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Nicotine and opioid co-dependence: Findings from bench research to clinical trials

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Abstract

Concomitant use of tobacco and opioids represents a growing public health concern. In fact, the mortality rate due to smoking-related illness approaches 50% among SUD patients. Cumulative evidence demonstrates that the vulnerability to drugs of abuse is influenced by behavioral, environmental, and genetic factors. This review explores the contribution of genetics and neural mechanisms influencing nicotine and opioid reward, respiration, and antinociception, emphasizing the interaction of cholinergic and opioid receptor systems. Despite the substantial evidence demonstrating nicotine-opioid interactions within the brain and on behavior, the currently available pharmacotherapies targeting these systems have shown limited efficacy for smoking cessation on opioid-maintained smokers. Thus, further studies designed to identify novel targets modulating both nicotinic and opioid receptor systems may lead to more efficacious approaches for co-morbid nicotine dependence and opioid use disorder.

Keywords

Substance use disorder; Opioids; Nicotine; Polydrug abuse; Rodent models; Clinical trials; Genetics; Neurobiology of addiction

1. Introduction

Nicotine dependence (ND) and opioid use disorder (OUD) are primary causes of preventable disease and premature death worldwide. Despite the increased public health campaigns and availability of smoking cessation and OUD aids, the successful smoking cessation rate remains lower than 8% (Creamer et al., 2019), while opioid-related overdose deaths have been escalating (O'Donnell et al., 2020). An overwhelming majority of individuals with opioid use disorder (OUD) report nicotine co-use, with over 80 % of OUD patients reporting cigarette smoking (Kalman et al., 2005). The rate of nicotine-opioid co-use appears even higher in untreated opioid users, with estimated co-use among 92 % of heroin users (Haas et

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al., 2008) and 91 % of syringe exchange participants not in treatment (Clarke et al., 2001). Furthermore, between 2002 and 2017, the prevalence of OUD has escalated among smokers and former smokers, while the prevalence of OUD has decreased among non-smokers (Parker and Weinberger, 2020). The high prevalence of nicotine-opioid co-use is particularly pressing since their interactions are largely unexplored and co-use may present an even greater risk for negative health effects.

Furthermore, smoking rates are higher in vulnerable drug-using populations, contributing to a 50 % mortality rate due to smoking-related illness among substance use disorder (SUD) patients (Hurt et al., 1996; Hser et al., 1994). For example, the smoking rates among hospitalized smokers with SUD are at least three times greater than hospitalized patients without SUD, particularly in opioid-dependent patients (Kathuria et al., 2019). Conversely, smoking cessation medications are less efficacious among individuals with OUD (Miller and Sigmon, 2015), possibly due to the higher severity of ND in this population (Parker et al., 2018). Moreover, smokers with OUD report low motivation to quit (Kathuria et al., 2019), possibly because they perceive smoking as less harmful and have limited access to treatment programs (Richter et al., 2004). Additionally, smokers with OUD report concerns about opioid relapse, since many use smoking to cope with negative affect and ameliorate other adverse events related to opioid withdrawal, which poses a risk to patient's adherence and compliance to smoking cessation programs. Chronic pain is also highly prevalent in both smokers and individuals with OUD compared to the general population (Plesner et al., 2016), likely representing a co-morbid driver for dependence. Individuals with chronic pain who are smokers under opioid therapy use more opioids than never smokers and are less sensitive to the adverse effects of opioids. Males with chronic pain consume an increased daily dosage of opioids, and therefore, are particularly vulnerable to misuse prescription opioids and potentially overdose leading to respiratory failure (Young-Wolff et al., 2017). However, while there are epidemiological data showing distinct interactions between ND and OUD, the mechanisms circumscribing this co-dependency are not well understood.

In this review, we will discuss current knowledge and recent developments linking rodent and human observations in nicotine-opioid interaction research, examining evidence of interdigitating roles of nicotine and opioids on reward, antinociception, and respiration. Reward was selected because this process underlies the abuse liability of both nicotine and opioids. Antinociception was selected because (1) nicotinic cholinergic mechanisms are known to be involved and (2) pain relief represents the main clinical use for opioids. Finally, respiration was selected because tobacco inhalation alters respiration rate and respiratory failure represents the main cause of death due to opioid overdose. Through this lens, we will then examine the neural and genetic mechanisms contributing to co-dependency and discuss their salience to current clinical trials data for integration of these mechanisms in evidence-based approaches for individuals suffering from co-morbid ND and OUD.

2. Nicotine dependence and opioid use disorder: reward

2.1. Anatomy of reward pertaining to nicotine and opioid co-use

The mesocorticolimbic or reward pathway is the key neural substrate for reward, including those behaviors underlying drug addiction. Nicotine and opioids are known to enhance

the effect of dopaminergic function in the mesocorticolimbic pathway that runs from the midbrain ventral tegmental area (VTA) to medium spiny neurons in nucleus accumbens (NAc) and the prefrontal cortex (PFC). Both nicotine and opioids are known to evoke dopamine release in this pathway (Nisell et al., 1994; Tanda and Di Chiara, 1998), a response known to be a principal neural framework shaping reward-related behaviors. With nicotine, burst firing of dopamine VTA neurons is increased directly via nicotinic acetylcholine receptors (nAChRs) located on cell bodies, as well as indirectly via GABAergic interneurons within VTA (Pistillo et al., 2015; Mansvelder and McGehee, 2002; Faure et al., 2014). Dopamine release is enhanced further via nAChRs in the terminal field (Exley et al., 2008; Lee et al., 2020). With opioids, there is a dopamine-dependent mechanism involving disinhibition of dopamine neurons via GABAergic interneurons in VTA, as well as a dopamine-independent mechanism involving modulation of medium spiny neurons in NAc (Nestler et al., 2020; Hjelmstad and Fields, 2003).

Repeated nicotine or opioid exposure is thought to change the sensitivity of the dopamine reward pathway via extensive glutamatergic input from various structures, including PFC, hippocampus, paraventricular thalamus and amygdala (Kruyer et al., 2020; Scofield et al., 2016). These areas are anatomically and functionally interconnected to exert motivation, reward, cognitive and emotional processing (Goto and Grace, 2008). In addition to reward processing and dependence, additional brain systems mediate drug-induced aversive states that counterbalance activity of the mesolimbic pathway. For example, kappa opioid agonists produce aversion by directly blunting the reward pathway (Knoll and Carlezon, 2010; Robles et al., 2014), whereas nicotine produces aversion by indirectly blunting the reward pathway by activation of the lateral habenula (Fowler and Kenny, 2014; Zuo et al., 2016). Thus, the complex interplay of these various systems broadly demonstrates both the circuitry-level regulation of reward, as well as a dissociations of the discrete symptoms of withdrawal and aversion that ultimately control nicotine and opioid drug-taking.

2.2. Nicotinic contributions to opioid reward

Underlying the co-morbidity of tobacco use and opioid use disorders, preclinical evidence shows a direct interaction between opioid and nicotinic receptor activation in the control of addiction-relevant behaviors measured by either conditioned place preference (CPP) or self-administration (SA). As summarized in Table 1, a number of preclinical studies have examined the role of nAChRs in modulating opioid reward. Most relevant for the co-morbidity of ND and OUD, nicotine pretreatment can have profound effects on opioid reward. When nicotine is administered in the drinking water for 7 weeks prior to conditioning, it sensitizes mice to morphine CPP (Vihavainen et al., 2008a). In contrast, when administered during conditioning, systemic or intra-insular cortex nicotine shifts the dose-effect curve for morphine CPP to the right (Loney et al., 2021), indicative of decreased sensitivity to opioid reward. Similarly, when administered on the test day, systemic and intracerebroventricular nicotine decreases the expression of morphine CPP (Shams et al., 2006). As a compensation for reduced reward sensitivity, acute nicotine pretreatment increases SA of morphine and remifentanil (Loney et al., 2021). Conversely, the use-dependent nicotinic antagonist 2,2,6,6-tetramethyl-4-piperidinyl [BTMPS] decreases morphine SA and seeking during abstinence (Hall et al., 2011). Interestingly, in contrast

to nicotine-induced increases in opioid SA, activation of muscarinic cholinergic receptors decreases heroin SA (Zhou et al., 2006).

Relative to SA, studies using CPP are more widely represented in the literature, with some results opposing the conclusion drawn above that nicotine decreases opioid reward sensitivity. For example, in contrast to the nicotine-induced decrease in reward sensitivity reported recently (Loney et al., 2021), other reports show *increased* sensitivity to opioid CPP when nicotine is administered into various brain structures, including VTA, dorsal hippocampus, and basolateral amygdala (Rezayof et al., 2007, 2006; Zarrindast et al., 2005). These latter studies also show that microinjection of mecamylamine (a non-selective nicotinic receptor agonist) into these same regions decreases morphine CPP, an effect that is also obtained with systemic mecamylamine (Zarrindast et al., 2003). It is difficult to reconcile the findings showing *decreased* sensitivity to opioid reward when nicotine is administered systemically or into insular cortex, but *increased* sensitivity when nicotine is injected into VTA, dorsal hippocampus and basolateral amygdala. However, it appears that nicotinic receptors from different brain structures exert both excitatory and inhibitory control on opioid reward systems.

There has also been work examining the role of nicotinic receptors in reinstatement of opioid seeking. While one study found that nicotine is ineffective in eliciting morphine seeking following extinction of morphine CPP (Feng et al., 2011), antagonism of either β-containing nAChRs with dihydro-β-erythroidine or α7 homomeric nAChRs with methyllycaconitine reduces drug-primed reinstatement of morphine CPP (Feng et al., 2011; Wright et al., 2019). The effect of methyllycaconitine is mediated, at least in part, by α7 receptors in ventral hippocampus (Wright et al., 2019). These results with reinstatement align more closely with the notion that nicotinic receptors primarily function to *increase,* rather than decrease, opioid reward sensitivity, although the neurocircuitry involved in excitatory vs. inhibitory nicotinic modulation of opioid reward mechanisms remains to be elucidated.

2.3. Opioid contributions to nicotine reward

As summarized in Table 2, many studies have examined the role of opioid systems in modulating nicotine reward. In mice, development of nicotine CPP is reliably blocked by naloxone (Zarrindast et al., 2003; Walters et al., 2005) and by genetic deletion of β-endorphin production (Trigo et al., 2009) or μ opioid receptor (MOR) expression (Walters et al., 2005; Berrendero et al., 2002), strongly implicating a role for MOR in the control of nicotine reward. Similarly, while some null findings have been reported (Corrigall and Coen, 1991; DeNoble and Mele, 2006), nicotine self-administration in rats is decreased by naloxone and the long-lasting μ_1 antagonist naloxonazine (Liu and Jernigan, 2011; Ismayilova and Shoaib, 2010). Reinstatement of nicotine seeking also involves MOR activation since a morphine prime reinstates nicotine CPP and naloxone blocks cue-induced reinstatement of nicotine seeking measured by SA (Biala and Budzynska, 2006; Liu et al., 2009).

Beyond MOR, genetic evidence also suggests involvement of the δ opioid receptor (DOR) in nicotine reward. In particular, DOR knockout mice fail to develop nicotine CPP and show

diminished SA compared to wild-type counterparts (Berrendero et al., 2012). Deletion of *enk* yields a similar loss of nicotine CPP (Berrendero et al., 2005). Despite this genetic evidence, however, there is only sparse pharmacological data to support a role for DOR in nicotine reward. While one study found that naltrindole slowed acquisition of nicotine SA in mice (Berrendero et al., 2012), this same study found no effect on progressive ratio breakpoint. Moreover, others have reported no effect of naltrindole on nicotine SA in rats (Liu and Jernigan, 2011), bolstering the conclusion that DOR blockade does not alter nicotine reward. Together, these results suggest that genetic deletion of DOR or *enk* may produce some compensatory neural change in non-DOR systems to alter nicotine reward, which does not translate into pharmacological effects at DOR in wild-types.

Similar to other non-opioid drugs of abuse such as alcohol and cocaine (Funk et al., 2014; Redila and Chavkin, 2008), considerable evidence supports a role for the κ opioid receptor (KOR) in the expression of stress-induced nicotine seeking following a period of extinction. Importantly, prodynorphin KO does not alter acquisition of nicotine CPP (Galeote et al., 2008) and KOR antagonists have no effect on acquisition or expression of nicotine CPP (Nygard et al., 2016; Jackson et al., 2010). In addition, KOR antagonists have no effect on drug- or cue-primed reinstatement of nicotine seeking using CPP (Nygard et al., 2016; Jackson et al., 2013; Grella et al., 2014). Instead, KOR antagonists have a selective ability to decrease stress-induced reinstatement induced by forced swim, footshock or administration of the sympathomimetic yohimbine (Nygard et al., 2016; Jackson et al., 2013; Grella et al., 2014; Smith et al., 2012). The KOR agonist U50,488 also induces reinstatement of nicotine seeking (Al-Hasani et al., 2013) and this effect is reversed by a KOR antagonists delivered either systemically or directly into the amygdala (Smith et al., 2012). Viral activation and genetic knockdown studies also support a specific role of KOR in central nucleus of amygdala in stress-induced nicotine seeking (Nygard et al., 2016).

There is little information on the potential role of nociceptin opioid peptide (NOP) receptors on nicotine reward. NOP receptor KO mice drink more nicotine in a 2-bottle choice (Sakoori and Murphy, 2009), although the effect is modest and occurs only with a dilute nicotine concentration (3 μg/mL) that may not be behaviorally relevant. Nonetheless, a recent study found that nicotine SA is increased by a NOP receptor agonist and decreased by a NOP receptor antagonist (Cippitelli et al., 2016), thus providing an impetus for more work with this opioid receptor subtype. Until then, the main conclusions to be drawn at this time are that: (1) MOR plays a key role in nicotine reward and reinstatement; and (2) KOR plays a specific role in stress-induced reinstatement of nicotine seeking.

3. Nicotine dependence and opioid use disorder: antinociception

3.1. Anatomy of nociception pertaining to nicotine and opioid co-use

Pain signals are detected by nociceptors in the periphery and are transmitted to the dorsal horn of the spinal cord via nociceptive primary afferents where they synapse with projection neurons, which in turn cross the anterior white commissure to ascend the spinothalamic tract for thalamic relay and somatosensory cortical processing. As a result of incoming pain information, opioid interneurons in the periaqueductal grey (PAG) inhibit PAG activity, disinhibiting serotonergic rostral ventral medulla (RVM) neurons, and noradrenergic

projections arising from the locus coeruleus (Al-Hasani et al., 2013; Ossipov et al., 2010). The heavy involvement of opioid receptors in the descending and ascending pain pathways allows exogenous opioids, such as morphine, heroin, and fentanyl, to inhibit pain signaling, resulting in a decrease in nociception (Al-Hasani et al., 2013).

Nicotine also works within some of the same pain neurocircuitry components in which opioids act. For example, one study found that intra-vlPAG injection of PHA-543613, an α7 nAChR selective agonist, produced a dose-dependent antinociceptive effect compared to vehicle as determined by a formalin assay in rats, an effect reversed by pre-treatment with an α7 nAChR antagonist (Umana et al., 2017). Additionally, intra-RVM injection of mecamylamine, prevents immobilization stress-induced antinociception in rats following carrageenan-induced mechanical hyperalgesia and formalin-induced paw flinch nociception (Tobaldini et al., 2020). This supports that nicotinic agonists produce antinociception by targeting opioid- and pain-associated brain areas and that nicotine and opioids may interact to alter pain perception.

3.2. Nicotinic modulation of opioid antinociception

Nicotine specifically mediates the antinociceptive properties of opioids by acting as an enhancer of opioid-induced antinociception and increases opioid antinociceptive tolerance when co-used. Fentanyl, oxycodone, and buprenorphine dose-dependently increase squirrel monkey tail-withdrawal latency to hot water, and pre-treatment with nicotine shifts the dose response to the left without altering opioid-induced decreases in milk self-administration (Barreto de Moura et al., 2019). In rodent models, co-administration of the nAChR β2* agonist A85380 (where * indicates the presence of other subunits in addition to the β2) and fentanyl similarly enhances the ability of fentanyl to decrease pain responsivity to thermal plate- and formalin-induced nociception (Ren et al., 2019). Acute nicotine also increases the percent of maximum possible effect (%MPE) of tail flick latency after tail heat exposure in rats given codeine.

In contrast to the enhancement in opioid-induced antinociception observed with acute nicotine, repeated nicotine exposure increases the rate of tolerance for a codeine/nicotine combination (McMillan and Tyndale, 2017). Similarly, human tobacco smokers may be more tolerant to the antinociceptive properties of opioids. A meta-analysis of results from humans suggests that nicotine reduces pain in humans to a small, but significant extent, with more robust effects found in studies using men (Ditre et al., 2016). However, continued nicotine use increases the need for pain relief with opioids after surgery. For example, one study found that smokers deprived of nicotine after coronary artery bypass graft surgery required more opioids for pain relief than non-smokers (Creekmore et al., 2004). A similar effect was found in male smokers following distal gastrectomy with gastroduodenostomy (Kim et al., 2017). Considering the increased rate for OUD among smokers (Kalman et al., 2005), research should examine compatible treatments to reduce the need for increased opioid use in patients with ND.

Overall, the evidence above collectively suggests that nicotine interacts with the opioid system to enhance opioid-induced antinociception when used in combination. However, the complexity of this question is apparent given the dissociable effects of acute and chronic

nicotine treatments on opioid-induced analgesia. One potential reason for these observations may be due to the peculiar pharmacology of nicotine action when delivered acutely versus chronically. For example, previous fundamental pharmacological studies both *in vitro* and *in vivo* examining the acute and chronic effects of nicotine at the receptor level suggest that while nicotine is a super-agonist at nAChRs, its agonist effects at non-α7 receptors rapidly results in long-lasting desensitization of the receptor (Hulihan-Giblin et al., 1990; Turner et al., 2013a). This effectively results in nicotine acting as a "time-averaged" antagonist. While this has not been directly evaluated in opioid nociceptive studies as yet, utilization of allosteric modulators rather than agonists or partial agonists, may be more effectively clinically.

3.3. Opioid modulation of nicotinic antinociception

Considering the role of endogenous opioids in pain pathway regulation, exogenous opioids are frequently used as treatment for pain in the medical setting (National Academies of Sciences, E. et al., 2017). However, the antinociceptive effects of nicotine may also be modulated by opioid use since opioid receptor manipulation alters nicotine-induced antinociception. When MORs are absent, nAChR agonists no longer produce or enhance antinociception. For example, MOR KO mice show reduced nicotine-induced antinociception compared to wild-type mice tested using either the tail-flick or hotplate assays (Berrendero et al., 2002). Another study found that MOR KO mice express accelerated tolerance to the antinociceptive effects of nicotine compared to wild-type mice (Galeote et al., 2006). However, DOR KO mice show similar tolerance to the antinociceptive effect of chronic nicotine across a 12-day period compared to wild-type mice as determined by tail-immersion tests (Berrendero et al., 2012). While most research examining the impact of opioid system manipulation on nicotine-induced antinociception has been performed in opioid receptor KO rodents, one study found that pretreatment with a MOR, DOR, or KOR-opioid antagonist (β-FNA, naltrindole, or nor-BNI) reduces the antinociceptive effect of i.c.v. nicotine on acetic acid writhing in mice (Kwon et al., 2008). Thus, while the evidence is relatively sparse, it indicates that manipulation of the opioid system may alter nicotine-induced antinociception and should be a target for future work.

4. Nicotine dependence and opioid use disorder: respiration

4.1. Anatomy of respiration pertaining to nicotine and opioid co-use

The neural control of respiration involves multiple neurotransmitters emanating from anatomically distinct clusters of brainstem neurons that descend the spinal cord to synchronize breathing. While a comprehensive description is beyond the scope of this review, as described in detail previously (McCrimmon et al., 2008), there are three main groups of respiratory neurons. The first is the dorsal respiratory group located in the nucleus of the solitary tract, which are primarily inspiratory neurons under glutamatergic control. The second is contained within the ventrolateral medullar column that extends from the spinal-medulla junction to the facial nucleus, which are both inspiratory and expiratory neurons that utilize glutamate, GABA and glycine. The third is the pontine respiratory group within the dorsolateral pons, which are heterogeneous neurons utilizing glutamate, enkephalin and catecholamines. These three groups receive top-down modulation by

serotonergic and catecholaminergic input from midbrain periaqueductal gray, hypothalamus and cortex. In addition, most relevant for this review, there is also modulatory control of medullary respiratory neurons through stimulation of α4β2 nicotinic receptors (Ren et al., 2019), as well as through inhibition via MOR of both the medullary and pontine respiratory groups (Varga et al., 2019).

4.2. Nicotinic modulation of opioid effects on respiration

Heroin is known to produce profound life-threatening respiratory depression that is reversed by naloxone (Jolley et al., 2015; Strang et al., 2016). Moreover, the recent accelerating opioid overdose crisis is related primarily to the introduction of high potency opioids such as fentanyl and carfentanil into the illicit drug market (Volkow et al., 2019). In addition to producing profound respiration depression similar to heroin, high-potency fentanyl analogues also induce vocal chord closure and wooden chest syndrome that contributes to lethality (Torralva and Janowsky, 2019) and all of these untoward effects on breathing involve multiple mechanisms beyond mere occupation of opioid receptors (Torralva et al., 2020).

Stimulation of nicotinic receptors has recently been advanced as a potential intervention for countering opioid-induced respiratory depression (Imam et al., 2020). Using whole-body plethysmography in anesthetized rats, recent studies found that fentanyl-induced respiratory depression is reversed by nicotine or A85380 (Ren et al., 2019), as well as by partial agonists such as varenicline (Ren et al., 2020). Interestingly, the reversal of respiration depression is not accompanied by a reversal of the motoric rigidity that also accompanies high-dose fentanyl exposure. The dissociation between respiratory and motoric depression likely reflects that nicotinic receptors modulate MOR in respiratory brainstem nuclei (Ren et al., 2019), but not in motoric striatal circuits (Havemann and Kuschinsky, 1981). Since the α7 agonist PNU282987 has no effect on fentanyl-induced suppression of respiratory circuits (Ren et al., 2019), β-containing nAChRs play the key role. However, some caution is needed in interpreting these results using an anesthetized rat preparation because a recent study using conscious rats failed to find an effect of A85380 in reversing sufentanil-induced respiratory depression (Dandrea and Cotten, 2021), thus begging for further work on this vital clinical problem related to opioid overdose.

4.3. Opioid modulation of nicotinic effects on respiration

Most work assessing the effects of nicotine on respiration in humans has used tobacco cigarettes as the delivery device, which can lead to either decreases or increases in respiration based on individual differences (Jones, 1987). Similarly, different inbred mouse strains show variable respiratory responses to nicotine, with dose- and time-dependent decreases or increases occurring based on the genetic strain assessed (Marks et al., 1989). In general, however, preclinical studies in rodents and monkeys indicate that exposure to either tobacco smoke or systemic nicotine initially inhibits breathing, followed by a rebound tachypnea (Bloom, 2019; Howell, 1995; Lee et al., 1990). In dogs, nicotine-induced tachypnea is potentiated by naloxone pretreatment (Kamerling et al., 1982), indicating the involvement of opioid receptors

Evidence also indicates that the initial respiratory depressant effect of nicotine is modulated by opioid receptors. For example, the respiratory depression produced by acetylcholinesterase inhibition in rats, while reversed by muscarinic antagonists, also involves a significant nicotinic receptor component that is sensitive to naloxone (Skrbic et al., 2017). Even more directly relevant, naltrexone administration prevents the respiratory depressant and lethal effects of intravenous nicotine in anesthetized rats (Sloan et al., 1989), supporting the notion that nicotine depresses respiration via central opioid mechanisms (Krause et al., 2018).

5. Neural mechanisms contributing to overlapping nicotine and opioid co-use

Several lines of evidence suggest a functional interaction of the nicotinic and opioidergic systems in the development and maintenance of drug-seeking. Human and rodent studies indicate a bidirectional relationship between nicotine and opioid systems that is critical for the development and establishment of their drug dependence (Young-Wolff et al., 2017; Krause et al., 2018; Almeida et al., 2000; Trigo et al., 2009); W For example, nicotine modulates opioid actions in the mesolimbic circuit by enhancing the anxiolytic effects (Zarrindast et al., 2008) and rewarding properties of MOR agonists (Rezayof et al., 2006; Zarrindast et al., 2003; Berrendero et al., 2002; Trigo et al., 2009),which are heavily implicated in relapse and the development of dependence. Similarly, a human laboratory study showed that opioid receptor non-selective antagonism with naloxone challenge dose-dependently promotes nicotine withdrawal signs and alters craving in nicotine-dependent subjects (Krause et al., 2018). This portion of the review will examine the interaction of these drugs at the receptor and circuitry levels, with some integration of behavioral endpoints for functional emphasis.

5.1. Nicotinic and opioidergic interactions: receptors and downstream signaling

Nicotinic and opioidergic receptors are often tandem co-regulators, whether on the same cell or on different cells within the same circuit. In fact, these receptors can even be activated by the converse drug; for example, an *in vitro* study in human cell lines suggests that morphine acts directly as a partial agonist of α4β2 nAChRs (Talka et al., 2013). However, the predominant observations at the receptor level relate to (1) expression changes of the receptors due to exposure to the converse drug or (2) alterations in common downstream signaling mechanisms. For example, nicotine treatment in mice lacking MOR does not activate the transcriptional factor CREB in the VTA, and, similarly, naloxone precludes nicotine-induced phosphorylation of CREB (Walters et al., 2005).

Notably, the findings regarding the effect of nicotine on MOR expression are are are mixed. For example, in rodents, while chronic high doses of nicotine (5 mg/kg, twice daily) decrease MOR density in the mice NAc and dorsal striatum (Galeote et al., 2006), other studies using lower doses (0.3 mg/kg, twice daily) show increased MOR expression in rat striatum (Wewers et al., 1999). This is also true in the human literature, as a series of studies using positron emission tomography (PET) imaging to assess MOR binding potential (BP) availability after smoking or placebo have yielded mixed results. For instance, some studies

showed increased C-carfentanil BP after smoking in areas such as the Nac, amygdala, and putamen, while decreased BP was observed in Nac, ACC, striatum, PFC, and, hippocampus, possibly indicating MOR up- or down-regulation according to the region (Domino et al., 2015; Nuechterlein et al., 2016; Scott et al., 2007). Moreover, some studies did not identify any differences in MOR binding between placebo and active cigarette groups in any region examined (Ray et al., 2007; Kuwabara et al., 2014). Despite these discrepant findings, one study in human smokers observed that MOR availability in reward-related brain areas was negatively correlated to Fagerstrom Test for Nicotine Dependence (FTND) scores (Domino and Hirasawa-Fujita, 2019). This suggests that inter-individual variability may play a role in the discrete regulation of MORs by nicotine and that the expression levels of MORs may directly impact nicotine dependence and withdrawal behavioral phenotypes. This is supported by the finding that expression of MORs and endogenous opioids are required for nicotine reward and dependence (Walters et al., 2005).

Conversely, opioids can also regulate nicotinic receptor expression. For example, naloxone decreases the activity and expression of $\alpha 4\beta 2$ and $\alpha 7$ nAChRs induced by nicotine treatment (Almeida et al., 2000) Studies have also found that naltrexone inhibits nicotine-induced up-regulation of nAChRs, a hallmark of nicotine exposure; this may indicate that opioid antagonism exerts direct effects on nAChRs, thus leading to decreased activity in the mesolimbic pathway and precipitation of withdrawal (Kenny and Markou, 2001). However, these effects may be MOR-specific, as a recent multicenter human laboratory study assessing the efficacy of a short-acting KOR antagonist in smokers found that the administration of a KOR antagonist was ineffective in altering smoking latency, consumption, and withdrawal, as well as any affective measures of smoking, compared to placebo (Jones et al., 2020).

In addition to the effects of nicotine and opioids on receptor expression, these drugs seem to also converge on common intracellular signaling pathways. As an example, the extracellular signal-regulated kinase (ERK) is a signaling pathway involved in the neuroadaptations caused by drugs of abuse. Both nicotine and morphine administration lead to increased ERK expression and activity in various regions within the mesolimbic system (for review, see Zhai et al., 2008). Once activated via phosphorylation, pERK translocates to the nucleus (Chen et al., 1992) and indirectly regulates several transcription factors, including the canonical transcription factor cAMP Response Element-Binding Protein (CREB) (Brami-Cherrier, 2007; Xing et al., 1998). In the nucleus, CREB activation culminates in the transcription of several genes, such as NRG3 (Turner et al., 2013b), that have been implicated in addiction processes (Fisher et al., 2017; Portugal et al., 2012). Interestingly, blood samples from smokers exhibit higher levels of both phosphorylated ERK (pERK) and CREB (pCREB) compared to never smokers (Lenz, 2012; Lenz et al., 2010, 2012). It remains to be determined if similar changes in blood occur among individuals with OUD.

5.2. Nicotinic and opioidergic interactions: regulation of dopamine and other neurotransmitter release

Extending these observations from the receptor level to the circuit level, both nicotinic and opioidergic receptors also contribute to dopaminergic signaling, which is critically important

for drug reward. While both receptors can regulate the release of other neurotransmitters, this function is a canonical role for nicotinic receptors, which are predominantly found presynaptically or preterminally in the central nervous system. Due to this positioning, their activation can elicit neurotransmitter release from the synaptic terminal without depolarization of the entire neuron.

With regards to dopaminergic co-regulation by nicotine and opioids, the predominant regions involved are within the mesolimbic circuitry, namely the nucleus accumbens (NAc) and the ventral tegmental area (VTA). There is considerable evidence that both nicotine and opioid agonists trigger the release of dopamine from terminals in the NAc and, more broadly, from striatal terminals, both of which have behavioral consequences (Di Chiara and Imperato, 1988). This is thought to be due to the effects of nicotine and opioids signaling in both the NAc, as well as the VTA. For example, microinfusion studies show direct effects of nicotine on dopamine release in both the VTA and NAc (Pistillo et al., 2015). In both the mesolimbic and nigrostriatal terminal fields, nicotine appears to modulate DA via activation of presynaptic β2-containing nAChRs (Mamaligas et al., 2016).

In addition to these isolated effects of nicotine on dopamine signaling, there is considerable evidence of overlapping regulatory mechanisms by both nicotine and opioids. For example, proenkephalin (PENK) genetic deletion reduces nicotine-induced dopamine release in the NAc, suggesting that nicotine's effects can also act indirectly via MOR activation (Berrendero et al., 2005). These effects may also encompass metabolic effects of nicotine, as neurochemical studies indicate that chronic nicotine sensitizes dopaminergic pathways to morphine, which augments dopamine turnover and metabolism in the striatum (Vihavainen et al., 2006).

However, there is cumulative evidence that synchronized action of nAChRs and opioid receptors results in more homeostatic modulation of dopamine outflow in the striatum. For example, electrochemical studies suggest that endogenous opioids are released in the NAc to modulate dopamine neurotransmission via MOR activation on NAc cholinergic interneurons (Britt and McGehee, 2008). This results in effective modulation of striatal dopamine by inhibiting acetylcholine release and reducing nAChR-mediated dopamine release (Britt and McGehee, 2008). This may be a salient point for clinical applications, as cigarette smoking produces dose-related increases of circulating β-endorphin in human subjects (Pomerleau et al., 1983). In addition to the opioid effects through MOR activation, KOR activation by opioids can have both direct effects by triggering dopamine release from presynaptic neurons, as well as indirectly by their inhibitory effects on cholinergic interneurons in the NAc (Mamaligas et al., 2016; Britt and McGehee, 2008).

The actions of nicotine and opioids within the VTA regulate the overall firing of dopaminergic neurons in the mesolimbic pathway, with MOR and nicotinic agonists enhancing net excitatory activity by disinhibition of dopaminergic neurons. For example, nicotine microinjection in the VTA enhances dopamine overflow in the NAc, an effect that is reversed by nAChR antagonism (Nisell et al., 1994). Further, activation of MORs in VTA GABAergic interneurons result in inhibited GABA release and subsequently increases dopamine firing and release in the NAc, an effect that is precluded by opioid antagonists

(Tanda and Di Chiara, 1998). Additionally, chronic nicotine exposure and withdrawal alters GABAergic transmission in the VTA and GABA response to morphine, possibly underlying the potentiation of locomotor behaviors (Vihavainen et al., 2008b)..

6. Genetic factors impacting both nicotine and opioid dependence

An intricate relationship of polygenic and environmental factors underlies SUD phenotypic manifestations (Walker and Nestler, 2018). For example, heritability accounts for upwards of 70 % of ND (Lessov et al., 2004), with data from familial and twin studies indicating that genetic liability for smoking initiation is estimated at 60 %. In comparison, the other 40 % of variance pertains to the influence of environmental factors due to individual characteristics or features of the twin pair (Sullivan and Kendler, 1999). Likewise, for OUD, genetic liability is estimated at around 70 % (Goldman et al., 2005). In this section, we will discuss some of the genetic contributors in common between ND and OUD, with an emphasis on variants in the nAChRs or MORs themselves. Furthermore, while the section will focus on tobacco and opioid use disorders, variation within these targets have also been implicated in SUDs broadly (Arias et al., 2006; Bart et al., 2005; Brynildsen and Blendy, 2021; Ide et al., 2004).

6.1. Polymorphisms in nAChR subunits and effects on nicotine and opioid dependence

Genetic association (GWAS) studies have identified numerous risk alleles for nicotine and opioid addiction. Among these genes, the most well described haplotype is in the nAChR gene cluster (*CHRNA5–CHRNA3–CHRNB4 locus*), encoding the α5, α3, and β4 nicotinic subunits. Variants in this nAChR gene cluster, particularly CHRNA5 (rs16969968), have been implicated in the addiction vulnerability across various addictive substances, including nicotine and opioid addiction (for review, see Brynildsen and Blendy, 2021). For example, SNPs in CHRNA5 are linked to both lifetime ND and OUD in European and Afro-American families (Sherva et al., 2010). For example, the A allele of the rs16969968 SNP within CHRNA5 is associated with a more severe OUD presentation (Erlich et al., 2010) and mechanistic fMRI studies of this variant found higher connectivity in the habenula-caudate circuitry in opioid users carrying the CHRNA5 G allele. Considering that the habenula is (1) enriched in both nAChRs and opioid receptors and (2) is known to modulate aversion, negative reinforcement and drug withdrawal, it was suggested that high-risk alleles might confer lower sensitivity to the aversive properties of opioids, increasing the susceptibility and severity of OUD (Curtis et al., 2017).

With respect to nicotine-specific endophenotypes, SNPs within the CHRNA5–CHRNA3–CHRNB4 cluster have been implicated in heavy smoking, the predisposition for ND, and smoking-related diseases (Bierut et al., 2008; Amos et al., 2008), nicotine withdrawal, craving, and inability to quit (Baker et al., 2009; Quach et al., 2020; Chen et al., 2020). Interestingly, the CHRNA5 risk allele attenuates the aversive properties of nicotine in both rodents (Fowler et al., 2013) and humans (Jensen et al., 2015), possibly increasing smoking consumption. Moreover, these CHRNA5 risk alleles also predict the failure to quit among untreated patients (Chen et al., 2012) or after discontinuation of pharmacotherapy (Sarginson et al., 2011). These findings highlight the important role of genetic variation

in the nicotinic receptor family to contribute to nicotine dependence and its associated endophenotypes.

6.2. Polymorphisms in MOR and effects on nicotine and opioid dependence

Evidence from transgenic mouse studies demonstrates that MORs are necessary for the somatic manifestation of nicotine- and morphine-induced rewarding and antinociceptive phenotypes (Berrendero et al., 2002; Matthes et al., 1996). This is in line with a number of human genetic studies implicating variants within the MOR gene (OPRM1) with both ND and OUD outcomes. Studies examining the well-described nonsynonymous OPRM1 SNP (termed A118G or rs10485057) have associated it with both ND (Zhang et al., 2006) and OUD (Tan et al., 2003; Bart et al., 2004; Kapur et al., 2007). This functional OPRM1 SNP (A118G) markedly increases the binding affinity of MOR to its ligand β-endorphin (Bond et al., 1998), while at the same time reduces mRNA and protein expression of MORs in rodent models (Mague et al., 2009). These complex effects result in the functional attenuation of the rewarding and antinociceptive effects of morphine (Mague et al., 2009). This rodent work has been replicated in human imaging studies, demonstrating reduced MOR binding in mesolimbic areas of G-carriers of the A118G polymorphism (Ray et al., 2011), and may underlie it's association with OUD (Tan et al., 2003; Bart et al., 2004; Kapur et al., 2007).

With regards to its contribution to nicotine dependence phenotypes, both GWAS and twin studies implicate polymorphisms in the OPRM1 gene in smoking susceptibility, ND, and relapse. For example, analyses from individuals recruited from a twin study database revealed a significant association of a three marker (rs2075572, rs10485057, and rs10485058) haplotype block within the OPRM1 gene and smoking initiation (Zhang et al., 2006). Additionally, the A118G polymorphism has also been associated with ND endophenotypes, such as the rewarding properties of tobacco smoking induced by negative mood, (Perkins et al., 2008), alterations in the self-reported rewarding effects of nicotine (Ray et al., 2011) and general nicotine reward in male mice and human subjects (Bernardi et al., 2016). Additionally, a recent GWAS study in individuals with or without an OUD diagnosis found that the A118G variant associated was associated with nicotine dependence in individuals with OUD (Zhou et al., 2020). However, the precise mechanism by which this variant contributes to increased nicotine dependence in this population is unknown.

7. Clinical trials and future directions for co-dependency of nicotine and opioids

Concurrent use of tobacco products and opioids is mutually reinforcing Story and Stark, 1991). (Clinical observations show that tobacco use promotes the escalation of methadone regimens for OUD patients (Schmitz et al., 1994). Conversely, methadone dose-dependently increases cigarette consumption. Thus, smoking rates are overwhelmingly high in OUD individuals relative to the general population. Despite the intent to quit, successful attempts at smoking cessation are markedly reduced in OUD individuals, rendering them vulnerable to health-related complications from tobacco use. In fact, the mortality rate due to smoking-related illness approaches 50 % among SUD patients (Hurt et al., 1996; Hser et al., 1994). Moreover, the efficacy of the currently available medications for tobacco cessation is modest

in opioid co-users (Miller and Sigmon, 2015), underscoring the critical gap in effective treatments for these individuals. This has led to a series of randomized controlled trials assessing pharmacological and multimodal interventions for smoking cessation in opioid-maintained patients has been conducted, with biochemically validated abstinence measures as the primary outcome in patients enrolled in opioid treatment programs (Table 3). We will briefly describe a subset of these studies below.

In a recent study, Hall and colleagues compared the effect of combined extended NRT with cognitive-behavioral therapy (CBT) and motivational intervention to standard control (counseling only) in buprenorphine-maintained smokers. Combined therapy showed only short-term efficacy for abstinence. However, it was superior to control treatment in providing motivation to quit smoking (Hall et al., 2018). Their findings corroborate previous studies indicating that smoking cessation approaches in opioid-maintained patients are only modestly efficacious in the first months of intervention. For example, one study in methadone-maintained smokers found a modest abstinence rate of 10.5 % and reduced daily cigarette consumption in varenicline-treated subjects compared to placebo. Abstinence in this study lasted for only three months, and it was not sustained beyond the intervention period (Nahvi et al., 2014). Varenicline displayed higher efficacy than NRT in promoting abstinence 3 months after treatment initiation in SUD patients (Rohsenow et al., 2017). Still, at the 6 months timepoint, cessation rates were similar between varenicline, NRT, and placebo (Stein et al., 2013). Similarly, another study evaluating the efficacy of combined CBT and NRT in methadone-treated smokers found a similar low, albeit significant abstinence rate (10 %) at three months of therapy that was no longer significantly different than placebo after treatment discontinuation (Reid et al., 2008). A study by Martin and colleagues provides a possible explanation for the lack of long-term efficacy of smoking cessation aids in OUD smokers. They found that smoking relapse may be partly attributable to inadequate medication and treatment adherence, decreased tolerance to physical discomfort, and escalated drug use while receiving varenicline compared to smokers with other SUDs (Martin et al., 2019).

Recent trials have focused on implementing individualized therapies in an attempt to achieve long-term tobacco abstinence among individuals with OUD. Cooperman et al. compared two interventions to improve smoking cessation outcomes. One consisted of eight sessions of Intervention-Motivation-Behavioral (IMB) model-based skills combined with NRT or a referral to a telephone-based service for follow-up as a control. Only a small subset of the IMB group achieved abstinence during the 6 months follow-up. Similar to other treatment strategies, IMB reduced the daily cigarette consumption, but the effects were short-lived (Cooperman et al., 2018).

Besides pharmacotherapies targeting nAChRs, other drug modalities have been explored as alternatives to improve tobacco cessation rates among OUD smokers. For example, individuals under a buprenorphine maintenance program underwent a 10-week regimen of bupropion treatment or placebo; participants also received contingency management to abstain from tobacco and illicit drugs during the intervention period. Bupropion was not well-tolerated and led to low adherence to treatment. Moreover, smoking and opioid abstinence rates were similar between the experimental and control groups (Mooney et

al., 2008). In another study, however, patients not allowed to smoke during treatment of opioid withdrawal using low-dose naltrexone and/or clonidine showed enhanced abstinence from cigarettes, but not from opioids, at a 1-week follow-up (Mannelli et al., 2013). Using a laboratory-based approach, it has been found that the severity of opioid craving and acute withdrawal correlates with ND and negative affect (Streck et al., 2020). This latter study suggests that opioid-maintained smokers may positively respond to a national nicotine reduction policy, such as increased taxation, for reducing smoking-related consequences.

Based on these clinical trials, it can be concluded that current pharmacotherapeutic approaches approved to treat nicotine and opioid addiction that target nAChR or MOR independently are of limited effectiveness in managing polydrug abuse. Further investigations designed *a priori* to identify unique mechanisms dictating nicotine and opioid co-abuse may lead to efficacious treatment for co-morbid ND and OUD. Increased coordinated translational efforts, spanning model systems to clinical trials, are needed for the development of individualized therapies to improve both smoking cessation and opioid discontinuation rates.

8. Summary

In summary, the evidence collected above indicates that nicotine-opioid interactions exist in reward, antinociception, and respiration. The rewarding effects of nicotine are moderated by manipulation of opioid systems, and nicotine amplifies opioid reward in CPP and self-administration models. Nicotine additionally produces opioid system-mediated antinociception and enhances the acute antinociceptive effect of opioids via nAChR activation. These interactions extend to respiration, where nicotine and other nAChR agonists may ameliorate opioid-induced respiratory depression. Conversely, however, nicotine alone generally produces transient respiratory depression, an effect modulated by opioid-receptors. Direct examination of these opioid-nicotine interactions at the cellular level indicates that nicotinic and opioidergic systems work bidirectionally and explain, at least in part, the behavioral and physiological effects observed with co-administration. Variants of genes encoding opioid and nicotinic receptors also underlie ND and OUD comorbidity, with the behavior observed in preclinical rodent models generally mimicking that found in human models. Despite this confluence of preclinical and clinical results, there is limited success in the treatment of nicotine-opioid co-use in clinical trials. Future research should delve into nicotine-opioid interactions further, considering their intricate cellular- and behavioral-level interconnectivity. Clinical trials that target nicotine-opioid co-use need to be continued, especially those intended to improve smoking cessation success among individuals with OUD.

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Table 1

Summary of preclinical studies examining the effect of nicotinic manipulations on opioid reward.

References	Species	Sex	Nicotinic Manipulation	Opioid Reward Test	Result on Opioid Reward
(Loney et al., 2021)	Long-Evans rats	male	1. nicotine 0.4 mg/kg, s.c.	1. SA FR-3 remifentanil 3.2 μg/kg, i.v. morphine 0.3 mg/kg, i.v. or CPP morphine 5, 10, or 20 mg/kg, s.c.	1. ↑ SA remifentanil and morphine ↓ CPP morphine 5 and 10 mg/kg ↑ CPP morphine 20 mg/kg
			2. nicotine 4 μg intra-IC	2. CPP morphine 5, 10 or 20 mg/kg, s.c.	2. ↓ CPP morphine 5 mg/kg ↑ CPP morphine 10 mg/kg ↔ CPP morphine 20 mg/kg
(Shams et al., 2006)	Swiss-Webster mice	male	1. nicotine 0.0006–0.1 mg/kg, i.p. during test	CPP morphine 5 mg/kg, s.c.	1. ↓ CPP expression
			2. nicotine 0.007–25 ng, i.c.v. during test		2. ↓ CPP expression
(Vihavainen et al., 2008a)	NMRI mice	male	nicotine 50–500 μg/mL, drinking water 7 weeks before conditioning	CPP morphine 5 or 10 mg/kg, s.c.	CPP obtained with 5 mg/kg morphine only in nicotine pretreated group, CPP obtained with 10 mg/kg in both nicotine pretreated and control groups
(Rezayof et al., 2007)	Wistar rats	male	1. nicotine 0.25, 0.5 or 1 μg, intra-VTA	1. CPP morphine 0.5 mg/kg, s.c.	1. morphine CPP obtained only with nicotine 0.5 or 1 μg
			2. mecamylamine 2.5, 5 or 7.5 μg, intra-VTA	2. CPP morphine 5 mg/kg, s.c.	2. ↓ morphine CPP with mecamylamine 5 or 7.5 μg
			3. nicotine 1 μg + mecamylamine 5, 7.5 or 10 μg, intra-VTA	3. CPP morphine 0.5 mg/kg, s.c.	3. morphine CPP obtained only with nicotine 1 μg, reversed by mecamylamine 7.5 or 10 μg
(Rezayof et al., 2006)	Wistar rats	male	1. nicotine 0.25, 0.5 or 1 μg, intra-dHipp	1. CPP morphine 0.5 mg/kg, s.c.	1. morphine CPP obtained only with nicotine 0.75 or 1 μg
			2. mecamylamine 2, 4 or 8 μg, intra-dHipp	2. CPP morphine 6 mg/kg, s.c.	2. ↓ morphine CPP with mecamylamine 2, 4 or 8 μg
			3. nicotine 0.5, 0.75 or 1 μg + mecamylamine 8 μg, intra-dHipp	3. CPP morphine 0.5 mg/kg, s.c.	3. morphine CPP obtained only with nicotine, ↓ by mecamylamine
(Hall et al., 2011)	Wistar rats	male	use-dependent nAChR antagonist BTMPS 0.1 or 0.5 mg/kg, s.c.	SA FR-1 morphine 0.25–1 mg/kg, i.	↓ SA ↓ morphine seeking during abstinence
(Zarrindast et al., 2003)	NMRI mice	female	mecamylamine 0.025, 0.05 or 0.1 mg/kg, i.p.	CPP morphine 5 mg/kg, i.p.	↓ CPP acquisition
(Zarrindast et al., 2005)	Wistar rats	male	1. nicotine 0.75, 1 or 2 μg, intra-BLA	1. CPP morphine 0.5 mg/kg, s.c.	1. morphine CPP obtained only with nicotine 0.75, 1 or 2 μg
			2. mecamylamine 1, 3 or 6 μg, intra-BLA	2. CPP morphine 7.5 mg/kg, s.c.	2. ↓ morphine CPP with mecamylamine 1, 3 or 6 μg
			3. physostigmine 1, 3 or 5 μg, intra-BLA + atropine 7 μg, intra-BLA or + mecamylamine 6 μg, intra-BLA	3. CPP morphine 0.5 mg/kg, s.c.	3. morphine CPP obtained with physostigmine, reversed by atropine but not mecamylamine

References	Species	Sex	Nicotinic Manipulation	Opioid Reward Test	Result on Opioid Reward
			4. nicotine 0.75, 1 or 2 ug, intra-BLA + atropine 7 μg, intra-BLA or + mecamylamine 6 μg, intra-BLA	4. CPP morphine 0.5 mg/kg, s.c.	4. morphine CPP obtained with nicotine, reversed by mecamylamine but not atropine
(Feng et al., 2011)	BALB/c mice	male	1. nicotine alone 0.5 mg/kg, s.c. as reinstating stimulus	CPP morphine 10 mg/kg, s.c.	1. no reinstatement with nicotine
			2. DHβE 5 mg/kg, s.c. or MLA 4 mg/kg, s.c. during drug prime reinstate physostigmine 0.5 mg/kg, s.c.		2. ↓ CPP reinstatement with either DHβE or MLA
(Zhou et al., 2006)	Sprague-Dawley rats	male	+ scopolamine (0.5 mg/kg, s.c.) or + mecamylamine (0.5 mg/kg, s.c.) or + saline	SA FR-5 heroin 0.05 mg/kg, i.v.	↓ SA physostigmine alone, reversed by scopolamine but not by mecamylamine
(Wright et al., 2019)	1. C57BL/6 mice	male			
	Wistar rats		1. methyllycaconitine, 4 mg/kg, s.c. during conditioning, test or drug prime reinstatement	1. CPP morphine 10 mg/kg, s.c.	1. ↔ CPP acquisition ↔ CPP expression ↓ CPP reinstatement
			2. methyllycaconitine 6.75 μg intra-dHipp, -vHipp or -mPFC during reinstatement	CPP morphine 5 mg/kg, s.c.	2. ↓ CPP reinstatement intra-vHipp only

Abbreviations: BLA=basolateral amygdala; CPP=conditioned place preference; dHipp=dorsal hippocampus; FR=fixed ratio; IC=insular cortex; i.c.v.=intracerebroventricular; i.p.=intraperitoneal; i.v.=intravenous; mPFC=medial prefrontal cortex; nAChR=nicotinic acetylcholine receptor; SA=self-administration; s.c.=subcutaneous; vHipp=ventral hippocampus.

Table 2

Summary of preclinical studies examining the effect of opioid manipulations on nicotine reward.

References	Species	Sex	Opioid Manipulation	Nicotine Reward Test	Result on Nicotine Reward
(Biala and Budzynska, 2006)	Wistar rats	male	morphine 10 mg/kg, i.p. as reinstating stimulus	CPP nicotine 0.5 mg/kg, i.p.	induces reinstatement
(Zarrindast et al., 2003)	NMRI mice	female	naloxone 0.5, 1 or 2 mg/kg, i.p.	CPP nicotine 1 mg/kg, i.p.	↓ nicotine CPP, CPA with naloxone alone
(Corrigall and Coen, 1991)	Long-Evans rats	male	naltrexone 0.1, 1 or 10 mg/kg, s.c.	SA FR-5 nicotine 0.03 mg/kg, i.v.	↔ SA
(Liu et al., 2009)	Sprague-Dawley rats	male	naltrexone 0.25,1 or 2 mg/kg, s.c. during SA or cue maintenance in extinction or cue reinstatement	SA FR-5 nicotine 0.03 mg/kg, i.v.	↔ SA ↓ cue maintenance ↓ cue reinstatement
(DeNoble and Mele, 2006)	Long-Evans rats	male	naloxone 0.75, 1.5 or 3 mg/kg, i.p.	SA FR-1 nicotine 0.32 mg/kg, i.v.	↔ SA 1. ↓ CPP ↔ CPA
Walters et al., 2005	C57BL6 mice	male	1. naloxone 1 mg/kg, s.c. during test day	CPP nicotine 1 mg/kg, s.c.	1. ↓ CPP ↔ CPA
			2. MOR KO vs WT	CPA nicotine 2 mg/kg, s.c.	2. CPP in WT only CPA in both KO and WT
(Trigo et al., 2009)	C57BL/6 J mice	male	β-endorphin KO vs WT	CPP nicotine 0.5 mg/kg, s.c.	CPP in WT only
(Berrendero et al., 2002)	C57/BL6 mice	female and male	MOR KO vs WT	CPP nicotine 0.5, 0.7 or 1 mg/kg, s.c.	CPP 0.5 or 0.7 mg/kg in WT only
(Ismayilova and Shoaib, 2010)	Lister rats	male	1. Naloxone 0.3, 1 or 3 mg/kg, s.c.	SA FR-3 nicotine 0.03 mg/kg, i.v.	1. ↓ SA 0.3, 1 or 3 mg/kg
			2. DOR antag naltrindole 0.3, 1 or 3 mg/kg, s.c.		2. ↔ SA
			3. KOR agonist U50,488 0.3, 1 or 3 mg/kg, s.c.		3. ↓ SA 3 mg/kg
(Liu and Jernigan, 2011)	Sprague-Dawley rats	male	1. MOR antag naloxonazine 5 or 15 mg/kg, i.p.	SA FR5 nicotine 0.03 mg/kg, i.v.	1. ↓ SA
			2. DOR antag naltrindole 0.5 or 5 mg/kg, i.p.		2. ↔ SA
			3. KOR antag GNTI 0.25 or 1 mg/kg, i.p.		3. ↔ SA
Berrendero et al., 2012	C57BL/6 J mice	male	1. DOR KO vs. WT	1. CPP nicotine 0.17 mg/kg, s.c. or SA FR-1 nicotine 0.015 or 0.03 mg/kg, i.v.	SA DOR < WT acquisition and intake
			2. DOR antag naltrindole 2.5 or 5 mg/kg, i.p.	2. SA FR-1 and PR nicotine 0.03 mg/kg, i.v.	2. SA ↓ FR acquisition ↔ PR breakpoint
(Berrendero et al., 2005)	C57BL/6 J mice	female and male	*enk* KO vs WT	CPP nicotine 0.25, 0.5 or 1	CPP in WT
(Al-Hasani et al., 2013)	C57BL/6 mice	male	KOR agonist U50,488 5 mg/kg, i.p. as reinstating stimulus	CPP nicotine 0.5 mg/kg, s.c.	induces reinstatement

References	Species	Sex	Opioid Manipulation	Nicotine Reward Test	Result on Nicotine Reward
(Grella et al., 2014)	Long Evans rats	male	1. KOR antag nor-BNI 10 mg/kg, i.p. during yoh reinstatement	SA FR-3 or -5 nicotine 0.03 mg/kg, i.v.	1. ↓ yoh reinstatement
			2. KOR agonist U50,488 1, 2.5 or 5 mg/kg, i.p. as reinstating stimulus		2. induces reinstatement
			3. nor-BNI 10 mg/kg, i.p. during cue reinstatement		3. ↔ cue reinstatement
(Smith et al., 2012)	C57BL/6 mice	male	1. KOR antag nor-BNI 10 mg/kg, i.p. during swim stress reinstatement	CPP nicotine 0.5 mg/kg, s.c.	1. ↓ stress reinstatement
			2. KOR agonist U50,488 2.5, 5 or 10 mg/kg, i.p. as reinstating stimulus + nor-BNI 10 mg/kg, i.p.		2. U50,488 induces reinstatement, reversed by nor-BNI
			3. U50,488 5 mg/kg, i.p. as reinstating stimulus + nor-BNI 2.5 μg intra-Amyg or intra-VPN		3. U50,488 induces reinstatement, reversed by nor-BNI intra-Amyg, but not intra-VPN
(Jackson et al., 2010)	ICR mice	male	KOR antag JDTic 8 or 16 mg/kg, s.c, on test	CPP nicotine 0.5 mg/kg, s.c.	↔ expression
Jackson et al., 2013	ICR mice	male	KOR antag nor-BNI 10 mg/kg, s.c. during drug prime or swim stress reinstatement	CPP nicotine 0.5 mg/kg, s.c.	↔ drug prime reinstatement ↓ stress reinstatement
(Galeote et al., 2008)	C57BL/6 J mice	male	proDYN KO vs. WT	CPP nicotine 0.5 mg/kg, s.c. or SA FR-1 or PR nicotine 0.0052-0.0855 mg/kg, i.v.	CPP KO = WT SA acquisition KO > WT at 0.0052 mg/kg dose PR breakpoint KO < WT at 0.0427 mg/kg dose
(Nygard et al., 2016)	C57BL/6 J mice	male	1. KOR antag nor-BNI 10 mg/kg, i.p. during footshock, yoh or drug prime reinstatement	CPP nicotine 0.5 mg/kg, s.c.	1. ↓ footshock reinstatement ↓ yoh reinstatement ↔ drug prime reinstatement
			2. KOR KO vs pre-pro-DYN KO vs WT during yoh or drug prime reinstatement		2. ↓ yoh reinstatement ↔ drug prime reinstatement each KO vs WT
			3. nor-BNI 2.5 μg, intra-BLA during acquisition or yoh reinstatement or drug prime reinstatement		3. ↔ acquisition ↔ drug prime reinstatement ↓ yoh reinstatement
			4. KOR cKO AAV-cre-GFP or AAV-GFP, intra BLA footshock and drug prime reinstatement		4. ↓ footshock reinstatement ↔ drug prime reinstatement AAV-cre-GFP vs AAV-GFP
			5. AAV5-CaMKIIa-hM4D(Gi)-mCitrine or control virus DREADD into BLA, CNO activation as reinstating stimulus		5. induces nicotine seeking, AAV5-CaMIIa-hM4D(Gi)-mCitrine DREADD only
(Cippitelli et al., 2016)	Sprague-Dawley rats	male	1. NOP agonist AT-202 0.3, 1 or 3 mg/kg, i.p.	SA FR-1 co-use nicotine 0.03 mg/kg, i.v. ethanol 10 % oral, 01. mL	1. ↑ nicotine SA ↔ ethanol SA
			2. NOP antag SB612111 1, 5 or 10 mg/kg, i.p.		2. ↓ nicotine SA 5 and 10 mg/kg ↓ ethanol SA 10 mg/kg only
(Sakoori and Murphy, 2009)	C57BL/6 mice	male	NOP receptor KO vs WT	SA 2-bottle choice nicotine 3, 6, 12, 25 or 50 μg/mL, oral	intake KO > WT 3 μg/mL KO = WT 6, 12, 25 or 50 μg/mL

Abbreviations: AAV=adeno-associated virus; Amyg=amygdala; BLA=basolateral amygdala; CaMKII=calcium/calmodulin-dependent protein kinase II; CNO=clozapine *N*-oxide; CPA=conditioned place aversion; CPP=conditioned place preference; DOR=delta opioid receptor; DREADD=designer receptor exclusively activated by designer drug; DYN=dynorphin; *enk*=enkephalin gene; FR=fixed ratio; GFP=green fluorescent protein; i.p.=intraperitoneal; i.v.=intravenous; KO=knockout; KOR=kappa opioid receptor; MOR=mu opioid receptor; NOP=nociception opioid peptide; nor-BNI=nor-binaltorphimine; PR=progressive ratio; SA=self-administration; s.c.=subcutaneous; VPN=ventral posterior thalamic nucleus; WT=wild-type; yoh=yohimbine.

Table 3

Summary of clinical trials assessing the effectiveness of pharmacotherapies for smoking cessation on opioid-maintained patients.

References	Participants	Intervention	Assessment:Primary and Secondary Outcomes	Follow-up time point for abstinence	Results
(Hall et al., 2018)	Buprenorphine-maintained smokers	1. Skills training + NRT (patch 7 mg, 14 mg or 21 mg), (lozenges 2 mg combination or varenicline + CBT)	1. CPD and biochemical: CO + urine	3, 6, 12, and 18 months	The interventional group had higher abstinence rates than controls at 3-months FU.
	N = 175	2. Information (control) 12 weeks	2. Questionnaires: FTND and others.		CPD and cannabis a month prior to FU as a predictor of smoking continuance
(Nahvi et al., 2014)	Methadone-maintained Smokers	1. Varenicline (2 mg)	1. CO abstinence at 12 weeks FU	2, 4, 8, 12, and 24 months	Varenicline higher abstinence rates at 12-weeks FU
	N = 112	2. Placebo 12 weeks	2. CO abstinence each FU, CPD, quit attempts >24 h, psychiatric or cardiac adverse events		Reduced CPD at 12 weeks
					No differences in psychiatric or adverse events between groups
(Rohsenow et al., 2017)	SUD, including OUD outpatient smokers	1. Varenicline (2 mg) or placebo	1. CO + urine cotinine	3, 6 months	Varenicline was more effective than NRT in promoting abstinence at a 3-months timepoint.
	N = 137	2. NRT (patch 7 mg, 14 mg or 21 mg) or placebo 12 weeks	2. CPD, or continuous abstinence assessment		
(Stein et al., 2013)	Methadone-maintained Smokers	1. Varenicline (2 mg)	1. CO + salivary cotinine at 3months	6 months	Varenicline was not more effective than placebo in promoting abstinence at a 6-month time point.
	N = 315	2. NRT combination (patch 21 mg or 42 mg; 4 mg gum)	2. CO at 6 months, and urine test, CPD, self-report abstinence for drugs		
(Reid et al., 2008)	Methadone-maintained Smokers	1. NTR (14 mg or 21 mg) + CBT	1. CO + urine	1–9, 13, and 26 weeks	NRT + CBT promotes a small but significant reduction of CPD and abstinence during the treatment period compared to the control group.
	N = 225	2. Treatment as usual 9 weeks	2.CPD		
(Martin et al., 2019)	OUD vs. non-OUD outpatient smokers	1. Varenicline (2 mg) or placebo	1. CO + cotinine saliva	3, 6 months	
	N = 137 (drawn from Rohsenow, 2017)	2. NRT (patch 7 mg, 14 mg or 21 mg) or placebo 12 weeks		2. CO at 6 months, and urine test, CPD, self-report abstinence for drugs	Smoking abstinence and CPD were not significantly different between OUD vs. NOUD at 3- and 6 months time points.
(Cooperman et al., 2018)	Methadone-maintained Smokers	1. IMB + NRT	1. CO abstinence	3, 6 months	The interventional group reported less CPD at 3 and 6months compared to the control.
	N = 83	2. Referral to Quitline (Control) 3 months	2. CPD, self-report quit attempts, number of days of abstinence		IMB + NRT was not more effective than placebo for abstinence at 3 or 6 months.

References	Participants	Intervention	Assessment:Primary and Secondary Outcomes	Follow-up time point for abstinence	Results
(Mooney et al., 2008)	Buprenorphine-maintained smokers N = 40	1. Bupropion (300 mg) 2. Placebo 10 weeks	1. Combined nicotine and illicit drugs abstinence (CO and urine). 2. Nicotine and Opioid WD	2, 4, 6, 8, and 10 weeks	Bupropion was not more effective than placebo for smoking and opioids abstinence.

Abbreviations: CO= carbon monoxide, CBT=cognitive behavioral therapy; CPD=cigarettes per day; FTND= Fagerstrom Test for Nicotine Dependence, FU=follow-up; IMB=model-based intervention, NRT=nicotine replacement therapy; WD=withdrawal.