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Current Treatment Options for Co-Morbid Anxiety and Alcohol Use Disorders: A Review

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Abstract

Anxiety and alcohol use disorders (AUD) are highly co-morbid and prevalent in the United States, yet optimal ways to diagnose and treat these co-occurring conditions have not been fully elucidated due to their inter-related features that create difficulties in determining causality of symptomatology. For instance, many clinicians struggle to distinguish whether or not recurrent withdrawal symptoms in AUD is causing anxiety, or anxiety is causing one to self-medicate with alcohol use. This complex set of the interactions between anxiety disorders and AUD has been associated with worsened outcomes for AUD and lower treatment retention in patients with co-morbid anxiety disorders. Given this, treatment of these co-morbid conditions must be thoughtfully planned and comprehensive to improve outcomes. It is critical that clinicians consider sequential, parallel, or integrated treatment modalities with respect to timing and deliverance of treatment. In this article, we will present a case study illustrating the multidimensional elements of co-morbid anxiety and AUD, and examine the current evidence regarding optimal treatment plans for patients with these dually-diagnosed conditions.

Keywords: Anxiety alcohol use disorder; Dual diagnosis; Co-morbidity; Treatment; Pharmacology; Combined behavioral therapy; AUD; Addiction

Case Description

The patient is a 43-year-old married Caucasian female who was referred to the UCLA-Harbor Dual Diagnosis Treatment Program (DDTP) by her primary care physician due to worsening symptoms of anxiety and escalating alcohol consumption. Upon intake at DDTP, she reported four primary concerns: persistent symptoms of anxiety, sleep disturbance despite treatment with zolpidem (Ambien) 10 mg at bedtime, escalating use of alcohol consisting of approximately 2 bottles of wine daily, and difficulty with her relationship. Specifically, she reported experiencing anxiety attacks with physical symptoms of chest tightness, increased heart rate, sweaty palms, and racing thoughts in response to severe worries about many different things in her life including financial and psychosocial stressors such as daily verbal abuse from her partner of 19 years. When the patient began to realize she had problematic drinking and sought treatment, she reported her boyfriend was unsupportive of her sobriety and would even make a point of offering her alcoholic beverages. She intentionally limited her interactions with him at home and slept in a separate bedroom in their 2-bedroom apartment. She described the sensation of feeling "stuck" and panicked many times throughout the day, especially when needing to interact with him. Historically, the patient reported having taken medications such as zolpidem to treat her insomnia related to underlying anxious ruminations at night-time, but noted the medication "doesn't always work" and she would drink wine because it was "the only thing in that moment that will calm me down." She went on to report many signs and symptoms concerning for an AUD, such as spending a great deal of time in activities necessary to obtain alcohol (i.e., walking to the liquor store multiple times daily) recurrent preoccupations and urges to drink, and repeated use of alcohol that resulted in failure to fulfil major role obligations within her work and marriage, as demonstrated by her unemployment and marital distress. Further, she reported continued use of alcohol despite evidence that her recurrent interpersonal problems were exacerbated by her alcohol use, a pattern of emotional coping with alcohol in response to the various stressors in her life, and needing to drink increasing quantities of alcohol in order to achieve the desired "mellowing out" effect. More alarmingly, she stated that she frequently experienced withdrawal symptoms of shaking, worsening anxiety, irritability and insomnia if she goes "a couple days" without a drink. At home, the patient was not the only one consuming alcohol on a regular

basis, as she reported her boyfriend also drinks throughout the week to "take the edge off." She was distressed that she would be unable to achieve abstinence from alcohol with its continuous presence in her household, and expressed concern her prescribed medication had become ineffective. Upon intake, it was clear the patient was suffering from a co-morbid generalized anxiety disorder and AUD within a context of significant psychosocial stressors and poor coping skills. Her initial treatment plan included participation in the DDTP three days per week, cognitive behavioral therapy (CBT), facilitated group therapy, regular Alcoholics Anonymous (AA) attendance to increase social supports, and use of low-dose chlordiazepoxide (Librium) 50 mg twice daily to manage her anxiety and alcohol withdrawal symptoms. Over the course of the following sixty days, the patient's anxiety symptoms gradually remitted and she achieved abstinence from alcohol. She was also started on Zoloft 50 mg po qd for treatment of her anxiety. During a recent follow-up conversation with the patient, she reported achieving forty-five days of abstinence and felt "more in control" of her life.

Introduction

Treatment strategies for co-morbid anxiety and alcohol use disorders (AUD) have been difficult to devise due to several confounding factors, such as the inability to distinguish whether symptoms are independent, induced from each other, and/or inter-related. Epidemiologic research suggests the prevalence of anxiety disorders in the United States is 11.08%, 8.46% for AUD, and 17.71% for co-morbid anxiety and AUD [1-4]. Since anxiety and AUD combined affect an estimated 106 million Americans, effective and integrated treatment options should be offered to this sizeable population. However, relatively little is known about the optimal settings or modes of delivering care for patients with co-occurring psychiatric and substance use disorders and the most efficacious pharmacological and psychosocial treatments to provide, even though there is consensus that treatment of both co-occurring disorders is paramount [5].

Anxiety is highly prevalent among all patients seeking addiction treatment, and for those with alcohol use disorders specifically, the prevalence of anxiety disorders is believed to be as high as 33% [6]. Often times, patients with AUD consume alcohol due to its sedative effect as a way to self-medicate anxiety they experience when they are not drinking, but at the same time their anxiety may be a manifestation of an AUD in the form of a withdrawal symptom. Regardless of the phenomenology, clinicians commonly recognize a vicious cycle that has been established in these patients to the point where both the anxiety and AUD require intensive treatment to improve functioning. This article aims to review the current scientific literature focusing on the efficacy of pharmacological and psychosocial treatment options for individuals with co-morbid anxiety and AUD, with the goal of elucidating optimal treatment strategies for these dual-diagnosis patients.

Current Treatment Options for Anxiety Disorders

Many epidemiological studies confirm that anxiety disorders are one of the most prevalent psychiatric conditions in the US. Based on the Epidemiological Catchments Area Study, one out of three people will meet criteria for an anxiety disorder at some point in their lives [7] Common anxiety disorders include Obsessive-Compulsive Disorder (OCD), Panic Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder (GAD), and Specific Phobias [8] Anxiety disorders typically manifest with extreme and continuous worrying, stress, and fear, and can be accompanied by physical symptoms such as muscle tension, tremulousness, palpitations, and chest tightness as well as psychological symptoms such as panic, irritability, restlessness, fatigue, insomnia, and difficulty concentrating [9]. Proper identification and treatment of anxiety disorders are essential since these disorders are responsible for significant impairments in quality of life, and may lend themselves to self-medication with alcohol and drugs [8]. Unfortunately, many anxiety disorders go unrecognized or are under-treated, failing to benefit from the many evidence-based treatments available at this time [10].

Pharmacological treatment options for anxiety disorders

Commonly used pharmacological treatments for anxiety disorders include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, buspirone (BuSpar), beta-blockers, gabapentinoids, atypical antipsychotics and benzodiazepines. Due to their relative safety and tolerability profile, SSRIs are commonly recommended as a first-line pharmacotherapy and should be used for at least one year, if tolerated [11]. SNRIs are recommended for patients who fail to respond adequately to SSRIs or for those who are unable to tolerate SSRIs. Benzodiazepines such as alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), and lorazepam (Ativan) are also often used for anxiety, ideally for short-term use given their risk of tolerance and dependence. Benzodiazepines have an efficacy rate of over 80% for treatment response and are FDA-approved for both GAD and panic disorder [9]. While benzodiazepines are effective at treating anxiety, they are not only ineffective for co-morbid depressive symptoms but may also contribute to depressive symptoms and result in undesirable side effects such as sedation, asthenia, cognitive impairment, psychomotor retardation, tolerance, dependence and subsequent withdrawal symptoms [7]. Due their abuse liability, it is recommended to restrict use of benzodiazepines to only four weeks or reserve them for patients who have not responded to at least two other treatments [11].

There are few head-to-head randomized controlled trials comparing the efficacies of medications such as SSRI *vs.* SNRI for the treatment of anxiety disorders. However, one meta-analysis conducted by Hidalgo et al. examined several pharmacological treatments for GAD, including both FDA-approved medications like SSRIs and SNRI, complementary/alternative medicines

(CAM) and off-label use of certain medications. Among the medications examined, they concluded that CAM such as kava-kava and homeopathic preparations had a negative effect size (d=-0.31), buspirone (BuSpar) had the smallest effect size (d=0.17), whereas hydroxyzine (Vistaril) and pregabalin (Lyrica) had the largest effect sizes (d=0.45 and d=0.50, respectively) [12]. Another recent study found that of the FDA-approved medications for GAD, duloxetine (Cymbalta) and escitalopram (Lexapro) had the highest response rates, while pregabalin (Lyrica) was the most tolerable medication [13].

Psychosocial treatments for anxiety disorders

Many experts advocate for the use of combined pharmacological and psychological treatments of anxiety disorders because there is strong evidence supporting combination treatments having more effectiveness than medications or psychosocial therapies alone [9]. Psychosocial treatments for anxiety disorders range from mindfulness to exposure-response prevention to CBT. In general, these treatments aim to restructure cognitive distortions, desensitize or challenge the autonomic/psychological responses to the feared stimuli and ensuing undesirable behaviors in order to promote more effective coping. CBT has been widely recognized as an effective treatment with response rates as high as 60-90% for anxiety disorders [9,14] Current CBT modules for anxiety disorders also involve varying combinations of the following elements: psychoeducation, self-monitoring of symptoms, somatic/cognitive exercises, cognitive restructuring, exposure-response prevention, and imaginal/*in vivo* exposure to distressful stimuli [15]. One current psychosocial treatment for anxiety disorders utilizes relaxation and meditation techniques combined with CBT to target the worrying process and bring it under the patient's conscious control [16]. In one study, researchers compared the efficacy of applied relaxation to other treatments like CBT and non-directive psychotherapy in patients with GAD [17]. At 12 months, the majority of patients receiving CBT improved symptomatically and regained a higher state of functioning compared to those who underwent applied relaxation or non-directive psychotherapy. In a 1992 study by Peterson and Pbert, which investigated the effectiveness of group therapy on patients with anxiety disorders, they found group stress reduction utilizing mindfulness meditation significantly reduced anxiety, depression and panic symptoms in patients with GAD, panic disorder, and panic disorder with agoraphobia when compared to a control group as usual [18].

Though CBT displays efficacy for treatment of patients with anxiety disorders in naturalistic settings as well as randomized controlled trials (RCT), between 10-40% of patients with anxiety disorders do not respond to psychosocial treatments and may experience debilitating residual symptoms. Given this, more research on pharmacological and psychosocial approaches to treatment-resistant anxiety disorders is warranted [9].

Current Treatment Options for Alcohol Use Disorders

Alcohol use disorders are among the most prevalent and disabling disorders worldwide, and represent the third leading cause of preventable death in the US [19]. The adversities facing those with AUD are manifold, including a scarcity of specialized, evidence-based addiction treatment centers and addiction specialists, unawareness and poor utilization of the FDA-approved medications for AUD, and a predominant moralistic view that patients with AUD should achieve abstinence through sheer willpower and 12-step groups. Other adversities consist of the fact that only 8% of the 17.3 million Americans with an AUD receive specialized treatment [20]. Further, patients with AUD often have co-morbid psychiatric disorders and physical health conditions that contribute to their poor outcomes and exceptionally high morbidity and mortality rates [21].

Pharmacological treatments for alcohol use disorders

Currently, there are four FDA-approved medications for the treatment of alcohol use disorders: oral naltrexone (ReVia), injectable extended-release naltrexone (Vivitrol), acamprosate (Campral), and disulfiram (Antabuse) [22]. Naltrexone is a selective μ-opioid antagonist that blocks the effect of endogenous opioids released within the nucleus accumbens in response to alcohol use [23]. In view of this mechanism of action, naltrexone's efficacy is thought to be due to its ability to reduce the hedonic response to alcohol, thereby decreasing its reinforcing and rewarding properties, which ultimately leads to reduced preoccupations and cravings for alcohol [24]. In a 12-week, double-blind RCT involving seventy recently detoxified alcohol-dependent men receiving oral naltrexone (50 mg/d) versus placebo, those receiving naltrexone reported significantly less alcohol cravings and fewer drinking days [25]. The naltrexone treated subjects also had significantly fewer relapses when compared to placebo over the 12-week study period. Importantly, naltrexone has positive data supporting its use in patients who are not necessarily seeking total alcohol abstinence but instead are trying to cut down gradually or reduce hazardous drinking.

While there are benefits to oral naltrexone, some studies have found small treatment effect sizes, as well as variations in its metabolism that can predispose to adverse effects in some patients due to high serum levels and inefficacy in others due to low serum levels [26-29]. One way to combat this is through injectable extended-release naltrexone (Vivitrol) [29]. With use of this medication formulation, naltrexone serum levels remain relatively stable for several weeks after a brief initial peak in serum levels following the injection, thereby reducing side effects and ensuring therapeutic serum levels and efficacy.

Another treatment option is acamprosate, a homotaurine analog with weak NMDA receptor antagonism and GABA receptor agonism that increases abstinence rates by restoring glutamatergic/GABA-ergic tone in alcohol-dependent patients who have already achieved abstinence and wish to maintain it

[23,30] In a RCT conducted by Whitworth et al. acamprosate was found to be an effective and well-tolerated pharmacological adjunct to psychosocial and behavioral treatments in alcohol-dependent patients [31]. In a meta-analysis by Carmen et al. researchers found that acamprosate was an effective therapeutic approach to target patients who wish to achieve abstinence [32]. However, acamprosate's effectiveness for improving abstinence rates has not been replicated in other RCTs. In fact, a RCT conducted by Berger et al. and the large COMBINE study did not find any superiority of acamprosate compared to placebo or psychosocial interventions alone, suggesting that acamprosate may not be effective for certain patients and alternative pharmacotherapies may need to be pursued [33].

Several studies have examined the effectiveness of pharmacotherapies for AUD head-to-head. A meta-analysis involving 135 studies comparing acamprosate and oral naltrexone found that both acamprosate and naltrexone have strong evidence for decreasing alcohol consumption in AUD [34]. In another study, researchers compared the effects of acamprosate and oral naltrexone on different symptomatic AUD cases and found that acamprosate had somewhat higher efficacy rates in promoting abstinence compared to naltrexone, whereas naltrexone was more effective at reducing heavy drinking days and cravings than acamprosate [30]. However, there is not enough established evidence indicating that one is better than the other, though it is worthwhile to consider each patient's particular symptoms of AUD and their stage of recovery to choose a medication that best accommodates their needs. For instance, in patients with heavy binge-drinking and strong cravings, naltrexone may be a more appropriate choice, whereas acamprosate may be more suitable for patients who have already achieved abstinence and wish to maintain it.

Another FDA-approved treatment for AUD with over 50 years of clinical use is disulfiram (Antabuse). Disulfiram is an aldehyde dehydrogenase inhibitor which, in the presence of alcohol consumption, causes accumulation of acetaldehyde [35]. As a result of this, a noxious physical reaction ensues that ultimately serves as a form of aversive behavioral conditioning. While some studies indicate that supervised administration of disulfiram has a positive short-term effect on abstinence rates and days until relapse [35], others reveal mixed efficacy results with positive outcomes only in those who adherence to regular disulfiram treatment [36].

Beyond the aforementioned FDA-approved medications for AUD, several off-label medications with mood-stabilizing, antiepileptic properties have been studied and used with varying degrees of success in AUD, including topiramate (Topamax), gabapentin (Neurontin), lithium, divalproex sodium (Depakote), carbamazepine (Tegretol) and oxcarbazepine (Trileptal). Amongst these, off-label topiramate and gabapentin appear to be the most promising pharmacotherapies for AUD. Topiramate is an antiepileptic drug that antagonizes AMPA kainate glutamatergic receptors, blocks voltage-dependent sodium and L-type calcium channels, and enhances GABA-ergic neurotransmission [37-39]. It has been shown to increase abstinence rates, reduce alcohol cravings, decrease heavy drinking days and drinks consumed per day in alcohol-dependent individuals in a 12-week RCT [38]. Gabapentin is a GABA analog that binds to the $\alpha_2\delta$-1 subunit of presynaptic voltage-gated calcium channels to enhance inhibitory neurotransmission via indirect $GABA_A$ and $GABA_B$ agonism [40]. Gabapentin's efficacy in AUD was demonstrated in a 12-week placebo-controlled, double-blind RCT conducted by Mason et al. that found it increased rates of alcohol abstinence (odds ratio (OR) 4.8, number needed to treat (NNT=8), decreased heavy drinking days (OR 2.8, NNT=5), decreased cravings, and decreased alcohol-related insomnia and dysphoria compared to placebo [41].

Psychosocial treatments for alcohol use disorders

Current psychosocial and behavioral treatments for AUD include but are not limited to the following: CBT, motivational enhancement therapy (MET), 12-step facilitation, marital and family counseling, brief interventions, contingency management and mutual support groups [42]. Many of these therapies are aimed at building insight, structural support for the patients, establishing personal goals, and identifying and preventing triggers that may cause relapse. Specifically, CBT focuses on managing emotional triggers, feelings and automatic thoughts that may lead to relapse. In a relatively large RCT combining pharmacotherapy and behavioral therapy for alcohol dependence conducted by Anton et al., they found that patients receiving naltrexone, combined behavioral interventions, or both improved significantly more on the outcome measures such as higher percent days abstinent and reduced risk of a heavy drinking day than patients who received acamprosate with or without cognitive behavioral interventions [43]. In view of these results, the authors concluded that naltrexone should be given to alcohol-dependent patients in health care settings and treatment with CBT is beneficial to patients as well.

MET is also used as a short-term treatment whereby the therapist collaborates with the patient to build and develop the patient's own motivation to change behaviors in relation to substances of abuse. The goal of MET is to allow the patient to build their own confidence and goals to gradually abstain from substances in a supportive and collaborative environment [44]. In a recent study, researchers decided to test the efficacy of MET on patients with AUD and co-morbid hepatitis C virus infection and found that use of MET increased the percentage of abstinent days for these patients over a 6-month period by approximately 38% compared to baseline, which was a dramatic increase compared to the control group [45].

Perhaps the most common and widely available form of psychosocial treatment is mutual support groups such as AA. AA is a 12-step group that serves to provide support for patients who are trying to limit or quit drinking, which is the only criteria for inclusion in the groups [46]. The 12 steps involved in AA consist of a series of psychospiritual stages in which the person acknowledges their powerlessness over alcohol, seeks help by submitting to the power of a higher being and engages in step-wise tasks to repair and rebuild self-integrity [47]. The clinical efficacy of AA is often confounded by the fact many AA participants also receive specialized treatment by healthcare

professionals simultaneously. However, in a study conducted by Humphreys et al. investigating the effectiveness of AA without the self-selection bias of individuals who choose whether or not to attend AA meetings, 5 out of 6 randomized trial datasets of those funded by the National Institutes of Health were found to have positively benefited from AA attendance due to its therapeutic social support and wealth of role models that may act as an inspiration of hope [48]. They also found that AA meetings are beneficial for short-term (3 months) and long-term (15 months) reductions in alcohol use.

Treatment of Co-Morbid Anxiety and Alcohol Use Disorders

The prevalence of co-morbid anxiety and AUD is among the five most commonly diagnosed psychiatric disorders in the US [49]. While extremely prevalent, co-morbid anxiety and AUD often go untreated due to failure to recover from either disorder [50]. At its most basic level, there are three classic treatment options for dual diagnosis disorders: treat one disorder at a time (i.e., serial/sequential treatment), treat both simultaneously in different programs (i.e., parallel treatment), or provide integrated treatment in a single, comprehensive program for dual-diagnosis [51,52]. While serial and parallel treatments have their respective benefits, they both may create conflict or stress for dually-diagnosed patients, as patients in serial treatment may be given conflicting or contradictory information after one treatment and patients in parallel treatment may experience inefficiency, stress, and added expenses due to need for multiple appointments in different venues, time off from work and transportation costs. In view of these limitations, integrated treatment for dual-diagnosis patients represents one of the more effective and efficient treatment strategies [51,53]. Thus, although current evidence supports treating both psychiatric and substance use disorders concomitantly, benefits and disadvantages to each approach should be considered in view of each patient's individual needs and constraints [54-56].

Pharmacological treatment options for co-morbid anxiety and alcohol use disorders

Few studies have investigated which pharmacological interventions are effective for co-morbid anxiety and alcohol use disorders. While the use of SSRIs, SNRIs, tricyclic antidepressants, buspirone, beta-blockers, gabapentinoids, atypical antipsychotics and benzodiazepines is effective for reducing anxiety symptoms, there is a paucity of clinical studies demonstrating their effectiveness in patients with co-morbid AUD [54,57,58]. One study by Randall et al. examined the effectiveness of the SSRI paroxetine (Paxil) in treating co-morbid social anxiety disorder and AUD. Patients in the placebo group and the paroxetine group underwent clinical interviews asking about social fears and avoidance each week. Physicians then rated each patient through the Clinical Global Impressions scale and after each week they were re-evaluated for improvements based on Clinical Global Impression scores. They found patients who were randomly assigned to the paroxetine group exhibited greater improvements in their social anxiety disorder symptoms based on fear/anxiety and avoidance subscales compared to the placebo group [59]. Moreover, participants in the paroxetine group were found to have significant differences in alcohol consumption by week 7, suggesting that longer courses of treatment (e.g., 12 weeks) may be necessary to achieve efficacy of paroxetine for AUD with co-morbid social anxiety disorder [59]. This study's findings are significant because it is among the first studies to show positive results for both social anxiety disorder and AUD outcomes using a single pharmacotherapy.

A commonly used off-label pharmacotherapy for co-morbid anxiety disorders and AUD worth addressing is gabapentin. Gabapentin was initially approved by the FDA in 1993 for the treatment of seizure disorders, but since then its use has expanded to treat neuropathic pain, post-herpetic neuralgia, and is now commonly used off-label to treat anxiety, sleep disturbances, vasomotor symptoms of menopause, substance use disorders and other psychiatric disorders such as bipolar disorder and PTSD [60,61]. Despite insufficient evidence supporting its use in GAD, gabapentin has shown benefits for the treatment of other anxiety disorders such as social phobias, anxiety in breast cancer, perioperative anxiety, and OCD [60-62]. In a double-blind randomized clinical trial, researchers founded that gabapentin 300 mg/d and 900 mg/d were more effective than placebo at reducing both hot flashes and anxiety in patients who had recently received chemotherapy [61]. As previously discussed, gabapentin monotherapy has proven efficacy in AUD and convincing evidence for effectiveness in treating alcohol withdrawal symptoms in AUD, even if it is not commonly used for this purpose [41,63] Due to its lack of significant drug-drug interactions, renal excretion and its favourable side effect profile, gabapentin can be used in combination with other pharmacotherapies for AUD and/or psychiatric conditions even in hepatic impairment. In a study of alcohol-dependent patients who received gabapentin in combination with naltrexone, the combination demonstrated greater improvement in delaying return to heavy drinking and reducing the number of drinking days compared to those who received placebo or naltrexone alone [63].

Other medications that have been studied for the treatment of anxiety and AUD include buspirone (BuSpar), a 5-HT1A partial agonist with D2 antagonism, and hydroxyzine (Vistaril), a first-generation antihistamine [55]. Studies on buspirone have mixed data in this patient population, as one study found greater retention, reduced anxiety, and slower return to heavy alcohol consumption [64]. In contrast, a 2006 study by Malcolm et al. found that buspirone did not provide any benefit compared to placebo in terms of anxiety scales and time to study drop-out, time to first drink, time to five consecutive drinking days, and time to first intoxication [65]. In another study, Tollefson et al. found that buspirone was effective at treating patients with co-morbid AUD and GAD through reducing the number of days craving alcohol [6]. Specifically, patients in the study were randomized to receive either buspirone 15 mg/d or placebo over a period of 24 weeks. Patients treated with buspirone were found to have significantly reduced drinking rates compared to patients who received placebo. Due to its sedative properties, hydroxyzine is often used as a short-term treatment for anxiety with positive effects, and has been shown to decrease alcohol

consumption in patients with co-morbid anxiety and AUD [66,67]. In a study by Darcis et al., they found that use of hydroxyzine 50 mg/d over a 4-week period significantly reduced anxiety symptoms as measured by the Hamilton Anxiety Rating Scale compared to placebo (41% *vs.* 18%) [68]. Moreover, buspirone and hydroxyzine are often chosen as treatments in patients with co-morbid anxiety and AUD due to their low abuse potential compared to benzodiazepines and lack of cross-tolerance with the GABA receptor [69].

Another potential pharmacotherapy for patients with co-morbid anxiety and alcohol withdrawal symptoms is short-term use of chlordiazepoxide (Librium) [69]. As a benzodiazepine, chlordiazepoxide is effective for decreasing anxiety, restlessness, tremors, and seizure frequency encountered during mild to moderate alcohol withdrawal. It is commonly prescribed in small quantities for outpatient detoxification due to its long half-life and relatively lower risk of respiratory depression if combined with alcohol. While effective, there are several drawbacks of this medication including its abuse liability, cross-tolerance with alcohol at the GABA receptor, and its long half-life, which carries an absolute risk of respiratory depression, coma and death if used in combination with excessive alcohol, other sedatives and/or opioids.

Psychosocial treatments of co-morbid anxiety and alcohol use disorders

Use of behavioral and psychosocial treatments in co-morbid anxiety and AUD have mixed results according to recent meta-analyses [53]. While many studies show that concurrent behavioral and psychosocial treatments are successful, other studies have inconsistent results indicating that simultaneous treatment of the co-morbid conditions may have no clear advantage over sequential treatment of the two disorders [50].

For instance, in a 2001 study by Randall et al., they tested the effects of CBT on patients with co-morbid social anxiety disorder and AUD versus CBT for the alcohol dependence symptoms alone [50]. They found that both groups showed significant reductions in social anxiety symptoms as well as alcohol consumption with use of CBT. However, the group treated for social anxiety disorder and AUD suffered worse outcomes on some of the alcohol-related measures such as alcohol use frequency, total quantity of alcohol consumed, and more frequent heavy drinking days. The authors attributed this unexpected outcome to the CBT homework assignments given to the dual-diagnosed group concerning feared situations, as they believed this may have resulted in drinking in order to cope with the imaginal exposure. Mixed results were also found in a literature review by Hesse, which analyzed the integrated psychosocial treatment of AUD and anxiety disorders such as panic disorder, OCD, and/or social anxiety disorder using cognitive behavioral therapy [56]. He found that of the four selected primary outcomes, only one had statistically significant results: percentage of days abstinent from alcohol at follow-up. A randomized controlled trial of integrated treatment versus standard of care in dual-diagnosis patients conducted by Wüsthoff et al. showed enhanced motivational status in participants receiving integrated care compared to control, but neither group had any significant reduction in psychiatric symptoms [70]. Given this, integrated treatment of dual-diagnosis conditions is promising, but further research is warranted [71-73].

Successful psychosocial treatment for co-morbid social anxiety disorder and AUD was discussed in a case study whereby Buckner et al. that utilized combination MET and CBT to treat a 33-year-old male. Their treatment plan consisted of 19 sessions of MET and CBT with a six-month follow-up after termination of treatment. Based on their report, the patient has been in remission for both disorders, has denied use of alcohol and has experienced clinically significant improvement in his social anxiety disorder. While further clinical and empirical work and larger sample sizes are necessary to confirm the efficacy of integrated MET and CBT on co-morbid social anxiety disorder and AUD, Buckner et al. results are promising and may be a potential successful treatment option for many patients [74]. Other effective studies utilize cognitive behavioral therapy such as guided imagery and relaxation techniques in order to teach patients to control their anxious states in absence of medications [75].

Another potential adjuvant to psychosocial treatment for patients with co-morbid AUD and GAD is to increase family involvement [76]. Engaging family members in a patient's treatment aims to provide a supportive network throughout the patient's recovery so that relapses can be swiftly identified and referred back for treatment planning. Familial involvement provides an active role to encourage treatment retention, support relapse prevention, monitor aftercare and promote treatment re-entry after relapse, all of which benefit the patient's overall treatment [77]. There are also skills-based programs to help improve families' involvement, such as the Community Reinforcement and Family Training (CRAFT) intervention, which not only has been found to significantly help reduce AUD and GAD symptoms, but also improves the lives of the involved family members [78].

Conclusion

Co-morbid anxiety and alcohol use disorders are highly prevalent and represent a significant clinical treatment challenge. Pharmacological and psychosocial treatments have displayed effectiveness in treating anxiety and alcohol use disorders independently and when these conditions co-occur. Though there are effective pharmacological treatments for co-morbid anxiety and alcohol use disorders, there is no clear consensus as to which ones or combinations to use. Currently, hydroxyzine, buspirone and gabapentin represent three off-label pharmacotherapies that have demonstrated efficacy in co-morbid anxiety and alcohol use disorders. Similarly, efficacious psychosocial treatments for AUD and anxiety disorders to consider include CBT and MET. In view of the effective pharmacological and psychosocial treatments to treat these co-morbid conditions, and the evidence that integrated treatment has promising outcomes compared to sequential or parallel treatment, we believe that integrated treatment is superior in treating co-morbid anxiety and alcohol use disorders. Therefore, treatment plans should involve judicious use of pharmacological

agents in combination with psychosocial treatments, ideally in a comprehensive dual-diagnosis capable setting. Since alcohol use disorders are a leading cause of preventable death in the United States and co-morbid anxiety disorders have been associated with worsened AUD outcomes, more studies are warranted to ascertain optimal treatments. As illustrated by our case presentation, integrated treatment involving a combination of active engagement in therapy in our DDTP, regular participation in AA, and short-term use of chlordiazepoxide (Librium) proved to be beneficial for improving our patient's abstinence rates even after completion of the treatment program. More high-quality studies investigating effective integrated pharmacotherapies and psychosocial interventions for specific co-morbid anxiety disorders and AUD are warranted, given the disproportionately large burden of disease these two disorders carry.

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