HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2017 March ; 43(2): 155–170. doi:10.1080/00952990.2016.1209513.

Interactions between nicotine and drugs of abuse: A review of preclinical findings

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Abstract

Polysubstance abuse is common among substance use disorder patients and nicotine is one of the most commonly co-used substances. Epidemiological and clinical laboratory studies suggest that nicotine, when combined with other drugs of abuse, increases intake of one or both substances. This review focuses on the preclinical literature regarding nicotine's interaction with alcohol, stimulants (i.e., cocaine, amphetamines), opioids (i.e., morphine, heroin) and Δ^9-tetrahydrocannabinol (THC). The current understanding of how these various classes of abused drugs may interact with nicotine on behavioral, physiological, and pharmacological indices that may be important in maintaining co-use of one or both substances in human populations are highlighted. Suggestions as to future areas of research and gaps in knowledge are offered.

Keywords

Polysubstance use; nicotine; cocaine; alcohol; opioids; THC; preclinical

Introduction

Nicotine-containing products are among the most widely used addictive substances in the U.S. The most recent Substance Abuse and Mental Health Administration (SAMHSA) report indicates that 67 million people (nearly 25% of the population) are current tobacco users [1]. Though the percentage of people using tobacco products has decreased over the past decade, the use of new products, such as nicotine containing e-cigarettes and other electronic nicotine delivery systems (ENDS), has risen dramatically [2]. In addition to the grave problem of nicotine dependence in the general population, cigarette smoking among individuals with substance use disorders presents a unique public health concern that has received inadequate attention, particularly in preclinical studies. Because nicotine is a legally used substance and its psychoactive effects are relatively mild, the full scope of nicotine polysubstance use is likely underreported. Even then, nicotine is often reported as a component of the most frequently used polysubstance combinations [3]. For example, in a European sample of school students, nearly three-quarters (73%) of last month polysubstance using adolescents reported both alcohol and cigarette use and one-fifth of

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The author has no conflicts of interest to declare.

those surveyed reported cannabis (Δ^9-tetrahydrocannabinol; THC) use concurrent with alcohol and/or nicotine [3].

The societal impact of nicotine polysubstance use is a major concern. Chronic health problems associated with nicotine dependence are among the most prominent causes of preventable death in the United States (e.g., ~480,000/year). Annual economic costs of cancer, cardiovascular disease, and other health risks associated with tobacco consumption exceed $289 billion [4]. In addition, the health consequences associated with combinations of drugs far exceeds that of either drug alone [5]. As such, polysubstance users often report, and laboratory-based studies confirm, that the combined use of multiple substances increases the use of one or both substances (e.g., cocaine [6], d-amphetamine [7], heroin [8], and alcohol [9,10]). This may lead to accelerated development of dependence or increased incidences of acute or long-term toxicity - decreased liver or kidney function, damage to cardiovascular or respiratory systems, etc. [11–13] – and underscores the urgency of this problem and the need for strategies to manage and/or counteract the effects of this form of polysubstance abuse.

This review focuses on studies of nicotine's interaction with alcohol, stimulants (i.e., cocaine, amphetamines), opioids (i.e., morphine, heroin, etc.) and THC. As should become clear, work in some of these areas is limited. While not intended to be an exhaustive review, the studies described below will highlight the current understanding of how these various classes of abused drugs may interact with nicotine on behavioral, physiological, and pharmacological indices that may be important in maintaining co-use of one or both substances. Some suggestions for future areas of research and gaps in knowledge are addressed.

It is recognized that nearly 80% of nicotine-dependent adult smokers report the initiation of smoking during teenage years [1]. Further, adolescents who smoke cigarettes are 7 times more likely to use an illicit substance compared to those that do not smoke cigarettes [14]. Likewise, sex/gender factors may play important roles in determining behavioral and/or neurochemical responses to drugs of abuse and resultant patterns of drug use [1]. A number of recent reviews have discussed the consequences of nicotine/tobacco or other drug exposure during critical developmental periods (prenatal or adolescent; [15–19] as well as sex/gender issues [20–26] on behavioral and neurobiological endpoints of drug exposure. Consequently, an extensive discussion of that literature is beyond the scope of this review.

Interactions between nicotine and drugs of abuse

Nicotine is thought to be the main psychoactive component of tobacco that maintains its persistent use and is responsible for many of the abuse-related behavioral and neurochemical effects of tobacco, including reinforcing effects and dependence induction [4]. Nicotine interacts directly with nicotinic acetylcholine receptors (nAChRs) as a full agonist. The nAChRs are pentameric ligand-gated receptors composed of α (α2–α7, α9–α10) and β (β2–β4) subunits with several possible configurations [27,28]. The majority of research on nicotine's behavioral effects have focused on α4β2, α3β4, α5-, α7-, and β2-containing subunits in mesolimbic brain regions such as the ventral tegmental area (VTA) and nucleus

accumbens (NAcc) (for review, see [29,30]). The ability of nicotine to increase levels of dopamine (DA) in discrete brain regions has been linked to a variety of its behavioral effects [31,32].

Animal models of substance abuse/addiction

There are several reasons why people may combine multiple substances. For example, one substance may enhance the positive subjective effects of another, one may overcome certain unwanted or adverse effects of another, or one may substitute for a preferred drug when unavailable. There is now considerable empirical support for each of these explanations being important for nicotine polysubstance use, and preclinical studies have applied a number of animal models to evaluate these potential interactive effects. Drug self-administration procedures, for example, are used to assess variables related to drug-taking behavior – the key feature of polysubstance use. It is well established that animals will self-administer most drugs that are abused by man [33,34]. In drug self-administration studies, a drug (e.g., nicotine, cocaine, alcohol, etc.) serves as a reinforcing stimulus for operant performance. Alterations in a drug's reinforcing effects by co-administration of, or exposure to, another drug are determined by changes in rate of acquisition of self-administration or the shape and position of the self-administered drug's dose-effect curve. Drug discrimination, a preclinical model of the subjective effects of a drug in humans [35,36], involves training animal subjects to make one response after pretreatment with a training drug and a separate, but analogous, response after vehicle administration [37]. The goal is to train the subject to use the interoceptive cue (i.e, discriminative stimulus) produced by the training drug to engage in the pretreatment appropriate response. Alterations in a training drug's discriminative stimulus effects are then determined by leftward or rightward shifts in the dose-response curve or as a result of substitution tests to determine whether other drugs reproduce the discriminative stimulus of the training drug. Additional details and procedural variations for drug self-administration, drug discrimination, as well as other procedures, such as conditioned place preference (CPP)/aversion (CPA) (thought to measure rewarding/aversive properties of drugs), locomotor sensitization (a measure of neural plasticity following drug exposure), etc. can be found elsewhere [38,39].

Nicotine + alcohol interactions

Nicotine and alcohol are the most widely available and commonly used substances in the world. In addition to their high rates of independent use, there is also a high comorbidity between alcohol and nicotine use. In fact, 80–90% of patients with alcohol use disorder (AUD) also reportedly smoke cigarettes [40–42] and cigarette use in AUDs is accompanied by higher rates and levels of intake compared to non-AUDs [40]. This relationship between nicotine and alcohol has also been demonstrated in a number of preclinical studies under a variety of nicotine exposure and drinking conditions. For example, repeated nicotine injections or exposure to continuous nicotine delivery has been shown to increase alcohol consumption in animals [43–46]. Moreover, the effect of nicotine on alcohol self-administration is often dose- and time-dependent and may be more robust after repeated nicotine exposure. These differences are clearly exemplified in a series of studies from Lê and colleagues. Repeated nicotine treatment immediately prior to alcohol access decreased

or had no effect on alcohol consumption early in treatment, but then gradually increased to levels above baseline consumption after several days of nicotine exposure [45,47] see also [48,49]. However, increases in alcohol intake may also occur early in treatment if nicotine is administered prior to alcohol access. For example, rats that received a single pretreatment with a moderate nicotine dose (0.4 mg/kg) 3-hr prior to the initial alcohol exposure significantly increased alcohol self-administration over the first four self-administration sessions [50,51]. Although it appears that exposure to nicotine may facilitate alcohol intake, these results have generally relied on passive, experimenter-administered nicotine injections. In contrast, a recent study used rats trained to self-administer both intravenous (IV) nicotine and oral alcohol in daily sessions separated by 5-hr to study the interaction between self-administration of the two drugs [52,53]. In this study, nicotine self-administration increased responding for alcohol when alcohol was available first but nicotine self-administration decreased when alcohol was available first [53], suggesting asymmetrical interactions between nicotine and alcohol on intake. Interestingly, when alcohol and nicotine were available in alternating 5-min periods within the same session, alcohol intake significantly increased compared to alcohol alone while nicotine self-administration was unchanged [53]. As with experimenter-administered nicotine, increases in alcohol self-administration during alternating access conditions emerged after about a week. Additional research is needed to determine which exposure conditions support or limit increased intake of one or both drugs as well as to document the neurochemical changes that occur during the course of nicotine exposure that leads to increased alcohol intake.

Nicotine may also alter factors associated with success in treatment of AUDs, such as cessation and relapse. Clinical reports addressing the question of whether treatment should include one or both drugs have produced mixed results. Some studies, for example, have shown that either smoking cessation [54] or continued smoking [55] may increase relapse to alcohol drinking, whereas others indicate that smoking cessation does not interfere with [56] or may aid in the treatment of AUD [57]. In preclinical studies, nicotine exposure during extinction has been shown to reinstate extinguished responding for alcohol, and this effect is greater in subjects that have a previous history of nicotine exposure [47] see also [52,58]. Further, in rats trained to self-administer IV nicotine and oral alcohol, co-administration of both drugs maintained levels of self-administration similar to that maintained by each drug alone [52]. When either the nicotine or alcohol component of the nicotine + alcohol condition was removed, responding for nicotine extinguished rapidly when alcohol was still available but responding for alcohol extinguished more slowly when nicotine was still available for self-administration. Additionally, in studies investigating nicotine and alcohol withdrawal, mice that received simultaneous exposure to nicotine (P.O. in drinking water) and alcohol (daily injections) displayed more somatic withdrawal signs that lasted longer (i.e., >72 hrs) than either drug alone (i.e., <48 hrs; see [59]). Finally, acute nicotine prevented withdrawal symptoms from alcohol discontinuation and acute alcohol prevented withdrawal symptoms from nicotine discontinuation [59]. Taken together, these findings may have important implications for treatment of comorbid nicotine and alcohol use disorders and suggest that the order of treatment may be an important consideration.

There have been several investigations into the behavioral basis for nicotine-induced alterations in alcohol consumption. In drug discrimination studies, nicotine does not

substitute for the alcohol discriminative cue and alcohol does not substitute for the nicotine cue [60–63]. However, as is the case in human studies [64], nicotine potentiates the discriminative stimulus effects of alcohol, particularly in combination with low or threshold doses of alcohol [60,63,65], while alcohol attenuates nicotine's discriminative cue [66] though see [62], possibly through overshadowing processes [60]. Nicotine + alcohol combinations, when trained as a discriminative stimulus, also have been suggested to produce a discriminative cue that is distinct from those of the individual drugs [61]. Taken together, drug discrimination studies may offer insight into why nicotine and alcohol are often co-used in human populations. First, nicotine intake (through cigarette smoking) enhances the positive subjective (or discriminative stimulus) effects of low levels of alcohol use [64]. However, as more alcohol is consumed, the effects of nicotine become less apparent, leading to increased cigarette smoking. Finally, distinct subjective effects emerge as levels of both nicotine and alcohol use has increased.

There is little evidence of a direct interaction between nicotine and alcohol in aversive or rewarding motivational measures as nicotine did not affect alcohol-induced conditioned taste aversions [67,68] and alcohol did not affect nicotine-induced CPP [67]; though nicotine and alcohol do cross-reinstate extinguished CPP [69]. Nicotine has been shown to attenuate alcohol-induced ataxia [70,71] suggesting that nicotine may attenuate some of the direct effects (e.g., motoric disruption) of higher alcohol doses (i.e., the descending limb of the dose-effect curve) allowing subjects to self-administer more drug. Nicotine co-administration with alcohol increases locomotor activity [72] and also enhances the development of alcohol (1 g/kg)-induced locomotor sensitization [73]. Taken together, these findings suggest that enhancement of alcohol drinking by nicotine exposure is likely related to their interactive effects on a complex array of behaviors.

In addition to their interactions on behavioral indices, nicotine and alcohol also appear to interact within common pharmacological, neurochemical, and molecular mechanisms. Research has primarily focused on nAChRs in the mesolimbic DA system as crucial mediators of these effects, though glutamate [74], GABA [50], and serotonin [75] may also play important roles. While nAChRs are the main target of action for nicotine, they also appear to be involved in many of the abuse-related effects of alcohol (reviewed by [76,77]). The nonselective nAChR antagonist mecamylamine has been shown to reduce alcohol-induced increases in extracellular DA in the NAcc [78] and decrease alcohol drinking in rodents [79–82]. Varenicline (Chantix), a nAChR receptor partial agonist and FDA-approved smoking cessation aid, has shown similar effects [83,84] and has been proposed as a treatment for AUD [85]. However, preclinical studies have produced mixed results showing that varenicline may reduce alcohol consumption under some [86–88] but not all [88–90] conditions. Varenicline has also been shown to have no effect on alcohol-induced CPP, though it did alter alcohol-induced changes in locomotor activity [91].

Nicotine and alcohol both increase Fos expression (a molecular marker of neuronal activation [92]) and other gene expression in addiction-related brain areas [93]. Neurobiological studies implicate the VTA as an important structure mediating the interactions between nicotine and alcohol. For example, injections of alcohol directly into the VTA increase NAcc DA levels, which is blocked by mecamylamine [94]. Further,

nicotine administered directly into the posterior VTA [75] or the basal forebrain, which receives input from the VTA [95], increases alcohol seeking in rats. VTA activation also increases extracellular DA in the NAcc shell, and combinations of nicotine + alcohol administered directly into the VTA produce an additive effect on DA levels in this region [96]. Finally, human genetic studies indicate shared genes associated with the development of nicotine and/or alcohol use disorder [97,98], and preclinical studies point to a corresponding association. In this regard, rats bred for high alcohol drinking (e.g., alcohol-preferring rats) self-administer more nicotine compared to rats bred for low alcohol drinking [44,75,99]. Those genes encoding for several nAChR subunits have been implicated as possible contributors (see Table 1 in [97]) because of their modulatory role on various neurotransmitter systems (e.g., DA, GABA, glutamate, etc.) that mediate behavioral responses to both nicotine and alcohol. However, risk for nicotine and alcohol co-use is likely the result of a complex interaction between multiple genes [98] and additional studies utilizing transgenic mouse models may shed light onto the contribution of specific genetic alleles to various aspects of nicotine and/or alcohol co-use.

Nicotine + stimulant interactions

Similar to the effects reported with nicotine and alcohol co-use, clinical studies suggest an interaction between nicotine and a variety of stimulants such as cocaine, methamphetamine (METH), and amphetamine. The prevalence of cigarette smoking among cocaine or METH abusers, in particular, is 3–4 times that observed in the general population, and most stimulant abusers report a history of cigarette smoking prior to the initiation of stimulant use [100–102]. Further, cocaine-dependent smokers use more cocaine than cocaine-dependent non-smokers [100,103], and rate of cigarette smoking increases during bouts of cocaine use [104]. Clinical studies also have found that concurrent use of nicotine and cocaine enhances several positive ratings of the drugs, and users report that nicotine enhances the reinforcing effects of cocaine [105].

Preclinical investigations into the effects of nicotine on stimulant intake have largely been concordant with clinical reports. Pretreatment with nicotine prior to cocaine self-administration sessions has been shown to accelerate the acquisition of [106] and increase overall levels of intake of both cocaine and amphetamine under a progressive ratio schedule of reinforcement in rats [107,108]. Interestingly, like the effects seen with alcohol described above, the effects of repeated nicotine treatment take several days before cocaine self-administration increases [107]. Studies in nonhuman primates also have assessed the possible interactions between nicotine and cocaine using mixtures of cocaine + nicotine self-administered concurrently. In these studies, monkeys were trained to self-administer IV cocaine and then, nicotine was combined with the cocaine solution to compare reinforcing effects of the mixtures with that of cocaine alone [109,110]. In both studies, adding nicotine to the cocaine solutions produced leftward shifts in the cocaine dose-effect curves suggesting an increase in potency. In contrast to studies with cocaine, the effects of nicotine on METH self-administration are less clear [111] though more research is needed to determine what conditions of nicotine administration, if any, affect METH self-administration. However, one study has shown that acute pretreatment with a low (0.3 mg/

kg), but not high (1–3 mg/kg), dose of METH significantly increased nicotine self-administration in rats [112].

Some studies also investigated whether acute nicotine exposure (priming) could reinstate extinguished stimulant-seeking behavior, but the results have been inconsistent [107,111,113]. However, Hiranita and colleagues [114–116] have extensively studied the effects of nicotine pretreatment on reinstatement of extinguished METH-seeking induced by METH priming or a METH-associated cue. These studies consistently show that nicotine has an inhibitory effect on METH reinstatement leading the authors to conclude that the nAChR system may play a role in relapse to METH-seeking. Interestingly, nicotine administration itself can also reinstate METH seeking after extinction, however, this effect may only occur in rats with previous history of nicotine exposure [111]. Rats with a previous exposure to nicotine were also more resistant to extinction of amphetamine self-administration [108].

Drug discrimination studies suggest some overlap in the behavioral and neurochemical effects of nicotine and abused stimulants, though these effects appear to be asymmetric and drug and species dependent. That is, nicotine substitutes for the discriminative stimulus effects of cocaine in rats [117,118] and METH in rats [119] and monkeys [120], but shows no substitution or incomplete substitution for cocaine in monkeys or pigeons [110,117,120]. Cocaine does not substitute for the nicotine discriminative stimulus in rats [117,118].

In addition to direct alterations in the reinforcing and subjective effects of cocaine that serve to maintain or enhance drug-taking behavior, cocaine users often report the use of nicotine-containing products because they “increase mental concentration” and “help them feel better physically” after cocaine use [121]. Results from preclinical studies also suggest that nicotine may alleviate some of the adverse consequences of chronic stimulant use. A recent series of studies found that nicotine exposure attenuated METH-induced disruptions in cognitive performance and striatal deficits possibly through activation of $\alpha 4\beta 2$ receptors [122–124]. Nicotine and other nAChR agonists have also been shown to ameliorate disruptions in cognitive performance in monkeys with a history of cocaine self-administration [125]. Collectively, these data indicate that while the positive reinforcing effects may serve to maintain nicotine-taking behavior, its role in polysubstance use may also be the result of a negative reinforcement process by which some of the adverse effects of repeated stimulant use are overcome by nicotine. More research in this area may shed light onto this important issue.

The facilitative effect of nicotine on stimulant self-administration may be related, at least in part, to adaptations in nAChR systems. In rats responding for cocaine under long-access conditions, which has been reported to produce an escalation of drug intake over several sessions (see [126]), mecamylamine prevented the escalation of cocaine self-administration when added to the cocaine solution [127]. However, when mecamylamine was removed, cocaine intake escalated in those same subjects. Radioligand binding studies have also shown that the distribution of nAChRs is altered in monkeys with a history of cocaine self-administration [125] and in human cocaine users [128]. Other behavioral effects associated with the interaction between nicotine and stimulants, such as cross-sensitization (a

neurobiological adaptive process that is thought to play a role in the development and maintenance of addiction; [129]) have been demonstrated. These include interactions between nicotine and amphetamine [130], methylphenidate [131], cocaine [132], and METH [133]. Related neurobiological changes have also been noted in rodents pre-exposed to nicotine. For example, nicotine exposure enhanced cocaine-induced reduction in long-term potentiation and gene transcription patterns in striatum that may be related to increased cocaine-induced locomotor sensitization and CPP [14]. However, the behavioral and neurochemical effects of nicotine were not enhanced following cocaine exposure. Consistent with these laboratory findings, epidemiological analysis suggests that most cocaine users initiate cocaine use after a history of tobacco smoking and while still smoking cigarettes [14]. These findings have prompted some to view nicotine as a “gateway drug” [134], though this characterization has not been sufficiently evaluated and several questions remain regarding its generality to human drug users.

Investigations into the neurochemical basis for nicotine + stimulant interactions have primarily focused on overlapping effects within the mesolimbic DA system – particularly the NAcc and other striatal regions [31,135]. Both nicotine and cocaine produce overlapping patterns of activation in mesolimbic DA pathways in rats trained to self-administer either nicotine or cocaine [136]. Microdialysis studies have found that nicotine, like cocaine and METH, increases extracellular DA levels in the NAcc [32,137]. Importantly, the interaction between nicotine and cocaine on extracellular DA is often described as additive [138–140], which mirrors the degree of change in most behavioral measures. It should be noted however, that maximal changes in extracellular DA levels induced by nicotine are relatively small (typically between 100–200% increase from basal values) compared to stimulant drugs such as cocaine and METH (>600%). Further, positron emission tomography (PET) studies in rhesus monkeys have found that nicotine, even up to a dose that increases cardiovascular responses, does not release sufficient DA to displace [11C]raclopride from DA receptors. In contrast, METH produces a robust, time-dependent displacement [141] see also [142]. While modest, nicotine-induced increases in extracellular DA may be sufficient to produce stimulant-like effects. In rats trained to discriminate cocaine [143] or METH [144] from saline, a low dose of the training drug that produced > ~125% of baseline DA in microdialysis studies was enough to produce stimulant-like discriminative stimulus effects suggesting a role for nicotine-induced DA release in its abuse-related effects and interactions with other drugs of abuse.

Nicotine + opioid interactions

Clinical reports indicate that approximately 83–95% of methadone maintained patients smoke cigarettes [145,146] and an association between smoking status and prescription opioid misuse has also been reported [147]. Laboratory based human self-administration studies have shown that nicotine and opiates (e.g., heroin, morphine, methadone) interact to increase total drug intake. For example, heroin [8] or methadone [148] administration increases smoking while methadone also increases the subjective ratings of smoking satisfaction [148]. Naltrexone, an opioid antagonist, decreases the number of cigarettes smoked and self-reports of smoking satisfaction [149]. Finally, laboratory studies have

shown that subjects consume more methadone following nicotine exposure [150,151]. These reports may explain the high rates of smoking in methadone-maintained patients [152].

Preclinical studies have not directly assessed the effects of nicotine on opiate self-administration (or vice versa) though nicotine self-administration in rats does not seem to depend on mu opioid receptor activity as antagonists such as naloxone or DAMGO do not alter nicotine intake [153,154]. Other measures related to drug reward have been studied however. Intracranial self-stimulation studies (ICSS) in rats show that pretreatment with morphine shifts the ICSS threshold for nicotine down and to the left, suggesting increased efficacy and potency [155]. Nicotine and opiates also produce cross-tolerance [156] or cross-sensitization [157] such that exposure to one drug increases or decreases the response to the other in CPP procedures, depending on the schedule and duration of administration. Further, acute administration of nicotine into the VTA [158], hippocampus [159], or basolateral amygdala [160] potentiates, while mecamylamine inhibits, morphine-induced CPP. Morphine also reinstates extinguished nicotine-induced CPP [161]. Seemingly at odds with these findings, it has also been shown that systemic or central (ICV) injections of “ultra-low doses” of nicotine (0.0012–0.01 mg/kg, intraperitoneal; 0.03 – 0.5 ng/mouse, ICV) reduce the expression of morphine-induced CPP [162]. While an explanation for these effects is not readily available, it may involve disruptions to memory processes as these same doses of nicotine have been shown to alter morphine state-dependent learning [163].

Drug discrimination studies have found that there is little overlap in the discriminative stimulus effects of nicotine and opioids. For example, morphine does not substitute for the discriminative stimulus effects of nicotine [164] and nicotine does not substitute for the morphine discriminative stimulus [165]. Further, the mu-opioid antagonists, naloxone and naltrexone did not significantly alter nicotine’s discriminative cue [165,166] and mecamylamine does not alter morphine’s discriminative cue [166].

One area that has received considerable attention is the apparent overlapping mechanisms in the development of tolerance and/or withdrawal from chronic treatment with nicotine or opiates [167]. Repeated nicotine treatment has been shown to attenuate the development of morphine tolerance determined by fewer opioid antagonist-precipitated withdrawal signs such as withdrawal jumping [168] or CPA [169,170] in morphine-treated mice. Acute nicotine also decreases antagonist-precipitated opioid withdrawal [171,172]. Overt signs of nicotine withdrawal appear to be less intense than the overt signs of opiate withdrawal [173] but some studies have found that endogenous opioids are involved in nicotine tolerance and withdrawal. For example, opioid antagonists prevent the development of nicotine tolerance [174], precipitate nicotine withdrawal in mice [174,175], and block nicotine-induced alleviation of nicotine withdrawal [176]. Nicotine withdrawal is also decreased by mu opioid receptor agonists [175].

Like nicotine’s interaction with other drugs, nicotine-induced changes in the reinforcing effects of opioids are likely due to alterations in the mesolimbic DA system as morphine-induced DA release in the caudate putamen and NAcc is significantly augmented by chronic nicotine administration [157]. Interactions between nicotine and opiates also extend beyond reinforcing effects of the drugs to other important effects such as antinociception though

these may not be mutually exclusive as patients with chronic non-malignant pain also co-use opioids and nicotine to manage pain (i.e., negative reinforcement; [177]). There is, for example, evidence that nicotine releases endogenous opioids [178,179] and that nAChRs play a role in opioid-induced antinociception [180], perhaps by potentiating opioid-induced antinociception through nAChR-induced release of endogenous opioid peptides [181]. Identifying the nature of nicotine's reinforcing effects using preclinical pain models is needed to understand the relevance of this interaction to nicotine + opioid co-use.

Nicotine + THC interactions

There is a close association between nicotine and THC use in humans, and cannabis users report that nicotine enhances the effects of THC, the active psychoactive component in marijuana [182]. In addition to these epidemiological findings, a double-blind cross-over experiment using transdermal nicotine (21 mg) significantly altered physiological and subjective effects of smoked marijuana (1.99 or 3.51% THC content). Measures including increases in heart rate and subjective reports of "stimulated" were significantly increased while subjects also reported that the effects of THC were longer lasting [183].

The results of preclinical studies have shown a similar interaction between the rewarding/reinforcing effects of THC or other cannabinoid (CB) receptor agonists and nicotine. For example, in nicotine-induced CPP studies, the CB receptor antagonist rimonibant (SR141617A) blocked the acquisition of nicotine CPP [184] as well as nicotine priming-induced reinstatement of extinguished nicotine CPP [69]. Consistent with these findings, nicotine fails to condition CPP in CB1 receptor knockout mice [185] suggesting a role for the endocannabinoid system in nicotine reward. In a self-administration study, rats were treated with escalating THC doses for 3 consecutive days and then trained to self-administer nicotine 7 days later [186]. A greater percentage of THC exposed rats (94%) acquired nicotine self-administration compared to vehicle-exposed rats (65%) and THC exposed rats also self-administered more nicotine after acquisition. Other CB1/2 agonists such as WIN55,212–2 have been shown to increase nicotine self-administration and to reinstate extinguished nicotine-seeking behavior [187]. Rimonibant has also been found to decrease nicotine self-administration in rats [188]. These changes in nicotine self-administration are likely related to reinforcing effects as CB receptor agonists and antagonists do not appreciably alter the discriminative stimulus effects of nicotine [188,189] though see [190]. As of this writing, no study appears to have directly investigated the effects of nicotine exposure on THC self-administration. Nonetheless, the available data suggest the ability of CB receptor activation to modulate various aspects of the rewarding and reinforcing effects of nicotine.

Nicotine may also facilitate some other pharmacological and behavioral effects of THC. For example, nicotine facilitated the hypothermic, antinociceptive, and hypolocomotive effects of THC administration in mice [191]. Further, co-administration of nicotine with THC attenuated THC-induced tolerance and enhanced the expression of CB receptor antagonist-precipitated THC withdrawal [191]. Interestingly, THC decreased the incidence of nAChR antagonist-precipitated nicotine withdrawal (i.e., decreased wet dog shakes, paw tremors, scratching) and reversed CPA associated with antagonist-precipitated nicotine withdrawal

[192]. Finally, drug discrimination studies in rodents have found that nicotine potentiates low dose THC discrimination [193].

There are several lines of evidence suggesting an interaction between endocannabinoid and nicotinic acetylcholine systems that may underlie behavioral and pharmacological interactions between THC and nicotine. A comprehensive review of the evidence for a role of the endocannabinoid system in nicotine addiction, which includes molecular biology, pharmacological, and behavioral studies, has recently been published [194]. However, it should be noted that while interactions between nicotine and alcohol or nicotine and abused stimulants appear to be associated with increases in extracellular DA in the NAcc (see above), the interaction between nicotine and THC is probably more complicated with studies showing decreases in nicotine-induced mesolimbic DA release [188,195] by CB receptor antagonists but no changes in NAcc DA activity [196]. Further research is needed to disentangle the complicated interactions between nicotine and THC on the DA system [194].

Nicotine's interaction with drugs of abuse: Commonalities and differences across pharmacological classes

To summarize, nicotine appears to interact with drugs from other pharmacological classes in several ways, all of which appear to be mediated through nicotine's pharmacological activity as a nAChR agonist. Nicotine's ability to increase extracellular DA levels through nAChR activation in mesolimbic brain regions is a likely common mechanism through which nicotine exposure or pretreatment alters the reinforcing or rewarding effects of other drugs. While interactions at the level of DA may be a principal reason for the high prevalence of nicotine co-use with drugs of abuse, nicotine (through activation of nAChRs) produces a complex array of behavioral effects, each of which may be differentially relevant for the various drug classes. For example, nicotine enhances stimulant effects (stimulants), alleviates drug withdrawal (opioids, THC, alcohol) and drug-induced cognitive deficits (stimulants, THC; [197]), or enhances tolerance (opioids) and antinociception (opioids, THC). These observations, that behavioral and neurochemical effects of nicotine overlap with the effects of drugs of abuse, point to the ubiquitous nature of nAChRs in brain function and suggest an important role in nicotine polysubstance use.

Associative factors in nicotine polysubstance use

There are other potential explanations for the high rates of nicotine polysubstance abuse that must be considered. First, it is now well accepted that, in addition to its direct reinforcing effects, nicotine also can enhance the effects of conditioned stimuli that likely play a major role in maintaining tobacco addiction and possibly polysubstance use. The idea of cross-drug generalization to nicotine-associated stimuli was recently demonstrated in studies of the reinforcing effects of amphetamine after nicotine exposure [108]. In these studies, nicotine or saline was administered every third day for five total injections in one of two environmental conditions – in the home-cage or in the self-administration chambers with response manipulanda removed. Rats were then trained to self-administer amphetamine under a progressive ratio schedule approximately two weeks later, followed by extinction, and amphetamine-induced reinstatement. Rats that received nicotine injections in the self-

administration chamber displayed enhanced amphetamine self-administration and significantly higher amphetamine-induced reinstatement than rats that received nicotine injections in the home-cage. Thus, the contextual stimuli previously associated with nicotine (i.e., the self-administration chamber) served as an associated cue that enhanced the reinforcing effects of other drugs of abuse (e.g., amphetamine).

Nicotine also has been shown to enhance responding for a conditioned reinforcer (CR) even when there was no temporal association between nicotine and the CR (see also [198,199]). In the study mentioned above, prior nicotine exposure, regardless of whether the exposure was in the home-cage or self-administration chamber, was found to delay extinction of non-reinforced responding in which nicotine was removed and only the accompanied visual stimulus was presented [108]. This is reminiscent of studies showing that responding for a visual stimulus in rats is enhanced by response independent administration of nicotine [200,201]. While research into these processes have been extensively applied to the study of nicotine and its role in tobacco addiction, few studies have applied it to the study of polysubstance use and abuse. Thus, more research into the role, if any, that nicotine-associated stimuli or nicotine's CR enhancing effects play in polysubstance abuse is likely to be a profitable direction for understanding nicotine's interaction with other drugs of abuse.

Future directions and challenges

Preclinical evaluations of the interaction between nicotine and drugs of abuse have been hampered by difficulties in establishing and maintaining nicotine self-administration in laboratory animals [202,203]. Despite its widespread use in human populations, the conditions that support nicotine self-administration in laboratory animals have been inconsistent across studies and are poorly understood. There have been a number of laboratories over the past decade that report acquisition and maintenance of nicotine self-administration in rats, but rodent studies often lack the longevity in intravenous catheter life required to fully and systematically characterize drug interactions using self-administration techniques in long-term experiments [204]. Progress in establishing nicotine self-administration in nonhuman primates has recently been reported [202,205,206]. Experimenter-administered, or passive exposure to nicotine has undoubtedly increased our understanding of the effects of nicotine in combination with other drugs (see above). However, experimenter-administered and self-administered drug exposures can have different behavioral and neuropharmacological effects [207,208]. Thus, it will be important to verify and complement the results of those studies employing experimenter-administered nicotine with those using animals trained to self-administer nicotine.

Related to difficulties in establishing nicotine self-administration in animals is the issue that preclinical studies have primarily examined the effects of nicotine (either passively administered or self-administered) on the self-administration of other drugs such as alcohol or stimulants (see above), while the impact of other drugs on nicotine self-administration has not been studied as rigorously. Nonetheless, some studies have found that indirect DA agonists such as methylphenidate, bupropion, or METH, and the adenosine antagonist caffeine increases nicotine self-administration when administered prior to self-administration sessions [131,209,210] suggesting a reciprocal influence of nicotine and

stimulants on drug intake. In contrast, Lê et al [52] found that alcohol intake before nicotine self-administration actually decreases nicotine self-administration, and similar results have also been reported with cocaine [211]. In apparent contrast to these laboratory studies, human tobacco users have reported smoking more cigarettes while taking other drugs [104]. A number of factors such as nicotine self-administration history, level of dependence, schedule of reinforcement, etc. may be important factors determining the nature of these interactions. Another intriguing possibility is that co-use of other drugs may decrease the aversive (e.g., noxious) effects of high doses of nicotine [212]. More research is needed to clarify these apparent discrepancies and to understand the conditions under which different classes of drugs may alter nicotine self-administration in preclinical studies.

Medication development for nicotine polysubstance use

Despite FDA-approval of several smoking cessation products, success rates remain low (5–35%) and there is clinical demand for more effective medications and new treatment strategies. This will require a more complete understanding of the interaction between nicotine and drugs of abuse at the behavioral and biochemical levels. Clinical studies suggest, however, that treatment for tobacco or nicotine use may also decrease the use or enhance treatment outcomes for other abused substances, such as cocaine, that may be used concurrently with nicotine [213]. Medication strategies for polysubstance abuse represent a unique challenge because combinations of drugs are often pharmacologically diverse. Studies in rhesus monkeys have begun to assess potential medications that may be effective for combined cocaine + nicotine use (e.g., buspirone, [214,215]; varenicline, [216]). In one study, chronic treatment with buspirone decreased self-administration of nicotine and cocaine alone as well as nicotine + cocaine combinations. However, decreases in drug self-administration were accompanied by reductions in food-maintained behavior, suggesting non-selectivity of treatment effects. Further, sedative effects were observed during the early phase of buspirone treatment which persisted in some cases [214,215] suggesting that buspirone is unlikely to be a clinically viable approach.

Varenicline has also been suggested as a potential polysubstance abuse medication. In rhesus monkeys, chronic varenicline treatment dose-dependently decreased self-administration of cocaine + nicotine combinations as well as nicotine alone to about 50% of baseline levels, but had no consistent effect on food-maintained behavior or the self-administration of cocaine alone. These data indicate that varenicline can effectively reduce nicotine self-administration in nonhuman primates and also suggest that its efficacy in reducing cocaine + nicotine self-administration is likely due to targeting the nicotine component of the combined drugs. Similar results were found in rats self-administering a combination of alcohol + nicotine [217]. In those studies, varenicline decreased nicotine self-administration and nicotine + alcohol combinations but did not alter alcohol self-administration (but cue + alcohol-primed reinstatement was blocked). Thus, medication mixtures, which target each component of polysubstance combinations, may offer an alternative approach [218]. Evaluations of other candidate medications or medication mixtures for polysubstance use are needed to advance clinical treatment.

Finally, medication approaches to polysubstance use have primarily focused on FDA-approved medications that modulate nicotinic and/or dopaminergic systems. However, polydrug interactions, including nicotine's interactions with alcohol, stimulants, opioids, and THC, at the level of neurochemical mediators other than dopamine (e.g., GABA, glutamate, serotonin, opioid) is not well characterized and research into the role of these neurotransmitter systems may provide insights into novel treatment approaches for nicotine polysubstance use and abuse.

Acknowledgments

The author thanks Drs. Roger Spealman and Rajeev Desai for helpful comments and suggestions on an earlier version of the manuscript.

This work was funded by NIH grants DA039306 and DA.

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