Alcohol and Mental Health: co-occurring Alcohol Use and Mental Health Disorders

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Abstract:

There is a strong link between alcohol use and mental health, yet research often fails to provide a comprehensive understanding of the complex interaction between the two aspects. In relation to treatment, alcohol and mental health services often work in a disjointed manner; likewise, policies and guidelines for the two sectors are generally developed in isolation from one another. The result of this silo mentality is that the needs of individuals with comorbid alcohol and mental health disorders, commonly referred to as "Dual Diagnosis", are often unmet, leading to serious harmful consequences for the affected individuals, their families and society as a whole. This generates further stigma and isolation for an already vulnerable and high-risk population. The present Chapter provides an overview of the epidemiology, and the main etiological theories of co-occurring Alcohol Use Disorders (AUD) and Mental Health Disorders (MHD). It is hoped that this chapter can inform treatment and policies for this population.

Key Words:

Dual Diagnosis, co-occurring disorders, comorbidity, alcohol dependence, mental health disorders, alcohol, mental health, depression, anxiety

[The prevalence of co-occurring Alcohol Use and Mental Health Disorders]

There is a strong linkage between alcohol use and mental health, with a wide range of mental health disorders being more prevalent in people who drink problematically. However, determining the prevalence of comorbid Alcohol Use Disorders (AUD) and Mental Health Disorders (MHD) is challenging because of the wide variation in the definitions, measurements, and instruments used to assess whether individuals met diagnostic criteria for AUD and any specific mental disorder (Boden & Fergusson, 2011; Anker & Kushner, 2019).

Mood disorders and Anxiety are particularly common in people with AUD (Kushner et al., 2012). The prevalence of depression in people seeking treatment for AUD ranges from 50 to 70% (Conner et al., 2009). A meta-analysis of 16 cross-sectional and longitudinal studies investigating the link between AUD and Major Depression (MD), confirmed that the presence of either condition doubles the risks of the second disorder, even after controlling for variations of measures of AUD and MD (Boden & Ferguson, 2011). Subjective measures of depression symptoms in the general population support the clinical findings. A survey based on 5828 respondents to the Health Survey for England found that the risk of alcohol dependence (determined by the amount of alcohol consumed) as well as the experience of alcohol dependence are significantly associated with higher levels of self-rated depression (Churchill & Farrell, 2017).

Research into the intersection between anxiety disorders (AD) and AUD found that up to 50% of individuals receiving treatment for problematic alcohol use also met diagnostic criteria for one or more AD (Chunk, Dennis & Funk, 2008; Kushner et al., 2005). Similarly, a synthesis of the major epidemiological studies showed that the risk for meeting diagnostic criteria for alcohol dependence more than doubled among individuals with an AD compared to those with no AD (Kushner et al., 2008). Individuals with social anxiety (SA) seem particularly vulnerable to develop AUD (Buckner, Heimberg, Ecker and Vinci, 2013). In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) in USA, 48% of individuals with a lifetime diagnosis of Social Anxiety Disorder (SAD) also met criteria for a lifetime diagnosis of an AUD (Grant et al., 2005). People with an AUD and lifetime history of SAD generally experience more severe alcohol dependence and report more major depressive episodes, less peer social support, and lower occupational status than patients without SAD (Buckner et al., 2013). Research on the co-existence of AUD and Obsessive-Compulsive Disorders (OCD) is relatively scarce in comparison to other subtypes. However, the development of the Obsessive–Compulsive Drinking Scale (Anton et al., 1996) signifies the existence of an overlap between OCD and AUD. Also, occurrence of obsessive–compulsive symptoms has been commonly reported among alcohol dependent patients (Lima et al., 2005). A cross-sectional study by Gentil et al., (2008) on 630 OCD patients from seven Brazilian university services, compared patients with and without AUD comorbidity. Out of the overall sample, 7.5% presented AUD comorbidity. Although the prevalence is lower than in other subtypes of AD, comorbidity showed clinical features that deserve special attention from mental health professionals, such as increased risk for suicidality, higher

comorbidity with generalized anxiety and somatization disorders, and compulsive sexual behaviour.

An issue in estimating and interpreting the prevalence of comorbid AUD and AD is that various subtypes (i.e., social phobia disorder, panic disorder, and generalized anxiety disorder) are often present at the same time in the same individual (Kushner et al., 2012). Another question is whether subtypes of anxiety disorders have a unique association with AUD, or whether each subtype individually contribute a similar increase in the overall risk for AUD. Modeling analysis on the NESARC database (N 43,093) was used to explore the relationship between risk for alcohol misuse and the shared versus unique components of several anxiety and depressive disorders. This analysis showed a strong positive relationship between risk for DSM-IV alcohol dependence and the shared components of the anxiety and depression diagnoses. However, the analysis also showed no relationship between risk for alcohol dependence and the unique components of those diagnoses. These findings are consistent with the idea that all anxiety and mood disorders contribute to general "negative emotionality", which, in turn, correlates with the risk for alcohol dependence (Kushner et al., 2012). These results support the development of a novel integrated "transdiagnostic" therapeutic protocol that focus on common processes underlying multiple disorders, for mood and anxiety disorders (Vujanovic et al., 2016).

Post-traumatic stress disorder (PTSD) is also highly associated with alcohol dependence (Suh & Ressler, 2018). Particularly vulnerable groups are individuals who have been victim of childhood trauma (Brady & Back, 2012) and women affected by domestic

violence (Kaysen et al, 2007). In addition, women have been found to be more likely to have experienced sexual abuse than men in both AUD and MHD clinical and community samples (Drapalski, Bennett & Bellack, 2011; Gearon, Nidecker, et al., 2003). Veterans are also particularly vulnerable to this comorbidity. In a nationally representative sample of Veterans in US, one of every five Veterans with AUD also screened positive for PTSD (Norman et al., 2018). The prevalence is even higher among Veterans seeking care, with up to two-thirds of those with AUD also having a diagnosis of PTSD (Seal et al., 2011). A high rate of AUD was also found in UK Veterans. For example, a recent UK study by Murphy & Turgoose (2019) investigated alcohol misuse and mental health in 403 treatment-seeking veterans, in comparison to the Armed Forces and the general population. They found that although both military samples reported significantly higher levels of AUD than the general population, treatment-seeking veterans were significantly more likely to report alcohol dependence and alcohol related harm than the two comparison groups.

Alcohol is also the most common substance of abuse amongst people with Bipolar Disorders, in a meta-analysis of 78 studies of comorbid bipolar disorder and substance use disorder, it was found that alcohol use was at 42%, followed by cannabis (20%), illicit drugs (17%), cocaine and amphetamine (11%) (Hunt et al*.,* 2016). With regard to psychosis, the comorbidity of schizophrenia and AUDs is particularly problematic, as it is associated with depression, suicidality, medication nonadherence, chronic physical problems, homelessness, aggression, violence, incarceration, and high rates of hospitalization (e.g. Hunt et al., 2018). Individuals with schizophrenia spectrum disorders

have three times the risk of heavy alcohol use relative to the general population (Hartz et al., 2014). One meta-analysis of individuals with schizophrenia found a lifetime prevalence of AUD of 24.3% and one American study reported that 36.4% of 404 participants had experienced AUD before their first episode of psychosis. A rarer but clinically significant psychotic disorder is alcohol-induced psychotic disorder (AIPD), which can occur with acute intoxication, alcohol withdrawal, as well as in patients with chronic alcohol use disorder (Jordaan & Emsley, 2013). A review of 21 studies found 0.4% lifetime prevalence of this disorder in the general population and 4.0% in patients with alcohol dependence (Engelhard, Touquet, Tansens and De Fruyt, 2015). Although relatively rare, AIPD is a serious condition and is associated with high comorbidity with other psychiatric disorders, high re-hospitalization, mortality rates and suicidal behaviour (Jordaan & Emsley, 2013).

Alcohol Use Disorders also co-occur at high prevalence with borderline personality disorder (BPD) and antisocial personality disorders (ASPD) (Helle, Watts, Trull, and Sher, 2019). In a recent review (Trull et al., 2018), of those individuals who met diagnostic criteria for BPD, 46% to 49% also met diagnostic criteria for current AUD, and 59% for lifetime AUD. Among the general population or clinical samples of individuals with a current diagnosis of AUD or alcohol dependence, the prevalence of a BPD diagnosis was approximately 12% to 17%. In the same population, ASPD diagnoses were slightly more prevalent than BPD diagnoses, ranging from 19% to 22%. However, the prevalence of AUD among those diagnosed with ASPD was as high as 68%.

The overlap between Attention Deficit Hyperactive Disorder (ADHD) and substance use disorders in general have been long documented (Magon & Müller, 2012). Data on adult ADHD comorbidity among individuals with AUD are limited, few studies have indicated that adult ADHD is comparatively low among individuals with AUD compared to those who use other substances (van de Glind, et al., 2013). Vice versa, the incidence of AUD in adults with ADHD has been found to be 33–44% (Rasmussen and Gilberg, 2000). While, in a German study of 91 adults with alcohol dependence, 20.9% (WURS-k) or 23.1% (DSM-IV diagnostic criteria) of the patients showed evidence of retrospective ADHD in childhood (Ohlmeier et al., 2008).

Finally, increased attention has recently been given to alcohol-related dementia in the elderly population. For example, a UK cohort study of people with a mean age of 56 found that drinking above 32 UK units of alcohol per week was associated with greater global impairment in cognitive function, as well as in memory and executive function 10 years later (Sabia et al., 2014), these data suggest that alcohol-related dementia represents an under-recognised mental disorder with both clinical and public mental health implications (Rao, 2014).

In conclusion, there is abundant evidence that the co-occurrence of AUD and MHD is highly prevalent and is associated with increased vulnerability, high level of risk to self and others, greater psychological and physical impairment and poor prognosis. Thus, failing to meet the needs of this population leads to serious consequences for the

individual and society as a whole, it is therefore paramount that the health and social care sectors treat comorbidity as the norm, rather than the exception.

[Etiological theories: what comes first?]

There are three main models that explain the etiology of comorbid mental health disorders (MHD) and substance use disorders (SUD): 1. The secondary substance use models, which suggests that MHD cause SUD; 2. The secondary mental health disorders model, which implies that SUD cause MHD; 3. the common risk factor model, which suggests that there might be shared neurological and psychosocial vulnerabilities that increase the risk of both MHD and SUD. This section will define each model in the context of alcohol use disorders (AUD).

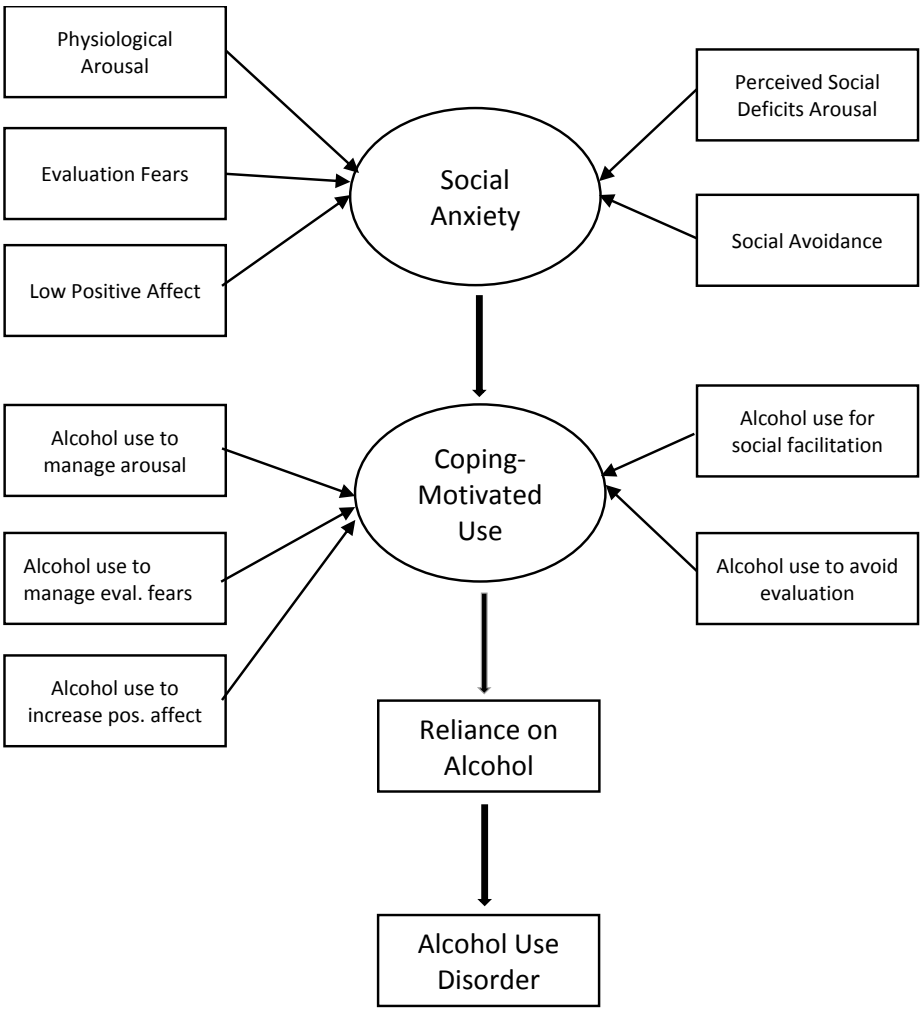
(1) The secondary substance use model

If MHD leads to AUD, by definition, a temporal association should be observed with the former preceding the latter. However, research on the order of onset produced inconclusive results. One limitation of this line of evidence is that the temporal sequence of the disorders does not necessarily imply causality (Anker and Kushner, 2019). In addition, it is difficult to establish the exact start of either MHDs or AUD because both disorders develop gradually, hence data on order of onset are not very helpful to determine causality, especially in regard to schizophrenia or bipolar disorders (Mueser et al.,1998). However, research on anxiety disorders (AD) has produced some supportive evidence of this direction of causality. For example, Kushner, Sher and Beitman (1990) have shown that the onset of AD preceded alcohol misuse in up to three-quarters of

individuals who had both conditions, subsequent studies demonstrated that this is true especially for those who had social anxiety disorders SAD (Buckner, et al. 2013). Grant et al. (2005) also found that the AD persisted following a period of abstinence from alcohol, indicating that it was an independent diagnosis. There are three explanatory models for the observed causal link: the "self-medication hypothesis" (Khantzian, 2013; Quitkin, Rifkin, Kaplan, & Klein, 1972), "tension reduction" (Conger, 1956) and "stressresponse dampening" (Sher & Levenson, 1982). These three models are based on the concept that people with AD attempt to relieve negative consequences of these conditions by drinking alcohol to cope with their symptoms, the "negative reinforcement" (an unpleasant state is successfully taken away in response to drinking) eventually leads to the later onset of AUD (Smith & Randall, 2019). Many studies investigating motivations for using alcohol, support this hypothesis (see Smith & Randall, 2012; Anker, & Kushner, 2019 for a review on the topic), however, most laboratory studies did not find a direct impact of alcohol on the physiological response among those with AD (see Tran & Smith, 2008). One possible explanation for these seemingly incongruent results is that a person's expectations about alcohol's effects can motivate drinking independently of alcohol's actual physiological effects, these expectations influence the likelihood of drinking to cope which in turn increases the risk of excessive drinking (e.g., Abrams & Kushner, 2004). In line with this explanation, men with elevated anxiety regarding heterosexual interactions who were told that alcohol enhances social performance reported less anxiety after drinking before a heterosexual social interaction than men who were told that alcohol impairs social, performance (Keane & Lisman, 1983). Also, men with SA who held stronger tension reduction expectancies reported less

anticipatory social anxiety than men who expected less tension reduction from drinking (Abrams & Kushner, 2004). Finally, individuals with AD who reported drinking to cope had a fivefold increased risk for developing alcohol dependence within 3 years; in contrary, people with AD who did not drink to cope showed the same level of risk for developing alcohol dependence as people with no anxiety disorders (Menary et al., 2011).

Buckner et al. (2013) proposed a biopsychosocial model for the comorbidity of substance use and social anxiety. Figure 4.1 is an adaptation of this model applied to alcohol use. The graph illustrates that socially anxious individuals may use alcohol to manage various components of social anxiety, for example to cope with unpleasant affective states as well as to increase positive affect (Abrams, Kusher, Reinertsen, 2002). Some may use alcohol to avoid negative evaluation by their peers (Byers, et al., 2010), some may use it to enhance enjoyment during social events (Alden &Wallace, 1995). Finally, the original model suggests that some socially anxious individuals may use substances to help decrease physiological arousal, for example, a study on people with social anxiety found that cannabidiol (CBD) decreased heart rate and decreased self-reported state of social anxiety prior to a speech task (Bergamaschi et al., 2011). However, as previously reported (Abrams & Kushner, 2004), the experience of anxiety attenuation following alcohol consumption seems to be determined more by individuals' expectancies, believes and motivations rather than the actual physiological response.



*** Insert Figure 4.1 ***

Caption: Proposed model of the relationship between social anxiety and substance used disorders.

Credit: Adapted from: Buckner, J. D., Heimberg, R. G., Ecker, A. H., & Vinci, C. (2013). A biopsychosocial model of social anxiety and substance use. Depression and Anxiety, 30(3), 276-284.

Research has shown that alcohol expectancies mediate alcohol consumption also in people with PSTD who have experienced trauma. A study by Nishith, Mueser and Morse,

(2019) compared a clinical sample of individuals with severe mental illness (SMI), PSTD and comorbid AUD with a sample of patients with similar mental health diagnosis but no AUD. They found that compared to people with SMI, PTSD, but no alcohol use disorder, those who had co-occurring AUD endorsed more positive expectancies for the effects of alcohol on increasing social and sexual behavior, and the experience of power and pleasure, but not for the effects on reducing tension and promoting relaxation. The authors suggest that AUD in individuals with SMI and PTSD may be related to attempts to cope with specific symptom clusters of PTSD, such as feelings of numbness and avoidance.

The "alleviation of dysphoria" model has been studied mainly in the context of bipolar disorders and schizophrenia (Mueser, Drake, & Wallach, 1998). This model holds that people with severe mental illness start drinking alcohol to alleviate the feelings of sadness, gloom, inadequacy, discontent, isolation, and boredom. Consistently with this model, Laudet, Magura, Vogel & Knight (2004) compared reasons for using substances in individuals suffering from bipolar disorder, schizophrenia, and depression. Overall, they found that alcohol was the most often cited as "substances used first" (65%). Those diagnosed with a bipolar disorder were significantly more likely to cite wanting to fit in with peers as the reason to start using alcohol. Contributively, and those with a primary diagnosis of schizophrenia showed a significantly lower likelihood of citing emotional or mental issues as a reason to start using drugs and alcohol in comparison to the other two groups. The role of alcohol as social lubricant for people with severe mental health disorders was demonstrated also by Thorton, et al. (2012). Their study showed that

reasons for using substances varied according to substance and mental disorder. As shown in Table x.1, overall, alcohol was primarily used to cope (79%), and for social motives (75%). Interestingly, "To be social/gives me a social life" was cited much more frequently by participants with psychosis (21.7%) as opposed to those with depression (6.4%), for whom cannabis was the preferred social lubricant. In addition, for the psychosis group, to "Take away sad feelings, cheer me up, loneliness" was the most frequently cited coping motive (28.3%). In line with Drake and colleagues (Drake, Wallach, Alverson, & Mueser, 2002) proposed that the emphasis on biological and pharmacological factors in the literature on "dual diagnosis" has diverted attention from important psychosocial issues. The authors suggest that factors such as social networks, expectancies of drug effects, boredom, dysphoria, unemployment, and poverty "are critically important in the presentation, development and course of substance abuse and in the process of helping people attain sobriety, stable abstinence and recovery" (p. 100).

Caption: Percentage of Study 5 participants endorsing reasons for tobacco, alcohol and cannabis use, collected via free response

Credit: Taken from: Thornton, L. K., Baker, A. L., Lewin, T. J., Kay-Lambkin, F. J., Kavanagh, D., Richmond, R., ... & Johnson, M. P. (2012). Reasons for substance use among people with mental disorders. *Addictive Behaviors*, *37*(4), 427-434.

Studies into gender differences suggested that women are more prone to drink to cope with symptoms of AD (negative reinforcement) (Norberg et al., 2010) whereas men are more likely to drink to enhance their experience (positive reinforcement) (Peltier et al,

2019). Recent research also demonstrated gender differences in stress-related alcohol use might be partly related to the role of ovarian hormones in regulating stress-response (see Peltier et al., 2019 for a review on gender differences in stress-related alcohol use).

In conclusion, there is evidence to support the secondary AUD model, however, this should be taken with caution as it is associated with at least two limitations: the analyses often rely on retrospective self-reported data and findings derive from clinical samples can inflate prevalence estimates of self-medication, especially if alcohol-dependent individuals are evaluated during acute alcohol withdrawal (Mueser et al., 1998). Despite these limitations, this line of research suggests that interventions for co-occurring AUD and AD, especially PTSD, should be gender sensitive and consider people's alcohol expectancies and reasons to drink.

(2) The secondary mental health disorders model

The second hypothesis proposes that AUD can induce MHD via biological, psychological, or social processes. For example, Boden & Ferguson's (2011) metanalysis found that the most plausible causal association between AUD and major depression (MD) is the one in which AUD increase the risk of MD, rather than vice versa. Churchill & Farrell's (2017) study on 5828 respondents from the Health Survey for England (HSE), confirmed the same direction of causality. They also found that higher levels of depression were associated with intensity (the volume of alcohol consumed) as opposed to frequency of alcohol consumption. There is some evidence that gender might moderate order of onset, whereby depression is often an antecedent of drinking problems among

women but is experienced as a consequence of drinking in men (Schutte et al., 1995; Churchill & Farrell, 2017).

AUD has also been found to precipitate or exacerbate anxiety disorders (AD) and psychosis. The section below illustrates some of the biological and mechanisms and neurological structures underpinning these causal links.

Biological and neurological mechanisms

One explanation of the biological mechanism through which AUD can cause MD is that alcohol exposure may generate metabolic changes that also increase the risk of MD. For instance, McEachin, Keller, Saunders, McInnis (2008) found evidence that exposure to ethanol leads to reductions in the production of MTHFR (methylenetetrahydrofolate reductase), an enzyme related to folate metabolism. Reduced folate levels have, in turn, been linked to increased risks of MD, indicating a possible causal link between AUD and MD through decreased MTHFR production. Another stream of research focuses on the effects that alcohol consumption has on the neurocognitive processes underlying MD. For example, trait rumination has been noted to be prevalent in those who suffer with depression (Mandell, et al., 2014). Mandell, and colleagues (2014) suggest that it is a risk factor towards more intense and harder to treat depressions. Trait rumination is the tendency to engage in sustained and repetitive thinking regarding negative thoughts about events that have happened in the past. The cognitive processes that have been suggested to be important to rumination are automatic attention to negative information, and difficulty disengaging from negative information. Therefore, it is hypothesised there is a lack of cognitive control mechanisms in place to aid regulation of attention, emotion, and emotional processing (Menke, 2019). Mandell, et al., (2014) examined this set of

mechanisms using 29 adults with a diagnosis of MD. The participants completed an FMRI protocol, self-report questionnaires (10 measures on rumination, emotional control, and intrusiveness) and qualitative data from clinical interviews. The study found that depressed individuals had primarily greater sustained amygdala activity and that related areas within the brain such as the hippocampus, dorsal lateral pre frontal cortex, anterior insula, medial frontal gyrus and posterior cingulate were activated depending on the type of rumination. However, notably the higher amygdala activation was most important as this can connote poorer emotional control, higher attention to stimuli that trigger negative emotional responses and dysfunctional control in response to internal feelings which may be ruminated upon. This may cause more emotional discomfort and distress for the individual. In people with chronic AUD, the amygdala is impaired in its function due to plastic changes dictated by gene expression such as down regulation of oxyreductases (Dager et al., 2015). This is important for energy stores and metabolism in the brain. With chronic alcohol use these functions are diminished suggesting reduced neuronal energy stores and additionally higher oxidative damage in the brain. In turn chronic alcohol use can lead to reduced neurogenesis which affects plasticity and therefore an individual's response to novel and stressful conditions (Kryger & Wilce, 2010). In consideration of this damage through alcohol use a circular issue may occur where stimuli become more stressful, emotional regulation becomes increasingly more difficult, and therefore this leads to more reliance of alcohol and its effects of dampening the amygdala when intoxicated (Roberto et al., 2012)., Therefore, an already dysfunctional hyperactive or hyper-reactive amygdala (as seen in dual diagnosis cases) will be further

compromised through use of alcohol in attempt to self-medicate rumination, sadness, to cope with anxiety or depression symptoms.

In reference to anxiety disorders, there is evidence that chronic alcohol dependence results in an overall GABA deficiency that may induce anxiety (Smith & Randall, 2012). Withdrawal periods also can induce changes in the brain, which can include excessive activity (i.e., hyperexcitability) of certain brain systems (i.e., the limbic system and the norepinephrine system) (Kushner et al., 1990), both of which are involved in triggering panic attacks (Graeff & Del-Ben, 2008). Repeated withdrawal episodes can lead to neural adaptation that makes the drinker more susceptible to anxiety and exacerbates stress-induced negative affect when alcohol intake stops (Breese et al., 2011). This explains why people with alcohol dependence who are recently abstinent report increased feelings of anxiety, panic, and phobic-like behaviors in the short term, and symptoms of autonomic activity (i.e., sympathetic activation, such as increased heart rate and faster/shallower breathing) and persistent anxiety across prolonged withdrawal.

The amygdala has been signified as one of the most supported regions that shows hyperactivity or hyperreactivity in people with AUD during fMRI and PET neuroimaging (Niciu & |mason, 2014). Withdrawal induced anxiety is part of the functional rebound changes from an excess of GABA from chronic use of alcohol and subsequent high glutamatergic expression. Considering the Amygdala is primarily GABAergic, the disinhibition of downstream brain regions can be problematic for the individual who has chronically used or is dependent on alcohol. Downstream brain regions that innervate the

central amygdala are outlined by Pitkanen, (2000) and include the ventral tegmental area (important for reward and production of forebrain dopamine), the locus coeruleus (important for stress response) and the medial pre frontal cortex (mPFC). The mPFC has been outlined as critical in processing emotionally salient information and facilitates behavioural responses to cues. Deregulation of this area has been implicated in addiction and in other neuropsychiatric disorders such as schizophrenia, depression, mood, and anxiety disorders (Stamatakis et al., 2014).

In reference to psychosis, alcohol can precipitate psychotic symptoms during acute intoxication, withdrawal, or chronic use (Archibald, Brunette, Wallin, & Green, 2019). In one study in emergency departments, 18.9% of those with a diagnosis of substance-induced psychosis had alcohol as the primary substance (Canton et al., 2005), patients with alcohol-related psychosis have a 5% to 30% risk of developing a chronic schizophrenia-like syndrome (Glass, 1989). In chronic alcohol dependent patients, lack of thiamine is a common condition. Thiamine deficiency is known to lead to Wernicke-Korsakoff syndrome, which is characterized by neurological findings on examination and a confusional-apathetic state (Peräl et al. 2010).

Psychosocial factors

From a psychosocial perspective, it can be argued that both anxiety and depression can be caused by the social and financial sequalae of alcohol dependence, for example loss of employment, financial difficulties, family breakdown, homelessness, ill health and isolation (e.g. Foster, Powell, Marshall and Peters, 1999). However, studies that have

accounted for the possible influence of a range of life circumstances in the causal link between AUD and major depression have found that these links persist even after controlling for social and environmental factors (Hasin & Grant, 2002; Paljarvi et al., 2009; Sihvola, et al., 2008). Whereas there is support evidence for life stressors to generate anxiety disorders. There are least two ways that can explain this causal link: first, the consistent presence of life stressors can intensify anxiety symptoms among already vulnerable individuals. Second, as explained in the earlier section, alcohol use in the presence of stress stimuli may interfere with extinction-based learning necessary for normal adaptation to stressors. Thus, AUD can lead to anxiety through a combination of greater levels of life stress coupled with poor coping skills (Smith and Randall, 2012).

(3) The common risk factors model

Recent research provides increasing support for the perspective that AUD and co-occurring MHD share underlying, mutually exacerbating, neurological and psychosocial processes.

Common biological risk factors have received considerable support in the context of Borderline Personality Disorders (BPD) and Antisocial Personality Disorders (ASPD). BPD and ASPD tend to relate similarly to AUD in terms of impulsivity, negative affect, and externalizing correlates; this commonality has been linked to the sharing of general personality traits, particularly antagonism and impulsivity (disinhibition) (Helle et al., 2019). For example, using a multivariate behavioral genetic twin design, Slutske et al., (2002) found that the genetic variance associated with impulsivity, novelty seeking, and aggression, accounted for 40% of the genetic variance in alcohol dependence. These

findings support the notion that the overlap of impulsivity and AUD originates from shared genetic mechanisms. Bornovalova, et al. (2013) have demonstrated the same for AUD and BPD. This common genetic mechanism appears to generate externalizing behavior and psychopathology generally, including AUD, other substance use disorder, conduct disorder, and antisocial behavior (Helle et al., 2019).

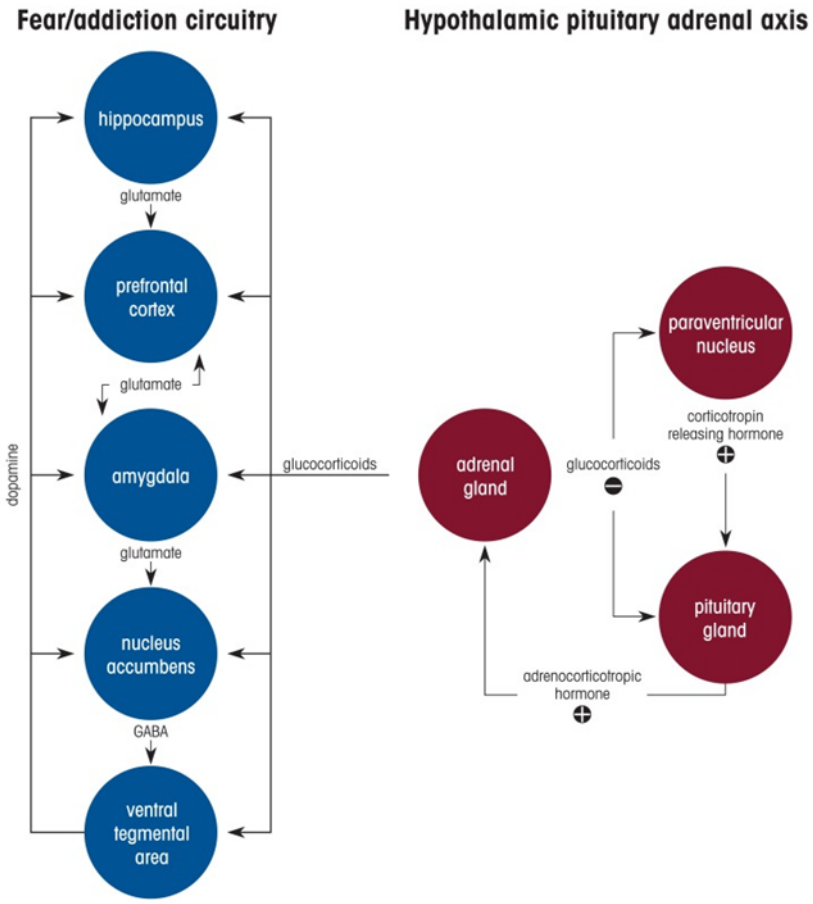
Genetic research has also found evidence of increased risks of both AUD and major depression (MD) among individuals with specific genotypes (Boden & Fergusson, 2011). For instance, studies by Wang et al. (2004) and Luo et al. (2005) found that variants of the muscarinic acetylcholine receptor M2 (CRHM2) gene are related to increased risks of both disorders. Similarly, several polymorphisms (genetic variations) of the brain-derived neurotrophic factor (BDNF) protein correlate with co-occurring schizophrenia and alcohol dependence but not with alcohol dependence alone, suggesting that these polymorphisms may contribute to a specific vulnerability to these co-occurring disorders (Hartz et al., 2017).

From a psychosocial perspective, trauma is a risk factor for both MHD and SUD, including AUD. Rates of trauma exposure in psychiatric inpatients range from 53% to 100% (McFarlane, Bookless, & Air, 2001), while about 90% of individuals with SMI (severe mental illness) report having experienced at least one traumatic event, most of whom have been multiply traumatised (Goodman et al., 1997; Mueser et al., 1998). As illustrated in the epidemiological section, rates of AUD among people with PTSD is high. There is growing evidence of the shared neurobiological mechanisms that link AUD and

PTSD. Neuroimaging studies have found that dysregulation in the hippocampus and the amygdala are implicated in both PTSD and AUD (Logue, et al., 2018; Norman, et al., 2012). The amygdala has been shown to be reduced in size within children who endured early life stress and/or trauma such as physical abuse, low socioeconomic status, and neglect (Hanson et al., 2015). Additionally, these structural changes have been identified in individuals who have survived a life-threatening illness or worked in critical care with life threatening or terminal illness and whom display PTSD symptoms from their ordeal (Matsuoka, et al., 2003; Stevens, et al., 2017). Hyperactive and or hyper-reactive activity in the amygdala (Gilpin & Weiner, 2017) have been shown in many studies concerning PTSD in combat veterans and inter-partner violence studies (Poirier, et al., 2013). Furthermore, women who have undergone intimate partner violence and who suffer with PTSD showed hyperactivation in the amygdala when exposed to fearful faces (Fonzo, et al., 2010). Like individuals diagnosed with PTSD, people who are diagnosed with AUD exhibit functional and structural changes in relation to the amygdala. Lower Amygdala volume has been reported in individuals with AUD (Dager, et al., 2015) and has been associated with higher alcohol drinking up to 6 months after imaging. However, to date there is a paucity of neuro imaging studies that investigate individuals with comorbid PTSD and AUD. One study by Nikolova, et al., (2016) used blood-oxygen-level-dependent functional magnetic resonance imaging to explore the relationship between alcohol use and levels of stress in a sample of 759 undergraduate students and demonstrated that problem drinking was highest in the context of stress. The study also showed that participants with higher levels of problem drinking displayed either high threat-related reactivity of the amygdala combined with low reward-related activity of the

ventral striatum (VS) or low threat-related reactivity of the amygdala combined with high reward-related activity of the VS. These results suggest that the relationship between neural activity and stress-related AUD may not be simply related to activity in one brain region, but rather may depend on convergent or divergent (re)activity in multiple brain regions. Semple, et al., (2000) used positron emission tomography to compare regional blood flow (rCBF) in patients with PTSD, alcohol and cocaine misuse at rest and during an auditory continuous performance task (ACPT). They found higher rCBF in the right amygdala and left parahippocampal gyrus, and lower blood flow in the frontal cortical regions for individuals with comorbid PTSD and alcohol or cocaine misuse in comparison to healthy controls, however one limitation of this study was that there were no PTSD-only and AUD-only comparison groups. A recent line of research has proposed that medial prefrontal cortex subregion (mPFC) projections to extended amygdala nuclei control fear and drug-seeking behaviours, and that dysregulation of these top-down PFC projections may lead to the abnormal fear conditioning that characterises PTSD and the compulsive drug-seeking behaviour in AUD (Peters et al. 2009). It has been suggested that the medial prefrontal cortex (mPFC) is impaired over time with excessive drinking and these impairments are similar to those seen in research regarding repeated stress. Accordingly, Holmes et al., (2012) examined the effects of excessive alcohol exposure on mice and found that there was a diminished capacity of the mPFC to mediate fear extinction. Below is a description of the fear/addiction circuitry to illustrate the connection. The mPFC is included in the pre-frontal cortex (PFC) and therefore is a part of this network. It has been suggested to be integral in working with the amygdala which is influenced by the Hypothalamus Pituitary Axis (HPA) Axis and other fear circuitry.

This circuitry is important in dampening emotional responses to fear, and its dysregulation plays a part in self-medication using alcohol to cope with internal and external stressors that are present for individuals who suffer with PTSD, see Figure x (Suh & Ressler, 2018).



*** Insert Figure 4.2 ***

Caption: Interactions between the fear/addiction neural circuitry and the hypothalamic pituitary adrenal (HPA) axis.

Credit: Suh, J., & Ressler, K. J. (2018). Common Biological Mechanisms of Alcohol Use Disorder and Post-Traumatic Stress Disorder. *Alcohol research: current reviews*, *39*(2), 131–145.

The above model is taken from Suh & Ressler (2018) and it shows the fear and addiction circuitry that is discussed in their review of common biological mechanisms of AUD and PTSD. The PFC and amygdala are mutually connected and the amygdala projects to the Nucleus Acumens via glutamatergic innervations. All areas illustrated above receive projections from dopamine neurons in the ventral tegmental area (VTA). The major components of the HPA include the paraventricular nucleus (PN) of the hypothalamus and the pituitary and adrenal glands. Corticotropin releasing hormone (CRH) from the PN stimulates release of adrenocorticotropic hormone (ACTH) from the anterior pituitary into the venal system. ATCH induces glucocorticoid release from the adrenal glands. Glucocorticoids mediate negative feedback regarding the HPA axis and directs it to reduce the stress response. Furthermore, Glucocorticoids affect the fear / addiction circuitry via their own receptors which can trigger physiological, cellular and molecular changes which in turn causes genetic alterations (epigenetic changes).

In summary, stress is a likely common neurobiological link between the processes of substance use disorders, including AUD, and anxiety disorders. Stress responses are mediated through the HPA axis, which in turn can influence brain circuits that control motivation. Higher levels of stress have been shown to reduce activity in the prefrontal cortex and increase responsivity in the striatum, which leads to decreased behavioral control, increased impulsivity, and increased compulsive behaviors. Early life stress, isolation, trauma and chronic stress can also cause long-term alterations in the HPA axis,

which affects limbic brain circuits that are involved in motivation, learning, and adaptation, which4are impaired in individuals with AUD and MHD.

Scientists are also beginning to understand the ways that genetic and environmental factors interact at the molecular level. Chronic stress caused by social factors such as isolation, homelessness, financial difficulties, trauma, or drug and alcohol exposure can induce stable changes that affect how genetic information is read and acted on by cells in the body (see Figure 4.3 and Wong, Mill & Fernandes, 2011, for a review on epigenetics in addiction). These alterations contribute to the development of MHD and addiction. However, there is also evidence that some of these changes can be reversed with interventions or environmental alteration (Guintivano & Kaminsky, 2016).

*** Insert Figure 4.3 ***

Caption: The proposed relationship between inherited predispositions, environmental factors, exposure to addictive substances and vulnerability to addictive disorders. When exposed to adverse environmental stimuli, individuals carrying susceptibility genes or epialleles predisposing to addictive behaviours may have an increased risk of developing addiction. Acute substance use may produce enduring alterations in gene expression via epigenetic changes that influence susceptibility to addictive disorders. Enhanced vulnerability to substances of abuse will then feed back into increased risk of future drug use (as shown by the dashed arrow) that bring about further modifications to the epigenome and gene expression

Credit: taken from: Wong, C.C.Y., Mill, J., Fernandes, C. (2011) Drugs and addiction: an introduction to epigenetics. *Addiction,* 106 (3), 480-489.

In conclusion, there is evidence to support all three main theoretical models of co-occurring AUD and MHD. However, it is becoming clear that the interaction between the two conditions is complex and, in many cases, bidirectional, with one reinforcing the other in a cyclic fashion (e.g. Suh & Ressler, 2018). Although it is important to try and disentangle the interaction between AUD and MHD, ultimately, regardless of the etiological model, these disorders are strongly associated. Thus, treatment must address both the MHD symptoms and AUD in an integrated fashion.

Research into the common underlying mechanisms indicates that interventions should aid individuals with such comorbidity develop skills to cope with the consequences of trauma and with stress. The evidence presented in this chapter also suggests that women are more likely to use alcohol to deal with symptoms of anxiety and stress in comparison to men, they are also more likely to have been victim of sexual abuse, they tend to display more severe psychiatric symptoms and more severe AUD related complications (see Gearon et al., 2011; Peltier, 2019). As a result, women have a greater number of service needs, especially for treatment related to family and trauma issues (Grella, 2003). Therefore, it is recommended that treatment interventions should be gender sensitive.

The strong connection between mental and alcohol use disorders indicates that transdiagnostic therapeutic protocols might be the way forward. The interplay between

the psychological and biological factors imply that therapeutic approaches may require a combination of pharmacological and psychosocial interventions. Finally, the complex and multiple needs of individuals with "dual diagnosis" can only be met if treatment and policy interventions adopt a joint and coordinated approach.

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