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Outside the typical anxiety disorder definition: Characterizing the role of impulsivity in comorbid substance use disorder

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ABSTRACT

Anxiety disorders and substance use disorders (SUDs) frequently co-occur, and individuals with this comorbidity demonstrate exacerbated impairment and poorer treatment outcomes compared to individuals with only one of the disorders. This paper reviews the potential mechanisms underlying this comorbidity, with a particular focus on the influence of impulsivity. There is an atypical subset of individuals with anxiety disorders that display elevated impulsivity, and it is suggested that these individuals account for the clinically relevant group of anxiety disorder patients that have a concurrent SUD. Patients with anxiety disorders that show increased impulsivity, particularly within the negative urgency (NU) sub-domain, appear to have a predisposition to engage in risky behaviours to cope with their anxiety symptoms, which includes substance use. Given the promise of impulsivity and NU as endophenotypes of this anxiety-SUD comorbidity, it is recommended that future research investigate gene variants that modulate impulsivity and NU to establish biomarkers predicting an increased risk of a concurrent SUD among anxiety disorder patients. This subtype and endophenotypic investigation may ultimately establish treatment targets that can lead to greater personalization of treatments for the subgroup of anxiety disorder patients that have comorbid SUDs.

1. Introduction

The anxiety disorders as a group are the most common class of mental disorders, with 11.6% of individuals globally having an anxiety disorder in a given year [1,2]. Individuals with these disorders are characterized as being predisposed to experiencing excessive fear and/or anxiety responses to perceived threats in a way that leads to significant distress and impairment in functioning [3]. Substance use disorders (SUDs) carry a worldwide prevalence of approximately 2.6%, and these disorders are characterized by the overuse of one or more psychoactive substances leading to deficits in physical and mental health [4]. Given the functional impairments and societal costs associated with the disorders alone, the high frequency of comorbidity between anxiety and SUDs is particularly worrisome [5]. The largest epidemiological study of this comorbidity conducted to date, the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), surveyed over 43,000 adults and found that 15% of individuals with a 12-month anxiety disorder concurrently have at least one SUD [6]. Similarly, approximately 18% of individuals with a current SUD also have at least one current anxiety disorder [6]. Of particular clinical relevance, among those seeking treatment for alcohol use disorder (AUD), 33% have an anxiety disorder, and among those seeking treatment for any SUD, 43% have an anxiety disorder. Among those seeking treatment for an anxiety disorder, 16% also have a SUD that was more likely to involve alcohol than other drugs. Overall, the epidemiological data presented suggest that anxiety and SUDs co-occur at greater rates than would be anticipated by chance, which introduces additional complications related to clinical presentation and treatment outcome due to the interaction between the disorders.

The anxiety and SUD comorbidity is particularly concerning due to the vicious cycle that occurs where the outcomes of anxiety perpetuate and exacerbate the SUD, and vice versa, in a continual cycle that extends suffering for the patient [7]. This concurrent anxiety-SUD presentation enforces a substantial burden on the individual, and to a

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greater degree than when these disorders exist separately. Compared to individuals with an anxiety disorder or SUD alone, those with comorbid anxiety and SUD are more likely to be unemployed, have an education that is less than or equal to high school level, be receiving financial aid, and be separated, widowed, or divorced [8–10]. As well, individuals with concurrent anxiety and SUD are more likely than those with only one of the disorders to perceive their mental health as poor, report higher psychological distress, and report their physical and mental health-related quality of life more negatively [8,9,11,12]. The existence of this comorbidity is also predictive of having a more severe psychiatric history, including a greater incidence of other comorbid mental disorders and increased self-reported illicit drug use [9,10].

In line with the greater burdens seen in comorbid compared to non-comorbid patients, individuals with an anxiety-SUD comorbidity are more likely to seek treatment than those with only one of the disorders [9]. However, they are also more likely to report that they have unmet needs in their mental health care [8]. This unmet need is reflected in the poor treatment outcomes that are commonly documented among this comorbid patient population. Compared to those with a SUD or AUD alone, those with a comorbid anxiety disorder have worse post-treatment smoking and drinking outcomes and increased craving during treatment [13–15]. Moreover, severity of anxiety symptoms is a predictor of recurrence among individuals with remitted alcohol dependence [16]. Similarly, the existence of a comorbid SUD greatly reduces the likelihood of remission from anxiety disorders and increases the likelihood of recurrence [17]. This overall lack of treatment efficacy may be causing, or be the result of, the higher rates of dropout and treatment compliance problems seen in this population when compared to non-comorbid populations [18,19]. Taken together, literature describing the epidemiology, clinical outcomes, and treatment response among individuals with comorbid anxiety and SUD supports the significant prevalence and clinical relevance of this co-occurrence. It is therefore paramount to explore the etiology of this comorbidity, which can allow for the establishment of novel treatment targets that are tailored to this particular comorbid population. The aim of this narrative review is to provide support for the use of impulsivity as an endophenotype that can explain the co-occurrence of SUDs among patients with anxiety disorders through presenting evidence delineating the interaction between anxiety symptoms and impulsivity, and how this interaction increases the susceptibility for substance use.

2. Etiological models explaining the anxiety and SUD comorbidity

There are three debated etiological models that have been proposed to account for the co-occurrence between anxiety and SUDs. It must be noted that the presumed causal pathways are not mutually exclusive, and comorbidity is inherently very complex [20]. However, understanding each of the basic pathway models by which an anxiety and SUD comorbidity may arise can be a useful starting point to commence further exploration. The first theory is the substance-induced model, which implicates the SUD as the primary disorder and the anxiety disorder as secondary, where anxiety symptoms arise as a result of substance use [21]. Support for this model is derived from studies showing that SUDs increase the risk for developing anxiety disorders [12,22], the anxiogenic effects of intoxication and withdrawal on individuals [23], enduring neurobiological deregulations that occur as a result of chronic substance use [24,25], and the negative psychosocial impact of SUDs [23]. The second theory explaining the anxiety-SUD comorbidity is the self-medication model, which claims that the anxiety disorder is primary, and substance use occurs to cope with anxiety symptoms [21]. This model has been supported by studies showing that anxiety disorders typically precede SUD onset [10,26–29] in addition to studies that report the motivation for using substances among patients with anxiety disorders, which is to cope with anxiety symptoms [30–35]. The third theory delineating the co-occurrence between anxiety and SUDs is the common vulnerability model, which states that both disorders occur together because they share a common cause [21]. One potential third variable is genetics, and there is support for a genetic role in this comorbidity. Family studies have discovered higher rates of anxiety disorders among relatives of patients with AUD, and vice versa, which suggests that these two disorders may share common genetic factors [36]. A twin study by Tambs and colleagues found that common genes explain the correlation between anxiety disorders and alcohol consumption [37]. Therefore, future studies may prove to be successful in identifying these shared genes. Another common vulnerability between anxiety and SUDs are personality traits. Personality traits that have been found to be present among individuals with comorbid anxiety and AUDs compared to individuals with anxiety alone are lower cooperativeness and conscientiousness, and higher neuroticism and openness to experience [27,38]. Of particular interest is the personality dimension of impulsivity. The trait of hyperactivity-impulsivity has a robust impact on smoking and drinking behaviours, but in one study, this relationship was found to be mediated by anxiety symptoms, and greater anxiety symptoms were associated with an increased risk of smoking and drinking behaviours [39]. This suggests that impulsivity is related to both anxiety symptoms and the propensity to use substances, which implicates it as a factor potentially explaining the linkage between anxiety and SUDs.

While elevated impulsivity predisposes substance abuse behaviour across psychiatric diagnoses, it may interact with pathological anxiety symptoms in a particularly insidious way. Although the anxiety disorders are heterogeneous conditions, the hallmark and unifying component of all anxiety disorders is the existence of pathological anxiety symptomatology (e.g. subjective anxious thoughts, physiological sensations, avoidance behaviours) and distress resulting from these symptoms [3,40]. Therefore, rather than considering each of the multifaceted anxiety diagnoses in a categorical manner, this review will focus on the dimensional excessive anxiety symptoms existing across these disorders, and how such symptoms interact with impulsivity. Specifically, we hypothesize that patients with anxiety disorders that also have underlying elevations in impulsive traits are predisposed to engage in impulsive behaviours, like substance use, in response to anxiety symptoms, which ultimately exacerbates anxiety due to consequences of substance abuse and leads to continued substance abuse to mitigate worsened anxiety symptoms. It is thus suggested that elevated trait impulsivity enables the anxiety disorder and SUD to co-occur by initiating substance use as a coping strategy consistent with the common vulnerability model, and subsequently leads to habitual self-medication of anxiety symptoms with substances and substance-induced anxiety symptoms, which perpetuate the reciprocal relationship of the disorders. Given the complexity of comorbid presentations across individuals, there is no single model that can account for all manifestations of co-occurring anxiety and SUDs. However, the evidence supporting the hypothesis that trait impulsivity may play an important role in the presentation of substance abuse among anxiety disorder patients warrants further investigation. This may uncover genetic markers related to etiological mechanisms that could be targeted for treatment development and more precise treatment selection for anxiety disorder subgroups. Other disorders, such as borderline personality disorder (BPD), also have a complex interplay of anxiety symptoms and impulsive traits that may been initiating the frequent comorbid presentation of substance abuse in patients [41]. While the hypothesis presented above may be relevant for these disorders as well, this is the subject of a larger discussion, and this review will remain focused on the interplay of anxiety symptoms and impulsivity within anxiety disorders.

3. Impulsivity

Impulsivity is defined as the tendency to engage in swift behaviours without adequate forethought of potential consequences [42,43]. This construct refers to a predisposition, reflecting a pattern of behaviours

rather than a single action at a particular time [42]. Impulsivity can be measured through behavioural tasks that model impulsive action and impulsive choice, and self-report methods that model trait impulsivity. One behavioural measure that probes impulsive action is the Stop-Signal Task, where participants must make rapid responses to a particular cue, and their success at inhibiting their rapid response when presented with a "stop" signal is determined [44]. A behavioural assessment that examines impulsive choice is the delay-discounting task, which measures the preference for smaller, immediate rewards over larger, delayed rewards [44]. Trait impulsivity is modeled via self-report questionnaires such as the Barratt Impulsiveness Scale [45] and the I-7 Impulsiveness Questionnaire [46]. Another empirically validated framework used to model impulsivity is the UPPS-P Impulsive Behavior Scale, which measures five impulsivity-related components: sensation seeking, lack of planning, lack of perseverance, negative urgency, and positive urgency [47–49]. There is no consensus on the most optimal measure to model impulsivity. However, the UPPS-P model most effectively and comprehensively captures the multifaceted nature of impulsivity by dividing this complex construct into five related empirical dimensions [50]. Furthermore, given that prior measures of impulsivity were used to create the UPPS-P model, it appears to be a framework that is particularly well suited for studies of the impulsivity construct [48,51].

Although impulsivity is a personality trait that can be recognized in healthy individuals, heightened impulsivity is more commonly seen among individuals with particular psychiatric disorders [42,52]. Impulsivity-related diagnostic criteria are present in SUD, behavioural addictions, BPD, antisocial personality disorder, mania, attention-deficit/hyperactivity disorder (ADHD), bulimia nervosa, the paraphilias, and across the impulse-control disorders [48]. Of particular relevance to this review, impulsivity is a risk factor for, and a consequence of, substance use [53]. Impulsivity is elevated among substance abusers compared to healthy individuals, and those dependent on multiple substances have higher impulsivity than those dependent on only one substance [42]. Impulsivity has been suggested to play a role in each step of the progression from casual substance use to dependence, including the initiation of substance use, the quantity and frequency of use, the rapid progression to habitual substance use, the failure to reduce substance use once it becomes a problem, and the likelihood of relapsing [43,51,53–56]. Similarly, stress impacts each stage of the addiction cycle through its creation of an allostatic state that dysregulates the function of the hypothalamic-pituitary-adrenal axis, leading to changes in neurocircuitry that can initiate, or worsen, an addiction [57]. Given this common influence of the seemingly contrasting elements of stress and impulsivity on addictions, their interaction may accelerate the development of a SUD, especially among those that are prone to feeling stress or anxiety.

4. The addition of impulsivity in anxiety disorders and subsequent risk for comorbid SUD

Traditionally, anxiety and impulsivity have been considered to have an inverse relationship, with anxiety-related traits being thought to be protective against impulsive behaviour [58,59]. The high degree of comorbidity between anxiety and SUDs thus appears to be counter-intuitive, given that anxiety disorders are typically associated with inhibition and a lack of novelty seeking, while substance abuse is associated with disinhibition and risk taking [60,61]. Much of the literature investigating the anxiety-SUD comorbidity focuses on the self-medication theory, and while this theory is useful to explain why some anxiety disorder patients use substances to cope with anxiety symptoms, which can lead to a SUD, it does not account for why all anxiety disorder patients do not use substances to cope. It is therefore conceivable that there is a unique subgroup of patients with anxiety disorders that are at an elevated risk for a concurrent SUD as a consequence of carrying an additional attribute that is related to a predisposition for substance use, particularly for coping with anxiety symptoms. Impulsivity is one such attribute, and it is a well-established personality trait related to SUDs, with higher trait impulsivity being associated with an increased tendency to engage in illicit substance use and binge drinking [62–64]. In fact, several studies have begun to address impulsivity as a dimensional characteristic that is heightened among a subset of individuals with anxiety disorders, effectively predisposing this subset of patients to engage in behaviours that can lead to a SUD. When comparing individuals with anxiety disorders to healthy controls, Del Carlo et al. found that the anxiety disorder patients were generally more impulsive as determined by psychometric and neurocognitive measures [58]. Despite this study's results, the prototypical anxiety disorder patient is non-impulsive, which introduces the possibility that there is a unique atypical group of patients with anxiety disorders that are impulsive accounting for this finding. Indeed, the presence of an impulsive subtype of anxiety disorder patients was first established in a group of social anxiety disorder (SAD) patients [65]. Specifically, in a sample of 60 adults with clinical SAD, two distinct groups were discovered based on their differing self-reported reactions to interpersonal events. One group demonstrated behaviours that are typically associated with anxiety, being avoidant and submissive during social situations, while the second group endorsed dominant and hostile behaviours. This initial finding thus suggests that there are qualitatively distinct problematic responses to social events among SAD individuals, with one group being unified by impulsive and approach-like responses to social events rather than inhibited ones. This finding in clinical SAD patients was replicated and extended in a subsequent study by Kashdan and Hofmann, who similarly discovered two separate groups of SAD patients based on the temperament trait of novelty seeking, which is linked to impulsivity [66]. Fifty-nine percent of their sample showed the traditional low levels of novelty seeking when compared to healthy controls, while 41% showed significantly higher novelty seeking. Lower and higher levels of impulsivity and exploratory excitability were associated with the low and high novelty seeking groups, respectively. The authors also found that the clinician-rated severity of comorbid SUDs was greater in the high novelty seeking group. These results have been validated in a larger sample by Kashdan and colleagues, who investigated impulsive behaviours among individuals with a current (n = 679) or lifetime (n = 1143) diagnosis of SAD [67]. Seventy-nine percent of their sample showed a prototypical pattern of risk aversion and behavioural inhibition, while 21% showed an atypical pattern of risk-prone and impulsive behaviours including elevated anger, aggression, sexual impulsivity, and substance use problems. This atypical group also displayed increased functional impairment, lower education and income, and more psychiatric comorbidities. Mörtberg et al. also identified these two subgroups in 84 SAD adults, finding that 24% of patients displayed anxious-impulsive traits, and additionally showed that this atypical group had low self-directedness and high levels of depressive symptoms [68]. This anxious-impulsive personality has also been shown to be elevated in stimulant-dependent individuals and their non-affected siblings, thus supporting this trait as a risk factor for drug abuse [69]. Another study delved into the two subgroups of anxious individuals further and discovered that the atypical impulsive subgroup of SAD (39%) was characterized by high harm avoidance and high novelty seeking, while the prototypical and more prevalent inhibited subgroup of SAD patients (61%) had high harm avoidance and low novelty seeking [70]. The atypical group reported more impulsive behaviours including substance use. This study thus provides evidence for a connection between the inhibited and impulsive subgroups via trait harm avoidance, yet a separation via novelty seeking. In each of the above studies identifying different SAD subgroups based on impulsive-related constructs, the subgroups did not differ in the severity or impairment from anxiety symptoms, which suggests that these novel subgroups reflect qualitatively different maladaptive coping responses to anxiety symptoms, leading to different behavioural implications. Although social anxiety has been the focus of explorations into the

atypical anxiety-impulsivity relationship, elevated traits related to impulsivity have also been identified in individuals with panic disorder and generalized anxiety disorder, and such elevations in these traits are associated with increased clinical severity [71,72]. Therefore, several studies have supported the existence of an anxious-impulsive subgroup among clinical anxiety disorder patients, with this group showing an increased risk of impulsive behaviours including substance abuse, in addition to showing elevated negative outcomes. Given the existence of an atypical impulsive anxiety disorder subgroup, the underlying interaction between anxiety symptoms and impulsivity should be investigated to determine how it leads to an increased risk of developing a SUD.

Studying categorical diagnoses established by the DSM limits the exploration to individuals that show high levels of symptomatology, based on arbitrary cut-offs [73]. As a result, this classification approach does not adequately represent the dimensional nature of problematic mental manifestations. Therefore, evidence of the existence of an anxious-impulsive subgroup must be replicated in those that show anxious tendencies in the general population to determine whether this subgroup also has an increased risk of substance abuse [73]. If there is truth to our hypothesis that impulsivity is interacting with anxiety symptoms within the anxiety disorders to increase the propensity to use substances as a coping mechanism, it would be expected that elevated trait impulsivity would similarly increase the likelihood of substance abuse among non-clinical populations that have elevated anxiety symptoms. In fact, grouping anxious individuals based on impulsivity levels has also been conducted in non-clinical samples. Among 772 young adults, 8% and 10% displayed anxious-impulsive and anxious-inhibited patterns, respectively, and these groups showed similar increased depressive symptoms and decreased life satisfaction compared to those only high in impulsivity or those low in both anxiety and impulsivity [73]. Further, Nicholls et al. tested whether an approach-motivated subtype of socially anxious individuals could explain the co-occurrence of social anxiety and substance abuse in 351 participants [61]. They identified four subgroups in their sample: a subclinical group, a subclinical SAD/risky alcohol use group, an avoidance-motivated social anxiety group, and an approach-motivated social anxiety group. The avoidance-motivated social anxiety group showed the expected levels of inhibition and risk avoidance, while the approach-motivated social anxiety group showed increased rash impulsiveness, risk-taking, reward sensitivity, and substance abuse. The subclinical SAD/risky alcohol use group displayed elevated substance abuse compared to the subclinical and avoidance-motivated social anxiety groups, but the approach-motivated social anxiety group showed the most substance abuse compared to the other three groups. In agreement with the studies in adult populations, non-clinical adolescent samples have also been examined to address the existence of the atypical anxious-impulsive subtype. In a three-year study of 714 adolescents, 6% of the sample was both socially anxious and impulsive, and this subgroup of adolescents showed increased intoxication frequency and delinquency compared to other adolescents at each follow-up [74]. This socially anxious-impulsive subtype has also been found in children, where 20% of children scoring high on social anxiety symptomatology also score high on impulsive behaviour, while 80% of the socially anxious children scored low on impulsivity [75]. Hence, ample evidence supports the presence of an anxious-impulsive subgroup of individuals with high levels of both anxiety and impulsivity across several age groups in the general population, and further shows that this subgroup is at an increased risk of substance abuse.

The identification of subtypes in both clinical and non-clinical anxious individuals upholds the idea that anxiety is not a homogenous dimension, and that the presence of additional elevated impulsivity among those with clinically relevant anxiety symptoms may be accounting for the significant subset of anxiety disorder patients with a comorbid SUD. Given the identification of this subtype, there has been a great degree of interest among researchers in understanding the cognitive differences between individuals who are anxious versus both anxious and impulsive. Although impulsivity is a trait considered to be at odds with the anxiety-associated trait of inhibition, perhaps impulsive behaviours serve the same underlying function as inhibited ones among anxiety disorder patients. Specifically, with both types of behaviours allowing the anxious individual to escape from their unpleasant thoughts and emotions related to anxiety [73]. However, despite the similar ultimate purpose that these inhibited and impulsive tendencies may have, there are contrasting underlying cognitions between the subgroups that lead to the different behaviours recognized, such as a group more versus less likely to abuse substances to cope with symptoms. In support of this cognitive differentiation, Kashdan and colleagues attempted to separate 280 socially anxious individuals based on their appraisals regarding the potential threats versus reward opportunities associated with engaging in several risky behaviours, including substance use [76]. Among their social anxiety sample, they were able to delineate two subgroups: an avoidance-oriented group characterized by the highest threat appraisals and a lack of recognition for rewards associated with risky behaviours including substance use, and an approach-oriented group characterized by high curiosity and recognition for rewards for engaging in such risky behaviours. An example of an appraisal endorsed by the approach-oriented subgroup was that involvement in risky behaviours carries the potential reward of increased social status. Over the three-month period in which these participants were studied, the approach-oriented group engaged in more social activity and risk-taking behaviours than the avoidance-oriented group, but these behaviours coalesced with more self-judgements during these activities, fewer social benefits, and increased psychological conflict over the recognition of potential threats and rewards for their risky behaviours. Another study investigating the different appraisals among socially anxious individuals found that the relationship between social anxiety and risk-taking was mediated by the expectancy of positive outcomes, where socially anxious participants expecting desirable outcomes had increased risk-taking intentions, and those expecting worse outcomes had fewer risk-taking intentions [77]. These studies overall suggest that various cognitions related to impulsivity can effectively differentiate the anxious-impulsive and anxious-inhibited subgroups, and this distinction implicates different resulting behaviours and outcomes.

Although many of the previously mentioned studies identify the different subgroups by measuring general trait impulsivity with different self-report scales, impulsivity is not a uniform construct. Consideration of the sub-domains that comprise impulsivity in the UPPS-P model can provide a more targeted explanation to describe how impulsivity may contribute to the anxiety-SUD comorbidity. Each of the five components of trait impulsivity as defined by the UPPS-P model have positive associations with SUD-related symptoms, but the associations with anxiety symptoms are not as clear [78–80]. Negative urgency (NU), defined as the tendency to engage in rash behaviours when feeling distressed, is the impulsivity component most consistently associated with anxiety symptoms [78,81–86]. Anxiety symptoms have also been associated with positive urgency (PU), lack of planning, and lack of perseverance [81–85]. However, these associations have not been replicated in other studies [78,83,85]. Sensation seeking is negatively correlated with anxiety symptoms [81,82]. The ability of these impulsivity sub-domains to moderate the relationship between anxiety symptoms and substance abuse behaviour has been assessed by Simons et al., who found that the association between anxiety symptoms and intoxication frequency was only significant among individuals with high NU or low PU, with NU moderating and strengthening the anxiety-intoxication relationship [83]. A similar moderation effect of NU has been found for anxiety and physiological alcohol dependence symptoms [87]. NU has also been shown to mediate the associations between anxiety symptoms and alcohol and cannabis use problems, as well as between anxiety sensitivity and alcohol- and cannabis-related problems [88–90]. Therefore, the evidence suggests that within the impulsivity

construct, it is elevated NU, when combined with pathological anxiety, that predisposes anxiety disorder patients to engage in rash behaviours to immediately terminate distress from anxiety symptoms. Due to the rash nature of this coping-like mechanism, resulting behaviours would likely have impulsive and maladaptive qualities such as substance use, which can lead to a SUD through continued negative reinforcement, and ultimately initiate mutual maintenance of both the anxiety and SUD.

5. Impulsivity as an endophenotype to identify SUD risk among anxiety disorder patients

The existence of anxiety disorder subtypes based on patients who are impulsive versus inhibited is well supported in the literature, with the NU sub-domain of impulsivity perhaps playing a more specific role in the anxiety and substance use relationship. The next step is to delineate the biological mechanisms behind this atypical anxious-impulsive subgroup to provide etiological insight on the comorbidity between anxiety and SUDs. Towards this goal, viewing trait impulsivity, or more specifically, NU, as an endophenotype that is responsible for linking anxiety disorders and SUDs may be fruitful for uncovering genes that predict which anxiety disorder patients will subsequently develop a concurrent SUD. The endophenotype approach has been increasingly used to clarify the genetics of psychiatric disorders due to the polygenic nature and heterogeneity of such diagnoses, where two individuals may have the same diagnosis, yet present with different and non-overlapping symptoms [91]. An endophenotype is a measurable and genetically-modulated characteristic that mediates the connection between genes and disorders, whereby genetic variation causes the endophenotypic variation, which then alters the risk for the disorder in question [91,92]. This approach thus serves to deconstruct complex psychiatric disorders into component parts that may be closer to genetic variation, which carries the potential to further explore the underlying liability for the disorder. For an endophenotype to be successfully established, it must show association with the disorder in question, expression as a state-independent trait, alterations in non-affected family members relative to the general population, and heritability [92,93]. As presented earlier in this review, elevated trait impulsivity and NU have been evidenced in both anxiety disorders and SUDs, and appear to influence the relationship between anxiety symptoms and substance use, where individuals with anxiety disorders that have increased impulsivity-related constructs have a higher likelihood of engaging in substance abuse than the anxiety disorder patients with low impulsivity. The ability of NU to fulfill the remaining endophenotype qualifications have not been explored. However, general trait impulsivity has been investigated in more depth, fulfilling the other endophenotype qualifications. Altered impulsivity has been shown to be stable and exist even when a disorder is not yet manifested, thus implicating trait impulsivity as a state-independent factor. Specifically, impulsivity as indexed by self-report and the delayed-discounting task has been shown to be stable over long periods of time in both adolescents and adults [91]. Elevated impulsivity at baseline has been able to predict which adolescents are more likely to develop heavy drinking behaviours two years later, which implies that alterations in this trait can be evidenced prior to disorder onset in addition to being stable over time [94]. As well, non-affected siblings show alterations in trait impulsivity, as shown by the study from Ersche et al. finding that relative to controls, self-reported impulsivity is significantly increased among siblings of stimulant abusers, with the stimulant abusers showing the highest levels of impulsivity [95]. Furthermore, impulsivity has been shown to be moderately heritable, which is similar to the disorders that impulsivity is often associated with, such as SUD [96]. Impulsivity measured via self-report is approximately 50% heritable, and response during the delayed-discounting task is 51% heritable [96,97]. Therefore, impulsivity is a trait that is disease-associated, stable, observed in non-affected siblings, and heritable, thus fulfilling the qualifications of an endophenotype that can aid gene discovery. Given the promise of impulsivity as an endophenotype, genes associated with variations in impulsivity levels may allow for the prediction of which individuals with anxiety disorders are at a higher risk of developing a comorbid SUD. Since NU is a component of impulsivity, it is expected that this sub-trait would show similar promise in endophenotype assessments.

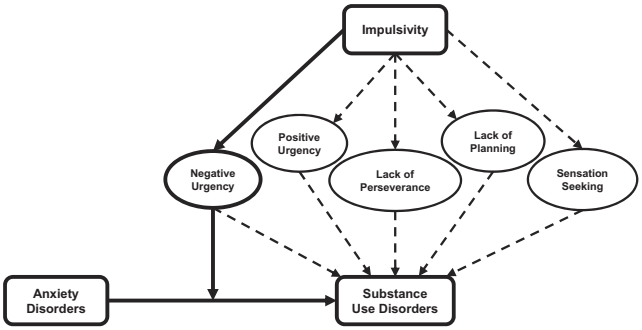

Fig. 1. Proposed pathway regarding how impulsivity elevates the risk of comorbid SUDs in patients with anxiety disorders.

The endophenotype approach can thus explain how impulsivity, and the sub-domain of NU, may be connecting SUDs to anxiety disorders, with the potential pathway illustrated with the solid bold arrows in Fig. 1. There is well-established literature implicating the endophenotype of impulsivity, along with each of the sub-domains, in SUD etiology. This review suggests that the impulsivity sub-domain of NU is responsible for the linkage between anxiety disorders and SUDs, with the anxiety disorder patients that have elevations in NU being at an increased risk of developing a SUD. Accordingly, the endophenotype approach would suggest that individuals with SUDs alone and individuals with comorbid anxiety and SUDs share similar impulsivity-related genetic variants. It thus follows that genetic variants related to impulsivity, or NU more precisely, may serve as biomarkers delineating risk for substance abuse among patients with anxiety disorders.

6. Genes associated with alterations in trait impulsivity

Given the promise of impulsivity as an endophenotype of the anxiety-SUD comorbidity, the next step is to identify genes related to impulsivity levels. Although genes related to NU would provide a more precise assessment of this comorbidity based on the figure discussed previously, there is currently a lack of genetic investigations on NU. The only genetic studies related to NU incorporate it as a mediator, with elevated NU being shown to mediate the associations between a single-nucleotide polymorphism (SNP) encoding for low functionality within the monoamine oxidase A (*MAOA*) gene and heightened aggression in one study, and the Taq1A A1 allele of the dopamine D2 receptor (*DRD2*) gene and smoking initiation in another study [98,99]. Trait impulsivity has received much more attention in genetic research. A recent genome-wide association study (GWAS) on 983 healthy young adults did not find any genome-wide hits associated with trait impulsivity scores [100]. However, upon testing 14 genetic variants that have been previously related to trait impulsivity, a significant association was found between impulsivity score and two SNPs in the serotonin 2A receptor (*HTR2A*) gene. Many other genetic studies on impulsivity have also found associations with variants related to serotonin neurotransmission. Variations in tryptophan hydroxylase 2 (*TPH2*), serotonin 1A receptor (*HTR1A*), serotonin 1B receptor (*HTR1B*), and the 5-HTTLPR polymorphism of the serotonin transporter (*SLC6A4*) have been associated with alterations in responses to behavioural and self-reported measures of impulsivity [96,101,102]. There is another polymorphism of *SLC6A4* located in intron 2 that has a 17-base pair variable number of tandem repeats (VNTR) thought to regulate transcriptional activity [70]. This polymorphism is called STin2, and

contains the alleles STin2.10 and STin2.12 that correspond to 10 or 12 repeats, respectively [70]. Interestingly, in the only published study investigating the genetic differences between inhibited versus impulsive SAD subgroups to date, this polymorphism was able to predict the SAD patients that were in each subgroup [70]. Specifically, the prototypical inhibited group had a higher proportion of individuals carrying the 10/10 or 10/12 genotypes, while the atypical impulsive group had a higher proportion of individuals carrying the 12/12 genotype.

Genetic variation related to dopamine has also been associated with variation in impulsivity levels. The dopamine transporter (*DAT1*) gene has been shown to predict trait impulsivity levels, and is involved in the risk for ADHD, a disorder characterized by elevated impulsivity [96,103]. Trait impulsivity has also been associated with polymorphisms in the dopamine D4 receptor (*DRD4*) and D2 receptor (*DRD2*) [101]. Among anxious-depressive alcohol dependent individuals, the presence of elevated novelty seeking was only seen in those with both the Taq1A A1 allele of *DRD2* and the S/S polymorphism of 5-HTTLPR [104]. The *DRD2* gene was also found to be uniquely associated with anxious-depressive alcohol dependent individuals, but not in those with only alcohol dependence or only anxiety and depression [105]. However, the effect of *DRD2* was under the control of the alcohol dehydrogenase (*ALDH2*) and aldehyde dehydrogenase (*ADH1B*) genes.

The neuropeptide S (NPS) system is also of interest as it has been implicated in each of the three phenotypes addressed in this review. Specifically, a functional SNP within the neuropeptide S receptor type 1 (*NPSR1*) gene has been associated with impulsivity [106] as well as panic disorder and anxiety symptom severity [107–109]. Although the NPS system has not been investigated in genetic studies of SUDs, preclinical evidence suggests that NPS reduces alcohol consumption through its anxiolytic properties [110]. The NPS system has also been shown to be involved in relapse and withdrawal, states often involving high anxiety [111,112].

Other genes that have been associated with impulsivity-related traits include catechol-O-methyltransferase (*COMT*), brain-derived neurotrophic factor (*BDNF*), μ-opioid receptor 1 (*OPRM1*), gamma-aminobutyric acid type A receptor alpha-2 subunit (*GABRA2*), cholinergic muscarinic receptor 2 (*CHRM2*), beclin1 autophagy regulator (*AMBRA1*), Fok I vitamin D receptor (*VDR*), neurexin-3 (*NRXN3*), and synaptosomal nerve-associated protein 25 (*SNAP-25*) [113–121]. Although these candidate genes require replication in larger samples, they are interesting targets that may modulate trait impulsivity levels. While some of the above genes have been investigated among patients with anxiety disorders [122–130], no studies to date have used variation in these genes to determine whether they can differentiate individuals with an anxiety disorder and SUD comorbidity from individuals with an anxiety disorder alone. Therefore, genetic analyses of these candidate markers may provide insight regarding SUD risk among patients with anxiety disorders.

7. Conclusion

Overall, this review has supported the notion that elevated impulsivity among a subset of patients with anxiety disorders carries the potential to explain the existence of the clinically relevant comorbidity between anxiety disorders and SUDs. The presence of an additional SUD among those with an anxiety disorder is associated with a decreased likelihood of achieving remission for the anxiety disorder, and vice versa. Outcome studies thus highlight the burdensome impact and treatment complications inherent in the concurrence of anxiety and SUD. This comorbidity is particularly insidious, as the anxiety disorder and SUD will interact in a synergistic manner to maintain each other. Understanding the mechanisms by which this detrimental interaction can occur, as discussed in this review, can aid treatment decisions tailored to this anxiety disorder patient subgroup, whether they be pharmacological or non-pharmacological such as cognitive behavioural therapy, mindfulness, or brain stimulation methods [3,131]. Although comorbidity is highly complex and there is no single model that can explain all forms of concurrent anxiety and SUDs, this review proposes an etiological conceptualization of this comorbidity that may provide promising pathways towards the establishment of personalized treatments for this patient population. The common vulnerability model introduces the possibility that elevated trait impulsivity is similarly predisposing individuals with and without anxiety disorders to engage in risky behaviours, such as substance use, which can lead to a SUD. Intriguingly, an atypical subset of anxiety disorder patients has been identified that shows elevated impulsivity, which is in contrast to the typically observed inhibited anxiety disorder patient. This atypical group displays increased substance abuse, thus implicating these impulsive anxiety disorder patients to be at a higher risk of developing a comorbid SUD as a result of their predisposition to risky behaviour. NU appears to be the sub-domain within impulsivity that is most relevant to this comorbidity, as it promotes the linkage between pathological anxiety symptoms and substance use, seemingly through the drive to use substances to cope with anxiety symptoms. Given this review supporting the use of impulsivity and NU as endophenotypes to assess risk of SUD among anxiety disorder patients, future studies should investigate genes that modulate impulsivity levels, and ideally a GWAS on NU should be performed. The impulsivity-modulating gene set may identify biomarkers predicting the anxiety disorder patients that are at an elevated risk of developing a comorbid SUD. The GWAS data may provide a set of novel risk genes for additional evaluation/validation in future studies. This etiological exploration can thus begin the creation of more precise treatment selection for this impulsive anxiety disorder patient subgroup. Such efforts may result in a reduction in the individual and societal burden of the anxiety and SUD comorbidity.

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Conflict of interest

JLK is a member of the Scientific Advisory Board of Myriad Neuroscience (unpaid), and holds several patents relating to pharmacogenetic tests for psychiatric medications. The remaining authors have no conflicts of interest to disclose.

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