences being predominant and changeable)(Smyth et al., 2011), but development of the alcohol abuse/dependence pattern in late adolescence or in early adulthood, may be subject to genetic influences (Kendler et al., 2009). In AUD, a number of genetic loci are of interest, and a number of endophenotypes (clusters of measureable symptoms or biological phenomena) that may also be of genetic interest (Dick et al., 2006); these include abnormal auditory P300 evoked response potential amplitude (a measurement of cerebral electrical activity) (Strat et al., 2008); increased or high tolerance to alcohol (Schuckit, 1994); high sweet-liking phenotype (Garbutt et al., 2009 ); abnormal personality characteristics including high novelty-seeking, low harm avoidance, and low reward dependence (Cloninger et al., 1987); early age of onset (Irwin et al., 1990) and alcohol typology (Babor et al., 1992).

In BD, there is an equal incidence of men and women, emphasising the genetic origin of the disorder. In AUD, while there is a higher incidence in men, the genetic component may be

more prominent in women (Kendler et al., 1992). There are neurochemical abnormalities in both disorders in the serotonin/dopamine pathways, which could suggest a similar pathology in both disorders (Yasseen et al., 2010).

## Neuroimaging

In neuroimaging studies, there are a number of areas of interest in BD and indeed in AUD that have emerged in different studies in different populations. In BD, numerous studies, including MRI studies. have identified areas including the pre-frontal cortex, the corpus striatum and the amygdala as being abnormal in early BD, potentially predating illness (Chang et al., 2004, Strakowski et al., 2005b). Abnormalities in the cerebellar vermis, lateral ventricles, and some prefrontal areas may develop with repeated affective episodes, and may represent the effects of illness progression (Strakowski et al., 2005b).

In AUD, various studies have also identified the frontal and prefrontal cortex, the anterior cingulate, the thalamus, and various basal ganglia as abnormal (Farren et al., 2001; Myrick et al., 2008; Volkow et al., 2007). While further investigations will explore the interrelationship between these various areas of interest, and the associated neurochemical abnormalities in these areas driving the disorders, there appears to be some crossover between them in origin of the disorders.

## Psychotherapeutic Interventions

In the past two decades, a large body of research has been devoted to the development and testing of manual-based psychotherapies for BD and for AUDs. The development of these psychotherapeutic interventions involves a rigorous process: structured therapist training and supervision, audiotaped or videotaped therapy sessions, rating of sessions to ensure that therapists are delivering the treatment as intended, and testing of the new treatment against either treatment-as-usual or another evidence-based treatment.

As a result of this process, a number of evidence-based psychotherapies have been developed for BD and for alcohol dependence. In the treatment of BD, cognitive-behavioral therapy (Lam et al., 2003), family-focused treatment (Miklowitz et al., 2003), interpersonal and social rhythm therapy (Frank et al., 2005), and group psychoeducation (Colom et al., 2003) have all been shown to be effective as adjuncts to pharmacotherapy. Similarly, motivational enhancement therapy, twelve-step facilitation therapy, and cognitive-behavioral relapse prevention therapy have all been shown to be effective in the treatment of alcohol dependence (Project MATCH Research Group, 1997). Notably however, patients with active substance use disorders (including alcohol dependence) are typically excluded from psychotherapy studies of BD, and patients with BD were excluded from the two largest studies examining behavioral therapies for alcohol dependence (Project MATCH Research Group, 1997; Anton et al., 2006). As a result, little psychotherapy research has focused on patients with co-occurring BD and alcohol dependence.

Psychosocial approaches (including psychotherapy) for patients with co-occurring psychiatric illness and substance use disorders typically involve one of three formats: sequential, parallel, or integrated. *Sequential* treatment involves focusing on the more acute disorder first, then treating the other disorder when the acute problem has been stabilized; this approach is most commonly utilized in a hospital setting. A limitation of sequential treatment, however, is the fact that the less acute disorder may not, in fact, be addressed in the future, despite intentions to do so during the acute hospitalization. *Parallel* treatment, which ordinarily takes place on an outpatient basis, consists of treating the two disorders in separate settings. Although the patients receive expert care for each disorder, they may hear potentially conflicting advice regarding the overlap between the two disorders. In *integrated*

treatment, a clinician or group of clinicians treats both disorders simultaneously. For many years, clinicians and researchers have cited the advantages of integrated treatment. However, there is no standardized method by which treatment of patients with co-occurring disorders is integrated. There are numerous models of integrated treatment, varying according to the patient population (i.e., the specific psychiatric disorder, substances of abuse, and sociodemographic characteristics of the population) and the philosophical orientation of the program. Integrated treatment models have been developed for a variety of different disorders, including posttraumatic stress disorder (Hien et al., 2004), schizophrenia (Ziedonis et al., 2005), and severe and persistent mental illness (Bellack et al., 2006). Patients with BD are sometimes grouped together with patients with major depressive disorder (Farren et al., 2010) or with patients with schizophrenia (Bellack et al., 2006) when conducting integrated treatment.

Integrated treatment can occur either at the programmatic level or at the individual or group patient level. In the programmatic level, as exemplified by the work of Farren et al. (Farren and McElroy, 2008, 2010; Farren et al., 2010), patients enter a comprehensive integrated treatment programme that focuses on both psychiatric illness and substance use disorders. This series of studies on bipolar subjects with alcohol dependence examined the response to an inpatient integrated four-week psychoeducational programme with appropriate individualised pharmacotherapy. The programme consisted of specifically developed relapse prevention group therapy, individualised interpersonal therapy, with psychoeducational video and group sessions, together with self-help groups including Alcoholics Anonymous, and Dual Recovery Anonymous. These treatment principles are outlined in Figure 1. When followed up at six months post-discharge, various positive prognostic factors were identified, including early abstinence, baseline low anxiety, and engagement with an aftercare programme (Farren and McElroy, 2010). By two years, however, different positive prognostic factors emerged including female gender (Farren et al., 2011). Interestingly, it appeared that the addictive disorder component determined the overall dual diagnosis outcome rather than the other way around; although this may have been driven by the fact that the treatment unit was historically an addiction treatment unit, and a significant number of the BD diagnoses were established after withdrawal in subjects originally admitted for alcohol use disorder treatment. However no difference in prognosis was found when subjects were divided by which disorder came first (Farren et al., 2011).

At the individual patient level (i.e., how one should intervene with a patient or group of patients that one is currently treating), the most systematic program of psychotherapy research involving patients with co-occurring bipolar and substance use disorders has focused on Integrated Group Therapy (IGT), in a series of studies by Weiss et al. (2000a, 2007, 2009). IGT (Weiss & Connery, 2011), based primarily on cognitive-behavioral therapy principles, is designed to serve as an adjunct to BD pharmacotherapy by focusing on the two disorders simultaneously, with a particular emphasis on their relationship. IGT has three major guiding principles. The first is the “single-disorder paradigm,” in which patients are encouraged to think of themselves as having a single disorder, i.e., “bipolar substance abuse,” rather than trying to tackle two discrete disorders at once. Thinking of themselves as having a single disorder aids in the process of acceptance.

A second key concept underlying IGT is a focus on common features in the recovery and relapse process in the two disorders. Patients are told that the same kinds of thoughts and behaviors that will facilitate their recovery from one disorder will also aid in the recovery process from their other disorder. Conversely, thoughts and behaviors that may increase the risk of relapse to one disorder will similarly elevate their chances of relapse to the other disorder. Thoughts and behaviors are therefore labeled “recovery thoughts” and “recovery behaviors,” or “relapse thoughts” and “relapse behaviors.” As with the single-disorder

paradigm, patients are encouraged to focus on the overall recovery process rather than the recovery process from each disorder.

A third feature of IGT is a discussion of the relationship between the two disorders. If commonalities in the recovery and relapse process in the two disorders can be seen as parallels between the two disorders, the focus on the relationship between the two disorders can be viewed as the intersection between BD and alcohol dependence. Thus, patients are told that drinking will negatively affect the course of their BD, and that non-adherence to their BD medication will increase their risk of relapse to drinking. Again, the focus on the intersection between the two disorders is consistent with the single-disorder paradigm.

An IGT session begins with a "check-in," in which patients have several minutes each to report on their substance use during the previous week, their overall mood, and their degree of medication adherence. Following this, a group topic is presented and discussed. Topics are designed to be relevant to both disorders (e.g., "Dealing with Depression without Abusing Substances," "Denial, Ambivalence, and Acceptance"), and the group leader refers back to the check-in reports frequently during the topic discussion. Toward the end of the group session, patients are given a handout with highlights of the group topic, and a skill practice sheet for patients to work on during the upcoming week. One of the guiding concepts of IGT is the so-called "central recovery rule": "No matter what, don't drink, don't use drugs, and take your medication as prescribed, no matter what."

## Research on Integrated Group Therapy

Weiss et al. (2000a, 2007, 2009) have conducted three studies of IGT, each of which supported its efficacy. In the initial pilot project (Weiss et al., 2000a), patients who received IGT were compared with patients who did not receive this treatment. In this study, all patients received "treatment as usual" in addition to being in the experimental or control condition. Importantly, all patients in this and in the two subsequent studies of IGT had to be taking a mood stabilizer to be eligible to participate in the research. Moreover, in all three studies, many patients participated in individual therapy and self-help groups (Weiss et al., 2000b). In the first study (N=45), patients who received IGT had significantly better substance use outcomes than those who did not receive the treatment, and were far more likely to maintain complete abstinence from drugs and alcohol for at least three consecutive months (61.9% vs. 20.8%, $p<0.004$).

Weiss et al. (2007) then conducted a randomized controlled study in which IGT was compared to an active control condition, Group Drug Counseling (GDC) (Daley et al., 2002). GDC, which had been used successfully in previous research (Crits-Christoph et al., 1999), is a manual-based treatment that represents the type of group therapy that would be delivered in a high-quality community-based substance abuse treatment program. GDC has the same structure as IGT (e.g., there is a check-in at the beginning and a session topic), but the content differs in that GDC addresses primarily substance use.

IGT patients had significantly better substance use outcomes than did those who received GDC: IGT patients had approximately half as many days of substance use as GDC patients (use on 5.3% vs. 10.0% of study days, $p<0.03$), and had fewer days of alcohol use ($p<0.001$) and fewer days of alcohol use to intoxication ($p<0.01$) during treatment. As with the pilot study, there were no significant differences in number of weeks ill with BD. Interestingly, patients receiving IGT did have more sub-threshold manic and depressive symptoms during treatment and follow-up.

A third study of IGT was designed to make this treatment more "community-friendly," to increase its chances of adoption in community-based addiction treatment programs. The

treatment was therefore reduced from twenty sessions to twelve sessions, to increase the likelihood that it would be funded by insurance companies and other payers. Moreover, the manual was modified to include more basic information on BD, substance use disorder, and cognitive-behavioral therapy, because many community-based treatment programmes do not have staff members with experience or expertise with BD or cognitive-behavioral therapy. Another study was then performed, comparing IGT with GDC, but with the twelve-week version conducted by front-line drug abuse counselors without cognitive-behavioral therapy experience or BD expertise. Again, IGT was shown to be more efficacious than GDC. Patients receiving IGT were significantly more likely to attain at least one month of total abstinence (71% vs. 40%, $p<0.02$) and were also more likely to abstain throughout all twelve weeks of treatment (36% vs. 13%, $p<0.05$). A composite measure of "good clinical outcome," consisting of abstinence and the absence of any mood episode in the previous four weeks, also favored IGT at the end of treatment (45% vs. 20%, $p<0.04$). Thus, IGT has been demonstrated to be efficacious for this common and difficult-to-treat population.

## Pharmacotherapeutic Interventions

Despite the considerable public health significance of co-occurring BD and alcohol dependence, there are few effective pharmacotherapeutic interventions. Pharmacotherapy clinical trials for BD and those for alcohol dependence have often excluded co-occurring disorders in an attempt to reduce confounding variables. As a result, there is a limited literature that clinicians can draw upon when treating patients with co-occurring BD and alcohol dependence.

Most pharmacotherapy studies in patients with co-occurring BD and alcohol dependence have utilized two groups of medications that can be used to treat mood symptoms: mood stabilizers and atypical antipsychotics. Valproate is promising in this regard due to established antimanic efficacy (Bowden et al., 1994), ability to alleviate alcohol withdrawal symptoms (Hillborn et al., 1989; Hammer and Brady, 1996), and reduction of alcohol use in those with AUD (Johnson et al., 2003; Brady et al., 2002). In the first study in patients with BD and AUD, Salloum et al. (2005) randomized 59 participants with BD maintained on lithium to receive valproate or placebo for 24 weeks. The valproate group had significantly fewer heavy drinking days and a trend toward fewer drinks per drinking day than the placebo group. A subsequent study of rapid cycling participants with bipolar I or II disorders and co-occurring substance abuse or dependence showed that, of the subset of participants with alcohol abuse or dependence, 58% no longer met criteria for alcohol abuse or dependence after a six month open-label trial of lithium and divalproex (Kemp et al., 2009).

Atypical antipsychotic pharmacotherapies may be efficacious in patients with both BD and AUD because they exert less dopamine antagonism than higher-potency typical antipsychotics (Drake et al., 2000; Zimmet et al., 2000; Littrell et al., 2001). In a double-blind, placebo-controlled pilot study in participants with AUD, quetiapine treatment resulted in significantly fewer drinking days as well as reduced craving in comparison to placebo (Kampman et al., 2007). Three studies have evaluated quetiapine in participants with co-occurring BD and AUD. In a randomized, double-blind, placebo controlled trial of quetiapine added to a regimen to treat BD in 115 outpatients with BD and alcohol abuse or dependence, Brown et al. (2008) found that the addition of quetiapine did not result in differences in alcohol use or on scores on the Young Mania Rating Scale (YMRS). They did, however, report a significant decrease in Hamilton Rating Scale for Depression (HAM-D) scores. Stedman et al. (2010) showed that quetiapine added to lithium or divalproex did not result in statistically significant changes in alcohol use as measured by mean proportion of heavy drinking days and mean change in proportion of heavy drinking days in 362 participants with BD and alcohol dependence compared to placebo over a twelve-week

period. Finally, quetiapine's effects upon AUD were also evaluated in participants with co-occurring psychiatric disorders characterized by high levels of mood and behavioral instability: BD, schizoaffective disorder, and borderline personality disorder (Martinotti et al., 2008). In this open-label study that did not provide outcomes for participants separated by disorder, twelve (42.8%) remained alcohol-free and significant reductions were reported in the Obsessive Compulsive Drinking Scale, the Visual Analogue Scale for craving, the Brief Psychiatric Rating Scale, the HAM-D, and the number of drinking days per week (Martinotti et al., 2008).

There have also been studies of pharmacotherapeutic interventions for AUD in those with BD and AUD. Encouraged by data suggesting a modest positive effect on alcohol consumption (effect size for percentage drinking days =−.191, p<.001; Kranzler and Van Kirk 2001), as well as studies suggesting that naltrexone is safe in patients with AUD and co-occurring severe mental illness (Croop et al., 1997; Salloum et al., 1998; Maxwell and Shinderman, 2000; Morris et al., 2001), two groups have examined naltrexone's efficacy in patients with BD and AUD. In a randomized twelve-week trial of naltrexone and disulfiram for alcohol use in 254 participants with alcohol dependence and co-occurring Axis I disorders (including 19.3% with BD), the medications produced significantly more weeks of abstinence and less craving than placebo (Petrakis et al., 2005). The results from this study also suggested that treatment with the combination of naltrexone and disulfiram did not have added benefit compared to treatment with either medication alone (Petrakis et al., 2005). In a sixteen-week, open-label, pilot study of naltrexone added on to existing regimens for 34 participants with BD and alcohol dependence, significant improvement was observed on both the HAM-D and YMRS, and days of alcohol use and craving decreased significantly (Brown et al., 2006). Brown et al. (2009) followed up with a randomized, double-blind, placebo controlled study of naltrexone added-on to pharmacotherapeutic regimens to treat participants with BD and alcohol dependence. No significant between-group differences on the primary outcome of drinking days were found, although naltrexone treatment showed trends ($p < .10$) toward a greater decreased in craving and some liver enzymes (aminotransferase and alanine aminotransferase, but not γ-glutamyltransferase)(Brown et al., 2009).

Acamprosate has also been evaluated in an open-label trial and a randomized controlled trial. In a small open-label trial of acamprosate added to a mood regimen in participants with BD and alcohol dependence, acamprosate produced a significant reduction in number of drinks per week, but no differences in mood symptoms when compared to placebo (Tolliver et al., 2009). However, these findings were not replicated in a slightly larger randomized, double-blind, placebo-controlled clinical trial of acamprosate add-on pharmacotherapy in participants with BD and alcohol dependence conducted by the same group (Tolliver et al., 2012). No statistically significant treatment differences were detected in drinking or mood outcomes. Post-hoc analysis showed that acamprosate treatment resulted in lower Clinical Global Impression scores of substance abuse severity in the last two weeks of the trial (Tolliver et al., 2012).

## Summary

This paper has examined the importance of the comorbidity of BD and AUD. It has explored the breath of the association, its complexity, the range of the associations between the disorders, and importantly the range and the limitations of the current knowledge of the psychotherapeutic and pharmacotherapeutic options available to the treating clinician. Unfortunately, the field is marred by a paucity of well-conceived, conducted, and published studies informing the clinician about how to manage a comorbidly diagnosed patient. Despite some ongoing studies, the research field still reflects the current therapeutic field;

namely there are few integrated treatment programmes in existence, and even fewer leading to therapeutic guidelines. It is only through demonstration of the effectiveness of treatment integration that there will be extensive therapeutic efforts to bridge psychiatric treatment programmes and services, and substance abuse treatment programmes and services. That treatment integration is still a long way off, despite the accumulating research demonstrating the benefits of integration.

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**Table 1**

The FIRESIDE Principles for an integrated treatment of bipolar disorder and alcohol use disorder. (Farren and McElroy, 2008).

- **F***ollow up*. The importance of aftercare strongly emphasised
- **I***nterrelationship of diagnoses*. Can't improve in one without the treating the other.
- **R***elapse Prevention*. The main addiction therapeutic intervention.
- **E***ducation*. Use of lectures, videos, and discussions.
- **S***tabilization of withdrawal and mood*. Pharmacotherapy used aggressively during and after the program.
- **I***ndividuation of program*. Flexibility of program to aid retention.
- **D***iagnostic equivalence*. Both diagnoses emphasised equally.
- **E***mpowerment*. Individual responsibility encouraged and demanded.