REVIEW PAPER

The Neurobiopsychology of Suicidal Behaviors among Persons with Substance Dependence: The Role of Impulsivity

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Abstract

Suicidal behaviors pose a major health challenge to persons with substance dependence (PSD). This article explores impulsivity as a potential determinant of suicide risk among PSD. By examining the neuropsychological and neurobiological factors involved in suicide and substance dependence/abuse, several theories were considered in relation to impulsivity. Laboratory measurements of neurocognitive capabilities combined with neuroimaging technologies, genetic and neurobiological approaches were used to provide insight regarding the potential roles of impulsivity in suicidal behavior among PSD. Our observations, as well as limitations and future research directions are discussed in this paper.

Keywords: Impulsivity, Suicidal Behaviors, Substance Dependence, Substance Abuse, Suicide, Impulse Control

Introduction

The bi-directional relationships between substance dependence and severity of suicidal behaviors are well established. Previous studies have shown that suicidal behavior rates have increased among those suffering from substance dependence1,2, and substance dependence has been found to increase the risk of future suicidal behaviors3-5. Impulsivity is a psychological construct often associated with suicidal behaviors and substance dependence, both independently and together1,6-12. Substance dependence particularly involving alcohol and other drugs is highly associated with impaired impulse control13-15.

Although defined in many ways, researchers agree regarding the main components of impulsive behavior: (a) poorly conceived action/reaction, (b) premature expression, (c) risky or inappropriate acts, and (d) no consideration of negative consequences16-17. The UPPS model18 uses these components to measure impulsivity based on the Five Factor Model of personality. Based on the model, the UPPS Impulsivity Scale has been developed to explore four facets of impulsivity: urgency, lack of premeditation, lack of perseverance, and sensation seeking. In a recent study involving suicidal drug and alcohol abuse inpatients, researchers observed the effects of a lack of premeditation and negative urgency and found a robust interaction between these
facets. They concluded that any model attempting to understand and predict suicidal behavior should consider these two impulsivity-related domains, both alone and together. Similar findings have been reported for non-suicidal PSD with high scores for dimensions of urgency, lack of perseverence, and lack of premeditation, but not for sensation seeking. These findings indicate that impulsivity plays a more significant role in substance dependence compared to suicidality.

One possible explanation for this is that suicidal acts can be impulsive or non-impulsive. The mechanisms involved in both are also likely to differ. A non-impulsive suicidal act is characterized by hopelessness, internalized anger, and depression. Supported by previous studies, the self-medication model suggests that non-impulsive attempters and completers abuse substance to medicate their depression up to the point where they fail to assess the consequences of overdose. The model however, lacks empirical support.

The impulsive type is more related to aggression, impulse control disorder and conduct disorder. The stress-diathesis model of suicidal behavior explains the dynamics of substance dependence, suicidality and impulsivity. In this model, life events with subjective states and traits interact. Specifically, PSD acts upon reasons for living/suicidal ideation, suicidal planning/intent, and impulsivity, leading to suicidal acts. The model agrees with state-dependent theories, in which impulsivity is seen as the product of cognitive distortion caused or at least influenced by substance use/dependence, resulting in a higher risk of suicide.

Adolescents and adults share similar risk factors associated with suicide, most of which are closely related to emotional burden. For example, researches found that substance dependence is associated with stress and co-occurring psychopathology, leading to a decision of suicide attempt – as a means of coping with an emotional burden. This explanation is supported by many studies which suggest that substance use can distort cognition by exacerbating depressive symptoms and aggressive/impulsive behaviors, particularly among adolescents. In adults, it has been proposed that suicidal behaviors are acts of reactive aggression ‘executed in the midst of distresses’.

Deficits in impulse control may explain why the prevalence of suicide (completion and attempt) in psychiatric patients, either alone or with co-morbid disorders, is significantly higher compared to in the normal population, particularly in those with substance dependence disorder, who are antisocial and with borderline personality disorder. Support for this claim is extensive. Moreover, one study found that polysubstance dependence is significantly associated with attempted suicide, impulsivity and aggression compared to monosubstance dependence. However, the opposite has also been reported; for example, a study compared cocaine and opiate patients who had attempted suicide and who had never attempted suicide using the self-reporting Barratt Impulsivity Scale (BIS) found no significant difference between groups. The research, however, suggested ceiling effects in which high impulsivity associated with samples may mitigate the utility of impulsivity in suicidal behavior assessment for such patients. Another study found that aggressive tendencies are a better predictor of suicidal behavior rather than impulsivity. This speculation may be valid but is difficult to prove since most studies in this area did not
treat impulse control and aggression as two separate entities.

Thus, this paper reviews the role of impulsivity to increase the understanding regarding the etiopathogenesis of suicidality in PSD. It is very important to understand the role of impulsivity as a predictor of suicidal acts in PSD. This will enable more effective intervention in addiction and substance dependence programs as well as suicidal risk assessment for those with impulse control problems as a prevention measure. Evaluating the neurobiological and psychological mechanisms of suicidal behaviors in PSD is crucial in this process, but not without difficulties. For instance, it is now known that both suicidal behaviors and substance dependence are observed within the same families. Secondly, compared to other biological markers for suicidal acts in substance dependence, dysregulation of the serotonin neurotransmitter system has been the most often-cited mechanism involved. However, how this system mediates impulsivity remains unclear. It is also important to point out here that the scope of substance dependence in this research is focused on substance dependence related to alcohol since only a few number of studies examining the relationship between drug dependence and suicide have been conducted. Additionally, disputes regarding traits and states perspectives between impulsivity and suicidal behaviors particularly among PSD remain unresolved. The scope of suicidality research is rather limited to help solve such disputes because of its dependency on retrospective self-reporting of suicide attempts and family history. Although self-reports are psychometrically established, inexpensive and valid, they require some degree of insight and are insensitive to state-dependent fluctuations in impulsivity. The level of agreement between impulsivity rating scales and laboratory measurements of impulsivity may disagree since they measure different aspects of impulsivity. Self-reporting measures are generally thought to reflect trait-like aspects of impulsivity, whereas laboratory-based measures are viewed as sensitive to state-dependent aspects of this construct. Thus, to generalize one finding with another can be faulty.

Neuropsychological aspects of suicidality in substance dependence disorders

Cognitive behavioral and neuroimaging findings

PSD with a history of suicidal behavior score higher on tests measuring impulsive traits compared to those that have not previously attempted suicide. Unfortunately, cognitive behavioral studies exploring the relationship between impulsivity and suicidality among PSD are rather limited. In one study done by Wojnar and colleagues, a total of 154 inpatients with alcohol dependence were assessed using the Barratt Impulsiveness Scale (BIS), a 30-item valid self-reporting questionnaire that measures impulsiveness as a personality trait. The Impulsiveness Facet of the Personality Inventory-Revised (NEO-PI-R) was also administered to measure the inability to resist cravings and urges, and is not directly related to spontaneity, risk-taking, or rapid decision time. Additionally, a computerized evaluation of inhibitory control, known as the Stop Signal task (a two-choice reaction time task), was also administered to measure behavioral impulsivity. In this task, a stop-signal occurs occasionally to indicate a withheld response. The task essentially tests the ability to stop competing activating and inhibiting processes. According to the cognitive model, an interpretation is made based on
the time it took the subject to react. Longer stop-signal reaction times indicate a higher difficulty to inhibit a response - thus greater impulsivity. The task has high construct validity and the findings were highly correlated with other measures of impulsivity in substance dependence literature8.

The researchers found that 43% of the sample population had attempted suicide, and 62% were impulsive in nature. Multinomial logistic regression analyses showed that non-impulsive suicide attempters scored higher on BIS compared to patients without suicide attempts, and impulsive suicide attempters scored higher on the Stop Signal Reaction Time (SSRT). Factors distinguishing suicide attempters and non-attempters were generally consistent with other findings for individuals with alcohol dependence11, 12, 37; for example, patients with a history of suicide attempts were younger and had severe substance dependence, higher rates of sexual or physical abuse, suicidal family history, and higher levels of impulsivity. Interestingly, the sensitivity of BIS was not sufficient to detect differences between impulsive attempters and non-impulsive attempters, demonstrating the limitation of self-reporting measurements to detect certain aspects of impulsivity in relation to suicidal behavior.

The neural processes involved in response inhibition are relevant to the neuropathology of suicidal symptom in substance dependence. Li and colleagues conducted fMRI during a Stop-Signal Task38. Results showed that subjects with alcohol dependence had lower left dorsolateral prefrontal cortex (DLPFC) activity than controls. Subjects with alcohol dependence also showed lower activation of the right DLPFC during post-error slowing (PES, an index for post-error behavioral adjustment) than controls. Moreover, lower activity was observed, particularly in the putamen, insula, and amygdala during risk-taking decisions in the Stop Signal test. Indeed, these results provided evidence for altered changes in the brain’s neural activity, affecting impulse control capability in patients with alcohol dependence.

Neuroimaging studies on suicidal patients appear to support this notion. Findings of dysfunction in the prefrontal cortex among suicide attempters indicate lack of impulse control as a mediator or even a predictor for suicidal behavior39-41. Generally, brain areas that have been implicated most frequently in suicide risk are found to overlap with brain areas associated with substance dependence/abuse and thus share similarities in neurobiopsychological characteristics. This suggests that substance dependence and suicidality share or have overlapping mechanisms. Areas involved in substance dependence and suicidality can include frontal cortical areas, DLPFC, orbitofrontal cortex (OFC), ventromedial cortex (VMC), nucleus accumbens, amygdala, hippocampus, and many more. Due to lesions or dysfunction in these areas, impaired neurocognitive abilities have been presented by suicidal populations, independently or together with substance abuse. Executive functions found to be most affected include those closely related to impulse control. These may include decrements in language skills, problem solving, emotional regulation, behavioral inhibition, verbal and non-verbal retention, working memory, and visuospatial performance42, 43.
Substance dependence/abuse and suicide may be regulated by similar processes. A recent study involved SPECT imaging analysis to compare psychiatric inpatients who committed suicide between 10 days and 36 months after the scan with non-suicidal depressed subjects and healthy controls highlighted several findings. Lower regional cerebral blood flow throughout the cortex was observed in suicidal patients compared to in controls. Reduced perfusion was detected in the corpus callosum, cingulate, and anterodorsal cortex, with a very significant area of low activity in the nucleus accumbens extending to the VMC and left and right putamen. Compared to non-suicidal depressed subjects, they found hemisphere asymmetries with increased perfusion in the right insular cortex in suicidal inpatients. Additionally, a significant decrease in the medial PFC and ventral tegmental area (VTA) were observed. These findings identify impulse control impairment and limbic dysregulation in suicide, - two major characteristics consistently found in PSD.

Based on these established neurocognitive and neuroimaging findings, the roles of impulsivity in substance dependence that can lead to suicidal behavior have been postulated. Abnormalities in the frontal cortex, amygdala, hippocampus, nucleus accumbens, and PFC, particularly in the OFC indicate that suicidal patients and substance-dependent groups are likely to have cognitive deficits, including impaired decision-making, lack of problem-solving abilities, negative emotions like hopelessness, and lack of impulse control, – which all may increase the urge to attempt suicide.

In short, neuropsychological and imaging studies have identified neurocognitive deficits in relation to abnormalities in specific brain regions, primarily the PFC, among suicide attempters and PSDs, independently or together. Lack of impulse control or high impulsive behavior appears to play a mediator role or even predictor of suicidal behavior among PSD.

Limitations of neuropsychological and imaging studies

First, cross-sectional study designs like Wojnar’s infer problems related to causality since there is no indication of sequential events before, after, or during the onset of suicidal behavior. Prospective and longitudinal studies may be useful for identifying potential variables such as onset, age, and experience or exposure effects related to impulsivity in PSD that are suicidal.

Secondly, as discussed above, the level of agreement between impulsivity rating scales and laboratory tasks of impulsivity can be conflicted, as demonstrated by some of the findings. An additional concern is that some behavioral measurements of impulsivity have not been validated. Thus, the studies may have reliability issues, and interpretation of findings is questionable.

Third, samples used in some studies did not exclude existing co-morbid conditions that may confound cognitive and neuronal functions; for example, one study included late-onset depression inpatients, while the other recruited bipolar disorder patients.

Fourth, because suicidal behavior is a symptom and not a psychiatric disorder, the definition of the impulsive nature associated with suicidal behavior varies greatly. For example, one study defined impulsive attempts based on 30 min interval while another used 1-week intervals and a third study used a shorter interval of 5 min. This
may explain the higher rates of impulsive attempts in some samples.

Finally, few women are recruited in these studies. Most studies focus on male samples. In fact, a low number of women participate in rehabilitation. This may be due to psychosocial obligations as mothers or wives, which may discourage them from participating in clinical studies.

Neurobiological aspect of suicidality in substance dependence disorders

Biogenetic influences

Twin and family studies’ findings

Laboratory studies measuring individuals’ vulnerability to alcohol and other drugs enable clinicians to identify at-risk populations. Such findings reported that the sons of alcoholics represent 4 to 9 times higher risk of developing substance use disorders compared to control subjects. Neuropsychological assessments of these samples show a higher incidence of neurocognitive deficits, particularly in behavioral dysregulation, which is one aspect of impulse control capabilities. Brent and colleagues supported these neuropsychological findings when they found that impulsive aggression could be used to predict familial (parent-child) transmission of suicide attempts, particularly at an early age. Furthermore, a study of alcohol dependence among young people identified a very strong familial link between higher levels of impulsivity or aggression and suicide attempt.

Findings from twin and family studies have been consistent in highlighting substance dependence as a significant predictor of suicide behavior, independently and together, and that both substance dependence/abuse and suicidality are genetically inherited. A study examined mono- and dizygotic twins (MZ and DZ twins) found that suicidal ideation was influenced by additive genetic (36%) and non-shared environmental (64%) effects, while suicide attempt was affected by additive genetic (17%), shared environmental (19%) and non-shared environmental (64%) effects. The study concluded that even without psychiatric disorder and impulsivity influences, the genetic susceptibility specific to both suicidal ideation and suicide attempt in men is possible.

Utilization of twin studies as a tool for studying genetic and environmental interactions towards outcome behavior is highly beneficial. Therefore, more research of monozygotic twins discordant for early substance use and impulsive personality are warranted to explore phenotypic differences in suicidality among PSD.

Studies of candidate genes

Neurobiological studies have shown that suicidal behavior, substance dependence, and impulsivity (alone and together) are strongly linked with abnormalities in the serotonergic system. Additionally, serotonin (5-HT) dysfunction has been associated strongly with impulsive/aggressive behaviors which can lead to both substance use problems and suicidal acts. Individual variations among PSD on serotonin may be related to genetic polymorphisms in different enzymes and proteins. Several candidate genes have been identified in relation to serotonergic genes including the serotonin transporter gene (5-HTT), tryptophan hydroxylase (TPH) gene, and the 5-HT1B receptor gene. Recently, the gene for the catechol-O-methyltransferase (COMT) enzyme also has
been shown to be related to degradation of catecholamines.

5-HTT is encoded by a gene located on chromosome 17q12. A polymorphism in this gene (known as 5-HTTLPR) consists of two alleles, long (l) and short (s), has been studied in relation to suicidality. In a study, 103 suicide attempters were followed over a one-year period to measure behavioral impulsivity as a personality trait. The BIS scale was administered to assess lifetime impulsivity history. The results showed that having the short allele increased the risk of subsequent suicide attempts, while the homozygous group or the s/s genotype was more at risk. Furthermore, subjects scoring higher on impulsivity measurements carried the s/s genotype. Subsequent studies confirmed the findings of this study. However, studies examining genotype have generally shown mixed results, indicating the complex nature of the relationship between suicidality and genetic polymorphism of the serotonin transporter gene. Therefore, additional studies examining the links between 5-HTT and impulsivity in suicidal behavior, particularly among PSD, are necessary.

The TPH gene encodes an enzyme involved in serotonin synthesis, which has consistently been associated with substance dependence/abuse and suicidality, particularly the A779C polymorphism type. Furthermore, this gene has been linked to behaviorally impulsive groups and cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) concentration. 5-HIAA is a major metabolite of serotonin, and decreased levels of 5-HIAA are commonly observed in suicide attempters and completers. For example, Nielsen and colleagues found that the 779C allele is likely to be carried by suicidal impulsive offenders compared to non-suicidal offenders. Despite these findings, this research area is still in its infancy, and additional studies should be conducted to explore the mechanisms involved before hypotheses can be developed regarding the relationship between 5-HIAA and impulsivity in suicidal behavior, particularly among PSD.

A polymorphism in the 5-HT1B receptor gene has been labeled as 861C. This allele was observed in two independent populations of alcoholics with suicidal history. Support for this, however, has only been demonstrated through animal studies, in which mice lacking the receptor were responded to alcohol and showed increase impulsive/aggressive behavior. The association between the 5-HT1B receptor gene and substance dependence in humans have not been demonstrated.

Because of these limitations and the conflicting findings of previous studies, a review study suggested that impulsivity may not be directly related to serotonergic dysfunction in patients with substance-dependence. The author argued that serotonergic dysfunction can be indirectly caused by alcohol consumption rather than behavioral impulsiveness. Secondly, serotonergic dysfunction may provoke suicidal attempts due to mood variations rather than due to impulsiveness; and finally, the candidate genes may play nonspecific role in increasing suicide attempt risks, regardless of whether substance use disorder has been diagnosed. Nevertheless, it is very clear that serotonin dysregulation plays a role in impulsivity, suicidality, and substance dependency, both independently and together.

Genetic polymorphisms in the dopaminergic system, particularly in genes functioning in
the frontal and limbic structure of the brain, can influence impulsive behavior and decision-making\textsuperscript{66}. For example, recent studies identified the COMT gene as a potential contributor to impulsivity, which can lead to suicide, substance dependence, or both\textsuperscript{67-69}. Previous studies have also found that only certain alcoholic subphenotypes are associated with specific COMT variation, suggesting that genes affecting impulsive behavior in substance dependence only interact with other psychiatric disorders with overlapping psychopathology (44), which may include suicidal symptoms. However, few studies examining the COMT have been conducted and additional studies are needed to understand its influence on suicidal risk among PSD.

In summary, although some contrasting findings have been found, biogenetic research involving twin and family studies and studies of candidate genes implicate genes and their components in impaired impulse control, suicidality, and substance dependence. Additional research is warranted to overcome some of the limitations that will be discussed below.

**Limitations of biogenetic studies**

There are some limitations to previous studies. First, there is a lack of adequate control for psychiatric disorders in some studies. There is a clear distinction between genetic predictions of suicidal behavior and genetic influences mediated by psychiatric disorders (substance dependence disorder, bipolar disorders, mood disorders, etc.), leading to an increased risk of suicidality. However, some studies of twins did not make this distinction\textsuperscript{70}, leading to unnecessarily complex findings. This concern is backed up by a report stating that some clinical genetic studies have observed that associations between suicidal behaviors and substance dependence are confounded by genetic vulnerabilities and psychiatric co-morbidities affecting both problems and not independently as separate entities\textsuperscript{51}.

Furthermore, genetic influences observed in twin studies and similar environmental factors involved in impulsivity leading to suicidal behavior among PSD do not explain variations found, even in monozygotic twins. Recent studies have highlighted the epigenetic mechanisms in which changes in gene expression occur without any altering DNA sequences, while DNA methylation patterns are changed\textsuperscript{71}. In the brain, epigenetic changes have been associated with several biological and cognitive processes, including drug dependence, neurodegeneration, learning, and memory\textsuperscript{71}. The discovery of epigenetic regulation is still recent, and additional studies are needed to explain epigenetic mechanisms in substance dependence, suicide, and impulsive behavior.

Finally, most relevant neurobiological studies have examined the effects of alcohol dependence on suicidal behavior mediated by impulsivity. These studies highlighted the importance of future research for exploring the effects of other type of drugs such as cocaine and opiates, in suicide behavior and how impulsivity relates to these phenomena.

**Abnormalities in the serotonergic system**

It is now known that hypoactivity of the serotonergic system affects impulsivity levels and the severity of suicidal behavior among PSD\textsuperscript{50, 72}. 5-HIAA levels in cerebrospinal fluid and the cerebral cortex with low serotonergic function have been implicated in substance use/dependence, risk of suicidality, and high impulsivity\textsuperscript{73}. This has been well-supported through many
animal studies using alcohol. One study further examined impulsive alcoholic offenders and the association between 5-HIAA levels and TPH gene. The study found that 779C allele carriers are more likely to have lower 5-HIAA levels compared to non-carriers. Thus, this study provided dual support for the independent relationships between the TPH gene and 5-HIAA in cerebrospinal fluid. Later, another study found that the 779C allele is more likely to be carried by those who are suicidal compared to those who are non-suicidal.

Fenfluramine challenge was also used to detect serotonin levels, in which fenfluramine (a serotonin agonist) was administered to stimulate serotonin release and inhibit reuptake. Prolactin levels were then measured to examine the degree of serotonin stimulation. In a study, higher decreased prolactin response (and thus low serotonergic activity) was observed in suicide attempters compared to drug-free depressed inpatients and controls. Indeed, results supporting fenfluramine studies have been rather consistent, with only few contrasting findings. More importantly, the PET imaging study confirmed relative hypometabolism in impulsive attempters compared to non-impulsive attempters in the ventral, medial and lateral PFC as examined by fenfluramine challenge.

To date, post-mortem analyses of suicide victims have been limited and reveal inconsistent findings. Using radioligand tracers specific to serotonin transporters, serotonin-1A receptor (5-HT1A), or serotonin-2A receptor (5-HT2A), functional imaging studies enable investigation of the binding index of these tracers to transporters or receptors. For example, samples of brain tissue from suicide completers with alcohol dependence revealed decreased serotonin transporter binding in the hippocampus. Compared to non-alcoholics, 5-HT1A receptors binding was also reduced in alcoholics.

One of the most well known post-mortem studies in this area was conducted by Pandey and colleagues. The study reported higher expression of 5-HT2A receptors, protein, and mRNA in post-mortem brains of teenage suicide victims, specifically in the prefrontal cortex and hippocampus, – which are areas that have been associated with emotion, stress, and cognitive functions. However, increased levels of the receptor binding in the nucleus accumbens area was not observed, indicating that a specific mechanism for suicidal behavior exists independently from substance dependency. Nevertheless, this mechanism needs more exploration – and it is possible that impulsivity can be related to the results of these studies. However, because of the non-specific samples used (i.e. drug-free or non-user; co-morbidities, etc.), the findings must be viewed with caution when applied to the drug-dependent population.

Other possible neurobiological markers

Dysfunction of the monoamine neurotransmitter system has long been associated with substance dependence and suicidal behavior. Monoamine oxidase A and B (MAO-A and MAO-B) are known as warrior genes due to their strong link with behavioral aggression and impulsivity. Both enzymes are known to be related to alcohol dependence, but exactly how these coding genes affect suicidality remains unknown. One review concluded that MAO is unspecific and unstable as a biomarker for suicidal risk in PSD and that it may indirectly reflect serotonin metabolism due to its involvement in serotonin catabolism. Vinod and colleagues studied the endocannabinoid system to better
understand the relationship between substance dependence and suicidal behavior, alone and together. Their findings suggest that in the ventral striatum (a critical area for drug reward and impulsivity), alcohol dependence is associated with the downregulation of CB1 receptors, while suicide is linked to the receptors’ upregulation. The precise role of the system remains unknown; however, recent findings have suggested an abnormal interaction between the endocannabinoid system and other neurotransmitters system involved in substance dependence, such as the serotonergic, glutamatergic and dopaminergic systems. Additionally, several animal and human studies also found that dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is related to the endocannabinoid system, thus strengthening the support for its role in developing impulsivity, substance dependence, and suicidal behavior, independently or together.

Because the nature of suicide is quite complex, it would be useful to consider other novelty biomarkers related to impulsivity and explore indirect relationships they may have with suicide risk among PSD. One such marker that has been recently explored is ΔFosB. Winstanley schematized a framework regarding the role of ΔFosB in substance dependence. Induction of the FosB gene by repeated cocaine administration may alter neuronal activation, impulsivity and other cognitive performances within the orbitofrontal cortex (OFC). Specifically, repeated exposure of cocaine leads to adaptive processes affecting cortical activity to counteract the excitatory effects of cocaine. Acute cocaine administration leads to tolerance of cognitive dysfunction. During withdrawal, activated inhibitory processes lead to low activity of OFC, which also leads to a decline in cognitive performance and a lack of impulse control abilities. These can lead to impulse control disorders. Although not yet proven, this theoretical model is plausible for explaining impulsive suicidality, particularly if the mode is drug overdose.

To conclude, the effects of serotonergic dysfunction in relation to impulsivity have been explored for suicidal risk among PSD. The exact relationships between serotonin with MAO, endocannabinoid receptors, and ΔFosB are unclear. Mixed results in most studies indicate complex pathways of impulse control in both suicidality and substance dependence.

Some limitations of the neurobiological studies

First, most neurobiological studies examining suicidality focus on impulsive types of suicide and suicide attempts. Another method for understanding suicidal behavior among PSD is to explore the neurobiological factors for the non-impulsive suicide and suicide attempts. Both spectrums/dimensions of impulsivity should be examined to assess its role in suicide and substance dependence, independently or together.

Second, researches highlight the difficulties to control psychiatric co-morbidities associated with suicide and substance dependence due to their complex nature. It is impossible to make a causal link due to possible confounding effects.

Third, most studies focus on alcohol compared to other type of drugs. Impulsivity in suicidal behavior among PSD may be significantly more directly influenced by specific drug types.
Finally, although post-mortem analysis of suicide victims offers direct brain sampling of neurotransmitter transporters and receptors, there are reports of rapid alterations in neurotransmitter concentrations post-mortem\textsuperscript{42} which may influence findings. This limitation highlights the needs of other investigation methods to support the findings of post-mortem analysis.

**Implications & future directions**

Although the exact mechanisms related to impulsivity in suicidal behavior among alcohol and other drug-dependents are not fully understood, studies have provided several psychological and research implications that are fairly important for mental health professionals. Some implications for managing impulsive-related suicidal behavior among PSD include:

a) Training general practitioners and mental health nurses to ask specific questions regarding suicidal ideation to identify persons at risk. Professionals should incorporate questions that probe impulsivity behavior among PSD when carrying out suicide risk assessment. With this in place, it is hoped that individuals can benefit from specialized prevention and awareness programs.

b) PSD who are at-risk (e.g. PSD with bipolar disorders) or those with a history of suicide attempts and/or history of aggressive/impulsive behavior may require management therapies involving teaching steps on suicidal behavior crisis, provision of problem solving, communication and coping skills, and techniques for managing aggression and impulsive behavior. It is helpful to discuss patients’ perception regarding the connections between their substance dependence problem, impulsivity proneness, and prior suicide attempts with or without CBT in therapy sessions.

c) Novel treatment approaches for suicidal PSD should be focused on emotional regulation\textsuperscript{19}. One type of structured cognitive behavior therapy focused on emotional regulation for treating impulsivity associated with suicidality and substance dependence disorder is known as dialectical behavior therapy (DBT). The DBT manual includes teaching the patients problem-solving skills, emotional regulation strategies, interpersonal skills, and distress tolerance\textsuperscript{17}. The DBT efficacy for this population has yet to be examined; thus, the approach is only encouraged for PSD with multiple, complex problems rooted in emotional dyscontrol who have not responded to other evidence-based approaches\textsuperscript{93}.

d) It is possible that suicidal acts are linked to relapse (9). Extensive studies have support this notion. One study found that PSD involved in suicidality are more likely to have high levels of impulsivity and depression, which are both significant predictors of relapse\textsuperscript{94}. Neurobiopsychological studies have revealed significant impairment of impulse control, emotional regulation, and parts of executive functions in PSD, demonstrating the importance of clinicians conducting routine assessments of suicidality. When the suicidal behavior symptom is recognized, clinicians must be aware of the increased risk of relapse.
as well, and a treatment plan must be formulated accordingly. This includes motivating individuals to undergo relapse prevention using pharmacotherapy intervention, increase therapy-client contacts, and increase the availability of support systems (family & friends).

Questions such as the heterogeneity and potential for subgroups in populations of suicidal PSD, the possibility of changing relationship between substance use and suicidality’s factors over time (e.g. from adolescence to young adulthood), and differences in poly-substance and mono-substance dependence interactions on suicidal behaviors are all related to impulsivity and should be addressed. Future studies should include:

a) Additional neuroimaging studies which focus on the underlying neurobiological and neuropsychological processes leading to suicidal thoughts and acts in PSD by identifying specific brain regions and neural circuits/pathways involved. This method is promising, particularly for evaluating pharmacotherapy and psychotherapy effects over time, i.e. efficacy studies - giving better prediction, prevention, and treatment strategies.

b) Multimodal impulsivity assessments such as the UPPS scale and laboratory tasks are necessary to fully explain the roles of impulsivity in suicidal behavior and substance dependence since previous studies indicate that different measures are useful for measuring different aspects of impulsivity, as the states and traits theories have suggested. These instruments must be scientifically validated to ensure the quality of data and research in this area. Multimodal impulsivity assessments can advance the development of theories and models of impulsivity, suicide and substance dependence, independently or together.

c) Different research designs can provide an increased understanding of suicidal behavior in PSD. Cross-sectional study designs are limited since they assess impulsivity and suicidal risk at a specific time, providing a state-like perspective. Longitudinal designs are more advantageous because they provide extensive information on age, biological, social, and trait-like psychological variations that may influence such behaviors in normal and PSD populations.

d) Future research should explore the roles of impulsivity in the effects and withdrawal states of other drug interactions (e.g. cocaine, cannabis, and opiate) on suicidal behaviors among PSD, since there are currently very limited studies about them.

e) Future research should also investigate neurobiopsychological differences of the impulsive and non-impulsive nature of suicide and protective factors that can prevent high-risk PSDs from engaging in suicidal ideation and behavior. Few studies have examined impulsivity specific to suicidality in substance-dependent groups.
f) Most neurobiopsychological research involves lower numbers of women in their studies and focus primarily on male sample. Li and colleagues claimed that gender differences in cognitive control during the Stop Signal Task were observed in their previous study; however, their findings cannot be generalized to the substance-dependent population due to sample differences. Another study reported that impulsive suicide attempts were more likely to be carried out by women. Based on such findings, gender-specific research in this area should be conducted to understand the role of gender in suicide risk among PSD.

g) Examining past suicidal acts and impulsive behavior to understand the psychopathology of relapse in PSD are useful because of its potential to delegate eclectic-style interventions in suicide and relapses prevention programs.

h) The difficulties associated with suicide research should be addressed. These include the definition of impulsive nature of suicide. Additionally, it is quite difficult to identify PSD at risk due to lack of warning signs given prior to an impulsive suicide attempt, and thus these individuals may be missed. A standardized definition of impulsivity with proper guidelines of warning signs specific to this group should be considered.

i) It is unequivocal that treating substance dependence (a disorder spectrum) and suicidal behavior (a symptom) has been a substantial challenge for both researchers and practitioners, complicated even further by impulsive behavior (another symptom) commonly observed in these groups. Future research is necessary to measure the effectiveness of either single or combined treatment programs for these individuals.

Conclusion

The role of impulsivity in substance dependence has long been established in the literature. Impulsivity has also been significantly associated with suicidal behaviors in suicide studies. Thus, suicidal behaviors among PSD may be directly/indirectly influenced by impulsive personality. The neuropsychological and neurobiological studies discussed in this article reveal reasonable support for this claim.

In regards to the neuropsychological aspect, neurocognitive tests have been used to measure impulsive behavior in suicide patients with and without substance dependence problems. Neuroimaging studies have identified many significant overlapping brain areas and neural circuits involved in substance dependence and suicidality, and these studies have implicated impulse control as one of the possible mechanisms.

On the neurobiological aspect, genetic studies involving twin and family studies and studies of candidate genes provided support for the involvement of impulsivity in suicide behavior among PSD, particularly for alcoholics. Serotonergic dysfunction in metabolism, turnover, its transporters, and receptors are possible mechanisms involved in PSD with suicide attempt history. Other possible biomarkers have been considered,
but the exact roles and mechanisms involved are unclear.

There are some limitations in these studies that require further attention. Integrating genetic, behavioral, psychological, and biological aspects of impulsivity, substance dependence and suicidality would be the most approachable way for directing future research.

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