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

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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
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-HT1A 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-HT1A and 5-HT1B 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 5-hydroxyindolacetic acid (SHIAA; a major metabolite of serotonin), and high lethality
attempts 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 promotor 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 serotonin functioning, implicated in the pathophysiology of depression and suicidality [62, 63], may also play a role in OUD [231]. Serotonin availability at postsynaptic 5-HT1A 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-HT1A 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 μ 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.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Centers for Disease Control and Prevention. National Center for Injury Prevention and Control. (2020). Web-based injury statistics query and reporting system (WISQARS). from www.cdc.gov/injury/wisqars. Accessed 01 Dec 2020

2. U.S. Department of Health and Human Services. (2010, August 10, 2020). Mental health and mental disorders objectives. Healthy People 2020. 2020, from https://www.healthypeople.gov/2020/topics-objectives/topic/mental-health-and-mental-disorders/objectives. Accessed 01 Dec 2020

3. Brown GK, Beck AT, Steer RA, Grisham JR. Risk factors for suicide in psychiatric outpatients: a 20-year prospective study. J Consult Clin Psychol. 2000;68(3):371–7.

4. Sokero TP, Melartin TK, Rytasla HJ, Leskela US, Lestela-Mielonen PS, Isometsa ET. Prospective study of risk factors for attempted suicide among patients with DSM-IV major depressive disorder. Br J Psychiatry. 2005;186(4):314–8.

5. Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM. Psychological autopsy studies of suicide: a systematic review. Psychol Med. 2003;33(3):395–405.

6. Pirkis J, Burgess P, Dunt D. Suicidal ideation and suicide attempts among Australian adults. Crisis. 2000;21(1):16–25.

7. Cottler LB, Campbell W, Krishna VAS, Cunningham-Williams RM, Ben Abdallah A. Predictors of high rates of suicidal ideation among drug users. J Nerv Ment Dis. 2005;193(7):431–7.

8. Borges G, Walters EE, Kessler RC. Associations of substance use, abuse, and dependence with subsequent suicidal behavior. Am J Epidemiol. 2000;151(8):781–9.

9. Bernal M, Haro JM, Bernert S, et al. Risk factors for suicidality in Europe: results from the ESEMED study. J Affect Disord. 2007;101(3–4):27–34.

10. Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug Alcohol Depend. 2004;76(Suppl):S11–9.

11. Cheek SM, Nestor BA, Liu RT. Substance use and suicidality: specificity of substance use by injection to suicide attempts in a nationally representative sample of adults with major depression. Depress Anxiety. 2016;33(6):541–8.

12. Espinet S, Corrin T, Balinunas D, et al. Predisposing and protective factors influencing suicide ideation, attempt, and death in patients accessing substance use treatment: a systematic review and meta-analysis protocol. Syst Rev. 2019;8(1):115.

13. Rizk MM, Galfalvy H, Miller JM, et al. Characteristics of depressed suicide attempters with remitted substance use disorders. J Psychiatr Res. 2020.

14. Esang M, & Ahmed S. A closer look at substance use and suicide. Am J Psychiatry Residents’. J. (2018). A brief review of risk for suicidal behavior in alcohol and substance use: findings from the 2005 youth risk behavior survey. J Adolesc Health. 2007:41(2):175–81.

15. Groves SA, Stanley BH, & Sher L Ethnicity and the relationship between adolescent alcohol use and suicidal behavior. Int J Adolesc Med Health. (2007).

16. Darvishi N, Farhadi M, Haghtalab T, Pooorolajal J. Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: a meta-analysis. PLoS One. 2015;10(5):e0126870.

17. Flensborg-Madsen T, Knop J, Mortensen EL, Becker U, Sher L, Gronbaek M. Alcohol use disorders increase the risk of completed suicide—irrespective of other psychiatric disorders. A longitudinal cohort study. Psychiatry Res. 2009;167(1-2):123–30.

18. Sher L. Alcohol consumption and suicide. Qjm. 2006;99(1):57–61.

19. Ramstedt M. Alcohol and suicide in 14 European countries. Addiction. 2001;96(1s1):59–75.

20. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001–2002 to 2012–2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. JAMA Psychiatry. 2017;74(9):911–23.

21. White AM, Castle IJP, Hingson RW, Powell PA. Using death certificates to explore changes in alcohol-related mortality in the United States, 1999 to 2017. Alcohol Clin Exp Res. 2020;44(1):178–87.

22. Hedegaard H, Curtin SC, & Warner M Increase in suicide mortality in the United States, 1999–2018. (2020).

23. Rossen LM, Hedegaard H, Khan D, Warner M. County-level trends in suicide rates in the US, 2005–2015. Am J Prev Med. 2018;55(1):72–9.

24. Hufford MR. Alcohol and suicidal behavior. Clin Psychol Rev. 2001;21(5):797–811.

25. Lewis MR. Alcohol-related risk factors for suicidal behavior: a review of the literature. Alcohol Clin Exp Res. 2004;28:18–28S.

26. Borges G, Bagge C, Cherpilte CJ, Borges GL, Wilcox HC. Acute alcohol use and suicidal behavior: a review of the literature. Alcohol Clin Exp Res. 2004;28:18–28S.

27. Borges G, Bagge C, Cherpilte CJ, Conner K, Ooroza R, Rossow I. A meta-analysis of acute alcohol use and the risk of suicide attempt. Psychol Med. 2017;47(5):949.

28. Sher L, Quinodo MA, Richardson-Velgaga R, et al. Effect of acute alcohol use on the lethality of suicide attempts in patients with mood disorders. J Psychiatr Res. 2009;43(10):901–5.

29. Centers for Disease Control and Prevention. (2014b). Surveillance for violent deaths—national violent death reporting system, 16 States, 2010. MMWR. 63(1). from http://www.cdc.gov/mmwr/pdf/ss/ss6301.pdf. Accessed 01 Dec 2020.

30. Norström T, Rossow I. Alcohol consumption as a risk factor for suicidal behavior: a systematic review of associations at the individual and at the population level. Arch Suicide Res. 2016;20(4):489–506.

31. Conner KR, & Bagge, CL Suicidal behavior: links between alcohol use disorder and acute use of alcohol. Alcohol Res: current reviews, 40(1). (2019)
32. Brady J. The association between alcohol misuse and suicidal behaviour. Alcohol Alcohol. 2006;41(5):473–8.
33. Bagge CL, Sher KJ. Adolescent alcohol involvement and suicide attempts: toward the development of a conceptual framework. Clin Psychol Rev. 2008;28(8):1283–96.
34. World Health Organization (WHO). World Health Organization (WHO) 2014 global status report on alcohol and health. from www.who.int/substance_abuse/publications/global_alcohol_report/en/
35. Kresnow MJ, Powell KE, Webb KB, et al. Assigning time-linked exposure status to controls in unmatched case-control studies: alcohol use and nearly lethal suicide attempts. Stat Med. 2001;20(9-10):1479–85.
36. Baumeister RF. Suicide as escape from self. Psychol Rev. 1990;97(1):90.
37. Shneidman ES. Suicide as psychache: a clinical approach to self-destructive behavior. Jason Aronson. 1993
38. Gonzalez VM, Reynolds B, Skewes MC. Role of impulsivity in the relationship between depression and alcohol problems among emerging adult college drinkers. Exp Clin Psychopharmacol. 2011;19(4):303.
39. Mann JJ, Watermanciu, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatr. 1999;156(2):181–9.
40. Mann JJ, Rizk MM. A brain-centric model of suicidal behavior. Am J Psychiatr. 2020;177(10):902–16.
41. McGinn A, Turecki G. The relationship of impulsive aggressiveness to suicidality and other depression-linked behaviors. Curr Psychiatry Rep. 2007;9(6):460–6.
42. Dick DM, Smith G, Olausson P, et al. Understanding the construct of impulsivity and its relationship to alcohol use disorders. Addict Biol. 2010;15(2):217–26.
43. Fulfiler C, Eckstine J, Kalsy S. Impulsive-aggressive traits, serotonin function, and alcohol-enhanced aggression. J Clin Pharmacol. 2005;45(1):94–100.
44. Turecki G, Ernst C, Jollant F, Labonté B, Mechawar N. The neurodevelopmental origins of suicidal behavior. Trends Neurosci. 2012;35(1):14–23.
45. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health. 2017;2(8):e356–66.
46. Braquehais MD, Oquendo MA, Baca-García E, Sher L. Is impulsivity a link between childhood abuse and suicide? Compr Psychiatry. 2010;51(2):121–9.
47. Caetano R, Schafer J, Cinardi CB. Alcohol-related intimate partner violence among white, black, and Hispanic couples in the United States. Alcohol Res Health. 2001;25(1):58.
48. Murphy CM, O'Farrell TJ, Fals-Stewart W, Feenan M. Correlates of intimate partner violence among male alcoholic patients. J Consult Clin Psychol. 2001;69(3):528.
49. Mulia N, Zemore SE, Murphy R, Liu H, Catalano R. Economic loss and alcohol consumption and problems during the 2008 to 2009 US recession. Alcohol Clin Exp Res. 2014;38(4):1026–34.
50. Stuckler D, Basu S, Suhrecke M, Coutts A, McKee M. The public health effect of economic crises and alternative policy responses in Europe: an empirical analysis. Lancet. 2009;374(9686):315–23.
51. Bagge CL, Littlefield AK, Conner KR, Schumacher JA, Lee H-J. Near-term predictors of the intensity of suicidal ideation: an examination of the 24 h prior to a recent suicide attempt. J Affect Disord. 2014;165:53–8.
52. Turecki G, Brent DA, Gunnell D, et al. Suicide and suicide risk. Nat Rev Disease Primers. 2019;5(1):1–22.
53. Conwell Y, Rotenberg M, Caine ED. Completed suicide at age 50 and over. J Am Geriatr Soc. 1990;38(6):640–4.
54. Fanning JR, Pietrzak RH. Suicidality among older male veterans in the United States: results from the National Health and Resilience in Veterans Study. J Psychiatr Res. 2013;47(11):1766–75.
55. Thompson JM, Zamorski MA, Sweet J, et al. Roles of physical and mental health in suicidal ideation in Canadian Armed Forces Regular Force veterans. Can J Public Health. 2014;105(2):e109–15.
56. Russell D, Turner RJ, Joiner TE. Physical disability and suicidal ideation: a community-based study of risk/protective factors for suicidal thoughts. Suicide Life Threat Behav. 2009;39(4):440–51.
57. Zhao Q, Pfefferbaum A, Podhajsky S, Pohl KM, Sullivan EV. Accelerated aging and motor control deficits are related to regional deformation of central cerebellar white matter in alcohol use disorder. Addict Biol. 2020;25(3):e12746.
58. Grüpper S, Spengler S, Stuke H, et al. Behavioral impulsivity mediates the relationship between decreased frontal gray matter volume and harmful alcohol drinking: a voxel-based morphometry study. J Psychiatr Res. 2016;83:16–23.
59. Noonberg A, Goldstein G. Premature aging in male alcoholics: “accelerated aging” or “increased vulnerability”? Alcohol Clin Exp Res. 1985;9(4):334–8.
60. Le Berre AP, Fama R, Sullivan EV. Executive functions, memory, and social cognitive deficits and recovery in chronic alcoholism: a critical review to inform future research. Alcohol Clin Exp Res. 2017;41(8):1432–43.
61. Richard-Devantoy S, Berlim MT, Jollant F. Suicidal behaviour and memory: a systematic review and meta-analysis. World J Bio Psychiatry. 2015;16(8):544–66.
62. van Heeringen K, Mann JJ. The neurobiology of suicide. Lancet Psychiatry. 2014;1(1):63–72.
63. Sher L, Stanley B, Grunebaum M, et al. Lower cerebrospinal fluid 5-hydroxyindolacetic levels in depressed high-lethality suicide attempters with comorbid alcoholism. Paper presented at the Biological Psychiatry. 2005
64. Pihl RO, Lemerquand D. Serotonin and aggression and the alcohol-aggression relationship. Alcohol Alcohol. 1998;33(1):55–65.
65. Underwood MD, Mann JJ, Arango V. Serotonergic and noradrenergic neurobiology of alcoholic suicide. Alcohol Clin Exp Res. 2004;28:578–69S.
66. Coppen A. The biochemistry of affective disorders. Br J Psychiatry. 1967;113(504):1237–64.
67. Nautiyal KM, Hen R. Serotonin receptors in depression: from A to B. F1000Research. 2017;6:123.
68. Placidi GP, Oquendo MA, Malone KM, Huang Y-Y, Ellis SP, Mann JJ. Aggressivity, suicide attempts and depression: relationship to cerebrospinal fluid monoamine metabolite levels. Biol Psychiatry. 2001;50(10):783–91.
69. Ballenger JC, Goodwin FK, Major LF, Brown GL. Alcohol and central serotonin metabolism in man. Arch Gen Psychiatry. 1979;36(2):224–7.
70. Linnola M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindolacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sci. 1983;33(26):2609–14.
71. Mann JJ. Neurobiology of suicidal behaviour. Nat Rev Neurosci. 2003;4(10):819–28.
72. Gorwood P, Batel P, Adès J, Hamon M, Boni C. Serotonin transporter gene polymorphisms, alcoholism, and suicidal behavior. Biol Psychiatry. 2000;48(4):259–64.
73. Sander T, Harms H, Lesch KP, et al. Association analysis of a serotonin transporter gene polymorphism, alcoholism, and suicidal behavior. Alcohol Clin Exp Res. 1997;21(8):1356–9.
74. Sander T, Harms H, Dufé P, et al. Serotonin transporter gene variants in alcohol-dependent subjects with dissociative personality disorder. Biol Psychiatry. 1998;43(12):908–12.
94. Brown RP, Stoll PM, Stokes PE, et al. Adrenocortical hyperactivity in depression: effects of agitation, delusions, melancholia, and other illness variables. Psychiatry Res. 1988;23(2):167–78.
95. Rizk MM, Galfalvy H, Singh T, et al. Toward subtyping of suicidality: brief suicidal ideation is associated with greater stress response. J Affect Disord. 2018;230:87–92.
96. Lovallo WR. Cortisol secretion patterns in addiction and addiction risk. Int J Psychophysiol. 2006;59(3):195–202.
97. Blaine SK, Sinha R. Alcohol, stress, and glucocorticoids: from risk to dependence and relapse in alcohol use disorders. Neuropsychopharmacology. 2017;122:136–47.
98. Brkic S, Söderpalm B, Gosh D. High cortisol responders to stress show increased sedation to alcohol compared to low cortisol responders: an alcohol dose–response study. Pharmacol Biochem Behav. 2016;143:65–72.
99. Braquehais MD, Picutto MD, Casas M, Sher L. Hypothalamo-pituitary-adrenal axis dysfunction as a neurobiological correlate of emotion dysregulation in adolescent suicide. World J Pediatr. 2012;8(3):197–206.
100. Lowry C. Functional subsets of serotonergic neurons: implications for control of the hypothalamo-pituitary-adrenal axis. J Neuroendocrinol. 2002;14(11):911–23.
101. Cornelius JR, Salloum IM, Cornelius MD, et al. Fluoxetine trial in suicidal depressed alcoholics. Psychopharmacol Bull. 1993;29(2):195–9.
102. Sher L, Stanley BH, Harvay-Kried Friedman JM, et al. Depressed patients with co-occurring alcohol use disorders: a unique patient population. J Clin Psychiatry. 2008;69(6):907–15.
103. Preuss U, Schuckit MA, Smith TL, et al. Comparison of 3190 alcohol-dependent individuals with and without suicide attempts. Alcohol Clin Exp Res. 2002;26(4):471–7.
104. Cornelius JR, Clark DB, Salloum IM, Bukstein OG, Kelly TM. Interventions in suicidal alcoholics. Alcohol Clin Exp Res. 2004;28:989–96.
105. Cornelius JR, Salloum IM, Mezzich J, et al. Disproportionate suicidality in patients with comorbid major depression and alcoholism. Am J Psychiatry. 1995;152(3):358–64.
106. Ilgen MA, Tiet Q, Finney JW, Harris AH. Recent suicide attempt and the effectiveness of inpatient and outpatient substance use disorder treatment. Alcohol Clin Exp Res. 2005;29(9):1664–71.
107. Miller KA, Hintsfield MJ, Lineberry TW, Palmer BA. How does active substance use at psychiatric admission impact suicide risk and hospital length-of-stay? J Addict Dis. 2016;35(4):291–7.
108. Loch AA. Discharged from a mental health admission ward: is it safe to go home? A review on the negative outcomes of psychiatric hospitalization. Psychiat Res Behav Manag. 2014;7:137.
109. Britton PC, Stephens B, Wu J, et al. Comorbid depression and alcohol use disorders and prospective risk for suicide attempt in the year following inpatient hospitalization. J Affect Disord. 2015;187:151–5.
110. Ilgen MA, Jain A, Lucas E, Moos RH. Substance use-disorder treatment and a decline in attempted suicide during and after treatment. J Stud Alcohol Drugs. 2007;68(4):503–9.
111. Wojnar M, Ilgen MA, Jakubczyk A, Wonrowska A, Klimkiewicz A, Brower KJ. Impulsive suicide attempts predict post-treatment relapse in alcohol-dependent patients. Drug Alcohol Depend. 2008;97(3):268–75.
112. Park LT, Zarate CA Jr. Depression in the primary care setting. N Engl J Med. 2019;380(6):559–68.
113. Tondo L, Baldessarini RJ. Suicidal behavior in mood disorders: response to pharmacological treatment. Curr Psychiatry Rep. 2016;18(9):88.
114. Dongier M. What are the treatment options for comorbid alcohol abuse and depressive disorders. J Psychiatry Neurosci. 2005;30(3):224.
115. DeVido JJ, Weiss RD. Treatment of the depressed alcoholic pa-
tient. Curr Psychiatry Rep. 2012;14(6):610–8. An integrative re-
view summarizing empirical research on various approaches
to the assessment and treatment of patients with co-occurring
alcohol use disorders and depressive disorders.
116. Benth JS, Solli KK, Opheim A, et al. Anxiety, depression, and
insomnia among adults with opioid dependence treated with
extended-release naltrexone vs buprenorphine-naloxone: a ran-
domized clinical trial and follow-up study. JAMA Psychiatry.
2019;76(2):127–34.
117. Cornelius JR, Salloum IM, Ehler JG, Jarrett PJ. Double-blind flu-
oxetine in depressed alcoholic smokers. Psychopharmacol Bull.
1997;33(1):165.
118. Torrens M, Fonseca F, Mateu G, Farré M. Efficacy of antidepress-
ts in substance use disorders with and without comorbid de-
pression: a systematic review and meta-analysis. Drug Alcohol
Depend. 2005;78(1):1–22.
119. Stokes PR, Jokinen T, Amawi S, et al. Pharmacological treatment of
mood disorders and comorbid addictions: a systematic review
and meta-analysis. Can J Psychiatry. 2020;65(11):749–69
0706743720915420. An important systematic metanalytic re-
view of 32 placebo-controlled randomized controlled trials in-
vestigating the effects of antidepressants in the treatment of
co-occurring alcohol/substance use disorders and mood disor-
ers (e.g., bipolar disorder, MDD).
120. Naranjo CA, Knoke DM. The role of selective serotonin reuptake
inhibitors in reducing alcohol consumption. J Clin Psychiatry.
2001;62(Suppl 20):18–25.
121. Getachew B, Hauser SR, Csoka AB, Taylor RE, Tizabi Y. Role of
cortical alpha-2 adrenoceptors in alcohol withdrawal-induced
depression and tricyclic antidepressants. Drug Alcohol Depend.
2017;175:133–9.
122. Iovino N, Tedeschini E, Bentley KH, Evins AE, Papakostas GL.
Antidepressants for major depressive disorder and dysthymic dis-
order in patients with comorbid alcohol use disorders: a meta-
analysis of placebo-controlled randomized trials. J Clin Psychiatry.
2011;72(8):1144–51.
123. Pedrelli, P., & Bentley, K. H. (2019). Co-occurring MDD and
problematic alcohol use The Massachusetts General Hospital
Guide to Depression (pp. 21-30: Springer.
124. Pettinati HM, Volpottelli JR, Luck G, Kranzler HR, Rukstalis MR,
Cnaan A. Double-blind clinical trial of sertraline treatment for
alcohol dependence. J Clin Psychopharmacol. 2001;21(2):143–
53.
125. Nunes EV, Levin FR. Treatment of depression in patients with
alcohol or other drug dependence: a meta-analysis. Jama.
2004;291(15):1887–96.
126. Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of
people with co-occurring depression and alcohol dependence.
Cochrane Database Syst Rev. 2018;4:CD008581.
127. Chick J. Unhelpful prescribing in alcohol use disorder: risk and
averting risk. Oxford: Oxford University Press; 2019.
128. Pettinati HM, Oslin DW, Kampman KM, et al. A double-blind,
placebo-controlled trial combining sertraline and naltrexone for
treating co-occurring depression and alcohol dependence. Am J
Psychiatr. 2010;167(6):668–75.
129. Stanley B, Brown GK, Brenner LA, et al. Comparison of the
safety planning intervention with follow-up vs usual care of sui-
cidal patients treated in the emergency department. JAMA
Psychiatry. 2018;75(9):894–900.
130. Miller IW, Camargo CA, Arias SA, et al. Suicide prevention in
an emergency department population: the ED-SAFE study. JAMA
Psychiatry. 2017;74(6):563–70.
131. NIDA. (2020). Motivational enhancement therapy (alcohol, mari-
jjuana, nicotine). https://www.drugabuse.gov/publications/prin-
ciples-drug-addiction-treatment-research-based-guide-third-
edition/evidence-based-approaches-to-drug-addiction-treatment/
behavioral-therapies/motivational-enhancement-therapy. Accessed 01 Dec 2020
132. Apodaca TR, Longabaugh R. Mechanisms of change in motiva-
tional interviewing: A review and preliminary evaluation of the
evidence. Addiction. 2009;104(5):705–15.
133. Ziedonis, DM, Krejić J, Westermeyer J, Weiss R, & Ziedonis D
(2003). Dual recovery therapy: blending psychotherapies for
depression and addiction: Integrated Treatment for Mood and
Substance Disorders. Edited by Westermeyer ....
134. Baker AL, Thornton IK, Hiles S, Hides L, Lubman DI. Psychological interventions for alcohol misuse among people with co-occurring depression or anxiety disorders: a systematic review. J Affect Disord. 2012;139(3):217–29.
135. Cornelius JR, Douaihy A, Bukstein OG, et al. Evaluation of cog-
nitive behavioral therapy/motivational enhancement therapy
(CBT/MET) in a treatment trial of comorbid MDD/AUD adoles-
cents. Addict Behav. 2011;36(8):843–8.
136. Prendergast M, Podus D, Finney J, Greenwell L, Roll J. Contingency management for treatment of substance use disor-
ders: a meta-analysis. Addiction. 2006;101(11):1546–60.
137. Baker AL, Kavanagh DJ, Kay-Lambkin FJ, et al. Randomized
tested controlled trial of cognitive–behavioural therapy for coexisting depression and alcohol problems: short-term outcome. Addiction. 2010;105(1):87–99.
138. Thase ME, Salloum IM, Cornelius JD. Comorbid alcoholism and
depression: treatment issues. J Clin Psychiatry. 2001.
139. Mack KA, Jones CM, Ballesteros MF. Illicit drug use, illicit drug
use disorders, and drug overdose deaths in metropolitan and non-
metropolitan areas-United States. Am J Transplant. 2017;17(12):
3241–52.
140. Oquendo MA, Volkow ND. Suicide: a silent contributor to
opioid-overdose deaths. N Engl J Med. 2018;378(17):1567–9.
141. An editorial perspective on the need to address the role of
suicidality in opioid-related deaths.
142. Braden JB, Edlund MJ, Sullivan MD. Suicide deaths with opioid
poisoning in the United States: 1999-2014. Am J Public Health.
2017;107(3):421–6.
143. Harris EC, Barraclough B. Suicide as an outcome for mental dis-
orders. A meta-analysis. Br J Psychiatry. 1997;170(3):205–28.
144. Maloney E, Degenhardt L, Darke S, Nelson EC. Are non-fatal
opioid overdoses misclassified suicide attempts?Comparing the
associated correlates. Addict Behav. 2009;34(9):723–9.
145. Roy A. Risk factors for attempting suicide in heroin addicts.
Suicide Life Threat Behav. 2010;40(4):416–20.
146. Tremeau F, Darreye A, Staner L, et al. Suicidality in opioid-de-
pendent subjects. Am J Addict. 2008;17(3):187–94.
147. Darke S, Ross J, Lynskey M, Teesson M. Attempted suicide
among entrants to three treatment modalities for heroin depen-
dence subjects. Am J Addict. 2008;17(3):187–94.
148. Darke S, Ross J, Lynchskey M, Teesson M. Attempted suicide
among entrants to three treatment modalities for heroin depen-
dence in the Australian Treatment Outcome Study (ATOS): prev-
ence and risk factors. Drug Alcohol Depend. 2004;73(1):1–10.
149. Kazour F, Soufia M, Rohayem J, Richa S. Suicide risk of heroin
dependent subjects in Lebanon. Community Ment Health J.
2016;52(5):589–96.
150. Icick R, Pecoć K, Ksouda K, et al. OPRM1 polymorphism and
lifetime suicide attempts among stabilized, methadone-maintained
inpatients. Psychiatry Res. 2014;218(1-2):259–60.
151. Murphy SL, Rounsaville BJ, Eyre S, Kleber HD. Suicide attempts
in treated opiate addicts. Compr Psychiatry. 1983;24(1):79
–88.
152. Darke S, Torok M, Kaye S, Ross J. Attempted suicide, self-harm,
and violent victimization among regular illicit drug users. Suicide
Life Threat Behav. 2010;40(4):416–20.
153. Apodaca TR, Longabaugh R. Mechanisms of change in motiva-
tional interviewing: A review and preliminary evaluation of the
evidence. Addiction. 2009;104(5):705–15.
154. Ziedonis, DM, Krejić J, Westermeyer J, Weiss R, & Ziedonis D
(2003). Dual recovery therapy: blending psychotherapies for
depression and addiction: Integrated Treatment for Mood and
Substance Disorders. Edited by Westermeyer ....
Kirby KN, Petry NM. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction. 2004;99(4):461–71.

Richard-Devantoy S, Berlim MT, Jollant F. A meta-analysis of neuropsychological markers of vulnerability to suicidal behavior in mood disorders. Psychol Med. 2014;44(8):1663–73.

Lin HC, Wang PW, Wu HC, Ko CH, Yang YH, Yen CF. Altered gray matter volume and disrupted functional connectivity of dorsolateral prefrontal cortex in men with heroin dependence. Psychiatry Clin Neurosci. 2018;72(6):435–44.

Lyoo IK, Pollack MH, Silveri MM, et al. Prefrontal and temporal gray matter density decreases in opiate dependence. Psychopharmacology. 2006;184(2):139–44.

Yuan K, Qin W, Dong M, et al. Gray matter deficits and resting-state abnormalities in abstinent heroin-dependent individuals. Neurosci Lett. 2010;482(2):101–5.

Liu H, Li L, Hao Y, et al. Disrupted white matter integrity in heroin dependence: a controlled study utilizing diffusion tensor imaging. Am J Drug Alcohol Abuse. 2008;34(5):562–75.

Li W, Li Q, Wang Y, et al. Methadone-induced damage to white matter integrity in methadone maintenance patients: a longitudinal self-control DTI study. Sci Rep. 2016;6:19662.

Lyoo IK, Streeter CC, Ahn KH, et al. White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. Psychiatry Res. 2004;131(2):135–45.

Qiu Y, Jiang G, Su H, et al. Progressive white matter microstructure damage in male chronic heroin dependent individuals: a DTI and TBSS study. PLoS One. 2013;8(5):e63212.

Ma N, Liu Y, Li N, et al. Addiction related alteration in resting-state brain connectivity. NeuroImage. 2010;49(1):738–44.

Liu J, Jiang J, Qin W, et al. Dysfunctional connectivity patterns in chronic heroin users: an fMRI study. Neurosci Lett. 2009;460(1):72–7.

Cheng GL, Zeng H, Leung MK, et al. Heroin abuse accelerates biological aging: a novel insight from telomerase and brain imaging interaction. Transl Psychiatry. 2013;3:e260.

Fu LP, Bi GH, Zou ZT, et al. Impaired response inhibition function in abstinent heroin dependents: an fMRI study. Neurosci Lett. 2008;438(3):322–6.

Schmidt A, Walter M, Gerber H, et al. Inferior frontal cortex modulation with an acute dose of heroin during cognitive control. Neuropsychopharmacology. 2013;38(11):2231–9.

Buhle JT, Silvers JA, Wager TD, et al. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cereb Cortex. 2014;24(11):2981–90.

Manes F, Sahabian B, Clark L, et al. Decision-making processes following damage to the prefrontal cortex. Brain. 2002;125(3):624–39.

Giakoumato CI, Tandon N, Shah J, et al. Are structural brain abnormalities associated with suicidal behavior in patients with psychiatric disorders? J Psychiatr Res. 2013;47(10):1389–95.

Soloff PH, Pruitt P, Sharma M, Radwan J, White R, Diwadkar VA. Structural brain abnormalities and suicidal behavior in borderline personality disorder. J Psychiatr Res. 2012;46(4):516–25.

Oquendo MA, Placidi GP, Malone KM, et al. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. Arch Gen Psychiatry. 2003;60(1):14–22.

Sublette ME, Milak MS, Galfalvy HC, Oquendo MA, Malone KM, Mann JJ. Regional brain glucose uptake distinguishes suicide attempters from non-attempters in major depression. Arch Suicide Res. 2013;17(4):434–47.

Le Merrer J, Becker JA, Befort K, Kieffer BL. Reward processing by the opioid system in the brain. Physiol Rev. 2009;89(4):1379–412.
Cleary DR, Heinricher MM. Adaptations in responsiveness of opioid involvement using opioid use. Am Soc Addict Med. 66. (2015)

Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9(5):358.

Fox L, Nelson LS. Emergency department initiation of buprenorphine for opioid use disorder: current status, and future potential. CNS drugs. 2019;33(12):1147–54.

Maremmanni AGI, Pacini M, Maremmanni I. What we have learned from the Methadone Maintenance Treatment of Dual Disorder Heroin Use Disorder patients. Int J Environ Res Public Health. 2019;16(3):447.

Molero Y, Zetzer-Yj, Binswanger JA, Hellner C, Larsson H, Fazel S. Medications for alcohol and opioid use disorders and risk of suicidal behavior, accidental overdoses, and crime. Am J Psychiatry. 2018;175(10):970–8.

Michel L, Lions C, Maradan G, et al. Suicidal risk among patients enrolled in methadone maintenance treatment: HCV status and implications for suicide prevention (ANRS Methaville). Compr Psychiatry. 2015;62:123–31.

O’Brien CP, Gastfriend DR, Forman RF, Schweizer E, Pettinati HM. Long-term opioid blockade and hedonic response: preliminary data from two open-label extension studies with extended-release naltrexone. Am J Addict. 2011;20(2):106–12.

Wardle MC, Bershad AK, de Wit H. Naltrexone alters the processing of social and emotional stimuli in healthy adults. Soc Neurosci. 2016;11(6):579–91.

Krupsky E, Zwartau E, Blokhina E, et al. Anhedonia, depression, anxiety, and craving in opioid dependent patients stabilized on oral naltrexone or an extended release naltrexone implant. Am J Drug Alcohol Abuse. 2016;42(5):614–20.

Miotto K, McCann M, Basch J, Rawson R, Ling W. Naltrexone and dysphoria: fact or myth? Am J Addict. 2002;11(2):151–60.

Croop RS, Faulkner EB, Labriola DF. The safety profile of naltrexone in the treatment of alcoholism. Results from a multicenter usage study The Naltrexone Usage Study Group. Arch Gen Psychiatry. 1997;54(12):1130–5.

Zaaijer ER, van Dijk L, de Bruin K, et al. Effect of extended-release naltrexone on striatal dopamine transporter availability, depression and anhedonia in heroin-dependent patients. Psychopharmacology. 2015;232(14):2597–607.

Myers DJ, Cheng WY, Nous E, Sullivan MA. The association between naltrexone treatment and symptoms of depression in opioid-dependent patients. Am J Drug Alcohol Abuse. 2011;37(1):22–6.

Dean AJ, Saunders JB, Jones RT, Young RM, Connor JP, Lawford BR. Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence. J Psychiatry Neurosci. 2006;31(1):38–45.

Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and state treatment need and capacity for opioid agonist medication-assisted treatment. Am J Public Health. 2015;105(8):e55–63.

Olsson M, Zhang VS, Schoenbaum M, King M. Trends in buprenorphine treatment in the United States, 2009-2018. JAMA. 2020;323(3):276–7.

Mack RP, Breen C, Kimber J, & Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev (2). (2014)

Latif ZE, Saltzeye Bendh J, Soli KK, et al. Anxiety, depression, and insomnia among adults with opioid dependence treated with extended-release naltrexone vs buprenorphine-naloxone: a randomized clinical trial and follow-up study. JAMA Psychiatry. 2019;76(2):127–34.

Bodkin JA, Zornberg GL, Lukas SE, Cole JO. Buprenorphine treatment of refractory depression. J Clin Psychopharmacol. 1995;15(1):49–57.

Nyhus PW, Gastpar M, Scherbaum N. Opiate treatment in depression refractory to antidepressants and electroconvulsive therapy. J Clin Psychopharmacol. 2008;28(5):593–5.

Serafini G, Adavastro G, Canapa G, et al. The Efficacy of buprenorphine in major depression, treatment-resistant depression and suicidal behavior: a systematic review. Int J Mol Sci. 19(8, 2018):2410 A multisite randomized double-blind placebo-controlled trial investigating the efficacy and safety of very low dosages of sublingual buprenorphine as a time-limited treatment for severe suicidal ideation.

Mamakwa S, Kahan M, Kanate D, et al. Evaluation of 6 remote First Nations community-based buprenorphine programs in northwestern Ontario: retrospective study. Can Fam Physician. 2017;63(2):137–45.

Coplan PM, Sessler NE, Harikrishnan V, Singh R, Perkel C. Comparison of abuse, suspected suicidal intent, and fatalities related to the 7-day buprenorphine transdermal patch versus other opioid analogues in the National Poison Data System. Postgrad Med. 2017;129(1):55–61.

Ahmadi J, Jahromi MS, Elsaei Z. The effectiveness of different singly administered high doses of buprenorphine in reducing suicidal ideation in acutely depressed people with co-morbid opiate dependence: a randomized, double-blind, clinical trial. Trials. 2018;19(1):462.

Striebel JM, Kalapatapu RK. The anti-suicidal potential of buprenorphine: a case report. Int J Psychiatry Med. 2014;47(2):169–74.

Yovell Y, Bar G, Mashiah M, et al. Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. Am J Psychiatry. 2016;173(5):491–8.

Emrich HM, Vogt P, Herz A. Possible antidepressive effects of opioids: action of buprenorphine. Ann N Y Acad Sci. 1982;398(1):108–12.

Karp JF, Butters MA, Begley AE, et al. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. J Clin Psychiatry. 2014;75(8):e785–93.

Ehrich E, Tumcliff R, Du Y, et al. Evaluation of opioid modulation in major depressive disorder. Neuropsychopharmacology. 2015;40(6):1448–55.

Kosten TR, Morgan C, Kosten TA. Depressive symptoms during buprenorphine treatment of opioid abusers. J Subst Abuse Treat. 1990;7(1):51–4.

Ahmadi J, Abtahi S. Eight-milligram single dose of buprenorphine as a time-limited treatment for severe suicidal ideation. N Engl J Med. 2017;376(2):137–45.

Falcon E, Maier K, Robinson SA, Hill-Smith TE, Lucki I. Effects of buprenorphine in major depression, treatment-resistant depression and suicidal behavior: a systematic review. JAMA Psychiatry. 2015;72(5):907–15.

Almatroudi A, Husbands SM, Bailey CP, Bailey SJ. Combined administration of buprenorphine and naltrexone produces...
antidepressant-like effects in mice. J Psychopharmacol. 2015;29(7):812–21.

268. Falcon E, Browne CA, Leon RM, et al. Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors. Neuropsychopharmacology. 2016;41(9):2344–51.

269. Bruchas MR, Land BB, Lemos JC, Chavkin C. CRF1-R activation of the dynorphin/kappa opioid system in the mouse basolateral amygdala mediates anxiety-like behavior. PLoS One. 2009;4(12):e8528.

270. Knoll AT, Muschamp JW, Sillivan SE, et al. Kappa opioid receptor signaling in the basolateral amygdala regulates conditioned fear and anxiety in rats. Biol Psychiatry. 2011;70(5):425–33.

271. Tejeda HA, Hanks AN, Scott L, Mejias-Aponte C, Hughes ZA, O’Donnell P. Prefrontal cortical kappa opioid receptors attenuate responses to amygdala inputs. Neuropsychopharmacology. 2015;40(13):2856–64.

272. Smoski MJ, Salsman N, Wang L, et al. Functional imaging of emotion reactivity in opiate-dependent borderline personality disorder. Personal Disord. 2011;2(3):230–41.

273. Mei W, Zhang JX, Xiao Z. Acute effects of sublingual buprenorphine on brain responses to heroin-related cues in early-abstinent heroin addicts: an uncontrolled trial. Neuroscience. 2010;170(3):808–15.

274. Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. J Addict Med. 2016;10(2):91.

275. Carroll KM, Weiss RD. The role of behavioral interventions in buprenorphine maintenance treatment: a review. Am J Psychiatr. 2017;174(8):738–47.

276. Sofuoglu M, DeVito EE, Carroll KM. Pharmacological and behavioral treatment of opioid use disorder. Psychiatric Res Clin Pract. 2019;1(1):4–15.

277. Davis JP, Prindle JJ, Eddie D, Pedersen ER, Dumas TM, Christie NC. Addressing the opioid epidemic with behavioral interventions for adolescents and young adults: a quasi-experimental design. J Consult Clin Psychol. 2019;87(10):941.

278. Day E, Mitcheson L. Psychosocial interventions in opiate substitution treatment services: does the evidence provide a case for optimism or nihilism? Addiction. 2017;112(8):1329–36.

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