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Review

Exploring the Impact of Recreational Drugs on Suicidal Behavior: A Narrative Review

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Abstract: Substance use/abuse and suicide are two closely related phenomena, mostly due to neurobiological, psychological, and social impairments. In the present narrative review, the relationship between suicidal behavior (SB) and the use and abuse of common recreational drugs, such as alcohol, cannabis, cocaine, methamphetamine, heroin, nicotine, ketamine, psilocybin, MDMA, and LSD, has been explored. Furthermore, potential mechanisms linking the two have also been examined. According to current research, all substances appear to have a deleterious effect on SB except for ketamine and psilocybin, which could potentially confer a protective effect. Further studies are needed to understand the relationship between MDMA, LSD, and suicide.

Keywords: suicide; drugs; alcohol; cannabis; cocaine; methamphetamine; heroin; nicotine; ketamine; psilocybin; MDMA

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1. Introduction

Suicide is a major health problem, accounting for 700.000 deaths annually across the globe. Moreover, it ranks as the second leading cause of injury worldwide, with a suicide death rate of 10.6 per 100,000 people [1]. Current research indicates that about 90% of people who attempt suicide suffer from a psychopathology [2]. Specifically, 13.3% suffer from a substance use disorder, which is often associated with unplanned suicide. The influence of substance use and abuse on suicide is unmistakable, especially considering that overdose is frequently employed as a method of attempting suicide. Indeed, as Oquendo and Volkow [3] remark, during the opioid crisis in the United States, many overdose deaths were not accidental.

Substance abuse disorders (SUDs), refer to a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using a specific substance despite significant substance-related problems. In addition, substance abuse refers to an unhealthy pattern of use of a substance that leads to significant impairment in the user's life [4].

SUDs are common among people who die by suicide. A recent meta-analysis of global data of psychological autopsy studies revealed that SUDs were present in 15% of cases examined and was associated with a fourfold increase in suicide risk (OR = 4.46; 95% CI 2.93; 6.77) [5]. Another meta-analysis identified a pooled prevalence of 20% (95% CI, 17% 23%) for suicide attempts in people with SUDs and 35% (95% CI, 22% 48%) for suicide ideation [6]. SUDs are also a predictor of multiple suicide attempts (more than two attempts) in adolescents [7] and adults [8]. Suicide risk is directly associated with both drug quantity and meeting the diagnostic criteria for SUDs [9]. For instance, in the case of alcohol, alcohol abuse is associated with a twofold increase in deaths by suicide, whereas alcohol dependence is associated with a fourfold increase [5,9].

Models of suicide include variables that are frequently affected in people with SUDs. The brain-centric model [10] proposes that suicidal behavior occurs when patients with

an existing predisposition (i.e., a diathesis) face acute or chronic stressors. Suicidal vulnerability involves brain and structural dysregulations, mostly related with serotoninergic, dopaminergic, adrenergic, and opioidergic systems. These dysregulations are mostly due to neuroinflammation, apoptotic processes, and hypothalamus–pituitary–adrenal (HPA) impairments. This leads to deficits in decision making, learning, memory, and social cognition, thereby facilitating suicidal behavior.

The purpose of this review is to analyze the impact of use and abuse of substances in suicidal behavior (SB). We will first analyze the mechanisms linking substance use and abuse with suicide. Afterwards, we will review the relationship between each substance (alcohol, cannabis, methamphetamine, cocaine, heroin, ketamine, psilocybin, etc.) and SB, evaluating whether this relationship tends to entail negative implications or if there is potential for therapeutic applications.

A literature search was conducted using PsychInfo, Pubmed, and Google Scholar using a combination of the drug names and the different impairments that relate them to suicide. Although we tried to mostly focus on systematic reviews and meta-analyses to provide the most extensive evidence possible, cross-sectional designs and case studies were also included when the former were not available.

2. Mechanisms Linking Substance Use and Abuse to Suicidal Behavior

2.1. Neurobiological Mechanisms

The brain-centric model [10] posits that several biological factors contribute to an individual's vulnerability to suicide. Some studies have shown evidence of structural, functional, and molecular alterations in the ventral prefrontal cortex (VPFC), the dorsal prefrontal cortex (DPFC), the anterior cingulate cortex (ACC), and the insula in suicidal patients [11]. These brain systems are mostly related to impulsivity, executive control, and emotion regulation [12–14]. In addition, these structures are also related to psychological pain and social exclusion [15,16]. Neurotransmitter deficiencies are also part of the neurobiological diathesis of suicide. A recent meta-analysis has shown that suicide attempters present diminished cerebrospinal fluid (CSF) levels of 5-HIAA and HVA, which are the metabolites of serotonin and dopamine, respectively [17].

These alterations in the neurocircuitry are mostly induced by neuroinflammation, oxidative stress, and HPA axis abnormalities. Neuroinflammation refers to the inflammatory response of the central nervous system to different disturbances, such as infections, traumatic brain injury, ischemia, etc. Two important immune cells in this process are glial cells and astrocytes [18]. Suicide has been related to increased neuroinflammation as measured by an increase in inflammatory markers such as interleukin-6 and other cytokines [19].

Another process to consider is oxidative stress (OS). OS is defined as the imbalance between the production of oxygen reactive species and the body's capacity to neutralize them [20]. Increased nitro-oxidative stress (a type of OS) has been related to SB [21].

Regarding the HPA axis, people with high intensity or variability in their suicidal ideation present hyper-reactivity in their cortisol response to acute stress [22–24]. Some studies have shown that suicide attempters present a blunted cortisol response to stress [25–27]. These results are not replicated in studies involving patients with current depression [28,29]. However, in line with the studies of suicidal ideation, impulsive–aggressive suicide attempters show a higher cortisol response to stress. In line with these results, two subtypes of suicidal patients have been proposed: those responsive to stress, mostly mediated by HPA alterations, lack of executive control, impulsive–aggressive traits, variable suicidal ideation, and impulsive suicide attempts; and those nonresponsive to stress, mostly mediated by serotoninergic release deficits, depressive traits, moderate and stable suicidal ideation, and planned suicide attempts [30].

In the same line, substance abuse also impacts the different neurobiological systems affected in suicidal patients. However, the degree and pattern of the impact varies depending on the specific substance involved.

First, substance abuse severely affects the prefrontal cortex. Concretely, some of the regions commonly affected are the prefrontal cortex (mPFC), lateral prefrontal cortex (lPFC), the anterior cingulate cortex (ACC), and the orbitofrontal cortex (OFC), which are mostly related to reward processing, attention, and behavioral inhibition [31].

Furthermore, there are specific impairments in neurotransmitter systems that significantly impact overall brain activity. First, addiction is heavily dependent on dopamine function. Imaging studies have shown that the reinforcing effects of drugs are dependent not only on dopamine increases in the striatum but also on the rate at which these increases occur. However, long-term drug use seems to be linked to diminished dopamine function as the brain of addicted subjects presents reductions in D2 DA receptors and DA release in the striatum [32]. Second, serotonin also plays a crucial role in the development and maintenance of addiction as it is involved in the modulation of impulsivity [33], which is a risk factor for addiction [34].

In addition, although the effects of illicit drugs on neuroinflammation depend on the drug in question, neuroinflammation has been proposed as a significant contributor in the genesis, maintenance, and treatment of SUDs [35].

Furthermore, patients with SUDs present higher oxidative damage markers and lower antioxidant components [36]. However, not all drugs present a detrimental effect on oxidative stress (e.g., cannabis) [37].

Finally, reactivity patterns of the HPA axis are also heavily dependent on the drug consumed. Moreover, categorizing drugs as stimulants or depressants does not help to classify their effect on the axis. However, a commonality among all drugs is their activation of the axis within the brain, with information converging in the paraventricular nucleus [38].

2.2. Psychological Mechanisms

The clinical profile of substance abusers who die by suicide is often complex. Comorbidities with both mood [39] and personality disorders, particularly cluster B, are frequent. Said comorbidity dramatically increases suicide risk compared to having a substance abuse disorder on its own [40].

Impaired decision making and impulsivity are key features in people with SUDs [34,41]. These factors function both as a precursor to addictive behavior and as a factor in maintaining the SUD [41]. In addition, they also underline related clinical features (such as cluster B personality traits) [42] and, of course, are also related to suicide attempts [43]. First-degree relatives of people who died by suicide show altered responses of the orbitofrontal cortex in risky decision-making tasks, even with no personal history of mood disorders or suicidal behavior. Specifically, differential activation of the left medial and right dorsomedial orbitofrontal cortex during safe and risky decision making was inverted in people with a family history of suicide compared to controls [44]. These findings support the existence of an impaired decision-making endophenotype [45], which would underlie both suicidal and addictive behaviors and their co-occurrence.

These traits are commonly present in people with SUDs, independent of the drug abused [46]. However, heavy drug use further aggravates pre-existing impairments. Most drugs, including alcohol, opioids, cannabis, and methamphetamine, are known for their long-lasting impact on the orbitofrontal cortex and associated neural networks [47–49], with adolescence being a period of great vulnerability for the development of these deficits [50].

Another characteristic that both SUDs and suicide share is a deficiency in reward processing [51,52]. Such a deficit is of considerable importance as it could contribute to a cycle of escalating substance use and suicidal tendencies as individuals struggle to attain fulfillment.

Finally, deficiencies in emotional facial recognition are also common in both substance users and suicide attempters. Current research suggests that both groups present difficulties in accurately perceiving and interpreting facial expressions, which could hinder their ability to navigate social interactions and seek appropriate support [12,53].

2.3. Psychosocial Mechanisms

One of the leading factors that contributes to the diathesis for SB in the brain-centric model is childhood trauma [10]. Childhood abuse is related to dysregulation in the HPA axis, which could persist until adulthood [54]. Said dysregulation could increase the reinforcing effect of drugs in an individual organism, increasing vulnerability for SUDs [55]. Childhood abuse, whether sexual, physical, or emotional, is also related to 2.5-fold greater odds for suicide attempts [56], as well as the development of impulsive and aggressive traits [57]. Childhood abuse is also related to post-traumatic stress symptomatology. Both drug use and suicidal behavior, as well as deliberate self-harm, have been described as strategies to deal with post-traumatic or dissociative symptoms [58].

The experience of psychological pain is an important variable in this pathway towards suicidal behavior. In fact, depressive symptoms and difficulties managing psychological pain have been reported to fully mediate the association between childhood abuse and suicide ideation in people with SUDs [59]. Additionally, psychological pain in individuals with SUDs predicts the severity of comorbid affective symptoms and treatment dropout rates [60].

In addition, social exclusion poses a significant challenge for individuals with SUDs. Those with SUDs often confront social stigma from various sources, including peers, family, and healthcare professionals, which can compromise their health outcomes [61]. Inability to deal with social exclusion may lead to suicidal behavior in people with SUDs in the same fashion as in any other physical and psychological pain.

3. The Impact of Use and Abuse of Substances on SB

3.1. Alcohol

In 2016, 2.3 billion people worldwide were reported to be current drinkers. Moreover, 283 million people in the world suffer from alcohol use disorders [62]. In a recent meta-analysis [9], alcohol use was associated with a 94% increase in overall risk of death by suicide (Table 1). This association remained consistent across different sample types (community, psychiatric, and military samples). Moreover, the quantity of alcohol consumed was more important than frequency of consumption. In addition, a diagnosis of alcohol use disorder had a significant impact on death by suicide [9], suicidal ideation, and suicide attempts ([63]). This association between alcohol and SB should be understood in the light of several neurobiological and psychological impairments that are commonly associated with alcohol use.

Alcohol use disorder has been related to increased risk taking (see review [64]). Such impairment does not seem to be task-specific as deficits were seen in numerous tasks (IGT, CGT, GDT, etc.). Moreover, the level of alcohol ingested by night predicts next-day impulsivity [65]. Therefore, both suffering from AUD, as well as causal consumption of alcohol, should be considered risk to be factors for SB. A possible pathway for this association is oxidative stress. It has been hypothesized that oxidative stress induced by alcohol coupled with a psychiatric diagnosis may increase impulsivity [66]. This is of significant importance as there is a clear association between suffering from anxiety and mood disorders and alcohol abuse [67,68].

Another pathway by which alcohol may be responsible for SB due to its impact in the PFC is neuroinflammation. Alcohol induces neuroinflammation through two main mechanisms. On the one hand, it activates neuroimmune cells (e.g., microglia) with the subsequent release of proinflammatory cytokines. On the other hand, it can also indirectly affect the brain through the gut–brain axis by introducing bacteria and bacterial endotoxins into the bloodstream [69]. Moreover, such neuroinflammation may also be responsible for a genetic predisposition to engage in binge drinking [70].

Furthermore, alcohol use disorder affects the HPA axis in several ways. Although the results are mixed for ongoing alcohol users, those in withdrawal clearly experience hyperactivity of the HPA axis. Early abstinent users (less than 6 months) show a blunted

cortisol response to stress (see review [71]). Therefore, this time period could represent a heightened risk for suicide.

In addition, social risk factors should not be undermined in the relationship between SB and suicide. Problematic alcohol use is associated with a history of childhood trauma [72], and early social isolation in rats seems to enhance the persistence of alcohol-seeking behaviors [73]. Moreover, it is also associated with bullying [74], racial discrimination [75], and unemployment [76].

3.2. Cannabis

Cannabis is one of the most used recreational drugs, with 4.3% of the population being reported as users [77]. Considering this, it is imperative to better understand the health-related dangers that its use might entail. A systematic review of other systematic reviews found a positive association between consumption of cannabis and both suicidal ideation and suicide attempts (Table 1). Moreover, initiating alcohol consumption at a younger age, as well as the duration and amount of alcohol consumed, were associated with a worse prognosis [78].

Cannabis is different from other drugs as research often highlights its anti-inflammatory and antioxidative stress effects [37,79]. However, the HPA axis of frequent cannabis users resembles that of suicide attempters as stress exposure is related to blunted HPA axis reactivity [80]. This finding suggests a potential link by which cannabis use may exacerbate susceptibility to SB.

Furthermore, its use is related to both neuroanatomical changes and neuropsychological impairments. An area notably affected by cannabis use is the frontal lobe [81], which is logical given that its main components, Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), bind to cannabinoid receptors CB1 and CB2, which are densely expressed in this area [82]. A part of the frontal lobe that is reduced in volume in cannabis users is the orbitofrontal cortex (OFC) [83]. A psychological trait that is negatively associated with OFC volume is impulsivity [84]. Indeed, cannabis misuse has been suggested to be a risk factor for increased impulsivity. Such a relationship is true for measures of both trait and behavioral impulsivity (although evidence is less clear for the latter) [85].

Other brain areas in which CB1 and CB2 receptors are densely concentrated are the prefrontal and limbic areas, which are related to reward motivation [86]. As could be expected, cannabis consumption affects reward processing. Although more studies are needed to draw definitive conclusions, there is evidence to suggest that cannabis consumption is related to reduced reward learning [87]. Regarding reward anticipation, in a longitudinal study [88], cannabis consumption was associated with blunted anticipatory nucleus accumbens activity. In the same line, suicide has also been related to impaired reward learning, which is defined as the inability to learn and adapt behavior based on rewards [89]. Another characteristic that could also be understood as a deficiency in reward processing is depression. Cannabis use is associated with a greater likelihood of suffering from depression [90].

Apart from biological and psychological factors, social factors are also key to understanding this relationship. Frequent cannabis use is associated with heightened levels of loneliness [91] and is related to family dysfunction [92], harsh parenting by fathers [93], parental separation, and early parental death [94]. Moreover, suffering from childhood physical and sexual abuse doubles the likelihood of consuming cannabis in adolescence [95]. Finally, its use is also related to unemployment [96] and lower socioeconomic status [97].

3.3. Methamphetamine

Methamphetamine (MA) is a recreational drug that accounts for a significant portion of people entering drug treatment, particularly in east and southeast Asia. Moreover, its use has increased, particularly in southeastern Europe [77].

A systematic review [98] found that MA was significantly associated with suicide (Table 1). However, the review did not specifically focus on suicide, and findings were based

on five studies (with three of them supporting the association). In a more recent review, both amphetamine and methamphetamine were analyzed collectively due to their similarity and the complexity of distinguishing between the two in self-reports. In the review, both suicide attempt and suicidal ideation were associated with methamphetamine use [99]. Apart from the evident bias that analyzing both drugs in conjunction entails, most of the studies included in the review were cross-sectional, therefore hindering causal inferences.

Although the evidence is not robust, there are some indications that MA might be related to an increased risk of suicide. Moreover, its impact in the social, psychological, and neurobiological domains strengthens this view.

First, MA use is associated with education problems, involvement with the judicial system [100], homelessness [101], and family dysfunction (history of crime or drug use) [102]. Furthermore, it has also been associated with a history of childhood abuse [103]. Indeed, MA mediates the relationship between childhood maltreatment and suicide [104]. This is of importance given that while MA alone can cause cognitive dysfunction, when combined with CM the impact could be exacerbated.

In the psychological domain, several impairments related to MA use must be highlighted. First, MA users are more likely to suffer from depression [105], with some authors arguing for a causal relationship [106]. Second, MA has been associated with increased impulsivity. In a systematic review of both behavioral and neuroimaging studies [107], MA users showed higher rates of delay discounting. Such impairment may derive from an inefficiency in cortical processing as participants presented lower activation in the PFC and higher activation in the striatum. Moreover, MA users also showed riskier behaviors in other tasks that measure risky decision making, such as the balloon analogue task, and the risky gains task.

Such impairment in impulsiveness might be mediated by dopamine. It has been proposed that PFC dopamine is related to cognitive stability, whereas striatum dopamine is related to cognitive flexibility [108]. Indeed, higher striatal dopamine transporter availability has been associated with heightened impulsivity in healthy controls [108]. Certainly, lower striatal D2 receptor availability has been found in MA users and has been related to greater impulsivity [109]. Indeed, the stress response of MA users resembles that of suicide attempters, exhibiting higher levels of impulsivity as they show a heightened cortisol response in comparison to controls in the Trier Social Stress Test (TSST) [110].

Finally, the different psychological impairments present in MA users could derive from the brain damage caused by the drug as MA use promotes neuroinflammation through several pathways, including neuron–glia and astrocyte–glia cross talk [111].

3.4. Cocaine

Cocaine is one of the most commonly used recreational drugs, with an estimated 22 million users in 2020 [77]. In a recent review regarding the prevalence of SB in cocaine users, it was found that cocaine was related to both suicide attempts and suicidal ideation (Table 1) [112]. Most of the studies included in the review were cross-sectional. However, cocaine is known to cause different impairments in the neurological, psychological, and social domains, which could account for this relationship.

Cocaine is a sympathomimetic stimulant of the central nervous system, which blocks the presynaptic transporters in charge of the reuptake of serotonin, noradrenaline, and dopamine. By blocking the dopamine transporter (DAT), an increase in extracellular dopamine occurs, which induces an overstimulation of the dopamine postsynaptic receptors [113].

In a recent review, a reduction of dopamine receptors, as well as higher DAT availability in the striatum, was found in chronic cocaine users [114]. Due to the relevance of the striatum in reward learning [115], it would be logical to assume that impairments in this structure lead to impairments in reward learning in cocaine users. One renowned method for evaluating reward learning is the Iowa Gambling Task. Cocaine users report impaired performance in the IGT in comparison to controls [116–118]. In the same

line, suicide attempters also present worse performance in reinforcement-learning tasks than controls [51].

Another brain region affected by cocaine is the prefrontal cortex. Cocaine has been found to induce changes in the orbitofrontal cortex [119], an area which is closely related to impulsivity [84]. Indeed, cocaine users present riskier decision making than controls, and this is even more pronounced in short-abstinence users [34]. Therefore, this short period of abstinence could suppose a period of increased susceptibility to SB.

A contributing factor to the deficits observed is neuroinflammation, which has been found to correlate with increased activation of microglia, macrophages, and astrocytes in human subjects [120].

Moreover, another potential pathway by which cocaine may contribute to SB is the HPA axis. In individuals with passive exposure to cocaine during prenatal development, a blunted response to the TSST in comparison to controls has been observed [121].

Furthermore, cocaine addicts also present a greater likelihood of suffering from psychosis [122], depression [123], and anxiety [124].

Finally, social risk factors for suicide in this population should not be underestimated as its use is related to childhood maltreatment [125] and low socioeconomic status markers such as neighborhood poverty [126].

3.5. Heroin

Heroin is the most commonly used illicit opioid and is responsible for a significant portion of the health burden linked to illicit drug consumption [77]. Considering this, a better understanding of the relationship between heroin and SB is imperative.

Heroin users present a higher prevalence of suicidal behavior than nonusers (Table 1) [127,128]. In a recent review [128], social factors are highlighted among the most common reasons for suicidal behavior in heroin users. Such association is logical due to their social context. First, its use is related to low socioeconomic status [129], greater odds of resorting to prostitution, criminal behavior [130], being victim of childhood trauma [127], parental rejection [131], and homelessness [132]. Considering all these different issues, the social context of heroin users is a perfect breeding ground for suicidal behavior.

Moreover, in the neurological and psychological domains, several factors need to be addressed. First, heroin use is related to an increased risk of depression, and some authors have hypothesized that this relationship could be bidirectional [133]. Second, heroin use has been associated with a dysfunction in impulsivity as reported by both behavioral and self-report measures. In a recent systematic review, the effects of heroin use on brain regions related to impulsive behavior were addressed. It was found that the brain circuits responsible for executive control over subcortical structures were weakened in those with heroin use disorder. In contrast, subcortical circuits associated with drives and motivations were heightened in comparison to healthy controls [134]. Moreover, some evidence has indicated that such an increase in impulsivity could be, at least partially, a consequence of consuming the drug [135]. These different psychological impairments could be due to neuroinflammation as heroin has been found to be associated with an increased expression of ICAM-1 and recruitment of CD3+ lymphocytes [136].

3.6. Nicotine

Nicotine is an addictive organic compound, which can be consumed by smoking regular cigarettes, electronic nicotine delivery systems (END-S), or even through second-hand smoke [137]. Due to the obvious difficulty in studying nicotine in isolation, most research focuses on these three methods of consuming nicotine, smoking regular cigarettes being the most common. The consumption of regular tobacco is a public health concern, with 8 million people dying from its use in 2019. Moreover, according to the WHO, the number of deaths is expected to increase in the next few years [138].

In a recent meta-analysis, tobacco use was associated with an increased likelihood of death by suicide, suicide attempts, and suicidal ideation in smokers compared to individu-

als who had never smoked [139]. Moreover, such a relationship could be independent from psychiatric diagnoses [137]. Furthermore, tobacco use disorder has also been related to an increased likelihood to attempt suicide [140].

The association between nicotine and suicide should be understood in the light of several neurobiological and psychological impairments that are commonly associated with nicotine consumption.

First, it is noteworthy to mention that both traditional cigarettes and END-S contribute to the generation of oxidative stress within the body, potentially heightening the risk of SB [141,142]. However, in contrast to other drugs, nicotine consumption does seem to reduce neuroinflammation [35]. Regarding HPA axis function, although smoking only two cigarettes increases the activity of the axis, regular smokers present a blunted cortisol responsivity to the TSST in comparison to nonsmokers [143].

Another key factor that may shed light on the connection between suicide and nicotine is serotonin. Post-mortem studies show a depletion of serotonin in the hippocampus of smoker brains, implying a potential association between nicotine use and alterations in serotonin levels, potentially contributing to the elevated risk of suicidal behavior among smokers [144].

Despite the observed alteration in serotonin levels, the relationship between tobacco use and depressive disorders is not clear. In the same line, there is also no consensus between tobacco and its relationship to anxiety disorders. In contrast, smoking has been related to an increased likelihood of suffering from eating disorders [145], obsessive compulsive disorder [146], and lower self-esteem [147].

In addition, it has been found that tobacco users are more impulsive than nonusers as measured by behavioral and trait measures of impulsivity. Moreover, chronic exposure to nicotine may also directly increase impulsivity. In the same line, nicotine deprivation may contribute to a propensity for impulsive behavior, potentially leading to a period of increased risk for suicide [148].

Finally, the social context of consumers should not be overlooked. There exists an inverse relationship between tobacco consumption and socioeconomic status, with individuals from lower socioeconomic backgrounds tending to exhibit higher rates of tobacco use compared to those from higher socioeconomic strata [149]. In the same line, individuals facing unemployment tend to have higher rates of tobacco use [150]. Finally, it has also been related to higher loneliness [151], family dysfunction [152], and a history of childhood trauma [153].

3.7. Ketamine

Among participants in the European Web Survey on Drugs [154], 13% of those who had used drugs in the past year had used ketamine. Moreover, in some European countries, there has been an increase in the number of patients entering treatment for problems associated with ketamine use [154]. Although illicit use of ketamine could lead to psychological impairments, such as increased impulsivity and increased likelihood of mental disorders [155], clinical use of the drug has shown beneficial effects for SB (Table 1) [156].

Literature exploring the efficacy of ketamine for treating suicidal thoughts and behaviors has grown in the last years. In a recent meta-analysis [156] it was found that intravenous racemic ketamine proved to be more effective than control drugs in the first 72 h. After 72 h, no significant differences between groups were usually found (mostly due to a reduction in SB in the control group). Due to the numerous limitations (poor blinding quality, large placebo effects, doubtful definition, and assessment of SB etc.) the authors call for caution as findings are yet not conclusive.

The mechanisms by which ketamine may be exerting its antisuicidal effects remain poorly understood. In their paper, Lengvenyte et al. [157] propose a theoretical background that could explain ketamine's effects. First, ketamine induces neuroplasticity by the activation of BDNF and mTOR pathways [158], which could repair dysconnectivity induced by stress in brain areas such as the PFC (responsible for decision making and inhibition)

and the anterior cingulate cortex (responsible for pain processing). Second, those who have suffered childhood maltreatment present greater impulsivity, a dysregulation of the HPA axis and not chronic SI (which is usually a consequence of stressful events) [24,30]. Due to the ketamine's effect of both PFC's and ACC's neuroplasticity, its stabilizing effect on the HPA axis, and its noneffects on chronic SI it could be helpful to treat patients with this pattern [159]. Third, ketamine's modulation of the opioid system could result in pain relief and restored reward processing. Finally, by inhibiting the overactivation of the lateral habenula [159] it could help to restore reward processing and decrease anhedonia.

Finally, although ketamine's effects on SB are promising in controlled settings, such an effect cannot be extrapolated to its illicit use. Although not much research has been conducted regarding the relationship between the recreational use of ketamine and suicide, the case report of a 29-year-old male who died by suicide under the influence of ketamine (and also alcohol) raises concerns about its detrimental effects [160].

3.8. Psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a serotonergic hallucinogen and the main psychoactive substance in psilocybe mushrooms [161]. Although its recreational use can entail adverse consequences such as development of psychotic symptoms and mood disorders [162] psilocybin has been proposed as an alternative treatment for suicidal behavior (Table 1) [163] due to its apparent efficacy in reducing suicidal thoughts and attempts [164–166]. The mechanisms by which psilocybin may be exerting such effects are still not clear. In their review, Strumila et al. (2021) propose several neurobiological and neuropsychological pathways by which psilocybin could ameliorate the usual impairments found in SB.

Regarding the neurobiological pathways, although the evidence is scarce [163], some studies hint that psilocybin may possess antioxidant effects [167]. Moreover, it has also been found that psilocybe mushrooms have anti-inflammatory properties [167]. Considering that oxidative stress and inflammation have both been related to suicidal behavior, it is plausible that reducing them could also reduce SB.

Regarding the psychological pathways, it has been proposed that psilocybin enhances cognitive flexibility [168] and reduces feelings of social exclusion [169]. Moreover, it also affects emotional processing by reducing the recognition of negative emotions (see review [170]). This is of great importance given that suicide is closely related to hyperactivity of negative facial expressions [14,171].

Apart from the several neurobiological and psychological pathways delineated in their paper, there are several domains that have yet not been explored by researchers due to the novelty of the research area which need to be investigated. First, to the best of our knowledge, no previous reports regarding how psilocybin administration regulates impulsiveness have been published. Prior studies with animal models report that serotonergic neuronal firing promotes waiting behavior when the possibility of a future reward arises [172]. Considering this, it would not be unexpected that serotonin agonists such as psilocybin could promote the same effect. In addition, the effects of psilocybin administration in social stress tasks such as the TSST should also be explored as suicide has been consistently related to increased social stress. Psilocybin could potentially moderate social stress as it has been associated with decreased amygdalar responses, a brain region which is key for regulating fear and stress [173].

Non-clinical use of psilocybin may entail some risks. In a recent case report, a 30-year-old man who consumed psilocybin attempted suicide. Moreover, he reported no previous thoughts of self-harm [174]. Therefore, further investigation of the use of psilocybin for treating suicidal behavior is needed.

3.9. Other Drugs

3.9.1. MDMA

MDMA (3,4,-Methylenedioxymethamphetamine) is a widely used recreational drug, with an estimated 20 million users in 2021 [77]. The literature regarding MDMA and suicide is scarce and inconclusive. A comprehensive systematic review that synthesizes all available evidence is lacking (Table 1). However, several papers that compile findings from different national surveys (U.S. and France) are available. In a sample of U.S. adults, MDMA was associated with reduced past-year suicidal thinking and past-year suicidal planning [165]. In an analogue study of adolescents [175], MDMA was not associated with any measure of SB. In another study consisting of adolescents (12–17 years old), the prevalence of past-year suicide attempts for those with lifetime MDMA use was nearly doubled compared to those who used other drugs, and was nine times higher than those with no drug use [176]. In a separate study with a nationally representative French adolescent sample, both MDMA and amphetamine were grouped to explore suicidal behavior, and a significant relationship with SB was found [177]. However, due to both drugs being analyzed as a group, it is impossible to infer the specific relationship that MDMA and SB share.

Taken together, the relationship between MDMA and suicide is inconclusive. Moreover, due to the cross-sectional nature of the studies presented, no inferences regarding causality can be made. Pre-drug differences in several social and psychological domains, as well as consumption of other drugs, could account for the differences observed. Longitudinal studies that aim to explore the casual relationship between SB and MDMA, as well as a further study of potential mediators and moderators, are needed.

3.9.2. LSD

According to the European Monitoring Centre for Drugs and Drug Addiction, 20% of those who had used drugs in the previous year had used LSD (lysergic acid diethylamide) [154]. LSD is a hallucinogenic drug that stimulates central serotonin receptors (5-HT_2) [178]. The literature regarding the relationship between LSD and suicide is inconclusive (Table 1) and dispersed. To our knowledge, a systematic study that compiles all available data to reach a definitive conclusion about its relationship is lacking. In a cross-sectional study comprising young adults, it was found that LSD users (either past year or lifetime) reported greater suicidal ideation than nonusers [179]. Moreover, several case reports of completed (violent) suicides following LSD consumption, in which no prior history of attempts or psychiatric comorbidities existed, have been published [180,181]. However, in a cross-sectional population-based study of adults in the United States (N = 135.095), LSD was not found to be associated with suicidal ideation, suicide planning, or suicide attempts [182].

More research is required in order to better understand the relationship between LSD and suicidal behavior. Further studies that measure suicidality, using proper scales and controlling for mental health issues, as well as longitudinal studies that track individuals over an extended period of time, are needed.

Table 1. Drugs and their relationship with suicide.

Drug	Relationship with Suicide	What Findings Are Based on
Alcohol	Highly plausible that it increases suicidal behavior	Findings based on a meta-analysis of longitudinal studies [9].
Cannabis	Plausible that it increases suicidal behavior	Findings based on a systematic review of systematic reviews [78]. Further longitudinal studies are needed.
Methamphetamine	Could increase suicidal behavior.	Findings based on two reviews that either did not focus on suicide [98] or analyzed the drugs in conjunction with another drug [99]. Moreover, most studies included were cross-sectional.
Cocaine	Could increase suicidal behavior.	Findings based on a systematic review and metanalysis [112] that analyzed mostly cross-sectional studies.

Table 1. *Cont.*

Drug	Relationship with Suicide	What Findings Are Based on
Heroin	Plausible that it increases suicidal behavior	Findings based on a systematic review and meta-analysis [128]. Further longitudinal studies are needed.
Nicotine	Could increase suicidal behavior	Findings based on a meta-analysis [139] of cohort studies.
Ketamine	Plausible that it decreases suicidal behavior	Findings based on a systematic review of double-blind randomized controlled trials [156]. Further studies are needed.
Psilocybin	Could decrease suicidal behavior	Findings based on a paper that proposes the drug as a potential treatment for suicidal behavior due to its properties [163]. No experimental studies were found.
MDMA	Not enough studies to conclude a relationship	
LSD	Not enough studies to conclude a relationship	

4. Discussion

The present review aimed to assess the relationship between different common recreational drugs and suicide while attempting to elucidate the potential neurobiological, psychological, and social mechanisms that may be influencing this association (summarized in Table 2). Alcohol, cannabis, methamphetamine, cocaine, heroin, and nicotine were related to greater SB, whereas there was insufficient scientific evidence to support effects of both MDMA and LSD on SB. In contrast, ketamine and (probably) psilocybin present potential therapeutic use for reducing suicidal behavior.

Table 2. Mechanisms linking drug consumption with SB.

Drug	Neurobiological Mechanisms	Psychological Mechanisms	Social Mechanisms
Alcohol	↑ Neuroinflammation ↑ Oxidative stress HPA axis: blunted cortisol response in early abstinence (<6 months)	↑ Both long-term and next-day impulsivity ↑ Anxiety and mood disorders	History of childhood trauma Bullying and racial discrimination Unemployment
Cannabis	Ø Neuroinflammation Ø Oxidative stress HPA axis: stress exposure is related to blunted HPA reactivity Impairments in frontal and limbic areas	↓ Reward learning Impaired reward anticipation ↑ Impulsivity ↑ Depression	History of childhood trauma Family dysfunction (parental separation, harsh parenting, early parental death) Loneliness Unemployment Low socioeconomic status
Methamphetamine	↑ Neuroinflammation HPA axis: pattern similar to high-impulsivity SA, with a heightened cortisol response to the TSST	↑ Depression ↑ Impulsivity (mediated by dopamine)	History of childhood trauma Criminality Homelessness Family dysfunction
Cocaine	↑ Neuroinflammation Reduction of dopamine receptors and higher DAT availability in the striatum Alterations in the OFC HPA axis: prenatal exposure leads to a blunted response to the TSST	↓ Reward learning ↑ Impulsivity ↑ Depression ↑ Psychosis ↑ Anxiety	History of childhood trauma Low socioeconomic status
Heroin	↑ Neuroinflammation Brain circuits responsible for executive control over subcortical structures are weakened Subcortical circuits associated with drives and motivations are heightened	↑ Impulsivity ↑ Depression ↑ Tendency to focus on negative facial expressions.	History of childhood trauma Parental rejection Prostitution Criminal behavior Homelessness

Table 2. *Cont.*

Drug	Neurobiological Mechanisms	Psychological Mechanisms	Social Mechanisms
Nicotine	↓ Neuroinflammation ↑ Oxidative stress HPA axis: blunted cortisol response to social stress	↑ Impulsivity ↑ Eating disorders ↑ Obsessive compulsive disorder ↓ self-esteem	Poverty Unemployment Loneliness Family dysfunction History of childhood trauma
Ketamine (clinical use)	Induced neuroplasticity in the PFC and ACC. Stabilizing effect on the HPA axis Beneficial effect on the opioid system Inhibits the activation of the lateral habenula	Relieving pain and decreasing anhedonia Restoring reward processing	
Psilocybin	Possible reduction of neuroinflammation and oxidative stress.	↑ cognitive flexibility ↓ recognition of negative emotions	↓ feelings of social exclusion

Note: ↑ increased, ↓ decreased, Ø: no effect.

Of all the drugs assessed, alcohol, cannabis, heroin, nicotine, and ketamine present the greatest scientific evidence that supports their association with SB. Longitudinal studies/randomized controlled trials suggest a strong relationship between the drugs and suicide, an assertion that is not feasible to make for the rest of the drugs as their findings mostly rely on cross-sectional studies.

Illicit and therapeutic drugs are usually used as a method for suicide by self-poisoning in western countries [183]. Previous research on autopsies of drug intoxication has demonstrated that people usually use prescribed drugs such as opioids, benzodiazepines, antidepressants, or neuroleptics rather than illicit drugs such as ethanol and cocaine [183,184]. However, some of the prescribed drugs can be used as illicit drugs, and all drugs function as facilitators for suicide by increasing the user's capability to attempt suicide [185].

The association between drug intake during life and suicide remains poorly understood. Targeting the different impairments found in the neurobiological, psychological, and social systems is crucial to provide a better treatment for suicidal patients. Some substances such as ketamine and psilocybin are proving effective in the treatment of SB, targeting key neurobiological mechanisms associated with suicide.

Additional research in the neurobiological domain that seeks a specific profile of impairment may serve to identify potential biomarkers. In the same line, further studies regarding the role of mental disorders and impulsivity on SB in this population could refine and refocus current therapeutical approaches such as cognitive behavioral therapy. In addition, understanding the different social-risk and protective factors is also crucial for implementing community-based strategies that aim to improve the social context.

Additionally, due to the current state of the art, conclusive evidence could not be established in this paper, as numerous variables exist within this research domain that complicate the attainment of consistent conclusions. First, drug users commonly use more than one drug [186], which hinders direct conclusions regarding the effect that a specific drug may have on SB. Thus, further research should aim to minimize the effect of co-consumption in their analyses to tackle the problem. Second, substance abuse is strongly linked to depression, anxiety, and psychotic disorders [187–189]. Due to the large comorbidity of mental disorders with SB, future research should consider the impacts these entail.

In conclusion, there is a need for further high-quality research utilizing longitudinal designs and controlling for potential confounding variables such as mental disorders and co-consumption. Additionally, a deeper investigation into the various impairments observed in this population is warranted. Finally, further studies should assess the bidirectionality of the relationship, which is currently not feasible due to the state of the art of the research.

Exploring the temporal sequence of this relationship can provide valuable insights into the development of both substance use disorders and suicidal tendencies.

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