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Treatment for comorbid borderline personality disorder and alcohol use disorders: A review of the evidence and future recommendations

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Abstract

There is a high degree of comorbidity between borderline personality disorder (BPD) and alcohol use disorders (AUDs) including alcohol abuse (AA) and dependence (AD). There is some evidence that this pattern of comorbidity may be associated with poorer prognosis. Although there are many different psychotherapeutic and pharmacological treatments for BPD and AUDs when they occur alone, there are very few treatment options when they occur together. The objective of this paper was to review the existing treatment options—both psychotherapeutic and pharmacological—for patients with dual diagnoses of BPD and AUDs and to explore alternative treatment options that warrant further study. There have been a number of studies that have examined the efficacy of specific psychotherapies targeting drinking among patients with comorbid BPD; however, their efficacy in reducing BPD symptoms is unknown. There are also three psychotherapies that were specifically developed for patients with BPD and SUDs, but only one of these (Dynamic Deconstructive Psychotherapy) has been tested among patients with dual diagnoses of BPD and AUDs. Research on pharmacotherapy for dual diagnoses of BPD and AUD is scarce, and no study has yet explored medication options that can concurrently manage symptoms of BPD and decrease alcohol consumption. Interestingly, there is growing evidence that anticonvulsants and second generation antipsychotics, the recent medications of choice for the management of anger in BPD, may also reduce alcohol craving and consumption. Although premature, these findings are encouraging especially for this population of patients for whom treatment options are very limited.

Keywords

Borderline Personality Disorder; Alcohol Dependence; Comorbidity; Psychotherapy; Pharmacotherapy

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There is substantial literature documenting the high co-occurrence of borderline personality disorder (BPD) and substance use disorders (SUDs) (e.g., Trull, Sher, Minks-Brown, Durbin & Burr, 2000; Links, Helsegrave, Mitton, van Reekum & Patrick, 1995; Zanarini et al., 1998). Evidence for this comes from a variety of sources including data from clinical samples and the general population. Of the SUDs, alcohol use disorders (AUDs) including both alcohol abuse (AA) and alcohol dependence (AD) are the most common among individuals with BPD (Trull et al., 2000; Verheul et al., 2000). Despite high comorbidity rates, little attention has been paid to treatments for these dually diagnosed patients. The objective of this paper is to review the existing treatment options for patients diagnosed with BPD and AUDs – both psychotherapeutic and pharmacological – and discuss alternative treatment options that warrant further study for this population.

Epidemiology and course

BPD is present in approximately 1% to 1.6% of the general population (Torgersen, 2009) and in about 20% of psychiatric patients (Gunderson & Links, 2008). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; APA, 2000), BPD is thought to be about three times more common among females than males. While this may be true in clinical settings, community-based studies have failed to find such gender differences (Grant et al., 2008; Lenzenweger, 2007; Torgersen, Kringlen & Cramer, 2001; Zimmerman & Coryell, 1990).

Both epidemiological and clinical studies have reported high comorbidity rates between BPD and AUDs. For example, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) suggest that among individuals with a lifetime diagnosis of BPD, 58.3% also had lifetime diagnoses of AUDs. In this same study, rates of co-occurrence of lifetime BPD among patients with AUDs ranged from 9.8% to 14.7%. Similarly high rates of comorbidity have been found in clinical samples. For example, in a review paper of BPD and AUD comorbidity in clinical samples, Trull et al. (2000) found that among individuals with BPD, the prevalence rate of AUDs was 48.8%, and among patients with AUDs, the prevalence rate of BPD was 14.3%. Comorbidity rates are even higher among female psychiatric patients, with 59% of women with BPD also carrying a lifetime diagnosis of either alcohol abuse or dependence (Zanarini et al., 1998).

Although it has been well-established that there is a high degree of comorbidity between BPD and AUDs, the nature of this relationship is poorly understood. Three etiological mechanisms have been proposed to explain this relationship. The first model infers a direct causal relationship in which the existence of one disorder leads to the development of the other. The second model infers an indirect causal relationship in which the existence of one disorder affects a third variable that in turn leads to the development of the second condition. The third model infers no causal relationship but rather postulates that common risk factors may lead to the development of both conditions. The research is limited, but there is some evidence in support of the causal link model (Siever & Davis, 1991; Zanarini, 1993; van Reekum, Links, & Fedorov, 1994; Links, Helsegrave & van Reekum, 1999) and the common factors model (Verheul, Ball & van den Brink, 1997).

This pattern of comorbidity of BPD and AUDs is also associated with poorer prognosis. Individuals diagnosed with BPD and AUDs have worse outcomes compared to those with either BPD or AUD alone (Links, Helsegrave, Mitton, Van Reekum & Patrick, 1995; Shea, Widiger & Klein, 1992; Morgenstern, Langenbucher, Labouvie & Miller, 1997; Miller, Abrams, Dulit & Fyer, 1993). Furthermore, BPD traits are significantly predictive of future problems associated with alcohol use, even after controlling for other Axis I disorders (including other current SUDs) and non-borderline personality disorders (Stepp, Trull, &

Sher, 2005). Additionally, the rate of new onset AUDs is at least twice as high among patients with BPD (13%) compared to those with other personality disorders (6%) (Walter et al., 2009).

Treatment

As with other psychiatric disorders, treatment options for individuals with BPD and AUDs can be broadly divided into psychotherapeutic or pharmacological interventions. There are many different psychotherapeutic and pharmacological interventions for the treatment of BPD and AUDs when the conditions present alone (e.g., Linehan et al., 1999; Paris, 2005; Mann, 2004; Garbutt, West, Carey, Lohr & Crews, 1999; Garbutt, 2009). In contrast, there are surprisingly few treatments that have been developed or tested for concurrently treating BPD and AUDs. Below, we present a review of treatments aimed to concurrently treat BPD and alcohol use disorders/problems. Table 1 provides a summary of the studies reviewed; only major findings relevant to alcohol use and/or BPD traits are included in this table.

Psychotherapy

A number of studies have examined the efficacy of AUD psychotherapies among patients with comorbid personality disorders. Although these psychotherapies have been tested in samples of patients with comorbid BPD or BPD-traits, the interventions were not designed specifically for patients with comorbid BPD and thus, do not generally examine their efficacy on reducing BPD symptoms (Nordholm & Nielsen, 2007; Conrod et al., 2000, 2006, 2010; Watt, Stewart, Birch & Bernier, 2006; Nielsen, Røjskjær & Hesse, 2007). For example, Nordholm and Nielsen (2007) conducted a study in which patients with personality disorders (PDs) were divided into three groups and compared to a group without personality disorders. Of the 363 patients, 124 had a PD diagnosis using ICD-10-R criteria (3 cluster A, 77 cluster B, 35 cluster C, 9 'other personality disorder'). Two hundred seventy-six (76%) participated in follow-up interviews; 253 of 276 had been assigned to one of three treatment conditions at the discretion of the treatment team: 1) cognitive behavioral therapy, 2) consultation/supportive therapy, or 3) family therapy. Analyses, conducted on a modified treated sample of 266 including 81 with either cluster B or C PDs and 185 without, revealed that all treatments were equally effective in reducing alcohol and drug use for patients with and without PDs.

Other studies have explored modified versions of established AUD treatments for patients with specific personality traits. For example, several randomized trials have found that targeting personality traits in brief coping skills interventions is effective in reducing alcohol and illicit substance use (Conrod et al., 2000, 2006, 2010). In their seminal study, Conrod and colleagues (2000) administered a 1-session coping skills intervention to female participants with AUDs and/or SUDs who were categorized into four groups depending on their personality and motivation profile: anxiety-sensitivity, introversion-helplessness, impulsivity, and sensation-seeking. Patients were randomly assigned to one of three conditions: motivation-matched intervention (MM) where motivational and coping skills training was designed based on the subject personality profile (e.g., a patient with impulsive personality/motivation profile receiving a treatment designed for impulsive personality/motivation profile); motivation-mismatched intervention (MMM) where motivational and coping skills training was designed based on a mismatched personality profile (e.g., a patient with impulsive personality/motivation profile receiving a treatment designed for anxiety-sensitivity personality/motivation profile); or motivational control intervention (MC) where subjects were shown a motivational film and engaged in supportive discussion with the therapist. Of the 243 participants, 198 women who had received one of three brief interventions completed the 6-month follow-up assessment and were included for analyses.

Six months after the brief intervention, patients who had received the MM intervention had moderately higher rates of alcohol abstinence (23%) compared to those in the MMM condition (11.4%) and significantly higher rates of alcohol abstinence compared to those in the MC group (6.4%). Similar results have been reported in subsequent studies by Conrod and colleagues (2006, 2010).

Others, like Watt and colleagues (2006), have found modest but not statistically significant effects when treatments were tailored for specific personality traits. In a sample of female students (n=221) selected on scores on the Anxiety Sensitivity Index (ASI; Peterson & Reiss, 1992) and treated with CBT or nonspecific treatment those that completed the study (n=148), had high AS scores and received CBT were less likely to report negative consequences from drinking than the other three groups.

Nielsen and colleagues (2007) developed the Personality-guided Treatment for Alcohol Dependence (PETAD), an approach that integrates cognitive therapy for addictive behaviors with strategic interventions for maladaptive personality features. PETAD's efficacy was compared against standard cognitive therapy among 108 inpatients with AD over a 12-week treatment period. Treatment in the PETAD group was individualized based on the Millon Clinical Multiaxial Inventory (MCMI-II; Millon, 1987) categorization of PDs among subjects who had at least one "serious personality disorder" of paranoid, schizotypal or borderline PD. Fifty-nine patients (29 PETAD, 30 control) completed the follow-up assessment and were included for analyses. Compared to those receiving standard cognitive therapy, those in the PETAD condition were more likely to stay in treatment, and had significantly more days of alcohol abstinence at their six-month follow up visit.

Others have developed psychotherapies specifically for the concurrent treatment of BPD and SUDs. To date, there are three such psychotherapies: Dialectical Behavior Therapy-S (DBT-S), Dual Focus Schema Therapy (DFST), and Dynamic Deconstructive Psychotherapy (DDP). While all three psychotherapies have been tested in samples of patients with BPD and SUDs, these trials have been conducted with very small samples, with an average of 7–15 completers per treatment condition. Furthermore, only DDP has been tested, again in a small sample of patients with comorbid BPD and AUDs.

Linehan and Dimeff (1997) developed a version of Dialectical Behavior Therapy (DBT) tailored for the treatment of patients with comorbid BPD and SUDs. This modified version of DBT, DBT-S, includes additional strategies for applying dialectics to abstinence issues and modified attachment strategies to keep difficult-to-engage or easily lost patients. While the efficacy of DBT-S for specifically treating comorbid BPD and AUDs is unknown, there are some promising findings regarding its efficacy for the concurrent treatment of BPD and SUDs.

Linehan et al. (1999) examined the efficacy of DBT-S in a sample of 28 female patients with BPD and SUDs, approximately half (52%) of whom also met diagnostic criteria for alcohol dependence. Patients were randomized to one year of either DBT-S (n=12) or treatment as usual (TAU; n=16). In addition, patients with stimulant or opiate dependence who were assigned to DBT-S were given replacement medications. Illicit stimulants were replaced with methylphenidate (maximum dose of 20mg daily) and opiates were replaced with methadone (maximum dose of 70mg daily). Of the original sample, 18 (7 DBT-S, 11 TAU) completed trial. Analyses conducted with the completer sample (those who had completed 6+ sessions of DBT-S or TAU) found that DBT-S patients reported a higher proportion of drug and alcohol abstinence days compared to those in TAU at 4 and 8 months, overall year total, and also at a 4-month post-treatment follow-up. There were no significant group differences on any of the psychopathology outcome measures during or at the end of

treatment. However, at their 16-month follow-up, DBT-S patients reported better social and global adjustment compared to the TAU group.

Another psychotherapy that has been developed for the concurrent treatment of PDs and SUDs is Dual Focus Schema Therapy (DFST; Ball, 1998; Ball & Young, 2000). Unlike DBT-S, DFST was developed for the treatment of a broader range of personality disorders that are often comorbid with SUDs and AUDs. This 24-week manual-guided individual cognitive behavioral therapy integrates relapse prevention techniques while addressing chronic, maladaptive personality functioning and coping styles. The efficacy of DFST for specifically treating patients with BPD and AUD is unknown, however, there are some encouraging findings regarding its efficacy among patients with dual diagnoses of personality disorders and SUDs.

Both DBT-S and DFST appear to be promising approaches for the concurrent treatment of BPD and SUDs. However, neither has been tested in the treatment of patients with comorbid BPD and AUDs. To date, the only form of psychotherapy that has been specifically tested for the concurrent treatment of BPD and AUDs is Dynamic Deconstructive Psychotherapy (DDP; Gregory & Remen, 2008), a time-limited, manual-based treatment based on object relations theory, deconstructive philosophy and neurocognitive research. Gregory et al. (2008) conducted the original trial of DDP with outpatients with BPD and AUDs (intent-to-treat (ITT) sample $n=30$: 15 DDP, 15 TAU). Analyses conducted with the ITT sample found no significant differences between groups during the course of the study. However, there were statistically significant improvements over time on measures of parasuicide behavior, alcohol misuse, and proportion of patients needing institutional care for those receiving DDP but not for those receiving TAU.

Gregory, DeLucia-Deranja and Mogle (2010) conducted a naturalistic follow-up of the patients involved in their seminal study above. The follow-up assessment occurred 18 months after the completion of the original study, and analyses were carried out using a modified ITT sample including those who had been in DDP or OCC (called TAU in previous study—Gregory et al., 2008) for at least 6 months ($n=24$: 12 DDP, 12 OCC). DDP group reported significant reductions in the severity of core BPD symptoms, depression and frequency of recreational drug use. There was, however, only a trend for between-group differences in their drinking behavior with the DDP group tending to report fewer heavy drinking days compared to those in OCC. Interestingly, when the 12-month data on the frequency of heavy drinking was re-analyzed, there were significant differences between the DDP and OCC groups, such that the DDP group was drinking less compared to the OCC group.

Summary and future directions for psychotherapy of comorbid BPD and AUDs

Several studies have been published on the efficacy of modified AUD psychotherapies for treating patients with comorbid BPD traits or diagnosis, including coping skills training and cognitive therapy. There are some encouraging findings regarding the efficacy of these modified psychotherapies in reducing alcohol use and increasing treatment compliance. However, as none reported changes in personality problems or BPD symptomatology, their efficacy in the treatment of BPD symptoms/traits remains untested.

There are three different psychotherapeutic interventions that have been developed for the concurrent treatment of BPD and SUDs. All three, however, have only been tested in small samples (completer sample sizes ranging from 7 to 15 participants). None of the three psychotherapies have they been extensively studied in patients with dual diagnoses of BPD and AUDs. Furthermore, of the three therapies, only Dynamic Deconstructive Psychotherapy (DDP) has actually been tested among patients with dual diagnoses of BPD

and AUDs. However, with only two studies, one of which was a follow-up of the first study, it is premature to draw conclusions on its efficacy. The other two psychotherapies, DBT-S and DFST have not been specifically tested among patients with dual diagnoses of BPD and AUDs. It is possible that they are effective treatment options for this patient population given the encouraging findings regarding their efficacy in patients with comorbid BPD and SUDs. Even amidst these studies, however, DBT-S and DFST appear to have only modest effects on drinking behavior. Further research is clearly indicated for all three psychotherapies. It will be important for future studies to explore the utility of these psychotherapies not only in bigger samples, but in samples of patients with dual diagnoses specifically of BPD and AUDs.

Pharmacotherapy

Pharmacotherapy is a common form of treatment for both BPD and AUDs when they occur alone. However, since the aims of pharmacotherapy in BPD versus AUDs are different, there has been little overlap in the use of specific medications when these two disorders co-occur. In treating patients with AUDs, for example, the main objective is relapse prevention. Thus, pharmacological strategies generally involve medications that deter alcohol use by moderating craving and/or producing adverse reactions when alcohol is consumed. The FDA (Food and Drug Administration) approved medications for alcohol relapse prevention are disulfiram [acetaldehyde dehydrogenase (ALDH-1 and -2 inhibitor)], oral and injectable naltrexone (mu-opioid antagonist), and acamprosate (NMDA receptor modulator).

On the other hand, there are no FDA approved medications for the treatment of BPD. Nevertheless, psychotropic medications, namely antidepressants, anticonvulsants, and antipsychotics, are often used to manage the anger, impulsivity and mood lability that are characteristic of BPD. Of these medications, anticonvulsants, namely topiramate and lamotrigine, and second generation antipsychotics, specifically aripiprazole and olanzapine, appear to be the most helpful. Antidepressants, although most commonly prescribed for patients with BPD, are only modestly effective in managing symptoms of BPD (Lieb, Vollm, Rucker, Timmer & Stoffers, 2010; Mercer, Douglas & Links, 2009).

Pharmacotherapy for concurrent treatment of BPD and AUDs

Research on pharmacotherapy for dual diagnoses of BPD and AUDs is scarce. In addition, no study has yet explored medication options that can concurrently manage symptoms of BPD and decrease alcohol consumption. To date, only two studies have explored pharmacotherapy options for these dually diagnosed patients, and both examined the efficacy of alcohol relapse prevention medications among patients with BPD.

The first and only randomized control study was conducted by Ralevski and colleagues (2007), which examined the efficacy of naltrexone and/or disulfiram for the treatment of AD in patients with comorbid psychiatric disorders. In this 12-week trial, 254 participants with diagnoses of AD and another Axis I disorder were randomized into four treatment groups: placebo, naltrexone only, disulfiram only, and disulfiram+naltrexone. Personality information was available for 225 participants, of whom 68 met current DSM-IV criteria for BPD. When participants with BPD were compared to those without BPD on various measures of alcohol use outcomes and psychiatric symptoms, there were no differences between the groups, thus suggesting that the presence of comorbid BPD did not affect alcohol treatment outcomes.

Most recently, Mutschler et al. (2010) presented a case history series of eight outpatients (two male, six female) with BPD and AD that had been provided supervised disulfiram treatment. Despite concerns that patients with BPD may use disulfiram to self-harm due to

their impulsive nature, no serious adverse events were reported and the overall tolerability and safety of disulfiram was considered to be good. Furthermore, two of eight patients remained completely abstinent under supervised disulfiram therapy over their respective treatment periods (4.5 and 14 months).

These studies provide evidence that relapse prevention medications may be similarly effective in reducing alcohol consumption for individuals with comorbid BPD. However, neither study reported on changes in BPD symptoms. Therefore, while relapse prevention medications may help to curb alcohol use, there is no evidence that they effectively manage BPD symptoms.

Future Considerations for Pharmacotherapy of BPD and AUDs

There is growing evidence that anticonvulsants and second-generation antipsychotics are most effective in the management of BPD symptoms (Lieb et al., 2010; Mercer et al., 2009). Interestingly, the very same medications may be helpful in the treatment of AUDs (Johnson, 2004). Of these classes of medications, most support has been found for topiramate and aripiprazole; however, encouraging findings have also been reported for lamotrigine and olanzapine. Brief reviews of studies that have tested these medications in patients with BPD/BPD-traits or alcohol use disorders/problems are provided below, organized by type of medication. Major findings relevant to alcohol use and/or BPD symptoms/traits are summarized in Table 2. Case reports, laboratory-based studies and those conducted with animals have been omitted from this table. It is important to note that a key limitation of the pharmacotherapy studies that have been conducted with BPD patients is that the majority excluded patients with active AUDs. Furthermore, the few that included patients with AUDs did not report subgroup results on patients with dual diagnoses of BPD and AUDs. As such, the generalizability of the findings to patients with dual diagnoses of BPD and AUDs is limited.

Anticonvulsants

Topiramate

Several studies have found that topiramate may be effective in reducing anger, one of the core symptoms of BPD. Nickel et al. (2004) evaluated the effects of topiramate on aggression in an 8-week randomized trial among females diagnosed with BPD (ITT sample $n=31$: 21 topiramate, 10 placebo; completer sample $n=29$: 19 topiramate, 10 placebo). Anger was measured using the State Trait Anger Experience Inventory (STAXI; Spielberger, 1988) - a self-report measure. Analyses conducted with the completer sample showed that participants receiving topiramate, when compared to those receiving placebo, reported greater reductions on four of the five STAXI subscales suggesting that topiramate may be useful in reducing the intensity of anger, and readiness to react with anger. These findings have been replicated among a sample of 42 male patients with BPD (Nickel et al., 2005). Topiramate was well-tolerated; however, particular caution may be warranted in patients with comorbid BPD and AUD. This includes dosing schedule and medication compliance, the potential for increased suicidality, fetal malformations, interactions with birth control medications, and for potential misuse, especially as weight loss agents.

Johnson et al. (2003) first demonstrated the utility of topiramate in reducing alcohol consumption among 158 adults seeking treatment for alcohol dependence. Analyses conducted with a modified ITT sample ($n=150$: 75 topiramate, 75 placebo) found that topiramate was more effective than placebo in increasing % abstinence days, and reducing drinks per day, drinks per drinking day, % heavy drinking days, and log plasma gamma-glutamyl transferase ratio (an objective index of alcohol consumption). In a separate 14-

week double-blind randomized clinical trial with 371 treatment-seeking adults with AD, analyses conducted with the ITT sample revealed that topiramate (n=183) was significantly more effective than placebo (n=188) in reducing % of heavy drinking days, drinks per drinking day, and plasma levels of the liver enzyme gamma-glutamyl-transferase (GGT) - a biomarker of drinking reduction (Johnson et al., 2007). Most recently, results from an open-label trial suggest that low-dose topiramate used in conjunction with psychotherapy may be more effective than psychotherapy alone in reducing alcohol cravings, and in decreasing anxiety and improving mood (Paparrigopoulos, Tzavellas, Karaiskos, Kourlaba & Liappas, 2011).

The mechanism by which topiramate reduces alcohol consumption is not yet clear. One hypothesis is that topiramate decreases mesocorticolimbic dopamine activity, and thus reduces the rewarding or reinforcing properties of alcohol (Johnson et al., 2003; 2007). This hypothesis was based largely on topiramate's neuropharmacological actions which include facilitation of GABA-mediated neurotransmission and blockade of AMP/kainate glutamate receptors. Both studies by Johnson and colleagues (2003, 2007) provided support for this hypothesis. It was, however, not supported by Miranda and colleagues (2008), a study conducted with non-treatment seeking heavy drinkers. Results, which were based on those who completed the study (n=61; 20 topiramate 200mg, 21 topiramate 300mg, and 20 placebo), demonstrated that topiramate reduced proportion of heavy drinking days but not self-reported craving scores or the frequency of alcohol consumption.

Based on the use of topiramate in the treatment of disorders characterized by impulsivity, another possibility is that topiramate reduces alcohol consumption by enhancing inhibitory control and attention (Rubio et al., 2009). This hypothesis was tested in a 12-week double-blind randomized clinical trial in a sample of 76 treatment-seeking men with alcohol dependence. Participants were randomly assigned to receive either topiramate (250mg/day) or placebo, and were asked to perform two laboratory paradigms that measured behavioral impulsivity. Analyses conducted with the completer sample (n=63; 31 topiramate, 32 placebo) found that compared to the placebo group, topiramate-treated subjects reported drinking less per drinking day, had fewer heavy drinking days, had greater number of abstinent days, and had a significant reduction in self-reported craving and plasma CDT (an indirect measure of alcohol consumption). These reductions in alcohol consumption were correlated moderately with improvement on behavioral inhibition tasks, thus suggesting that the reduced alcohol use was most likely due to the topiramate's ability to improve inhibitory control.

Lamotrigine

The use of lamotrigine in patients with BPD was first reported by Pinto and Akiskal (1998) in a case history series of eight patients with BPD who had failed to respond to other pharmacological treatments. Over the course of a year, lamotrigine decreased sexual impulsiveness, substance abuse, and suicidal behaviors. Other studies have also found lamotrigine to reduce impulsivity, mood lability and anger associated with BPD. For example, Preston and colleagues (2004) found that among female patients with comorbid bipolar disorder and BPD (n=35), lamotrigine decreased impulsivity and mood instability. Additionally, in a double-blind trial of lamotrigine among female patients with BPD (n=27; 18 lamotrigine, 9 placebo), Tritt et al. (2005) using the ITT sample found significant improvements in anger (as measured by the STAXI) after 8 weeks of treatment. In these studies, lamotrigine has been well-tolerated; however, similar to topiramate, particular caution may be warranted in patients with comorbid BPD and AUD. This includes dosing schedule and medication compliance, the potential for increased suicidality, fetal malformations, and for potential misuse, especially as weight loss agents.

The utility of lamotrigine in reducing alcohol craving was first documented in a series of case reports of three patients with resistant schizophrenia and comorbid AD (Kalyoncu et al., 2005). All were given lamotrigine to augment clozapine, a second-generation antipsychotic medication that has been used in the treatment of patients with schizophrenia and comorbid AD (Albanese, Khantzian, Murphy & Green, 1994; Buckley, Thomson, Way & Meltzer, 1994; Zimmet, Strous, Burgess, Kohnstamm & Green, 2000). All three patients reduced their alcohol consumption when they began taking lamotrigine in combination with clozapine. Rubio, Lopez-Munoz and Alamo (2006) were the first to systematically study the utility of lamotrigine in treating AD. In this 12-week open-label study, 28 outpatients with dual diagnoses of bipolar disorder and AD reported that lamotrigine as adjunctive therapy improved mood symptoms, and decreased both alcohol craving and consumption. Despite these encouraging results, very little research has been conducted with lamotrigine. The only other study that has examined the effects of lamotrigine on drinking behavior was conducted with animals (rats) – the study found that lamotrigine reduced alcohol seeking and relapse-like drinking behaviors (Vengeliene, Heidbreder & Spanagel, 2007).

Second-generation Antipsychotics

Aripiprazole

There is some evidence suggesting that aripiprazole can reduce anger in patients with BPD. For example, Nickel and colleagues (2006, 2007) evaluated the efficacy of aripiprazole among patients with BPD (n=52: 26 aripiprazole, 26 placebo). Analyses conducted with the ITT sample revealed that aripiprazole resulted in a significantly greater rate of change than did placebo on the aggressive symptoms of borderline psychopathology after 8 weeks. More specifically, aripiprazole decreased the intensity of anger, and readiness to react with anger while improving their self-reported ability to control anger. These improvements were sustained over an 18-month follow-up period, thus suggesting that aripiprazole may be an effective long-term treatment option for BPD.

The efficacy of aripiprazole in treating alcohol use disorders has been supported through several alcohol-cue-based clinical laboratory studies. Kranzler et al. (2008) found that a single dose of aripiprazole given prior to alcohol exposure produced significant dose-dependent effects of increasing the sedative and decreasing the euphoric effects of alcohol. It was also well-tolerated and reduced drinking in a sample of non-treatment seeking alcoholics, especially among those with lower impulse control in a 6-day laboratory study (Voronin, Randall, Myrick & Anton, 2008). It has been speculated that the utility of aripiprazole in reducing alcohol consumption may be due to its ability to break the link between alcohol-induced stimulation and subsequent alcohol consumption.

The clinical application and utility of aripiprazole in reducing alcohol use and craving was first reported in a case study of a middle-aged male patient who had been diagnosed with schizophrenia and alcohol dependence (Warsi, Sattar, Bhatia & Petty, 2005). Since then, there has been growing interest in studying the utility of aripiprazole in treating AD. In one of the first randomized clinical trials aripiprazole for the treatment of AD, 295 adult outpatients with AD were provided weekly psychotherapy, and were randomized to receive aripiprazole (n=149) or placebo (n=146) (Anton et al., 2008). Analyses conducted with the ITT sample revealed that while there were no differences between aripiprazole and placebo in the proportion of abstinent days, the aripiprazole group had fewer drinks per drinking day, greater reduction in overall severity of AD, and a larger decrease in carbohydrate-deficient transferrin-a biomarker of heavy alcohol consumption. In a separate randomized clinical trial, the safety and efficacy of aripiprazole (n=29) was compared against naltrexone (n=28) among alcoholics (Martinotti, Di Nicola, Di Giannantonio & Janiri, 2009). Analyses conducted with the ITT sample found that while relapse and treatment-retention rates were

comparable between aripiprazole and naltrexone, patients treated with aripiprazole remained abstinent from alcohol use for a longer period of time compared to those in the naltrexone group.

Olanzapine

Several studies have found olanzapine to reduce anger among patients with BPD. For example, Zanarini and Frankenberg (2001) conducted a 6-month study with 28 female patients with BPD in which participants were randomly assigned to olanzapine (n=19) or placebo (n=9). Analyses conducted with the ITT sample found that olanzapine effectively reduced impulsive aggression, interpersonal sensitivity, anxiety, and paranoia. Similarly encouraging findings were reported by Bogenschutz and Nurnberg (2004) in which 40 patients with BPD were randomly assigned to olanzapine (n=20), or placebo (n=20). Analyses conducted with 35 patients who had completed at least one post-baseline assessment revealed treatment with olanzapine was associated with significant improvements in all BPD symptoms, especially anger, after four weeks of treatment.

Other studies have explored the efficacy of combining olanzapine with another medication or psychotherapy. Zanarini, Frankenburg and Parachini (2004) compared the efficacy of fluoxetine, olanzapine and the combination of the two (olanzapine+fluoxetine) in the treatment of 45 female outpatients with BPD in an 8-week trial. Patients were randomly assigned to olanzapine (n=16), fluoxetine (n=14) or olanzapine-fluoxetine combination (OFC; n=15). Analyses conducted with the completer sample (16 olanzapine, 13 fluoxetine, 13 OFC) showed that while all three treatment options decreased impulsive aggression, the two olanzapine groups (olanzapine alone, and olanzapine+fluoxetine) produced significantly more improvements in impulsive aggression compared to those treated with fluoxetine alone. Most recently, Soler et al. (2005) compared the efficacy of olanzapine versus placebo in a combined treatment with dialectical behavior therapy. In this 12-week trial, all patients received dialectical behavior therapy and were randomly assigned to receive either olanzapine (n=30) or placebo (n=30). Analyses conducted with the ITT sample revealed that combined treatment (DBT+Olanzapine) was associated with significant improvement over DBT alone (DBT+placebo) in impulsivity/aggressive behavior.

Olanzapine's ability to alter the relationship between alcohol consumption and craving was first reported by Hutchinson et al. (2001). In a sample of heavy social drinkers, olanzapine attenuated the effects of alcohol cues on urge to drink in an alcohol challenge paradigm. A recent study, however, suggests that the effects of olanzapine may be dependent on genetics. Hutchinson and colleagues (2003) found that olanzapine was differentially effective at reducing cue-elicited cravings based on individual differences in the variable number of tandem repeats (VNTR) in the D4 dopamine receptor gene (DRD4). Olanzapine reduced cravings for all individuals, but only reduced cravings after exposure to alcohol cues and after a priming dose of alcohol for individuals who were homozygous or heterozygous for the 7 (or longer) repeat allele of the DRD4 VNTR.

Conclusions and future recommendations

BPD and AUDs are highly comorbid, and this pattern of comorbidity has been associated with particularly negative prognosis. Yet, there are very few treatments that concurrently treat symptoms of both BPD and AUDs. To date, psychotherapies used for the treatment of AUDs have been modified to better serve patients with comorbid BPD and AUDs. Although these modified psychotherapies have been associated with less alcohol use and increased treatment compliance, their effects on personality problems or BPD symptomatology is unknown. There are three psychotherapies that have been designed to concurrently treat BPD and SUDs. However, only one of these psychotherapies (Dynamic Deconstructive

Psychotherapy) has been specifically evaluated for the concurrent treatment of BPD and AUDs, and although it may be effective in reducing symptoms of BPD, its efficacy in reducing alcohol consumption may not be sustained over a longer period of time. In addition, despite some encouraging findings regarding the efficacy of the other two psychotherapies (Dialectical Behavior Therapy and Dual Focus Schema Therapy) in simultaneously reducing substance use and managing symptoms of BPD, their efficacies in specifically reducing alcohol use have not been established. Thus, it is premature to conclude whether or not they may be helpful for this population.

Pharmacotherapeutic interventions that target symptoms of BPD and AUDs would be valuable. There is evidence that some anticonvulsants and antipsychotics may significantly reduce anger (one core symptom of BPD), and some like lamotrigine have been shown to reduce other core symptoms of BPD including impulsivity and mood lability. Other studies suggest that the same medications may also reduce alcohol craving and consumption in patients with alcohol use disorders/problems alone. Although premature, these findings are encouraging, especially for this population of patients for whom treatment options are very limited. Considering the evidence, further study of the role of anticonvulsants and second-generation antipsychotics is warranted, and future studies aimed at exploring other treatments that simultaneously treat both symptoms of BPD and AD are recommended.

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Table 1

Summary of studies designed to treat comorbid Borderline Personality Disorder (BPD) or BPD-traits and Alcohol Use Disorders/problems.

Study	Subjects	Treatments/Conditions	Treatment retention and sample size used in analyses	Results specific to AD and BPD
Conrod et al. (2000)	243 female outpatients with AUDs and/or SUDs.	<ol style="list-style-type: none"> 1 Motivation-matched Intervention (MM) (n=94) 2 Motivation-Mismatched Intervention (MMM) (n=97) 3 Motivational film (Control) Intervention (MC) (n=52) 	198 completed 6-month follow-up. Attrition rates did not differ across 3 treatment groups. Analyses conducted with completer sample.	Alcohol use: MM resulted in significantly higher abstinence rate compared to MC.
Conrod et al. (2006)	297 secondary school students with one of three personality profiles (anxiety sensitivity, hopelessness, sensation seeking).	<ol style="list-style-type: none"> 1 Relevant personality-targeted intervention (n=166) 2 No-intervention control group (n=131). 	265 completed 4-month follow-up assessments. No significant group differences in attrition. Analyses conducted with ITT sample. Baseline observations were carried forward for missing data.	Alcohol use: Intervention group had less binge drinking, lower level of alcohol use, and less problem drinking symptoms. Personality measures: Significant reductions on personality dimensions on which they were most deviant.
Gregory et al. (2008)	30 adult outpatients with BPD and active AUDs.	<ol style="list-style-type: none"> 1 Dynamic Deconstructive Psychotherapy (DDP) (n=15) 2 TAU (n=15). 	10/15 DDP completed 12-month follow-up. 9/15 TAU completed 12-month follow-up. Analyses conducted with ITT sample. Most recent observations were carried forward for missing data.	Alcohol use: Significant improvement over time on alcohol misuse for DDP but not TAU.
Gregory, DeLucia-Deranja & Mogle (2010)	Follow-up study to Gregory et al. (2008). 24 adult outpatients with BPD and AUDs who completed 6-months of DDP or OCC.	<ol style="list-style-type: none"> 1 DDP (n=11) 2 OCC (n=13) 	Analyses conducted with modified ITT sample (from Gregory et al., 2008).	Alcohol use: DDP had less heavy drinking at 12 months than OCC. Core BPD symptoms: DDP had significantly more meaningful improvement by 12 months compared to OCC.
Linehan et al. (1999)	28 female outpatients with BPD and SUDs. 52% with AD.	<ol style="list-style-type: none"> 1 DBT-S+replacement medications* (n=12) 2 TAU (n=16). <p>*Replacement medications only given to those with stimulant or opiate dependence.</p>	7/12 (58.3%) of DBT-S, and 11/16 (68.8%) of TAU completed 6+ sessions of DBT-S or TAU.	Drug/alcohol use: Significantly higher proportion of drug and alcohol abstinence days for DBT-S versus TAU.
Nielsen, Rojskjaer & Hesse (2007)	108 adult inpatients with AD. 55% with > 1 PD.	<ol style="list-style-type: none"> 1 Personality-guided Treatment for Alcohol Dependence (PETAD) (n=47) 2 Control (standard cognitive based therapy) (n=61) <p>Quasi-random assignment.</p>	PETAD: 29/47 completed follow-up. Control group: 30/61 completed follow-up. Analyses conducted with completer sample.	Alcohol use: PETAD had higher proportion of days abstinent compared to control.

Study	Subjects	Treatments/Conditions	Treatment retention and sample size used in analyses	Results specific to AD and BPD
Nordholm & Nielsen (2007)	363 outpatients with AUDs. 34% (n=124) met ICD-10-R criteria for a PD.	253 of 276 assigned to therapy. 1 Cognitive behavioral therapy (n=147) 2 Family therapy (n=41) 3 Supportive consultation (n=65)	276/363 (76%) participated in follow-up interview. Analyses conducted with 266 (185 without PDs and 81 with PDs).	Alcohol use: No significant difference between 3 therapy types or between pts with and without PDs.
Watt, Stewart, Birch & Bernier (2006)	221 undergraduate females selected based on their Anxiety Sensitivity Index scores.	1 High AS/Brief cognitive behavioral therapy (CBT) (n=51) 2 Low AS/CBT (n=61) 3 High AS/Non-specific Treatment (NST) (n=56) 4 Low AS/NST (n=53)	148 completed 10-week follow-up assessment. No significant differences in attrition across groups. Analyses conducted with completer sample.	Alcohol use: No significant effect of treatment across groups.
Pharmacotherapy study: Dual Diagnoses of BPD+AUD				
Ralevski et al. (2007)	254 adult outpatients with AD and another Axis I disorder seeking treatment for AD. Personality data available for 225 participants including 68 with BPD.	1 placebo 2 naltrexone (50mg) only 3 disulfiram (250mg) only 4 disulfiram (250mg)+naltrexone (50mg) 12-week trial.	No differences among personality groups regarding treatment retention or medication compliance. Overall, 82% compliance. Analyses conducted with ITT sample with personality data.	Alcohol use: No differences between the treatment groups.

Note. BPD=Borderline Personality Disorder; AUD=Alcohol Use Disorder; AD=Alcohol Dependence; SUD=Substance Use Disorder; PD=Personality Disorder; TAU=Treatment As Usual; DBT-S=Dialectical Behavioral Therapy-S (for substance abusers); DDP=Dynamic Deconstructive Psychotherapy; PETAD=Personality-guided Treatment for Alcohol Dependence; OCC=Optimized Community Care; NST=Non-specific Treatment; ITT=Intent-to-treat sample.

Table 2

Summary of studies that have tested anticonvulsants and second-generation antipsychotics in individuals with Borderline Personality Disorder or Alcohol Use Disorders/Problems.

Study	Subjects	Treatments/Conditions	Treatment retention and samples used in analyses	Results
Topiramate and BPD				
Nickel et al. (2004)	31 female outpatients with BPD.	1 Topiramate (n=21) 2 Placebo (n=10).	29/31 (19 topiramate, 10 placebo) completed. Analyses conducted with completer sample.	Anger: Topiramate had significantly greater rate of improvement on 4 of 5 STAXI subscales.
Nickel et al. (2005)	44 male outpatients with BPD.	1 Topiramate (n=22) 2 Placebo (n=22).	42/44 completed (2/22 in placebo dropped out). Analyses conducted with completer sample.	Anger: Significant improvement on 4 of 5 STAXI subscale scores for topiramate.
Topiramate and alcohol use				
Johnson et al. (2003)	158 adult outpatients with AD.	1 Topiramate (n=78) 2 Placebo (n=80).	103/158 (48 placebo, 55 topiramate) completed. Analyses conducted with modified ITT sample (n=150; 75 topiramate, 75 placebo).	Alcohol use: Topiramate was significantly more effective than placebo in reducing drinks per day, drinks per drinking day, % heavy drinking days, and log plasma gamma-glutamyl transferase ratio, and increasing % days abstinent.
Johnson et al. (2007)	371 adult outpatients with AD.	1 Topiramate (n=183) 2 Placebo (n=188).	256/371 (144 placebo, 112 topiramate) completed. Analyses conducted with ITT sample. Baseline observations were carried forward for missing data.	Alcohol use: Topiramate had significant reductions in drinks per drinking day, % heavy drinking days and log plasma gamma-glutamyl transferase ratio, and increasing % abstinent days.
Miranda et al. (2008)	78 adult heavy drinkers. 60% met criteria for AUDs.	1 Topiramate 200mg (n=20) 2 Topiramate 300mg (n=21) 3 Placebo (n=20)	61/78 completed. Analyses conducted with completer sample.	Alcohol use: Topiramate was associated with significant reduction in proportion of heavy drinking days but not self-reported craving scores or the frequency of alcohol consumption.
Rubio, Martinez-Gras & Manzanares (2009)	76 adult men with AD.	1 Topiramate (n=38) 2 Placebo (n=38) All offered supportive group therapy.	63/76 (31 topiramate, 32 placebo) completed. Analyses conducted with completer sample.	Alcohol use: Topiramate group had fewer drinks per drinking day, lower % of heavy drinking days, lower craving, lower plasma CDT and had more abstinence days. Impulsivity: Topiramate group performed significantly better on most impulsivity measures.
Lamotrigine and BPD/BPD symptoms				
Preston et al. (2004)	56 outpatients with BPD symptoms.	Patients originally treated with lamotrigine in open-label manner.	35/56 completed retrospective interview. Analyses conducted with completer sample.	Dimensions of BPD: In patients with and without comorbid BPD, treatment reduced symptom burden in all dimensions of BPD.

Study	Subjects	Treatments/Conditions	Treatment retention and samples used in analyses	Results
Tritt et al. (2005)	27 adult female outpatients with BPD.	1 Lamotrigine (n=18) 2 Placebo (n=9).	24/27 (7 placebo, 17 lamotrigine) completed. Analyses conducted with ITT sample.	Anger: Significant reduction in all STAXI subscale scores for lamotrigine group.
Lamotrigine and alcohol use				
Rubio, Lopez-Munoz & Alamo (2006)	28 adult outpatients with bipolar disorder and AD.	Open-label trial of lamotrigine as adjunctive therapy. All received weekly relapse-prevention program.	26/28 completed. Analyses conducted with ITT sample.	Alcohol use: Lamotrigine reduced craving and alcohol consumption.
Aripiprazole and BPD				
Nickel et al. (2006)	52 adult outpatients with BPD.	1 Aripiprazole (n=26) 2 Placebo (n=26).	No drop-outs reported. Analyses conducted with ITT sample.	Anger: Aripiprazole was associated with a significantly greater rate of change compared to placebo.
Nickel et al. (2007)	18-month follow-up to Nickel et al. (2006).	1 Aripiprazole (n=26) 2 Placebo (n=26).	39/52 (22 aripiprazole, 17 placebo) completed. Analyses conducted with ITT sample. Most recent observations were carried forward for missing data.	Anger: Reductions in anger associated with aripiprazole was sustained over 18-month follow-up.
Aripiprazole and alcohol use				
Anton et al. (2008)	295 outpatients with AD.	1 Aripiprazole (n=149) 2 Placebo (n=146). All received weekly psychotherapy.	59.1% of aripiprazole, 73.3% of placebo group completed. Analyses conducted with ITT sample. Most recent observations were carried forward for missing data.	Alcohol use: Aripiprazole group reported fewer average drinks per drinking day, and greater reduction in overall severity of AD and carbohydrate deficient transferrin. Placebo group had significantly more % of abstinent subjects.
Martinotti et al. (2009)	57 patients who completed alcohol detox.	Random assignment stratified by psychiatric diagnosis. 1 Aripiprazole (n=29) 2 Naltrexone (n=28) All offered supportive self-help group.	43/57 (22 aripiprazole, 21 naltrexone) completed. Analyses conducted with ITT sample.	Alcohol use: No differences between groups on most alcohol use measures, but aripiprazole group remained abstinent for longer compared to naltrexone.
Olanzapine and BPD				
Bogenschutz & Nurnberg (2004)	40 outpatients with BPD.	1 Olanzapine (n=20) 2 Placebo (n=20)	23/40 (10 olanzapine, 13 placebo) completed. Analyses conducted with 35 pts with 1+ post-baseline assessment. Most recent observations were carried forward for missing data.	BPD symptoms: Olanzapine reduced BPD symptoms; significant effects appeared at 4 weeks.
Soler et al. (2005)	60 outpatients with BPD.	1 Dialectical behavior therapy +placebo (n=30) 2 Dialectical behavior therapy +olanzapine (n=30)	42/60 (70%) completed. No difference in attrition between groups. Analyses conducted with ITT sample. Most recent observations were carried forward for missing data.	Impulsivity/aggression: Olanzapine group had greater decrease in frequency of impulsivity/aggressive behavior.

Study	Subjects	Treatments/Conditions	Treatment retention and samples used in analyses	Results
Zanarini & Frankenberg (2001)	28 female outpatients with BPD	<ol style="list-style-type: none"> 1 Olanzapine (n=19) 2 Placebo (n=9) 	12/28 (8 olanzapine, 4 placebo) remained in study through week 20. Analyses conducted with ITT sample.	Interpersonal sensitivity, anger/hostility: Olanzapine group had a significantly greater rate of change on measures of interpersonal sensitivity, and anger/hostility.
Zanarini, Frankenburg & Parachini (2004)	45 female outpatients with BPD.	<ol style="list-style-type: none"> 1 Fluoxetine (n=14) 2 Olanzapine (n=16) 3 Olanzapine-fluoxetine combination (OFC) (n=15) 	42/45 (16 olanzapine, 13 fluoxetine, 13 OFC) completed. Analyses conducted with completer sample.	Aggression: OFC and olanzapine were associated with significantly greater improvement over time than fluoxetine.

Note. BPD=Borderline Personality Disorder; AUD=Alcohol Use Disorder; AD=Alcohol Dependence; MDD=Major Depressive Disorder; OFC=Olanzapine-Fluoxetine Combination; ITT=Intent-to-treat sample; STAXI=State-Trait Anger Expression Inventory.