Current Addiction Reports (2021) 8:194–207
https://doi.org/10.1007/s40429-021-00361-z

EMOTION & ADDICTION (K MORIE, SECTION EDITOR)

Suicide Risk and Addiction: The Impact of Alcohol and Opioid Use Disorders

Mina M. Rizk[1,2,3] · Sarah Herzog[1,2] · Sanjana Dugad[2,4] · Barbara Stanley[1,2]

Accepted: 23 February 2021 / Published online: 14 March 2021

Abstract

Purpose of Review Suicide is a major public health concern and a leading cause of death in the US. Alcohol and opioid use disorders (AUD/OUD) significantly increase risk for suicidal ideation, attempts, and death, and are the two most frequently implicated substances in suicide risk. We provide a brief overview of shared risk factors and pathways in the pathogenesis of AUD/OUD and suicidal thoughts and behaviors. We also review clinical recommendations on inpatient care, pharmacotherapy, and psychotherapeutic interventions for people with AUD/OUD and co-occurring suicidal ideation and behavior.

Recent Findings Among people with an underlying vulnerability to risk-taking and impulsive behaviors, chronic alcohol intoxication can increase maladaptive coping behaviors and hinder self-regulation, thereby increasing the risk of suicide. Additionally, chronic opioid use can result in neurobiological changes that lead to increases in negative affective states, jointly contributing to suicide risk and continued opioid use. Despite significantly elevated suicide risk in individuals with AUD/OUD, there is a dearth of research on pharmacological and psychosocial interventions for co-occurring AUD/OUD and suicidal ideation and behavior.

Summary Further research is needed to understand the effects of alcohol and opioid use on suicide risk, as well as address notable gaps in the literature on psychosocial and pharmacological interventions to lower risk for suicide among individuals with AUD/OUD.

Keywords Alcohol use · Opioid use · Suicidal behavior · Suicidal ideation · Suicide risk · Neurobiology

Introduction

Suicide rates rose by 35% in the US over the past two decades [1] despite significant efforts to reverse this pattern by identifying risk factors and preventative interventions [2]. While mood disorders are among the most important risk factors for suicide [3–5], comorbidity with alcohol and substance use disorders (AUD/SUD) vastly increases vulnerability to suicidal ideation [6, 7], attempts [8, 9], and deaths [5, 10, 11]. Additionally, suicidal ideation and behavior are significant clinical concerns among those seeking treatment for AUD/SUD [12], and risk for highly lethal suicide attempts remains to be elevated even after remission from SUD [13]. While all substances elevate the risk for suicidal behavior, alcohol and opioids are the most common substances identified in suicide decedents (22% and 20%, respectively), far above rates of marijuana (10.2%), cocaine (4.6%), and amphetamines (3.4%) [14•]. In this review, we summarize literature on the role of AUD and opioid use disorder (OUD) in contributing toward the risk of suicidal thoughts and behavior and discuss treatment interventions.

Alcohol

Alcohol misuse is robustly linked to heightened risk for suicidal ideation, attempts, and deaths in youths and adults [10, 15–17], a phenomenon not accounted for by comorbid

This article is part of the Topical Collection on *Emotion and Addiction*

Mina M. Rizk and Sarah Herzog are Co-first authors

✉ Mina M. Rizk
mina.rizk@nyspi.columbia.edu

[1] Department of Psychiatry, Columbia University Irving Medical Center, Columbia University, New York, NY, USA

[2] Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, 1051 Riverside Dr., Unit 42, New York, NY 10032, USA

[3] Department of Psychiatry, Faculty of Medicine, Minia University, Egypt, Egypt

[4] Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA

psychiatric disorders [18]. Cross-national studies indicate a linear relationship between suicide rates and per-capita alcohol consumption [19, 20], suggesting that alcohol may be a key factor in suicide. Indeed, rates of alcohol misuse have escalated over the last two decades [21, 22] in parallel with rising suicide rates [23, 24]. Since 2001, past-year prevalence of high-risk drinking has increased by 29.9%, and alcohol use disorder (AUD) by an alarming 49.4% [21]. Importantly, rising rates of alcohol misuse are accompanied by a 35% increase in alcohol-related suicide deaths [23].

Two forms of alcohol use are implicated in the elevated risk for suicidal thoughts and behavior—acute alcohol intoxication and chronic alcohol use or dependence [25, 26]. The 24-hour period following alcohol intoxication is associated with a seven-fold increase in the risk for suicidal behavior [27]. Moreover, alcohol intoxication is related to greater lethality of attempt methods, making suicide fatalities more likely [28]. Over a third of suicide decedents test positive for alcohol; 63.5% of whom have blood concentrations demonstrating intoxication [29], and more suicide decedents test positive for alcohol than other substances. Chronic alcohol use/dependence is similarly an important population-level risk factor for suicidal behavior [17, 30]. AUD is associated with a 10-fold higher risk for suicide compared to the general population [10] and trails mood disorders as the second most common psychiatric diagnosis in complete suicides [31].

Models of Suicide—Alcohol Relationships and Shared Risk Factors

Conceptual models accounting for causal mechanisms between AUD and suicide risk largely fall into two categories: a proximal pathway through the acute effects of alcohol intoxication, and a distal (i.e., predisposing) pathway through chronic alcohol use [32]. For example, the acute effects of alcohol intoxication, e.g., increased dysphoria, myopia, agitation, and impaired perception and motor control [33, 34], may render an individual prone to risk-taking or impulsive behavior and less likely to seek alternative solutions to self-regulate [25], thereby precipitating suicidal behavior. Intoxication also promotes behavioral disinhibition and affective numbing, potentially lessening fear of death that might otherwise act as a psychological barrier to suicide [35]. Suicide and alcohol use also share indirectly precipitating risk factors. For example, consistent with models of suicide as an escape aversive self-awareness [36], AUD and suicidal behavior may not be causally related but arise as a function of a third proximal factor such as motivation to avoid painful internal states [37]. Accordingly, acute intake might reflect maladaptive efforts at coping with negative affect [38] that paradoxically exacerbate dysphoria and suicidal ideation due to the depressogenic effects of alcohol [25]. Suicidal urges might prompt acute alcohol intoxication, for instance, as a means to lower inhibitions for self-inflicted violence.

Alcohol and suicide also share a number of distal, predisposing risk factors that may interact with immediate, proximal factors to produce suicidal outcomes. For example, according to the stress-diathesis model of suicidal behavior [39, 40], alcohol use might trigger suicidal behavior in those with an underlying vulnerability, such as a propensity toward stress-reactive impulsivity. Externalizing traits in particular may reflect an underlying vulnerability that promotes both impulsive aggression and suicidal behavior [41], and might also dispose an individual toward alcohol misuse [42, 43]. Additionally, childhood maltreatment is a shared predisposing factor for both alcohol misuse and suicidality [44, 45] that is likewise associated with impulsive and aggressive behavior [46]. Over time, chronic alcohol use can heighten the risk for suicide by promoting social isolation, corroding relationships and support systems, and precipitating or aggravating psychosocial stressors (e.g., homelessness, financial insecurity) [25, 32]. Indeed, heavy drinking is associated with aggressive behavior, intimate partner violence, economic hardship, and job loss [47–49], all of which predict both suicide and alcohol-related deaths [50–52]. Of particular concern in older adults for whom physical illness and disability constitute a major risk factor for suicide [53–56], chronic AUD can also accelerate aging processes [57, 58] and produce toxic physiological effects [59]. Moreover, cognitive deficits that emerge from repeated alcohol misuse may impair emotion regulation, decision-making and behavioral control [60], contributing to increased suicide risk [61].

Shared Neurobiological Features of Suicide and Alcohol Use

Individuals with AUD share a number of neurobiological characteristics with suicidal individuals. Evidence of impaired serotonin (5-hydroxytryptamine; 5-HT) transmission has been found *postmortem* in the brains of suicide decedents [62], as well as in the cerebrospinal fluid (CSF) of nonfatal attempters [63, 64]. Reductions in binding of 5-HT_{1A} receptors and serotonin transporter have likewise been found in prefrontal brain regions of alcoholic individuals [65]. Importantly, serotonergic dysfunction may be central to the pathogenesis of depression [66], specifically with regard to 5-HT_{1A} and 5-HT_{1B} receptors [67] thought to play a role in mood and reward sensitivity, and regulation of impulsivity and aggression [67]. Thus, serotonergic dysfunction may reflect a common pathway to suicidal outcomes and AUD, perhaps mediated by underlying depression or impulsive aggression. Studies of serotonin metabolites support this; for example, in high- and low-lethality attempters, trait aggression is related to lower concentrations of CSF 5hydroxyindolacetic acid (5HIAA; a major metabolite of serotonin), and high lethality

attempters demonstrated lower CSF 5-HIAA [68]. Lower concentrations of 5HIAA have also been found in alcoholic individuals compared to controls [69] and in impulsive violent offenders compared to premeditated offenders [70]. In the latter study, the lowest levels of CSF-5HIAA were found in impulsive offenders with a past suicide attempt, perhaps suggesting that impulsivity and suicidality are independently and additively related to serotonergic dysfunction.

AUD and suicidal behavior might share a genetic association with the promoter region of the serotonin transporter gene (SLC6A4), referred to as 5-HTTLPR [71]. The functional polymorphism of the 5-HTTLPR, specifically, the "short" (S) allele, is linked to a deficiency in serotonin reuptake and has been associated with suicidal behavior [72], particularly multiple and highly lethal attempts. The S allele of SLC6A4 has also been found in greater frequency in patients with severe alcohol dependence compared to controls [73] and is related to greater novelty-seeking in individuals with alcohol dependence compared to those without the S variant [74].

Individuals with history of suicidal behavior and those with AUD exhibit overlapping brain morphometric alterations. Suicidal behavior is associated with reductions in gray matter volume in various parts of the dorsolateral prefrontal cortex (dlPFC) implicated in decision-making and inhibitory control [75, 76]. Persons using alcohol likewise show reduced gray matter volume in these areas [77–79], as well as reward-related regions, such as the amygdala, anterior insula, and nucleus accumbens [80]. Additionally, adolescents with both AUD and suicidality have smaller prefrontal cortices compared to controls [81, 82]. Diffusion tensor imaging studies also show lower white matter integrity in the frontal and limbic regions in both suicide attempters [83, 84] and youths with AUD [78, 85]. Those structural brain changes in gray matter volume and white matter tracts integrity may be related to the neurotoxic effects of alcohol [78, 86, 87], with some evidence suggesting a dose–response relationship between white matter microstructural integrity and peak blood-alcohol concentrations in alcohol users [85].

Dysfunction of the biological stress response as suggested by hyperactive hypothalamic-pituitary-adrenal (HPA) axis responses has been evinced in both heavy alcohol users [88–90] and suicidal individuals [91] alike. Specifically, a subtype of suicide attempters high in trait impulsivity and aggression exhibited heightened cortisol responses to a lab-induced social stressor, compared to suicide attempters low on either aggression, impulsivity, or both [92, 93]. Hyperactive cortisol responses have also been demonstrated in individuals with major depression [71], particularly in relation to symptoms of psychomotor agitation [94], and in individuals with highly variable patterns of suicidal ideation compared to those with stable suicidal thoughts [95]. Moreover, acute alcohol intoxication is associated with stress-like increases in cortisol response [96]. Conceivably, HPA axis dysregulation may heighten the risk of both alcohol misuse and suicidality. Alternatively, alcohol intake might stimulate HPA activity [97] that then contributes to greater likelihood of risky, impulsive, or suicidal behavior. To this point, individuals who demonstrated increased sedative effects with higher dosing of alcohol also mounted greater cortisol responses to a social stress test, suggesting that alcohol intoxication contributes to hyperreactive cortisol responses [98]. Serotonergic dysfunction might also be a cross-cutting link between alcoholism, suicide, and HPA axis dysregulation [99], as serotonergic systems regulate HPA functioning by inhibiting or stimulating stress-related activity [100].

Treatment Interventions for Co-occurring Suicidality and AUD

There is a pressing need to develop effective interventions for co-occurring suicidal ideation and behavior and alcohol misuse because this high-risk population tends to have a more severe course of alcoholism, increased psychiatric and substance use comorbidity, and greater psychosocial impairment (e.g., unemployment, divorce, lower educational attainment), than individuals with AUD alone [101–103]. Additionally, suicide decedents with AUD tended to drink chronically until their deaths and had a recent alcohol binge in close proximity to, or as part of, a suicide attempt [104].

Acute Stabilization

Clinical recommendations suggest inpatient care for individuals with alcohol misuse who present with suicidal plans or intent, preferably in a dual-diagnosis facility (i.e., treatment setting for AUD/SUD and comorbid mental illness) [104, 105]. Evidence suggests that suicidal individuals with comorbid AUD significantly benefit from inpatient treatment relative to outpatient settings [106]. Additionally, acutely intoxicated individuals with suicidal urges appear to stabilize quickly in inpatient care [107]. However, relapse and suicidal behavior following discharge remain significant concerns [108]. Transfer to another inpatient setting following acute stabilization may decrease the risk of postdischarge suicide attempts [109], and longer treatment courses, whether inpatient or outpatient, may lower the posttreatment risk of suicidal behavior [110]. Notably, impulsive suicide attempts may be a strong indicator of relapse risk after discharge. Individuals with alcohol dependence who are hospitalized for an impulsive suicide attempt have higher rates of postdischarge relapse, and relapse faster, than those without an impulsive attempt [111]. This lends support to the clinical utility of targeting suicidality and alcohol misuse simultaneously in the acute stages of treatment.

Pharmacological Interventions There are many FDA-approved medications for treatment of depression [112] and primary among them are selective serotonin reuptake

inhibitors (SSRIs). As yet, however, there are no FDA-approved medications specifically indicated for suicidal ideation, urges, or behavior [113]. A few pharmacotherapies have been approved for the treatment of alcohol misuse [114, 115]. They include disulfiram, which produces aversive symptoms following alcohol intake; acamprosate, thought to mitigate withdrawal-related symptoms; and naltrexone, a nonselective opiate receptor antagonist that reduces alcohol cravings. These drugs primarily operate by targeting reinforcement mechanisms involved in alcohol misuse; however, extended-release naltrexone has also shown some benefits in reducing attendant anxiety and depressive symptoms [116].

Although not specifically indicated for suicidal ideation or behavior, SSRIs have been used with some success in decreasing suicidal ideation alongside other depressive symptoms, and reducing alcohol misuse in depressed alcohol users [101, 117–119]. SSRIs consistently produce a modest 15–20% reduction in alcohol consumption [120], however intra-individual reductions in alcohol intake range widely from 10 to 70% [120]. In addition to SSRIs, tricyclic antidepressants are thought to mitigate depressive-like alcohol withdrawal symptoms [121] and may be effective for co-occurring depression and AUD [122, 123]. Double-blinded, randomized, placebo-controlled trials for co-occurring MDD/dysthymia and AUD indicate that antidepressants—particularly non-SSRIs—outperform placebo in the treatment of depression [122], while SSRIs only demonstrate efficacy when restricted to participants without AUD [124]. Additional meta-analytic research similarly suggests lower performance of SSRIs relative to tricyclics in comorbid MDD and AUD/SUD [119, 125], but results should be interpreted cautiously given the potentially mediating roles of study design and sample selection. Additionally, findings regarding depressive symptom reduction are equivocal when controlling for study quality and bias [126], and antidepressants may not be justified for treatment of alcohol misuse in the absence of MDD [118, 127]. Lastly, studies combining pharmacotherapies for depression and alcohol dependence (e.g., sertraline and naltrexone) suggest better results for mood symptoms and abstinence than either mood or AUD treatment alone [123, 128]. To date, however, there are insufficient trials comparing one medication to another [126], and few that examine the effects of pharmacotherapy on suicidality in alcohol users.

Psychotherapeutic Interventions Brief interventions for suicidal crises (e.g., Safety Planning Intervention; SPI) often implemented in healthcare settings typically involve a written compilation of STB triggers, coping strategies, and sources of support [129]. Similar variations may include a risk assessment component (e.g., ED-SAFE) or intermittent outreach (e.g., SPI+) [130]. These interventions have shown success in reducing imminent suicide risk [52] and may be potentially adapted to address simultaneous risk of alcohol misuse. However, there is a dearth of research evaluating their effectiveness in co-occurring suicidality and AUD.

A variety of longer-term psychotherapies for AUD may be relevant in populations with co-occurring suicidality. Motivational enhancement therapy (MET) is a time-limited intervention that utilizes motivational interviewing (MI) principles to resolve ambivalence about treatment engagement and clarify goals relating to alcohol use [131, 132]. Cognitive behavioral therapy (CBT) for co-occurring mood and AUD focuses on dysfunctional, distorted, or self-defeating schemas or beliefs that may be contributing, jointly or severally, to depressed mood, suicidality, and alcohol misuse [133]. MI and CBT interventions have shown the greatest success among psychotherapeutic interventions used in populations with co-occurring alcohol misuse and depression and/or anxiety, even in brief interventions [134], and longer-term treatments produce still better outcomes. In combination, MET/CBT interventions have shown effectiveness in adolescent populations with co-occurring MDD and AUD [135]. Other interventions, such as relapse prevention therapy (RPT) and contingency management (CM), directly target the psychological reinforcement mechanisms that maintain addictive behavior. While they have been effective in populations with AUD/SUDs, there is limited evidence of their utility in co-occurring suicidality/depression and alcohol misuse [136].

Psychotherapy in combination with psychopharmacological treatment may also benefit from the advantages of each of these modalities [137]. For example, in a study of adolescents with AUD receiving fluoxetine for depression, those who also received a manualized CBT/MET protocol had superior outcomes for depression and alcohol-related symptoms compared to those who did not [135]. However, extant data are not conclusive [115•], and further research is necessary to evaluate the combined effectiveness of psychotherapy and pharmacology in co-occurring suicidality and AUD [138].

Opioids

The US is currently in the midst of an opioid epidemic. In 2016 alone, 11.8 million people misused opioids and 42,000 died by opioid-overdose [139]. Recent research suggests that a suicidal element may play a significant role in opioid overdose deaths [140, 141]. People who use opioids are 14 times more likely to die by suicide compared to the general population [10, 142], perhaps the highest odds of all substances. Indeed, estimates of lifetime suicide attempt rates among individuals with OUD are gravely elevated, ranging between 17% and 48% [143–152].

Co-use of alcohol and opioids can significantly increase the risk of death from overdoses due to respiratory depression [153], and in fact, many OUD-related deaths involve alcohol use [154]. There are a number of predisposing risk factors that

contribute to both AUD and OUD, and some pharmacological treatments are indicated for both AUD and OUD (e.g., naltrexone). However, despite the high cooccurrence of AUD and OUD [155], research on the contribution of this comorbidity to suicide risk is lacking. The below review therefore primarily concerns research on the cooccurrence of OUD and suicidality, without specifically accounting for comorbidity with other substances.

Models of Suicide—OUD Relationships and Shared Risk Factors

The association between OUD and increased suicide risk may be attributed to several factors. Social and environmental disadvantages, such as lack of family support, unemployment, and homelessness [144, 156–158] are highly prevalent among persons with OUD, as well as suicidal individuals. Childhood trauma (e.g., physical or sexual abuse) is a particularly significant early risk factor for suicide [159] and is highly prevalent in OUD [160–162]. Indeed, a history of childhood abuse significantly increase the risk for suicidal behavior in individuals OUD [144, 149, 157].

In addition, suicide may be an extreme expression of the negative affective states [163] that result from the neurobiological changes associated with chronic opioid use [164–166]. Around 75% of individuals dependent on opioids meet criteria for at least one comorbid psychiatric diagnosis [167, 168], predominantly mood and anxiety disorders (35-50%). These rates are much higher than those in the general population [169], and are associated with worse psychosocial and medical status and poorer outcome in OUD [168, 170]. Both OUD and mood and anxiety disorders may share common risk factors, including genetic liability or environmental stressors [171]. Alternatively, psychiatric comorbidities in OUD may result from tolerance and neuroadaptations to chronic opioids use [164–166, 172]. Moreover, because opioids often alleviate emotional, as well as physical, pain, they provide a powerful source of negative reinforcement [173] in the self-medication of negative affective states [174]. The negative reinforcement of psychological pain in opioid use is itself a risk factor for suicidal behavior [175], since with increasing levels of distress, patients may reach a point wherein suicide is perceived to be the only means of escape [163, 176, 177].

Shared Neurobiological Features of Suicide and Opioid Use

Chronic opioid use leads to increasing tolerance, which is associated with allostatic changes to limbic and striatal brain circuitry. These alterations may cause persistent and escalating negative affect [165], thereby contributing to the mental pain that frequently precedes or accompanies suicidal behavior [176–178]. Opioid-induced aversive mental states, a possible byproduct of changes to neural connectivity, are characterized by increased sensitivity to negative emotions, greater stress and pain, and decreased sensitization to natural rewards [164, 165]. Enhanced amygdala activation is one possible correlate of suicidal ideation in OUD, since amygdala activity is implicated in negative emotional reactivity in healthy adults [179, 180] and suicidal ideation in depressed patients [181, 182]. Individuals with OUD have enhanced activation of the amygdala in response to emotional faces [166], relative to controls. Alternatively, persistent negative affective states associated with OUD may disrupt inhibitory control functions, increasing the likelihood that individuals with OUD act on their suicidal impulses. Compared to healthy controls, patients with OUD show impairments in several domains of executive control and decision-making [183–193] that are also linked to an increased risk for suicidal behavior [194]. Specifically, dlPFC and orbitofrontal cortex (OFC) in OUD show lower gray matter volume [195–197], damage to white matter [198–201] and decreased resting-state functional connectivity [195, 202–204], compared with healthy controls. Further, when engaging in tasks requiring response inhibition [205, 206], OUD patients exhibit impaired activation of dlPFC and dorsal anterior cingulate cortex, which are involved in inhibitory control and cognitive regulation of emotions [207]. These impairments may result in dysfunctional decision-making [208], and are also linked to lifetime history of suicidal behavior [209–212].

Some evidence points to the specific role of kappa opioid receptors in mediating negative affective states in OUD. The euphoric effects of most abused opioids (e.g., heroin, oxycodone, and morphine) are due to their *mu* receptors agonism [213]. Chronic opioid use, tolerance, and stress may mobilize the kappa receptors system [214, 215]. Animal studies suggest that an activated kappa receptor system is a key mediator of dysphoria-related symptoms and depressive-like behavior [215–220], both relevant to mood disorders and chronic drug use/dependence [221–228]. In humans, increased expression of kappa receptors has been found *postmortem* in the brains of suicide victims [229]. Moreover, kappa receptors availability in the amygdala-anterior cingulate-striatal circuitry were shown to mediate the phenotypic expression of dysphoria [230].

Reduced serotonergic functioning, implicated in the pathophysiology of depression and suicidality [62, 63], may also play a role in OUD [231]. Serotonin availability at postsynaptic 5-HT1 A receptors modulates pain levels by inhibiting firing of sensory neurons. Opioid drugs enhance this effect by overriding GABA-mediated inhibitory control of serotonergic neurons, causing increased serotonin release that contributes to the drug's analgesic effects. Additionally, activation of 5-HT1 A receptors modulates dopamine transmission, thereby inhibiting the reinforcing or euphoric effects of opioids [232]. Over time, opioid abuse may lead to adaptive changes in the brain that impair serotonergic modulation of

pain and reward, resulting in increased pain sensitivity and opioid dependence [231, 233].

Treatment Interventions for Co-occurring Suicidality and OUD

Acute Stabilization Clinical guidelines recommend initiating pharmacological treatment for opioid withdrawal (e.g., methadone) in an inpatient setting or opioid treatment program, particularly for individuals presenting with suicidal ideation or other unmanaged psychiatric symptoms [234, 235]. Individuals with OUD frequently present to the emergency room with complications from opioid use, including withdrawal-related symptoms or overdose [236], and therefore emergency room-based intervention reflects a key point of linkage to care for this population.

Pharmacological Interventions Few medications are available for prevention of relapse in OUD. Methadone is a long-acting full opioid receptor agonist that has been long used for treatment of individuals with OUD [237]. Although methadone treatment in persons with OUD and comorbid depression may lead to modest improvement in depressive symptoms, they often require antidepressant medications to produce meaningful reductions in depressed mood [237]. Additionally, while a recent epidemiological study reported that individuals receiving methadone experienced a 40% reduction in SB compared to periods when they were not on the medication [238], other studies show that patients may continue to experience SI or engage in SB (e.g., overdose) while on methadone [239]. Extended-release naltrexone hydrochloride (XR-NTX) is a nonselective opioid receptor antagonist that has been also widely used for treatment of OUD and AUD, among other indications. Although initial dysphoria and anxiety have been reported when starting treatment with naltrexone, presumably a result of unmasking symptoms of psychiatric distress concealed by daily intake of opioids, these symptoms gradually subside in participants adherent to treatment [240–247]. Some studies report an improvement in depressive symptoms in patients with OUD after 4 weeks of adherence to naltrexone treatment [242, 246].

Buprenorphine, a *mu* opioid receptor partial agonist and *kappa* receptor antagonist, has become one of the most prescribed treatments for OUD relapse prevention in the US [248, 249]. Induction of buprenorphine in the emergency room for individuals with OUD who present with opioid overdoses has been shown to decrease the risk for future overdose [250]. Interestingly, buprenorphine has shown efficacy in treating depressive symptoms during the course of treatment of OUD [251], as well as in treatment-resistant depression [252–254]. Additionally, buprenorphine has shown promise in reducing suicidal ideation [255, 256]. Some case reports reported significant reduction in suicidal ideation with the start of buprenorphine treatment for OUD [257, 258]. Even in individuals without OUD, Yovell et al. [259] found that a very low dose of buprenorphine (0.1–0.8 mg/day) significantly reduced suicidal ideation in 2 weeks, compared with placebo. Interestingly, prior studies provided evidence for the rapid antidepressant and anti-suicidal action of buprenorphine, which seemed to act within a week after the first administration [252, 254, 258, 260–264]. Collectively, this may support the beneficial effect of buprenorphine as a rapid-acting treatment for high-risk suicidal individuals, particularly in those with OUD. Accumulating evidence suggests that kappa antagonism properties of buprenorphine may underlie its antisuicidal properties via reducing negative affect responses in the amygdala and enhancing activity of regulatory frontal regions. In preclinical models of depression, buprenorphine produced antidepressant and anxiolytic responses [265–268] driven by its kappa antagonist properties [267, 268]. More specifically, agonism to the amygdala kappa receptors mediated anxiogenic-like behavior [269] whereas antagonism to kappa receptors in the amygdala [269, 270] and prefrontal cortex [271] produced anxiolytic effects. Relative to controls, patients with OUD treated with buprenorphine demonstrated reduced amygdala activation in response to negative stimuli [272]. In addition, buprenorphine causes decreased amygdala responses to heroin-related cues in heroin-dependent patients [273].

Psychotherapeutic Interventions There is some evidence to support the incremental utility of psychosocial interventions in combination with pharmacotherapy for OUD [274, 275]. These interventions include contingency management (CM) and other cognitive-behavioral therapies (CBT), as well as supportive psychotherapy [276]. In opioid-using adolescents and young adults, motivational enhancement therapy (MET) and CBT, as well as combined MET/CBT, have demonstrated efficaciousness in compared to a community reinforcement approach, although findings appeared to be mediated by sex and age [277]. Other meta-analytic work conclude that structured psychosocial interventions contribute little to opiate substitution programs beyond the routine counseling provided with pharmacological treatment [278]. However, such studies do not account for the utility of psychosocial treatment in reducing suicidal ideation and behavior in individuals with OUD, and research on psychosocial interventions for opioid use and co-occurring suicidality remains an outstanding area of study.

Conclusion

Alcohol and opioid use are the two most common substances implicated in suicidal behavior [14•]. This review briefly surveys the literature on the overlap of these disorders, highlighting the complex and multidirectional relationships between them. A meaningful understanding of the different roles that

alcohol and opioid use can play in suicidal behavior, however, will require continued study of their shared risk factors, mechanisms, and interventions. For example, further empirical research is necessary to differentiate the acute effects of alcohol and opioid intake on suicidality, separably from chronic or dependent use. Additionally, the gaps in intervention research on co-occurring suicidality and AUD/OUD are substantial, and pharmacological studies do not frequently account for the effects on suicidality, specifically, in addition to mood improvements in mood, in alcohol/opioid users. Given the high prevalence of alcohol/opioid use alongside escalating rates of suicide, there is a compelling need for attention to their cooccurrence.

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