Current Addiction Reports (2019) 6:114–125
https://doi.org/10.1007/s40429-019-00245-3

TOBACCO (K GARRISON, SECTION EDITOR)

Mechanisms and Clinical Features of Co-Occurring Opioid and Nicotine Use

Sarah D. Lichenstein[1] · Yasmin Zakiniaeiz[2] · Sarah W. Yip[3] · Kathleen A. Garrison[4]

Published online: 27 April 2019

Abstract

Purpose of Review To review the literature addressing shared pathophysiological and clinical features of opioid and nicotine use to inform etiology and treatment, and highlight areas for future research.

Recent Findings Opioid and nicotine use co-occur at an alarmingly high rate, and this may be driven in part by interactions between the opioid and cholinergic systems underlying drug reward and the transition to dependence. Pain, among other shared risk factors, is strongly implicated in both opioid and nicotine use and appears to play an important role in their co-occurrence. Additionally, there are important sex/gender considerations that require further study. Regarding treatment, smoking cessation can improve treatment outcomes in opioid use disorder, and pharmacological approaches that target the opioid and cholinergic systems may be effective for treating both classes of substance use disorder.

Summary Understanding overlapping etiological and pathophysiological mechanisms of opioid and nicotine use can aid in understanding their co-occurrence and guiding their treatment.

Keywords Opioid use · Nicotine · Smoking · Pain · Comorbidity · Treatment

Introduction

Both opioid and nicotine use independently represent enormous public health problems, associated with staggering morbidity and mortality worldwide. Furthermore, opioid and nicotine use often co-occur, and their comorbid presentation has implications for their progression and treatment prognosis. Here, we review what is known about shared pathophysiological mechanisms of co-occurring opioid and nicotine use, including factors implicated in the etiology, illness course, and treatment of these conditions, and recommend directions for further research.

Opioid Epidemic

The prevalence of non-medical opioid use has risen dramatically over the past decade, for example, increasing by greater than 300% in the USA [1]. These rates are highest among young adults ages 25 to 34—with one in five deaths in this age group attributable to opioids—and opioid misuse in older adults also continues to rise [1, 2]. Rates of perinatal opioid exposure and of opioid-associated neonatal abstinence syndrome have also increased in recent years [2]. Thus, the current opioid epidemic is a pervasive public health problem affecting individuals of all ages.

This article is part of the Topical Collection on *Tobacco*

✉ Sarah D. Lichenstein
sarah.lichenstein@yale.edu

Yasmin Zakiniaeiz
yasmin.zakiniaeiz@yale.edu

Sarah W. Yip
sarah.yip@yale.edu

Kathleen A. Garrison
kathleen.garrison@yale.edu

[1] Department of Radiology and Biomedical Imaging, Yale School of Medicine, 1 Church Street, 7th Floor, Suite 721, New Haven, CT 06511, USA

[2] Department of Radiology and Biomedical Imaging, Yale School of Medicine, 330 Cedar Street, Suite LMP85, New Haven, CT 06510, USA

[3] Department of Psychiatry, Yale School of Medicine, 1 Church Street, Suite 731, New Haven, CT 06510, USA

[4] Department of Psychiatry, Yale School of Medicine, 1 Church Street, Suite 730, New Haven, CT 06510, USA

While opioid use is particularly prevalent in the USA and Canada, opioid use disorder (OUD) is the second most prevalent illicit drug use disorder worldwide, affecting 15.5 to 16.8 million people globally [3, 4]. In addition to its increasing prevalence, the clinical profile of OUD has changed in recent decades. Within the USA, this has included a sharp increase over the past two decades in the number of individuals reporting misuse of opioid analgesics prior to heroin initiation [5•, 6], as well as a more recent increase in the intentional and unintentional misuse of synthetic opioids with very high overdose potential, such as fentanyl [7, 8].

Tobacco Use

Tobacco smoking is a leading cause of preventable death worldwide [9] and costs the global economy $422 billion in healthcare expenditures annually due to smoking-attributable diseases [10]. Despite knowledge of severe health consequences, less than half of smokers worldwide have attempted to quit in the past year [11]. Smokers with comorbid medical conditions (e.g., substance use disorders, SUD) have been identified as important targets for treatment [12], and some medical conditions (e.g., pain) may serve to maintain tobacco dependence [13]. Furthermore, as with OUD, the clinical and demographic profile of tobacco/nicotine use may be changing with emerging products such as electronic cigarettes (e-cigarettes), which have both potential for harm reduction and abuse liability [14].

Co-Occurrence of Smoking and Opioid Misuse

Smoking and opioid misuse co-occur at strikingly high rates. Approximately 85% of patients in methadone treatment for OUD smoke cigarettes [15]—a much higher rate than those with alcohol use disorder [16]. Additionally, tobacco-related disease and mortality rates are high among individuals who use opioids [17]. Furthermore, nicotine and opioid use are thought to be mutually reinforcing, such that individuals with OUD are more likely to smoke [18•, 19] and smokers are likely to misuse opioids [20].

In addition to a more general link between smoking and opioid use, smoking status is a strong predictor of risk for non-medical use of prescription opioids in particular [18•], and tobacco smokers have a high frequency of non-medical use of prescription opioids [21]. While the greatest risk factor for non-medical use of prescription opioids is a history of substance or polysubstance abuse [22], recent evidence has singled out tobacco smoking as the strongest predictor [18•]. Daily/intermittent smokers are three times more likely to report past-year non-medical prescription opioid use compared to never smokers [23•]. Likewise, a population-based survey found that the odds ratios for prescribed opioids increased with severity of nicotine dependence (OR = 3.1) [24]. In line with this, smoking rates are higher among individuals who use prescription opioids than in the general population [19, 24, 25]. A recent study using the US National Survey on Drug Use and Health found that opioid-dependent smokers exhibited greater severity of nicotine dependence compared to non-opioid-dependent smokers [26]. Taken together, these studies suggest that smoking is a risk factor for prescription opioid use. Tobacco smoking may increase risk for opioid misuse because of the prior establishment of nicotine use as a "gateway" to illicit drug use [27], especially among adolescents [28].

Interactions Between the Endogenous Opioid and Cholinergic Systems

Smoking might also be a risk factor for opioid dependence because of neurobiological interactions between the endogenous opioid and cholinergic systems. Preclinical and clinical evidence point to a neurobiological link between nicotine- and opioid-related neurotransmitter systems [29]. With respect to nicotine dependence, nicotinic-acetylcholine receptors (nAchRs) mediate nicotine reinforcement by stimulating the release of dopamine as well as opioid neuropeptides in the striatum that act on *mu*-opioid receptors (MORs), which facilitate psychological nicotine dependence [30, 31•], and act on *delta*- (DORs) and *kappa*-opioid receptors (KORs), which facilitate physical nicotine dependence [32]. With respect to opiates, in vitro studies show that prescription opioids bind to MORs and DORs [33] and interact with nAchRs [34], suggesting possible mechanisms by which opioids might produce reinforcing/euphoric effects. One in vivo mouse study showed that opioid-induced striatal dopamine release, locomotor activity, and reinforcement are enhanced by nicotine treatment [35]. Thus, nicotine reinforcement is partly dependent on the opioid system and opioid reinforcement is partly regulated by the nicotinic-acetylcholine system. Furthermore, nicotine use may enhance the rewarding properties of opioids in the brain [36], promoting nicotine and opiate co-use. These complex nicotine–opioid interactions may explain why nicotine and opioids independently prime the use of other drugs of abuse [27] and might bidirectionally prime one another.

Pain as a Candidate Mechanism Underlying Co-Occurring Smoking and Opioid Misuse

Opioid Use Disorder and Pain

It has also been shown that chronic nicotine exposure dysregulates the endogenous opioid system and leads to greater pain and cross-tolerance to opioids [37, 38], suggesting that pain may contribute to comorbidity between smoking and opioid misuse, particularly among individuals with chronic pain. However, it is important to note that rates of tobacco smoking are also elevated among individuals with OUD without chronic pain. Both the therapeutic (i.e., analgesic) and

rewarding (e.g., euphoric) effects of opioids are largely due to their activation of MORs [39]. Within the brain, MORs are widely expressed and overlap with regions implicated in both nociceptive and reward processes, e.g., insula, thalamus anterior cingulate, and striatum [39]. These brain regions are activated in response to painful stimuli, and these effects are reduced following administration of opioid agonists [40, 41]. However, despite significant evidence for short-term efficacy of opioid analgesics for acute pain management, the evidence for the efficacy of these medications to treat chronic pain is limited [42]. In addition, in some individuals, repeated opioid exposure can result in the development of hyperalgesia—heightened pain sensitivity (see "Smoking and Pain" section for nicotine-induced hyperalgesia) [39].

OUD is relatively common among individuals with chronic pain. Recent data indicate that approximately 35% of patients receiving opioid treatment for non-cancer chronic pain also meet criteria for OUD [43]. Despite this, the majority of individuals who are prescribed opioids do not develop OUD [39]. Similarly, chronic pain is common among individuals with OUD, with estimates indicating that between 37% and 61% of individuals engaged in medication-assisted treatment (MAT) for OUD have a form of chronic pain [44–47]. Among MAT patients, chronic pain is associated with negative clinical symptoms including anxiety, depression, overall psychiatric distress, sleep disturbances, and trauma [44, 48]. As each of these factors is also associated with poorer clinical outcomes in OUD, further work to address chronic pain in MAT patients is urgently needed.

Smoking and Pain

There is also a significant association between smoking and pain (e.g., [21]). Smoking prevalence among pain patients is twice that observed in the general population (e.g., [49]). Whereas smoking rates have declined in recent years in the general population, rates do not appear to have declined among persons with chronic pain [50]. Smoking is associated with increased risk of chronic pain [51], and tobacco smokers report pain in more locations and at a higher intensity than non-smokers [20], and also experience more pain-related disability [21]. Furthermore, smokers with significant pain consume more cigarettes per day [52], are more dependent on tobacco, and are less confident in their ability to quit smoking [53] than smokers who do not report significant pain symptoms.

Pain and smoking have been proposed to interact in a reciprocal manner in a positive feedback loop that results in greater pain and increased smoking [13]. In this proposed model, effects of pain on smoking include psychosocial factors, smoking expectancies for pain coping and affect regulation [54], negative reinforcement (e.g., relief from pain, stress, negative affect [55]), positive reinforcement (e.g., positive affect, energy/arousal, cognitive enhancement), activation of the mesolimbic dopamine reward system and neural stress system, and other pain-related factors [13]. In line with this, an ecological momentary assessment study has provided evidence that pain triggers smoking [56], and a number of studies have provided evidence for a positive association between pain intensity and cigarettes per day [13]. Pain manipulation has also been associated with greater smoking urge and higher likelihood of smoking [57].

The proposed model likewise accounts for the effects of smoking on pain, including psychosocial factors, interactions with other risk factors for pain, pain from tissue damage from smoking, modulation of neurological processes related to pain, and altered pain processing, the latter involving activation of nAChRs and endogenous opioid systems, cardiovascular pressor actions, changes in attention, and nicotine withdrawal effects [13]. Nicotine administration has acute analgesic effects [reviewed in 13], and this is heightened in men [58••]. Despite these short-term analgesic effects, chronic smoking may sensitize pain receptors and increase pain sensitivity over time (i.e., nicotine-induced hyperalgesia). In fact, greater nicotine dependence is associated with more severe pain symptoms [59], likely contributing to greater opioid use [20, 60].

Furthermore, nicotine withdrawal is associated with a blunted stress response and increased pain sensitivity [21, 61]. Even among smokers who do not report pain, those who abstained from smoking reported greater pain intensity and were nearly 3.5 times more likely to endorse pain following a pain manipulation [62]. Therefore, there may be specific challenges to smoking cessation for pain patients. There is an association between positive pain status, reduced self-efficacy, and greater difficulty quitting smoking [63]. Pain-related anxiety is associated with greater smoking severity and barriers to quitting [64], and anxiety and depression may worsen the effects of pain on smoking cessation due to more severe withdrawal and increased pain sensitivity [65]. Nevertheless, smokers with chronic pain appear to be motivated to quit and amenable to pharmacologic intervention [66]. Other studies are testing cognitive-behavioral therapy for smoking cessation in treatment for chronic pain [67] to address these issues.

Interactions Between Pain, Smoking, and Opioid Misuse

Critically, smokers with chronic pain are more likely to use opioids and at higher doses (among men) [54], and smoking status may indicate risk for problems with prescription opioids [21]. One study found that pain patients who smoked perceived fewer problems with prescription opioid use, despite higher odds of having an OUD and using opioids at greater doses (among men) [21]. Another study of pain patients found that smoking was associated with greater pain intensity and less decline in daily opioid use at follow-up [68]. Smokers as well as former smokers using nicotine have been found to use opioids more frequently and at higher doses versus never smokers or former smokers not using nicotine [49]. Finally, although smoking abstinence may complicate short-

term efforts to treat pain, smoking cessation does not cause poorer opioid treatment outcomes [21] (see "Quitting Smoking Improves OUD Treatment Outcomes" section). However, medications for smoking cessation may be less effective among opioid-dependent smokers [69]. Together, the data suggest that pain plays an important role in opioid misuse, as well as smoking maintenance and escalation, and may also relate to the high co-occurrence of smoking and opioid misuse.

Additional Risk Factors for Opioid and Nicotine Use and Co-Use

Additionally, several other factors have been implicated in risk, illness course, and treatment prognosis of comorbid opioid and nicotine use disorder, including adverse childhood experiences, stress, and depression, reviewed below.

Adverse Childhood Experiences

Adverse childhood experiences (ACEs), including household dysfunction, physical, sexual, and emotional abuse, are robustly associated with a wide range of substance use behaviors, as well as other mental and physical health problems across the lifespan [70]. In particular, exposure to ACEs has been linked to increased risk for opioid use [71] and smoking [72], and a strong body of evidence demonstrates that individuals exposed to multiple ACEs are at particularly high risk for both [71, 73]. A recent meta-analysis reports that individuals with multiple ACEs are approximately 3 times more likely to smoke and 10 times more likely to engage in problematic drug use (including intravenous substance use, heroin, or crack cocaine use) [74]. Increased impulsivity has been proposed as one potential mechanism whereby ACEs give rise to later substance abuse [75]. Another potential mechanism is suggested by studies indicating that severe child abuse is associated with epigenetic changes in opioid receptor expression [76•]. However, additional research elucidating factors mediating these relationships is needed. Beyond risk for substance use/abuse, ACEs have also been associated with a more severe course of illness. ACEs have been linked to higher likelihood of overdose among individuals with OUD [71], more withdrawal symptoms and distress among newly abstinent smokers [77], and adverse psychosocial and health outcomes among inpatients with comorbid substance use and mental health disorders [78].

Stress

Stress has also been linked with the development of both opioid and nicotine use disorders [79], as well as poorer treatment engagement and outcomes in OUD [80]. In particular, stress has been robustly associated with relapse in opioid, nicotine, and other SUDs [81], and opioid administration reduces acute stress responses [82]. It has been proposed that learned associations between opioid use and relief from aversive states of opioid withdrawal potentiate individuals' vulnerability to relapse when faced with stressful life events [83••]. Nicotine use may exacerbate this vulnerability, as nicotine withdrawal increases acute stress responses among smokers [84] and higher stress severity has been linked to increased opioid craving [85]. Notably, the relationship between stress and drug reinstatement may be stronger among women compared to men, as greater associations between stress and opioid craving [85] and heightened stress-induced negative affect, stress, and nicotine craving [86] have been reported among women. Additional research is necessary to delineate potential mechanisms of sex differences in stress-induced reinstatement [81], as well as sex differences relevant to co-occurring opioid and nicotine use more broadly (see "Sex Differences" section).

Depression

Depression is frequently comorbid with both OUD [87, 88] and smoking [89], and may be an important contributor to their high rate of co-occurrence. Individuals with depression are significantly more likely to abuse prescribed opioid medication [90, 91], and depressive symptoms are associated with greater opioid craving and use among individuals with OUD [92, 93]. Similarly, negative affect predicts craving to smoke among current smokers [94]. Furthermore, comorbid mood disorders are associated with reduced opioid pharmacotherapy adherence among individuals in treatment for OUD [95] and poorer quit outcomes for individuals taking nicotine replacement therapy [96]. Among individuals with OUD, comorbid mood disorders are associated with smoking status [97], and depressive personality features are associated with fewer smoking quit attempts [98].

Pain may be another important mechanism linking depression with opioid and nicotine use. One study [98] found that higher depressive symptoms and current smoking status were both associated with higher opioid dose among pain patients, yet the effect of depressive symptoms was no longer significant when pain severity was included in the model, suggesting that altered pain perception may be a potential mechanism linking depressive symptomatology to opioid use, as described above. However, these findings could alternatively be interpreted as evidence that pain and depression explain common variance in opioid use. Nonetheless, negative mood has been shown to increase pain sensitivity among healthy volunteers [99], and individuals with depression display lower thresholds for certain types of pain [100•] and poorer responses to opioid pain treatment [101]. Negative affect induction increases withdrawal-related pain sensitivity among individuals with heroin dependence [102], and nicotine withdrawal has also been associated with acute increases in pain

sensitivity among daily smokers [62]. Collectively, these results suggest that depression plays an important role in the etiology and treatment of opioid and nicotine use, which may be mediated in part by negative mood related alterations in pain perception.

Influences of Sex/Gender on Opioid and Nicotine Use and Co-Use

Sex/gender differences (with the understanding of the American Psychiatric Association's [103] definitions of sex as a person's biological status such as male or female, and gender as the attitudes, feelings, and behaviors associated with biological sex such as men and women) in tobacco smoking and smoking-related behaviors are well established [104], whereas the literature on sex/gender-related differences in opioid use has yielded mixed findings [105]. With respect to tobacco smoking, men are better able to detect nicotine in cigarettes [106, 107] and women are more reinforced by nicotine-associated sensory cues and stress than nicotine itself [107, 108]. Women also metabolize nicotine and cotinine faster (partially due to estrogen) [109], which may explain why women typically experience more adverse nicotine-related effects [110] and worse smoking cessation outcomes [111]. With respect to opioid use, there is evidence that women's progression to opioid dependence is "telescoped" relative to men—women initiate use of opioids at an older age but progress to disease faster than men [112]. For women, emotional problems conferred risk for opioid misuse among individuals with chronic pain, whereas legal and behavioral problems predicted opioid misuse among men with chronic pain [113]. Gender-specific factors also predict non-pain-related opioid use—alcohol and illicit drug use predict opioid use in men while tobacco smoking and psychological stress predict opioid use in women [114, 115]. As mentioned above, among women, former daily smokers were more likely to have met criteria for past-year OUD than never smokers [23•], and among men, smokers report higher daily doses of opioids than non-smokers [21]. More research on the neurobiological bases of these sex/gender differences is needed to advance sex/gender-appropriate screening and treatment options for tobacco smoking, OUD, and nicotine-opioid co-use.

Effects of Early Exposure to Nicotine and Opioids

Perinatal Nicotine and Opioid Exposure

Perinatal nicotine and opioid exposure have significant negative health consequences for mother and infant, though the negative effects of smoking on fetal development may exceed those of opioid exposure [116]. Within the USA, approximately 14–22% of women are estimated to use tobacco during pregnancy [117]; however, smoking prevalence estimates among pregnant women receiving treatment for OUD are markedly higher at 88–95% [116, 118, 119]. In addition to numerous adverse physical health consequences, perinatal tobacco use is also linked to increased depression during pregnancy in the general population, as well as among individuals receiving MAT [97, 120]. MAT is recommended to treat opioid use in pregnant women and recognized to improve pregnancy outcomes, but does not address co-occurring tobacco smoking [116, 121]. Thus, further interventions to address the high rates of tobacco use in MAT patients during pregnancy are urgently needed (for a review of existing treatments, see [116]).

Adolescent Nicotine Exposure Increases OUD Susceptibility in Adulthood

A growing body of preclinical literature suggests that adolescent nicotine exposure may increase risk for opioid use in adulthood. In one report [122•], mice exposed to nicotine in early adolescence displayed enhanced conditioned place preference for morphine in adulthood, whereas nicotine exposure in late adolescence and adulthood was not associated with the same effect. These results are consistent with a larger literature implicating adolescence as a sensitive period when nicotine exposure can exert long-lasting effects on neurodevelopment, with substantial implications for addiction vulnerability in adulthood [for review, see [123]. Adolescent nicotine exposure may also potentiate risk for opioid use in adulthood via alterations in MOR expression [124], increased sensitivity to stress, and heightened depressive symptomatology [28, 125, 126]; effects that may vary by sex [28, 124, 125]. However, additional research is necessary to clarify these mechanisms and to establish these findings in human subjects.

Treatment Implications for Co-Occurring Opioid and Nicotine Use Disorders

Quitting Smoking Improves Opioid Use Treatment Outcomes

Smoking accounts for a significant proportion of mortality among individuals with SUD, yet nicotine dependence is rarely addressed in SUD treatment [17]. There is evidence to suggest that both providers [127] and patients [128] may abstain from addressing smoking based on concerns that it will interfere with sobriety from their primary drug of abuse. Contrary to this perceived barrier, smoking cessation appears to improve outcomes in SUD treatment overall [129•] and among individuals with OUD specifically [130]. A meta-analysis of seven studies with long-term follow-up data found that receiving a smoking cessation intervention during SUD treatment was associated with a 25% higher likelihood of long-term abstinence from alcohol and other substance use, including but not limited to opioids [130]. Other indirect evidence supports that smoking cessation may benefit OUD treatment. For example, among smokers with OUD, those who smoked during detoxification reported significantly higher opioid craving and had lower rates of retention as compared with those who were not allowed to smoke during detox as well as non-smokers [131]. Similarly, among methadone-maintained individuals, there is a

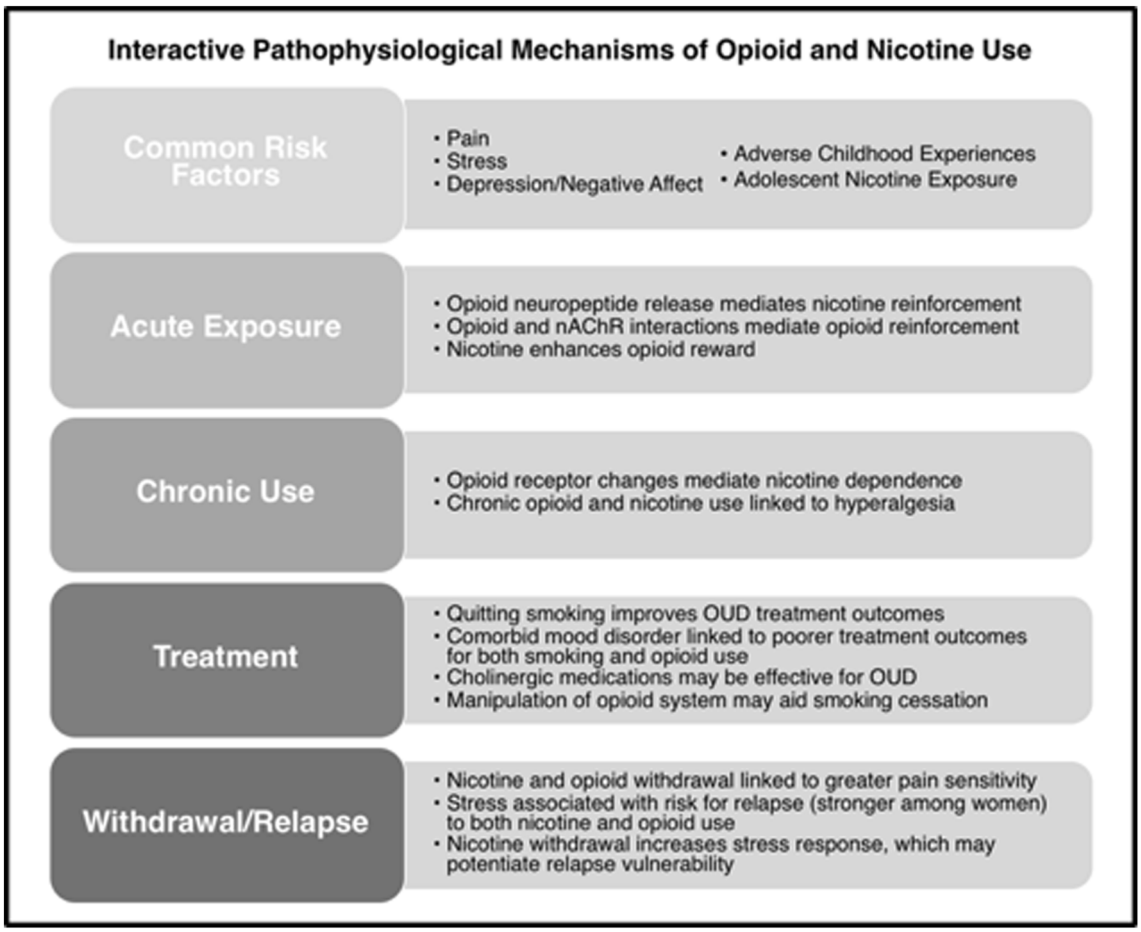

Fig. 1 Interactive pathophysiological mechanisms of opioid and nicotine use. Highlights selected findings related to mechanisms underlying opioid and nicotine use and their co-occurrence. nAChR, nicotinic acetylcholine receptor; OUD, opioid use disorder

positive association between smoking and opioid use [25, 132], and individuals who smoked more cigarettes on a preceding day were more likely to report that their methadone dose was inadequate [133]. In line with this, one small study has found smoking status to be a stronger predictor of opioid use during methadone maintenance than daily methadone dose [25]. Together, these data suggest smoking abstinence improves opioid treatment outcomes and support providing smoking cessation interventions with OUD treatment [17].

Implications for Pharmacological Treatment of Opioid and Nicotine Use Disorders

The functional interactions between the cholinergic and endogenous opioid systems described above have important implications for pharmacological treatments of opioid and nicotine use disorders [134••, 135••]. For example, medications targeting the cholinergic system have been found to be effective for smoking cessation [136, 137]. Animal research suggests that cholinergic medications may also be effective for treating OUD; however, there is very limited literature in humans [134••]. Nonetheless, preliminary data suggest that cholinergic agents are well tolerated [138], attenuate opioid withdrawal symptoms [138], increase time to relapse [139], and may also reduce symptoms of depression and anxiety [139] in human subjects in treatment for OUD [134••].

Similarly, preclinical literature indicates that manipulation of various opioid receptor subtypes may aid smoking cessation, but human data are also limited [135••]. There are currently no medications approved by the US Food and Drug Administration that specifically target DORs or KORs, and research with MOR manipulation has yielded mixed results. Meta-analyses have reported that there is not strong evidence for the efficacy of MOR antagonists for smoking cessation across studies [140, 141]. However, there are data to suggest that MOR antagonists may be more effective among subpopulations, including heavy drinkers [142] and individuals with comorbid depression [143]. Therefore, additional research is necessary to identify who may benefit most from medications targeting MORs, as well as to evaluate the safety, tolerability, and efficacy of medications that selectively target DORs and KORs, to aid in smoking cessation. Nevertheless, these promising preliminary findings suggest that further investigation into the potential of cholinergic and opioidergic agents for the treatment of opioid and nicotine use disorders is warranted.

Conclusions

There have been a number of recent advances in our understanding of the magnitude and mechanisms of co-occurring nicotine and opioid use and misuse. The available literature emphasizes pain as a critical mechanism underlying co-use and contributing to negative treatment outcomes for either disorder, in particular the interaction of pain and smoking with opioid use and treatment. Also highlighted are the roles of depression, stress, sex/gender, early exposure, and other factors that impact the effects of acute exposure, chronic use, treatment, and withdrawal/relapse of either substance (Fig. 1). Continued development in our understanding of nicotine and opioid use and co-use, including at neurobiological and genetic levels, should inform the development of more optimal prevention and treatment. In particular, continued consideration should be given to the impact of tobacco smoking on individuals in treatment for opioid use disorder, and the potential role of smoking cessation in improving opioid treatment outcomes. Such efforts may have substantial public health benefits in both domains.

Funding Funding for this work was provided by T32DA022975, K01DA039299, and K12DA00167.

Compliance with Ethical Standards

Conflict of Interest S.L., Y.Z., S.Y., and K.G. declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Gomes T, Tadrous M, Mamdani MM, Paterson J, Juurlink DN. The burden of opioid-related mortality in the United States. JAMA Netw Open. 2018;1(2):e180217. https://doi.org/10.1001/jamanetworkopen.2018.0217.
2. Klaman SL, Isaacs K, Leopold A, Perpich J, Hayashi S, Vender J, et al. Treating women who are pregnant and parenting for opioid use disorder and the concurrent care of their infants and children: literature review to support national guidance. J Addict Med. 2017;11(3):178–90. https://doi.org/10.1097/adm.0000000000000308.
3. Degenhardt L, Charlson F, Mathers B, Hall WD, Flaxman AD, Johns N, et al. The global epidemiology and burden of opioid dependence: results from the Global Burden of Disease 2010 study. Addiction. 2014;109(8):1320–33. https://doi.org/10.1111/add.12551.
4. Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction. 2018;113(10):1905–26. https://doi.org/10.1111/add.14234.
5. • Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiatry. 2014;71(7):821–6. https://doi.org/10.1001/jamapsychiatry.2014.366. **This study reports on changes in demographic and clinical characteristics of patients entering substance abuse treatment for OUD**.
6. Muhuri P, Gfroerer J, Davies M. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. SAMHSA. 2013. <http://www.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.htm>. Accessed 19 April 2019.
7. Peterson AB, Gladden RM, Delcher C, Spies E, Garcia-Williams A, Wang Y, et al. Increases in fentanyl-related overdose deaths—Florida and Ohio, 2013–2015. MMWR Morb Mortal Wkly Rep. 2016;65(33):844–9. https://doi.org/10.15585/mmwr.mm6533a3.
8. Marshall BDL, Krieger MS, Yedinak JL, Ogera P, Banerjee P, Alexander-Scott NE, et al. Epidemiology of fentanyl-involved drug overdose deaths: a geospatial retrospective study in Rhode Island, USA. Int J Drug Policy. 2017;46:130–5. https://doi.org/10.1016/j.drugpo.2017.05.029.
9. World Health Organization. WHO global report: mortality attributable to tobacco. Geneva, Switzerland. 2012. http://www.who.int/tobacco/publications/surveillance/rep_mortality_attributable/en. Accessed 04/14/15.
10. Goodchild M, Nargis N, Tursan d'Espaignet E. Global economic cost of smoking-attributable diseases. Tob Control. 2018;27(1):58–64. https://doi.org/10.1136/tobaccocontrol-2016-053305.
11. Ahluwalia I, Smith T, Arrazola R, Palipudi K, Garcia de Quevedo I, Prasad V et al. Current tobacco smoking, quit attempts, and knowledge about smoking risks among persons aged ≥15 years—Global Adult Tobacco Survey, 28 Countries. 2008–20162018.
12. Fiore M, JaÈn C, Baker T, Bailey W, Benowitz N, Curry S et al. Treating tobacco use and dependence: 2008 update—clinical practice guidelines. US Department of Health and Human Services, Rockville, MD. 2008. http://bphc.hrsa.gov/buckets/treatingtobacco.pdf. Accessed Sept 1 2015.
13. Ditre JW, Brandon TH, Zale EL, Meagher MM. Pain, nicotine, and smoking: research findings and mechanistic considerations. Psychol Bull. 2011;137(6):1065–93. https://doi.org/10.1037/a0025544.
14. World Health Organization, editor. Electronic nicotine delivery systems. WHO Framework Convention on Tobacco Control; 2014 13–18 October 2014; Moscow, Russian Federation.
15. Zirakzadeh A, Shuman C, Stauter E, Hays JT, Ebbert JO. Cigarette smoking in methadone maintained patients: an up-to-date review. Curr Drug Abuse Rev. 2013;6(1):77–84. https://doi.org/10.2174/1874473711306010009.
16. Soyka M. Alcohol use disorders in opioid maintenance therapy: prevalence, clinical correlates and treatment. Eur Addict Res. 2015;21(2):78–87. https://doi.org/10.1159/000363232.
17. Baca CT, Yahne CE. Smoking cessation during substance abuse treatment: what you need to know. J Subst Abus Treat. 2009;36(2):205–19. https://doi.org/10.1016/j.jsat.2008.06.003.
18. • Yoon JH, Lane SD, Weaver MF. Opioid analgesics and nicotine: more than blowing smoke. J Pain Palliat Care Pharmacother. 2015;29(3):281–9. https://doi.org/10.3109/15360288.2015.1063559 **This review discusses interactions between nicotine and opioids among individuals prescribed opioids for pain.**
19. Guydish J, Passalacqua E, Tajima B, Chan M, Chun J, Bostrom A. Smoking prevalence in addiction treatment: a review. Nicotine Tob Res. 2011;13(6):401–11. https://doi.org/10.1093/ntr/ntr048.

20. John U, Alte D, Hanke M, Meyer C, Völzke H, Schumann A. Tobacco smoking in relation to analgesic drug use in a national adult population sample. Drug Alcohol Depend. 2006;85(1):49–55.
21. Young-Wolff KC, Klebaner D, Weisner C, Von Korff M, Campbell CI. Smoking status and opioid-related problems and concerns among men and women on chronic opioid therapy. Clin J Pain. 2017;33(8):730–7. https://doi.org/10.1097/ajp.0000000000000461.
22. Morasco BJ, Turk DC, Donovan DM, Dobscha SK. Risk for prescription opioid misuse among patients with a history of substance use disorder. Drug Alcohol Depend. 2013;127(1):193–9. https://doi.org/10.1016/j.drugalcdep.2012.06.032.
23.• Zale EL, Dorfman ML, Hooten WM, Warner DO, Zvolensky MJ, Ditre JW. Tobacco smoking, nicotine dependence, and patterns of prescription opioid misuse: results from a nationally representative sample. Nicotine Tob Res. 2015;17(9):1096–103. https://doi.org/10.1093/ntr/ntu227 **This study provides epidemiological evidence for the association between smoking and opioid medication misuse in a nationally representative sample.**
24. Skurtveit S, Furu K, Selmer R, Handal M, Tverdal A. Nicotine dependence predicts repeated use of prescribed opioids. Prospective population-based cohort study. Ann Epidemiol. 2010;20(12):890–7. https://doi.org/10.1016/j.annepidem.2010.03.010.
25. Frosch DL, Shoptaw S, Nahom D, Jarvik ME. Associations between tobacco smoking and illicit drug use among methadone-maintained opiate-dependent individuals. Exp Clin Psychopharmacol. 2000;8(1):97–103. https://doi.org/10.1037/1064-1297.8.1.97.
26. Parker MA, Streck JM, Sigmon SC. Associations between opioid and nicotine dependence in nationally representative samples of United States adult daily smokers. Drug Alcohol Depend. 2018;186:167–70. https://doi.org/10.1016/j.drugalcdep.2018.01.024.
27. Tuesta LM, Fowler CD, Kenny PJ. Recent advances in understanding nicotinic receptor signaling mechanisms that regulate drug self-administration behavior. Biochem Pharmacol. 2011;82(8):984–95. https://doi.org/10.1016/j.bcp.2011.06.026.
28. Klein LC. Effects of adolescent nicotine exposure on opioid consumption and neuroendocrine responses in adult male and female rats. Exp Clin Psychopharmacol. 2001;9(3):251–61. https://doi.org/10.1037/1064-1297.9.3.251.
29. Xue Y, Domino EF. Tobacco/nicotine and endogenous brain opioids. Prog Neuro-Psychopharmacol Biol Psychiatry. 2008;32(5):1131–8. https://doi.org/10.1016/j.pnpbp.2007.12.012.
30. Berrendero F, Robledo P, Trigo JM, Martín-García E, Maldonado R. Neurobiological mechanisms involved in nicotine dependence and reward: participation of the endogenous opioid system. Neurosci Biobehav Rev. 2010;35(2):220–31. https://doi.org/10.1016/j.neubiorev.2010.02.006.
31.• Kuwabara H, Heishman SJ, Brasic JR, Contoreggi C, Cascella N, Mackowick KM, et al. Mu opioid receptor binding correlates with nicotine dependence and reward in smokers. PLoS One. 2014;9(12):e113694. https://doi.org/10.1371/journal.pone.0113694 **This study demonstrates associations between MOR availability and nicotine reward and dependence severity among human subjects.**
32. Kishioka S, Kiguchi N, Kobayashi Y, Saika F. Nicotine effects and the endogenous opioid system. J Pharmacol Sci. 2014;125(2):117–24. https://doi.org/10.1254/jphs.14R03CP.
33. Merrer JL, Becker JAJ, Befort K, Kieffer BL. Reward processing by the opioid system in the brain. Physiol Rev. 2009;89(4):1379–412. https://doi.org/10.1152/physrev.00005.2009.
34. Talka R, Salminen O, Whiteaker P, Lukas RJ, Tuominen RK. Nicotine–morphine interactions at α4β2, α7 and α3∗ nicotinic acetylcholine receptors. Eur J Pharmacol. 2013;701(1):57–64. https://doi.org/10.1016/j.ejphar.2013.01.005.
35. Vihavainen T, Mijatovic J, Piepponen TP, Tuominen RK, Ahtee L. Effect of morphine on locomotor activity and striatal monoamine metabolism in nicotine-withdrawn mice. Behav Brain Res. 2006;173(1):85–93. https://doi.org/10.1016/j.bbr.2006.06.004.
36. Vihavainen T, Piltonen M, Tuominen RK, Korpi ER, Ahtee L. Morphine–nicotine interaction in conditioned place preference in mice after chronic nicotine exposure. Eur J Pharmacol. 2008;587(1):169–74. https://doi.org/10.1016/j.ejphar.2008.03.028.
37. Shi MDMPHY, Weingarten MDTN, Mantilla MDPDCB, Hooten MDWM, Warner MDDO. Smoking and pain: pathophysiology and clinical implications. Anesthesiology. 2010;113(4):977–92. https://doi.org/10.1097/ALN.0b013e3181ebdaf9.
38. Zarrindast M-R, Faraji N, Rostami P, Sahraei H, Ghoshouni H. Cross-tolerance between morphine- and nicotine-induced conditioned place preference in mice. Pharmacol Biochem Behav. 2003;74(2):363–9. https://doi.org/10.1016/S0091-3057(02)01002-X.
39. Volkow ND, McLellan AT. Opioid abuse in chronic pain—misconceptions and mitigation strategies. N Engl J Med. 2016;374(13):1253–63. https://doi.org/10.1056/NEJMra1507771.
40. Lanz S, Seifert F, Maihofner C. Brain activity associated with pain, hyperalgesia and allodynia: an ALE meta-analysis. J Neural Transm (Vienna, Austria: 1996). 2011;118(8):1139–54. https://doi.org/10.1007/s00702-011-0606-9.
41. Moningka H, Lichenstein S, Worhunsky PD, DeVito EE, Scheinost D, Yip SW. Can neuroimaging help combat the opioid epidemic? A systematic review of clinical and pharmacological challenge fMRI studies with recommendations for future research. Neuropsychopharmacol. 2018. https://doi.org/10.1038/s41386-018-0232-4.
42. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4):276–86. https://doi.org/10.7326/m14-2559.
43. Boscarino JA, Rukstalis MR, Hoffman SN, Han JJ, Erlich PM, Ross S, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis. 2011;30(3):185–94. https://doi.org/10.1080/10550887.2011.581961.
44. Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. J Clin Psychiatry. 2009;70(9):1213–8.
45. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. JAMA. 2003;289(18):2370–8. https://doi.org/10.1001/jama.289.18.2370.
46. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. J Pain Symptom Manag. 2000;19(1):53–62.
47. Dunn KE, Brooner RK, Clark MR. Severity and interference of chronic pain in methadone-maintained outpatients. Pain Med. 2014;15(9):1540–8. https://doi.org/10.1111/pme.12430.
48. Barry DT, Beitel M, Cutter CJ, Garnet B, Joshi D, Rosenblum A, et al. Exploring relations among traumatic, posttraumatic, and physical pain experiences in methadone-maintained patients. J Pain. 2011;12(1):22–8. https://doi.org/10.1016/j.jpain.2010.04.006.
49. Plesner K, Jensen HI, Hojsted J. Smoking history, nicotine dependence and opioid use in patients with chronic non-malignant pain.

Acta Anaesthesiol Scand. 2016;60(7):988–94. https://doi.org/10.1111/aas.12741.
50. Orhurhu VJ, Pittelkow TP, Hooten WM. Prevalence of smoking in adults with chronic pain. Tob Induc Dis. 2015;13(1):17. https://doi.org/10.1186/s12971-015-0042-y.
51. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between smoking and low back pain: a meta-analysis. Am J Med. 2010;123(1):87 e7–35. https://doi.org/10.1016/j.amjmed.2009.05.028.
52. Hahn EJ, Rayens MK, Kirsh KL, Passik SD. Brief report: pain and readiness to quit smoking cigarettes. Nicotine Tob Res. 2006;8(3):473–80. https://doi.org/10.1080/14622200600670355.
53. Ditre JW, Kosiba JD, Zale EL, Zvolensky MJ, Maisto SA. Chronic pain status, nicotine withdrawal, and expectancies for smoking cessation among lighter smokers. Ann Behav Med. 2016;50(3):427–35. https://doi.org/10.1007/s12160-016-9769-9.
54. Hooten WM. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. Mayo Clin Proc. 2016;91(7):955–70. https://doi.org/10.1016/j.mayocp.2016.04.029.
55. Kosiba JD, Zale EL, Ditre JW. Associations between pain intensity and urge to smoke: testing the role of negative affect and pain catastrophizing. Drug Alcohol Depend. 2018;187:100–8. https://doi.org/10.1016/j.drugalcdep.2018.01.037.
56. Dhingra LK, Homel P, Grossman B, Chen J, Scharaga E, Calamita S, et al. Ecological momentary assessment of smoking behavior in persistent pain patients. Clin J Pain. 2014;30(3):205–13. https://doi.org/10.1097/AJP.0b013e31829821c7.
57. Parkerson HA, Asmundson GJG. The role of pain intensity and smoking expectancies on smoking urge and behavior following experimental pain induction. Drug Alcohol Depend. 2016;164:166–71. https://doi.org/10.1016/j.drugalcdep.2016.05.007.
58.•• Ditre JW, Heckman BW, Zale EL, Kosiba JD, Maisto SA. Acute analgesic effects of nicotine and tobacco in humans: a meta-analysis. Pain. 2016;157(7):1373–81. https://doi.org/10.1097/j.pain.0000000000000572 **Meta-analysis of acute nicotine effect on pain in line with proposed reciprocal model of pain and smoking as a positive feedback loop that results in greater pain, increased smoking, and maintenance of tobacco addiction.**
59. Weingarten TN, Moeschler SM, Ptaszynski AE, Hooten WM, Beebe TJ, Warner DO. An assessment of the association between smoking status, pain intensity, and functional interference in patients with chronic pain. Pain Physician. 2008;11:643–53.
60. Ditre JW, Brandon TH. Pain as a motivator of smoking: effects of pain induction on smoking urge and behavior. J Abnorm Psychol. 2008;117(2):467–72. https://doi.org/10.1037/0021-843X.117.2.467.
61. Nakajima M, Al'Absi M. Nicotine withdrawal and stress-induced changes in pain sensitivity: a cross-sectional investigation between abstinent smokers and nonsmokers. Psychophysiology. 2014;51(10):1015–22. https://doi.org/10.1111/psyp.12241.
62. LaRowe LR, Kosiba JD, Zale EL, Ditre JW. Effects of nicotine deprivation on current pain intensity among daily cigarette smokers. Exp Clin Psychopharmacol. 2018;26(5):448–55. https://doi.org/10.1037/pha0000218.
63. Zale EL, Ditre JW, Dorfman ML, Heckman BW, Brandon TH. Smokers in pain report lower confidence and greater difficulty quitting. Nicotine Tob Res. 2014;16(9):1272–6. https://doi.org/10.1093/ntr/ntu077.
64. Ditre JW, Langdon KJ, Kosiba JD, Zale EL, Zvolensky MJ. Relations between pain-related anxiety, tobacco dependence, and barriers to quitting among a community-based sample of daily smokers. Addict Behav. 2015;42:130–5. https://doi.org/10.1016/j.addbeh.2014.11.032.
65. Zale EL, Maisto SA, Ditre JW. Anxiety and depression in bidirectional relations between pain and smoking: implications for smoking cessation. Behav Modif. 2016;40(1–2):7–28. https://doi.org/10.1177/0145445515610744.
66. Zale EL, Ditre JW. Associations between chronic pain status, attempts to quit smoking, and use of pharmacotherapy for smoking cessation. Psychol Addict Behav. 2014;28(1):294–9. https://doi.org/10.1037/a0032515.
67. Hooten WM, Townsend CO, Hays JT, Ebnet KL, Gauvin TR, Gehin JM, et al. A cognitive behavioral smoking abstinence intervention for adults with chronic pain: a randomized controlled pilot trial. Addict Behav. 2014;39(3):593–9. https://doi.org/10.1016/j.addbeh.2013.11.010.
68. Montbriand JJ, Weinrib AZ, Azam MA, Ladak SSJ, Shah BR, Jiang J, et al. Smoking, pain intensity, and opioid consumption 1–3 months after major surgery: a retrospective study in a hospital-based transitional pain service. Nicotine Tob Res. 2018;20(9):1144–51. https://doi.org/10.1093/ntr/ntx094.
69. Miller ME, Sigmon SC. Are pharmacotherapies ineffective in opioid-dependent smokers? Reflections on the scientific literature and future directions. Nicotine Tob Res. 2015;17(8):955–9. https://doi.org/10.1093/ntr/ntv030.
70. Herzog JI, Schmahl C. Adverse childhood experiences and the consequences on neurobiological, psychosocial, and somatic conditions across the lifespan. Front Psychiatry. 2018;9(420). https://doi.org/10.3389/fpsyt.2018.00420.
71. Stein MD, Conti MT, Kenney S, Anderson BJ, Flori JN, Risi MM, et al. Adverse childhood experience effects on opioid use initiation, injection drug use, and overdose among persons with opioid use disorder. Drug Alcohol Depend. 2017;179:325–9. https://doi.org/10.1016/j.drugalcdep.2017.07.007.
72. Shin SH, McDonald SE, Conley D. Patterns of adverse childhood experiences and substance use among young adults: a latent class analysis. Addict Behav. 2018;78:187–92. https://doi.org/10.1016/j.addbeh.2017.11.020.
73. Anda RF, Croft JB, Felitti VJ, Nordenberg D, Giles WH, Williamson DF, et al. Adverse childhood experiences and smoking during adolescence and adulthood. JAMA. 1999;282(17):1652–8.
74. Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health. 2017;2(8):e356–e66. https://doi.org/10.1016/S2468-2667(17)30118-4.
75. Oshri A, Kogan SM, Kwon JA, Wickrama KAS, Vanderbroek L, Palmer AA, et al. Impulsivity as a mechanism linking child abuse and neglect with substance use in adolescence and adulthood. Dev Psychopathol. 2018;30(2):417–35. https://doi.org/10.1017/S0954579417000943.
76.• Lutz PE, Gross JA, Dhir SK, Maussion G, Yang J, Bramoulle A, et al. Epigenetic regulation of the kappa opioid receptor by child abuse. Biol Psychiatry. 2018;84(10):751–61. https://doi.org/10.1016/j.biopsych.2017.07.012 **This study reports epigenetic changes in KOR expression in association with child abuse, suggesting a novel mechanism whereby adverse childhood experiences may influence risk for opioid and nicotine use, as well as other psychopathology, later in development.**
77. al'Absi M, Lemieux A, Westra R, Allen S. Early life adversity influences stress response association with smoking relapse. Psychopharmacology. 2017;234(22):3375–84. https://doi.org/10.1007/s00213-017-4724-4.
78. Wu NS, Schairer LC, Dellor E, Grella C. Childhood trauma and health outcomes in adults with comorbid substance abuse and mental health disorders. Addict Behav. 2010;35(1):68–71. https://doi.org/10.1016/j.addbeh.2009.09.003.

79. Verplaetse TL, Moore KE, Pittman BP, Roberts W, Oberleitner LM, Smith PH, et al. Intersection of stress and gender in association with transitions in past year DSM-5 substance use disorder diagnoses in the United States. Chronic Stress (Thousand Oaks). 2018;2. https://doi.org/10.1177/2470547017752637.
80. Jaremko KM, Sterling RC, Van Bockstaele EJ. Psychological and physiological stress negatively impacts early engagement and retention of opioid-dependent individuals on methadone maintenance. J Subst Abus Treat. 2015;48(1):117–27. https://doi.org/10.1016/j.jsat.2014.08.006.
81. Mantsch JR, Baker DA, Funk D, Le AD, Shaham Y. Stress-induced reinstatement of drug seeking: 20 years of progress. Neuropsychopharmacology. 2016;41(1):335–56. https://doi.org/10.1038/npp.2015.142.
82. Bershad AK, Miller MA, Norman GJ, de Wit H. Effects of opioid- and non-opioid analgesics on responses to psychosocial stress in humans. Horm Behav. 2018;102:41–7. https://doi.org/10.1016/j.yhbeh.2018.04.009.
83.•• Evans CJ, Cahill CM. Neurobiology of opioid dependence in creating addiction vulnerability. F1000Res. 2016;5. https://doi.org/10.12688/f1000research.8369.1 **This review presents a mechanistic model highlighting various ways that opioid exposure potentiates the development of addiction.**
84. Van Hedger K, Bershad AK, de Wit H. Pharmacological challenge studies with acute psychosocial stress. Psychoneuroendocrinology. 2017;85:123–33. https://doi.org/10.1016/j.psyneuen.2017.08.020.
85. Moran LM, Kowalczyk WJ, Phillips KA, Vahabzadeh M, Lin JL, Mezghanni M, et al. Sex differences in daily life stress and craving in opioid-dependent patients. Am J Drug Alcohol Abuse. 2018;44(5):512–23. https://doi.org/10.1080/00952990.2018.1454934.
86. Tomko RL, Saladin ME, Baker NL, McClure EA, Carpenter MJ, Ramakrishnan VR, et al. Sex differences in subjective and behavioral responses to stressful and smoking cues presented in the natural environment of smokers. Nicotine Tob Res. 2018. https://doi.org/10.1093/ntr/nty234.
87. Kidorf M, Solazzo S, Yan H, Brooner RK. Psychiatric and substance use comorbidity in treatment-seeking injection opioid users referred from syringe exchange. J Dual Diagn. 2018:1–8. https://doi.org/10.1080/15504263.2018.1510148.
88. Anderson RE, Hruska B, Boros AP, Richardson CJ, Delahanty DL. Patterns of co-occurring addictions, posttraumatic stress disorder, and major depressive disorder in detoxification treatment seekers: implications for improving detoxification treatment outcomes. J Subst Abus Treat. 2018;86:45–51. https://doi.org/10.1016/j.jsat.2017.12.009.
89. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000;284(20):2606–10.
90. Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. The association between severity of depression and prescription opioid misuse among chronic pain patients with and without anxiety: a cross-sectional study. J Affect Disord. 2018;235:293–302. https://doi.org/10.1016/j.jad.2018.04.058.
91. Grattan A, Sullivan MD, Saunders KW, Campbell CI, Von Korff MR. Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. Ann Fam Med. 2012;10(4):304–11. https://doi.org/10.1370/afm.1371.
92. Serre F, Fatseas M, Denis C, Swendsen J, Auriacombe M. Predictors of craving and substance use among patients with alcohol, tobacco, cannabis or opiate addictions: commonalities and specificities across substances. Addict Behav. 2018;83:123–9. https://doi.org/10.1016/j.addbeh.2018.01.041.
93. Fatseas M, Serre F, Swendsen J, Auriacombe M. Effects of anxiety and mood disorders on craving and substance use among patients with substance use disorder: an ecological momentary assessment study. Drug Alcohol Depend. 2018;187:242–8. https://doi.org/10.1016/j.drugalcdep.2018.03.008.
94. Heckman BW, Kovacs MA, Marquinez NS, Meltzer LR, Tsambarlis ME, Drobes DJ, et al. Influence of affective manipulations on cigarette craving: a meta-analysis. Addiction. 2013;108(12):2068–78. https://doi.org/10.1111/add.12284.
95. Litz M, Leslie D. The impact of mental health comorbidities on adherence to buprenorphine: a claims based analysis. Am J Addict. 2017;26(8):859–63. https://doi.org/10.1111/ajad.12644.
96. Zawertailo L, Voci S, Selby P. Depression status as a predictor of quit success in a real-world effectiveness study of nicotine replacement therapy. Psychiatry Res. 2015;226(1):120–7. https://doi.org/10.1016/j.psychres.2014.12.027.
97. Chisolm MS, Tuten M, Brigham EC, Strain EC, Jones HE. Relationship between cigarette use and mood/anxiety disorders among pregnant methadone-maintained patients. Am J Addict. 2009;18(5):422–9. https://doi.org/10.3109/10550490903077721.
98. Cooperman NA, Lu SE, Richter KP, Bernstein SL, Williams JM. Influence of psychiatric and personality disorders on smoking cessation among individuals in opiate dependence treatment. J Dual Diagn. 2016;12(2):118–28. https://doi.org/10.1080/15504263.2016.1172896.
99. Boettger MK, Schwier C, Bar KJ. Sad mood increases pain sensitivity upon thermal grill illusion stimulation: implications for central pain processing. Pain. 2011;152(1):123–30. https://doi.org/10.1016/j.pain.2010.10.003.
100.• Thompson T, Correll CU, Gallop K, Vancampfort D, Stubbs B. Is pain perception altered in people with depression? A systematic review and meta-analysis of experimental pain research. J Pain. 2016;17(12):1257–72. https://doi.org/10.1016/j.jpain.2016.08.007 **This review presents results from a meta-analysis of 32 studies on pain perception in depression and highlights an important influence of painful stimulus type (cutaneous vs. ischemic pain).**
101. Wasan AD, Davar G, Jamison R. The association between negative affect and opioid analgesia in patients with discogenic low back pain. Pain. 2005;117(3):450–61. https://doi.org/10.1016/j.pain.2005.08.006.
102. Carcoba LM, Contreras AE, Cepeda-Benito A, Meagher MW. Negative affect heightens opiate withdrawal-induced hyperalgesia in heroin dependent individuals. J Addict Dis. 2011;30(3):258–70. https://doi.org/10.1080/10550887.2011.581985.
103. American Psychological Association. Guidelines for psychological practice with lesbian, gay, and bisexual clients. Am Psychol. 2012;67(1):10–42.
104. Perkins KA, Donny E, Caggiula AR. Sex differences in nicotine effects and self-administration: review of human and animal evidence. Nicotine Tob Res. 1999;1(4):301–15. https://doi.org/10.1080/14622299050011431.
105. Zakiniaeiz Y, Potenza MN. Gender-related differences in addiction: a review of human studies. Curr Opin Behav Sci. 2018;23:171–5. https://doi.org/10.1016/j.cobeha.2018.08.004.
106. Perkins KA, Jacobs L, Sanders M, Caggiula AR. Sex differences in the subjective and reinforcing effects of cigarette nicotine dose. Psychopharmacology. 2002;163(2):194–201. https://doi.org/10.1007/s00213-002-1168-1.
107. Perkins KA, Gerlach D, Vender J, Meeker J, Hutchison S, Grobe J. Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. Nicotine Tob Res. 2001;3(2):141–50. https://doi.org/10.1080/14622200110043059.
108. Perkins KA. Sex differences in nicotine versus nonnicotine reinforcement as determinants of tobacco smoking. Exp Clin

Psychopharmacol. 1996;4(2):166–77. https://doi.org/10.1037/1064-1297.4.2.166.

109. Johnstone E, Benowitz N, Cargill A, Jacob R, Hinks L, Day I, et al. Determinants of the rate of nicotine metabolism and effects on smoking behavior. Clin Pharmacol Ther. 2006;80(4):319–30. https://doi.org/10.1016/j.clpt.2006.06.011.
110. Sofuoglu M, Mooney M. Subjective responses to intravenous nicotine: greater sensitivity in women than in men. Exp Clin Psychopharmacol. 2009;17(2):63–9. https://doi.org/10.1037/a0015297.
111. Bjornson W, Rand C, Connett JE, Lindgren P, Nides M, Pope F, et al. Gender differences in smoking cessation after 3 years in the Lung Health Study. Am J Public Health. 1995;85(2):223–30.
112. Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. Drug Alcohol Depend. 2004;74(3):265–72. https://doi.org/10.1016/j.drugalcdep.2004.02.001.
113. Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender differences in risk factors for aberrant prescription opioid use. J Pain. 2010;11(4):312–20. https://doi.org/10.1016/j.jpain.2009.07.016.
114. Back SE, Payne RL, Simpson AN, Brady KT. Gender and prescription opioids: findings from the National Survey on Drug Use and Health. Addict Behav. 2010;35(11):1001–7. https://doi.org/10.1016/j.addbeh.2010.06.018.
115. Back SE, Lawson KM, Singleton LM, Brady KT. Characteristics and correlates of men and women with prescription opioid dependence. Addict Behav. 2011;36(8):829–34. https://doi.org/10.1016/j.addbeh.2011.03.013.
116. Akerman SC, Brunette MF, Green AI, Goodman DJ, Blunt HB, Heil SH. Treating tobacco use disorder in pregnant women in medication-assisted treatment for an opioid use disorder: a systematic review. J Subst Abus Treat. 2015;52:40–7. https://doi.org/10.1016/j.jsat.2014.12.002.
117. SAMHSA. Substance use among women during pregnancy and following childbirth. In: The NSDUH Report: Office of Applied Studies, Substance Abuse and Mental Health Services Administration; 2009.
118. Chisolm MS, Fitzsimons H, Leoutsakos JM, Acquavita SP, Heil SH, Wilson-Murphy M, et al. A comparison of cigarette smoking profiles in opioid-dependent pregnant patients receiving methadone or buprenorphine. Nicotine Tob Res. 2013;15(7):1297–304. https://doi.org/10.1093/ntr/nts274.
119. Jones HE, Heil SH, O'Grady KE, Martin PR, Kaltenbach K, Coyle MG, et al. Smoking in pregnant women screened for an opioid agonist medication study compared to related pregnant and non-pregnant patient samples. Am J Drug Alcohol Abuse. 2009;35(5):375–80. https://doi.org/10.1080/00952990903125235.
120. Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. J Women's Health (2002). 2003;12(4):373–80. https://doi.org/10.1089/154099903765448880.
121. Tran TH, Griffin BL, Stone RH, Vest KM, Todd TJ. Methadone, buprenorphine, and naltrexone for the treatment of opioid use disorder in pregnant women. Pharmacotherapy. 2017;37(7):824–39. https://doi.org/10.1002/phar.1958.
122.• Kota D, Alajaji M, Bagdas D, Selley DE, Sim-Selley LJ, Damaj MI. Early adolescent nicotine exposure affects later-life hippocampal mu-opioid receptors activity and morphine reward but not physical dependence in male mice. Pharmacol Biochem Behav. 2018;173:58–64. https://doi.org/10.1016/j.pbb.2018.08.006 **This study finds adolescent nicotine exposure impacts MORs and opioid reward later in adulthood.**
123. Smith RF, McDonald CG, Bergstrom HC, Ehlinger DG, Brielmaier JM. Adolescent nicotine induces persisting changes in development of neural connectivity. Neurosci Biobehav Rev. 2015;55:432–43. https://doi.org/10.1016/j.neubiorev.2015.05.019.
124. Marco EM, Granstrem O, Moreno E, Llorente R, Adriani W, Laviola G, et al. Subchronic nicotine exposure in adolescence induces long-term effects on hippocampal and striatal cannabinoid-CB1 and mu-opioid receptors in rats. Eur J Pharmacol. 2007;557(1):37–43. https://doi.org/10.1016/j.ejphar.2006.11.013.
125. Thanos P, Delis F, Rosko L, Volkow ND. Passive response to stress in adolescent female and adult male mice after intermittent nicotine exposure in adolescence. J Addict Res Ther. 2013;(Suppl 6):007. https://doi.org/10.4172/2155-6105.S6-007.
126. Iniguez SD, Warren BL, Parise EM, Alcantara LF, Schuh B, Maffeo ML, et al. Nicotine exposure during adolescence induces a depression-like state in adulthood. Neuropsychopharmacology. 2009;34(6):1609–24. https://doi.org/10.1038/npp.2008.220.
127. Gentry S, Craig J, Holland R, Notley C. Smoking cessation for substance misusers: a systematic review of qualitative studies on participant and provider beliefs and perceptions. Drug Alcohol Depend. 2017;180:178–92. https://doi.org/10.1016/j.drugalcdep.2017.07.043.
128. McHugh RK, Votaw VR, Fulciniti F, Connery HS, Griffin ML, Monti PM, et al. Perceived barriers to smoking cessation among adults with substance use disorders. J Subst Abus Treat. 2017;74:48–53. https://doi.org/10.1016/j.jsat.2016.12.008.
129.• McKelvey K, Thrul J, Ramo D. Impact of quitting smoking and smoking cessation treatment on substance use outcomes: an updated and narrative review. Addict Behav. 2017;65:161–70. https://doi.org/10.1016/j.addbeh.2016.10.012 **This review reports that smoking cessation does not negatively impact substance use outcomes as previously thought, rather the literature suggests a positive effect of treating smoking.**
130. Prochaska JJ, Delucchi K, Hall SM. A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. J Consult Clin Psychol. 2004;72(6):1144–56. https://doi.org/10.1037/0022-006X.72.6.1144.
131. Mannelli P, Wu LT, Peindl KS, Gorelick DA. Smoking and opioid detoxification: behavioral changes and response to treatment. Nicotine Tob Res. 2013;15(10):1705–13. https://doi.org/10.1093/ntr/ntt046.
132. Shoptaw S, Rotheram-Fuller E, Yang X, Frosch D, Nahom D, Jarvik ME, et al. Smoking cessation in methadone maintenance. Addiction. 2002;97(10):1317–28 discussion 25.
133. Tacke U, Wolff K, Finch E, Strang J. The effect of tobacco smoking on subjective symptoms of inadequacy ("not holding") of methadone dose among opiate addicts in methadone maintenance treatment. Addict Biol. 2001;6(2):137–45. https://doi.org/10.1080/13556210020040217.
134.•• Jensen KP, DeVito EE, Yip S, Carroll KM, Sofuoglu M. The cholinergic system as a treatment target for opioid use disorder. CNS Drugs. 2018. https://doi.org/10.1007/s40263-018-0572-y **This review presents preclinical and clinical data highlighting the potential of different cholinergic medications for the treatment OUD.**
135.•• Norman H, D'Souza MS. Endogenous opioid system: a promising target for future smoking cessation medications. Psychopharmacology (Berl). 2017;234(9–10):1371–94. https://doi.org/10.1007/s00213-017-4582-0 **This review presents an overview of data suggesting that manipulation of the endogenous opioid system may aid smoking cessation from both animal and human literatures.**
136. Diehl A, Nakovics H, Croissant B, Smolka MN, Batra A, Mann K. Galantamine reduces smoking in alcohol-dependent patients: a

randomized, placebo-controlled trial. Int J Clin Pharmacol Ther. 2006;44(12):614–22.
137. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006;296(1):47–55. https://doi.org/10.1001/jama.296.1.47.
138. Hooten WM, Warner DO. Varenicline for opioid withdrawal in patients with chronic pain: a randomized, single-blinded, placebo controlled pilot trial. Addict Behav. 2015;42:69–72. https://doi.org/10.1016/j.addbeh.2014.11.007.
139. Liu S, Li L, Shen W, Shen X, Yang G, Zhou W. Scopolamine detoxification technique for heroin dependence: a randomized trial. CNS Drugs. 2013;27(12):1093–102. https://doi.org/10.1007/s40263-013-0111-9.
140. David SP, Lancaster T, Stead LF, Evins AE, Prochaska JJ. Opioid antagonists for smoking cessation. Cochrane Database Syst Rev. (2013, 6):CD003086. https://doi.org/10.1002/14651858.CD003086.pub3.
141. David SP, Chu IM, Lancaster T, Stead LF, Evins AE, Prochaska JJ. Systematic review and meta-analysis of opioid antagonists for smoking cessation. BMJ Open. 2014;4(3):e004393. https://doi.org/10.1136/bmjopen-2013-004393.
142. Ray LA, Courtney KE, Ghahremani DG, Miotto K, Brody A, London ED. Varenicline, low dose naltrexone, and their combination for heavy-drinking smokers: human laboratory findings. Psychopharmacology. 2014;231(19):3843–53. https://doi.org/10.1007/s00213-014-3519-0.
143. Walsh Z, Epstein A, Munisamy G, King A. The impact of depressive symptoms on the efficacy of naltrexone in smoking cessation. J Addict Dis. 2008;27(1):65–72. https://doi.org/10.1300/J069v27n01_07.