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Review

The co-use of nicotine and prescription psychostimulants: A review of their behavioral and neuropharmacological interactions

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ABSTRACT

Background: Nicotine is commonly co-used with other psychostimulants. These high co-use rates have prompted much research on interactions between nicotine and psychostimulant drugs. These studies range from examination of illicitly used psychostimulants such as cocaine and methamphetamine to prescription psychostimulants used to treat attention deficit hyperactivity disorder (ADHD) such as methylphenidate (Ritalin™) and D-amphetamine (active ingredient of Adderall™). However, previous reviews largely focus on nicotine interactions with illicitly used psychostimulants with sparse mention of prescription psychostimulants. The currently available epidemiological and laboratory research, however, suggests high co-use between nicotine and prescription psychostimulants, and that these drugs interact to modulate use liability of either drug. The present review synthesizes epidemiological and experimental human and pre-clinical research assessing the behavioral and neuropharmacological interactions between nicotine and prescription psychostimulants that may contribute to high nicotine-prescription psychostimulant co-use.

Methods: We searched databases for literature investigating acute and chronic nicotine and prescription psychostimulant interactions. Inclusion criteria were that participants/subjects had to experience nicotine and a prescription psychostimulant compound at least once in the study, in addition to assessment of their interaction.

Results and conclusions: Nicotine clearly interacts with D-amphetamine and methylphenidate in a variety of behavioral tasks and neurochemical assays assessing co-use liability across preclinical, clinical, and epidemiological research. The currently available research suggests research gaps examining these interactions in women/female rodents, in consideration of ADHD symptoms, and how prescription psychostimulant exposure influences later nicotine-related outcomes. Nicotine has been less widely studied with alternative ADHD pharmacotherapy bupropion, but we also discuss this research.

1. Introduction

1.1. Background

Nicotine is the primary addictive chemical in cigarettes and e-cigarettes (Benowitz, 2010). Nicotine-containing products are one of the most highly used substances in the United States. Roughly 21% of people aged 12 or older used nicotine-containing products in 2020, including cigarettes, cigars, smokeless or pipe tobacco, and e-cigarettes (Substance Abuse and Mental Health Services Administration [SAMHSA] 2023). The use of nicotine products creates a significant public health concern, causing increased rates of asthma, cancer, and heart disease. These smoking-related illnesses lead to 480,000 deaths per year in the United States alone.

The use of nicotine products is also associated with increased rates of substance use disorders and increased rates of other substance use more generally (Crummy et al., 2020; Lyzwinski and Eisenberg, 2022). Nicotine use is particularly comorbid with the use of other psychostimulants; roughly 70–95% of individuals who use psychostimulants also use nicotine (Brecht et al., 2007; Weinberger and Sofuoglu, 2009). High rates of co-use between nicotine and other psychostimulants have prompted extensive research on their interactions. Studies range from examination of illicitly used psychostimulants such as cocaine and methamphetamine (e.g., Alajaji et al., 2016; Harmony et al., 2020) to

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prescription psychostimulant drugs used in the treatment of attention deficit hyperactivity disorder such as D-amphetamine (Dexedrine™; Adams et al., 2013; Henningfield and Griffiths, 1981), L-amphetamine (Vyvanse ™; Kollins et al., 2014), a mix of d- and L-amphetamines (Adderall ™; Gehricke et al., 2011), or methylphenidate (Ritalin ™; Shanks et al., 2015).

Despite the body of research on nicotine interactions with both illicit and prescription psychostimulants, previous reviews have largely focused on the interaction between nicotine and illicitly used psychostimulants such as methamphetamine or cocaine. Surprisingly, there has been little to no mention of nicotine-prescription psychostimulant compound interactions (e.g., Crummy et al., 2020; Cross et al., 2017; Kohut, 2017). The lack of reviews in this area may be due to the common misconception that prescription psychostimulants do not hold significant use liability (Weyandt and Bjorn, 2018), and as such, presumed low co-use liability. However, even when examining smoking rates among people using or misusing prescription psychostimulants specifically, smoking rates are higher among those who use or misuse prescription psychostimulants than among those who do not (Barrett et al., 2006; Compton et al., 2018; Silveira et al., 2018).

Over 50% of people misusing prescription psychostimulants also consume nicotine-containing products (Compton et al., 2018; Silveira et al., 2018). Further, in the general population, a 2006 survey identified that 67% of people who used amphetamine and 56.8% of people that used methylphenidate reported co-using with nicotine in the same poly-substance use session (i.e., where someone uses multiple drugs in tandem). An estimated 84% of these individuals increased their smoking while using amphetamine and 56% reported doing so while using methylphenidate (Barrett et al., 2006). Individuals with ADHD have a roughly 2–3 times higher smoking rate than the general population (van Amsterdam et al., 2018), likely producing high lifetime rates of co-use between nicotine and prescription psychostimulant treatments for ADHD. Indeed, evidence suggests prior stimulant treatment for ADHD increases the likelihood of future substance use, including nicotine (Kristin and Bradley, 2009; McCabe et al., 2016). Additionally, because nicotine users have a 3–4 times higher probability of being diagnosed with a substance use disorder (Chou et al., 2016), nicotine use represents an important risk factor for escalation to *any* problematic substance use and therefore should be examined for its interactions with any commonly misused substance. The examination of prescription drugs of this nature is particularly important given their widespread use for ADHD treatment.

Basic and preclinical research, in general, corroborate the observations from the correlational and epidemiological studies we just described. For example, in rodents and humans, pre-exposure to nicotine can modulate behavioral and neurochemical systems in response to later administered prescription psychostimulant compounds (Cortright et al., 2012; Santos et al., 2009; Zakiniaeiz et al., 2019). Acutely co-administered nicotine and D-amphetamine or methylphenidate also interact in behavioral tasks assessing use liability such as increasing smoking behavior in humans and enhancing self-administration, locomotor activity, or place conditioning in rodents (Jutkiewicz et al., 2008; Kim et al., 2011; Wooters et al., 2008). Given the evidence we just described, it is surprising that reviews have not incorporated the vast majority of research with nicotine and prescription psychostimulant compounds.

A substantive literature review that focuses on prescription psychostimulant interactions with nicotine is also needed given the differentiation between use trajectories of prescription psychostimulants and illicitly used psychostimulants that may warrant different research questions. For example, psychostimulants such as methamphetamine or cocaine are not typically used until late adolescence or adulthood (Alcover and Thompson, 2020). In contrast, prescription drugs for ADHD can be prescribed as early as age six (Heal et al., 2013), in addition to their frequent recreational use starting in late adolescence or adulthood (Compton et al., 2018). Because the average age of smoking onset is 15 years-old (Barrington-Trimis et al., 2020; United States Surgeon General, 2014), individuals are likely co-exposed to nicotine and prescription psychostimulants in a variety of temporal patterns. That is, individuals may smoke before ever taking prescription psychostimulants or vice versa. As such, understanding the effects of nicotine on the behavioral effects of prescription psychostimulant compounds is just as important as understanding the effects of prescription psychostimulant exposure on nicotine-related outcomes.

The point made in the previous paragraph is even more salient given that prior basic research in mice and rats has repeatedly suggested that different neurobiological and behavioral effects are observed with different exposure patterns (Kandel and Kandel, 2014; McNealy et al., 2022). For example, nicotine exposure before cocaine exposure enhanced the addiction-related behavioral and neurobiological effects of cocaine, whereas cocaine exposure before nicotine did not enhance addiction-related effects of nicotine. These behavioral changes were parallel with epidemiological patterns showing that over 95% of people began smoking before ever using cocaine (Levine et al., 2011). In contrast, when we examined the effects of order of nicotine and D-amphetamine exposure, nicotine exposure before D-amphetamine did not enhance the behavioral effects of D-amphetamine, while D-amphetamine before nicotine did enhance the behavioral effects of nicotine (McNealy et al., 2022).

Many prior reviews of nicotine-psychostimulant interactions have primarily considered nicotine pre-exposure given the evidence suggesting nicotine as a "molecular gateway" to substance use (Cross et al., 2017; Ren and Lotfipour, 2019). However, the above research suggests that not all stimulants are created equal. Further, early epidemiological and basic research of this kind did not include prescription psychostimulant compounds, nor amphetamines of any kind. Thus, there is increasing importance in understanding the interaction between nicotine and prescription-psychostimulants on use/co-use liability measures in a variety of exposure patterns. This understanding would allow researchers to determine how these different exposure patterns disparately impact measures of use and misuse liability. A critical first step in this understanding is synthesizing the available research to determine our current gaps in knowledge.

At present, we have a collection of exemplary reviews that synthesize the wide variety of interactions between nicotine and other commonly misused substances. However, these tend to include little to no mention of nicotine interactions with prescription psychostimulant compounds (Cross et al., 2017; Crummy et al., 2020; Kohut, 2017). In the current review, we will remediate this gap. To do so, we will summarize epidemiological and experimental human and pre-clinical research assessing the acute or chronic interactions between nicotine and prescription psychostimulants used in the treatment of ADHD, as well as disclose existing gaps in our current knowledge in this area of study. We define chronic administration as the persistent impacts of prior or concurrent repeated drug exposure (such as a 5-day pre-exposure regimen in rats or long-term stimulant administration consistent with ADHD pharmacotherapy for humans). In contrast, acute administration refers to the effects of a substance when administered in close proximity to the test, such as a pre-session administration of amphetamine before measuring nicotine intake. This review will specifically focus on nicotine interactions with amphetamine and methylphenidate. Nicotine has been less widely studied with alternative ADHD pharmacotherapy bupropion, but we will also include a discussion of this research. All nicotine doses are reported as freebase and prescription psychostimulant compounds are reported as salt weight per field standard. Note that we acknowledge that methamphetamine can be prescribed for ADHD in limited cases; however, currently available epidemiological, clinical, and basic research still focuses on illicit use. Further, methamphetamine interactions with nicotine are well-reviewed elsewhere (see Cross et al., 2017; Crummy et al., 2020; Kohut, 2017) and are thus not a focus of the present review. We further note that nicotine when consumed via smoking or vaping, is delivered with a myriad of other

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pharmacologically active constituents that could impact use and co-use liability of nicotine (Harris et al., 2019; Hoffman and Evans, 2013; Majdi et al., 2019). However, the research explicitly examining the role of these constituents in nicotine interactions with prescription psychostimulants does not exist. Thus, our silence reflects the lack of research and not the potential importance of these constituents.

1.2. Methods

We searched PubMed, Google Scholar, and ResearchRabbit for available literature investigating acute and chronic nicotine and prescription psychostimulant interactions. Search terms included nicotine-related terms, such as "nicotine," "tobacco," "cigarettes," "vaping," and "smoking," as well as prescription psychostimulant-related terms. These included the prescription name, such as "Ritalin," or "Adderall," but also the active ingredient, such as "methylphenidate," and "amphetamine." Criteria for inclusion of each publication included that the participants/subjects had to experience nicotine and a prescription psychostimulant compound at least once in the study. Even when both were administered, studies also had to take at least one measure of their interaction.

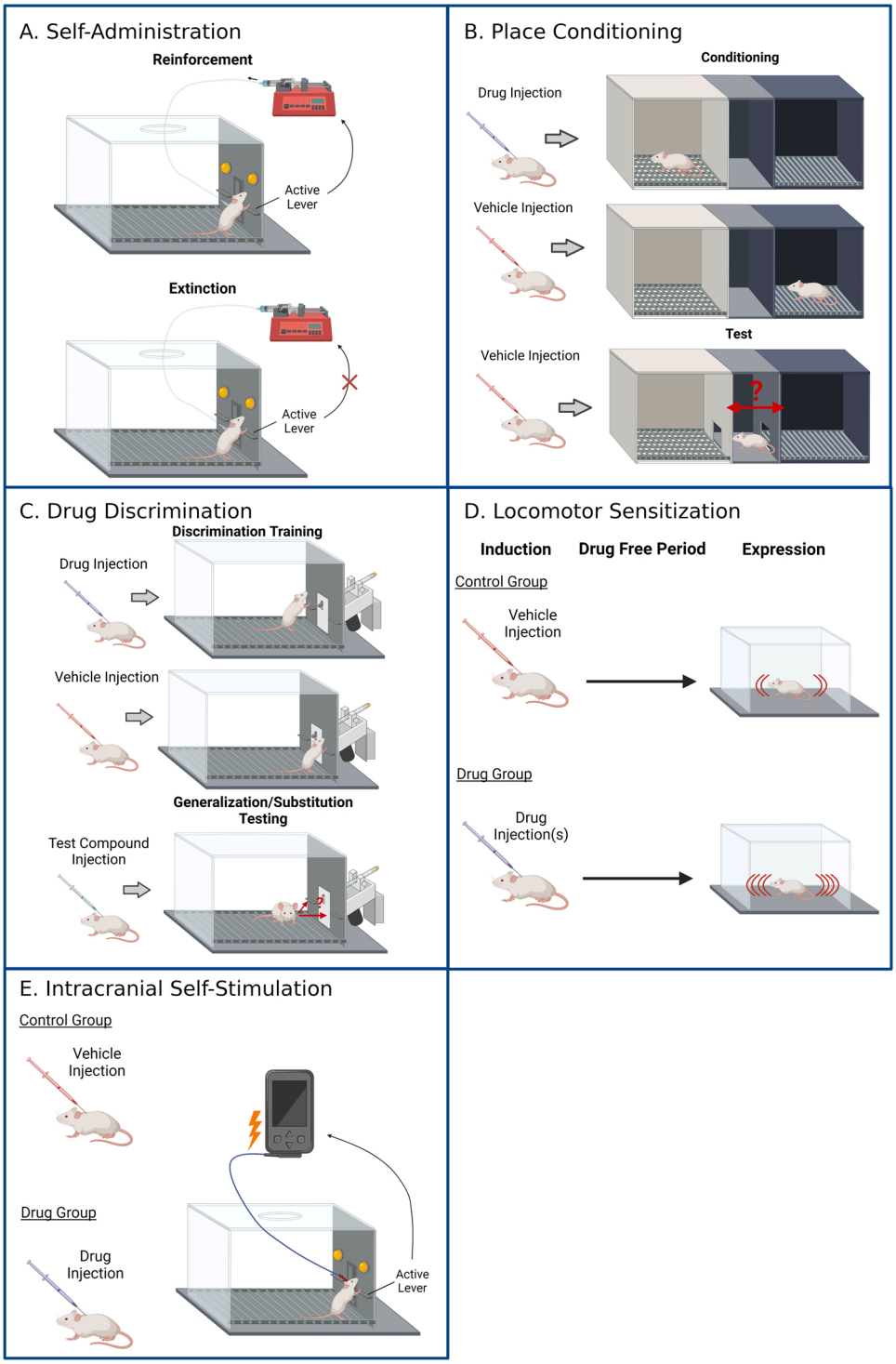

Fig. 1. Preclinical use liability tasks. Diagram of select preclinical behavioral tasks. Created with BioRender.com.

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For example, studies examining only the separate effects of nicotine and the prescription stimulant or that were not properly controlled to assess the interaction were not included in this review. Additionally, studies that examined methamphetamine rather than d- or l- amphetamine were excluded for being outside the scope of the present review. We conducted searches during multiple timeframes beginning in January 2021, with the final search conducted in March 2023. During the search process, a provisional eligibility was determined by reading the abstract, and the total count of publications deemed eligible was 135 papers. After detailed reading and synthesis of the literature, a total of 97 studies were included in the current review.

1.3. Behavioral mechanisms of use or co-use liability

A large majority of the literature reviewed herein reflects preclinical research with rats or mice. The different tasks employed to study drug interactions are thought to represent distinct behavioral mechanisms of use liability. To increase accessibility of this review, we start with a summary of the main experimental tasks used in this area of research – self-administration, reward-enhancement, place conditioning, intracranial self-stimulation (ICSS), drug discrimination, and locomotor sensitization.

Intravenous self-administration procedures are generally the gold-standard for determining whether a drug can serve as a reinforcer and thus hold misuse potential (Kuhn et al., 2019). In these experiments, the animal is implanted with a jugular catheter. Subsequently, the animal is attached to a drug pump via a tube within a chamber (see Fig. 1a), sometimes more colloquially referred to as a "Skinner box." In the chamber, there are generally two available operant devices (e.g., levers or nose-poke holes). One device is designated as the active operant for which responding on the programmed schedule of reinforcement produces an intravenous drug infusion. Brief stimuli such as light or audiovisual presentations typically occur following the infusion to signal a timeout where the animal cannot earn additional infusions. The second operant device is designated as inactive. Responding on the inactive device has no programmed consequence. A drug is interpreted to have reinforcing effects if response levels for drug infusions are significantly greater than saline infusions or if active operant responding is greater than inactive operant responding.

Some self-administration studies also examine extinction of drug-maintained responding to measure the degree to which drug-seeking behavior persists even when the drug is no longer available (Charntikov et al., 2017; Maher et al., 2021; Swalve et al., 2015). The extinction phase is often followed by a reinstatement session, where these data together are often used to provide an animal model of substance use recurrence after an abstinence period (Epstein et al., 2006; Knackstedt et al., 2010; Reichel and Bevins, 2009). While many experimental variations exist to examine extinction and reinstatement of drug-seeking, in the present report we specifically discuss procedures used for extinction before a drug-primed reinstatement test given our focus on drug interactions. In this variation, extinction sessions typically take the form of the same schedule of reinforcement and timeout stimuli used in the self-administration phase being associated with responding on the active operant, but the drug infusion withheld. The inactive operant still produces no consequence. For drug-primed reinstatement, the experimenter administers a low dose of either the initial self-administration drug or a test drug of interest to the animal before an extinction session. The reintroduction of this drug stimulus often induces a relatively specific increase in active operant responding toward pre-extinction self-administration levels (cf. Epstein et al., 2006; Harmony et al., 2020; Swalve et al., 2015).

Psychostimulants such as nicotine and amphetamine, in addition to their primary reinforcing effects, can also enhance the rewarding value of other environmental stimuli or outcomes (Barrett and Bevins, 2012; Winterbauer and Balleine, 2007). Reward-enhancement can be measured by examining operant response rates for weakly reinforcing visual stimuli. In this case, the animal is injected with a drug or vehicle control, then placed in a conditioning chamber (much like the one in Fig. 1a) and allowed to respond for a weak to moderate reinforcer such as low concentration sucrose (Barret and Bevins, 2013) or a brief light presentation (Barrett and Bevins, 2012; McNealy et al., 2021; Raiff and Dallery, 2008). In these studies, nicotine and other psychostimulants produce roughly two-fold increases in responding for visual stimuli (Barrett and Bevins, 2012; Winterbauer and Balleine, 2007). Reward-enhancement is thought to be a particularly important for use liability of nicotine given the role of reward-enhancement in nicotine intake. That is, nicotine is not readily self-administered when available on its own. However, when nicotine is delivered with weak reinforcers, self-administration is dramatically increased (Caggiula et al., 2009, 2002; Chaudhri et al., 2005). In turn, any prescription psychostimulant compound that augments the reward-enhancing effects of nicotine would be particularly relevant as a potential mechanism of nicotine-psychostimulant co-use.

Place conditioning, sometimes referred to as "conditioned place preference," is a measure of the conditioned rewarding effects of a drug. In the conditioning phase, there are intermixed paired and unpaired days. On paired days, the animal is injected with the drug and confined to one of two distinct contexts. On unpaired days, the animal is injected with vehicle control and confined to the other context (see Fig. 1b). As such, one context comes into association with the drug while the other context does not. In the most common variation of this task, the two contexts are separated by a divider during training. After repeated pairings of the drug with a context, the rodent is tested for which context they prefer. For this preference test, the contexts are no longer divided and the animal is placed between them and allowed to roam freely. More time in the drug-associated context would be interpreted as the drug having conditioned rewarding effects or the paired-context evoked anticipatory approach towards drug-associated stimuli. If the organism spends less time in the drug-associated context than the unpaired context then the drug is said to have conditioned aversive effects (Bardo and Bevins, 2000; White, 1989).

Like self-administration, extinction and reinstatement of the drug-context association is sometimes conducted following the place conditioning test. This task provides a model of substance use recurrence in relation to the drug's conditioned rewarding effects (e.g., Biala and Budzynska, 2008). Extinction is either conducted by repeated sessions where the animal is allowed to roam drug-free in the entire place conditioning apparatus (Biala and Budzynska, 2008) or sessions where the animal is placed in the previously drug-paired context in the absence of the initial training drug (McKendrick and Graziane, 2020). Drug-primed reinstatement can similarly be conducted by administering the training drug or a low dose of an alternate test compound (Biala and Budzynska, 2008; McKendrick and Graziane, 2020).

Drug discrimination is often utilized as a preclinical analog to measure the subjective or interoceptive (internal) stimulus effects of a drug (McMahon, 2015). As an example, consider the jitters after consuming too much of a caffeinated beverage or the sleepiness following an allergy medicine with sedative side effects. The most common variant of the drug discrimination task consists of two phases – training and substitution testing. During training, there are intermixed sessions where an animal (rats, mice, or primates) is injected with either drug or vehicle and subsequently placed into an experimental chamber. The chamber is equipped with two response options (e.g., left and right lever; see Fig. 1c). On days when the drug is injected, responding on only one of the levers or operant devices is reinforced; responding on the opposite lever is reinforced on saline days. The ability to discriminate the drug from saline is measured by the distribution of responding on the lever appropriate to the injection. Namely, discrimination between the drug and vehicle is said to have occurred when a greater proportion of responses occur on the injection-appropriate lever.

Once the discrimination has been acquired, animals move to substitution testing. In this phase, the animal is tested with various

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compounds to determine the degree to which the compounds substitute for the training drug. The general consensus for no, partial, and full substitution for the training drug stimulus is as follows: No substitution is declared if the test compound produces responding on the drug-appropriate operant comparable to saline. If the test drug produces responding on the drug-appropriate operant to a greater degree than saline but to a lesser degree than the training drug, then partial substitution is often declared. If the test drug engenders responding on the drug-appropriate operant to the same degree as the training drug, full substitution is interpreted. Partial or full substitution is generally taken as evidence that the drugs have similar or identical interoceptive stimulus effects, respectively (McMahon, 2015; Stolerman, 2002; Young, 2009).

Locomotor sensitization, or increases in drug-evoked activity following prior drug exposure, is thought to reflect potentiation of addiction-related neurochemical pathways (Kuhn et al., 2019). Most common variations of this experimental task involve a single or repeated non-contingent injection of a drug or saline over one or several days. Locomotor activity is measured following drug administration (see Fig. 1d). This phase can be referred to as "induction" of sensitization. The later "expression" phase is where sensitization can be observed. The expression phase occurs after a withdrawal period that can range from one day to several months. During the expression phase, the animals are tested with a drug challenge to determine whether activity has increased as a function of the prior drug exposure (DiFranza and Wellman, 2007). A significant increase in locomotor activation evoked by the injected drug in the previously drug exposed animals relative to the saline animals represents locomotor sensitization.

The rewarding effects of drugs in rodents can also be measured via intracranial self-stimulation (ICSS; Negus and Miller, 2014; see Fig. 1e). An electrode is first implanted into a brain reward center such as the medial forebrain bundle (see Fig. 1e). This behavioral task consists of acute administration of a drug or saline prior to placement in an ICSS chamber. The threshold for which animals will respond for this brain stimulation reinforcer is determined using a discrete trial operant task. For each trial, a noncontingent electrical impulse is delivered followed by a waiting period. The trial is complete once the animal either emits a response or the waiting period has elapsed. Trials continue with successively increasing magnitudes of electrical impulses until the threshold for electrical stimulation or the highest electrical impulse that produces reinforcement is determined. Drug challenges can then be administered before ICSS sessions to determine whether the threshold for ICSS reinforcement is increased or decreased, which indicates a decrease or increase in drug reward, respectively (Negus and Miller, 2014).

2. Amphetamine and nicotine

2.1. Primary reinforcement

There has been a wealth of human research examining the effects of D-amphetamine administration on smoking-related outcomes (see Table 1). Among these outcome measures, acute D-amphetamine administration has increased responding on a progressive ratio schedule maintained by cigarette puffs (Sigmon et al., 2003), the number of cigarettes smoked during an *ad libitum* session (Chait and Griffiths, 1983; Cousins et al., 2001; Henningfield and Griffiths, 1981; Tidey et al., 2000), cue- and abstinence-induced smoking craving (Alsene et al., 2005), and number of choices made for cigarettes over money in a discrete-trial choice task (Tidey et al., 2000). These findings suggest a clear enhancement of nicotine intake by acute D-amphetamine. However, one study using chronically administered amphetamine, similar to the long-term administration associated with the treatment of ADHD, found a decreased smoking rate and enjoyment (Low et al., 1984). No other experimental or clinical study has explicitly examined the effects of D-amphetamine on smoking cessation outcomes. This gap is surprising given the body of smoking cessation research examining prescription psychostimulants methylphenidate and bupropion (discussed in detail later). That being said, amphetamine-containing drugs such as Adderall™ are perceived to, and may very well have, greater misuse liability effects than methylphenidate, particularly in individuals without ADHD who smoke (Kollins, 2003).

However, one study examined L-amphetamine, the less potent amphetamine isomer and the main active component of Vyvanse™ and one of the active components of Adderall™, as a smoking cessation aid. In this study, L-amphetamine did not alter smoking behavior (Kollins et al., 2014). No other study described in the present review examined L-amphetamine, so hereafter D-amphetamine and amphetamine will be used interchangeably.

Interestingly, self-administration research in non-human animals seems to have had a different focus. We could not find self-administration studies that examined the impact of amphetamine pre-exposure on later nicotine intake. Rather, the limited extant preclinical literature has only examined the impact of nicotine exposure on later D-amphetamine self-administration (Cortright et al., 2012; Stairs et al., 2017). Cortright et al. found that nicotine exposure in adult rats enhanced D-lamphetamine self-administration and amphetamine-primed reinstatement only when prior nicotine exposure occurred in the self-administration chamber. Equal nicotine exposure in the home cage had no effect on amphetamine self-administration (Cortright et al., 2012). This pattern of results might suggest that the neurochemical effects from prior nicotine exposure were not driving enhanced amphetamine intake. Rather, nicotine's association with the drug-taking environment was required to enhance amphetamine-taking and seeking. Interestingly, another study found that home cage nicotine exposure during the rat adolescent period enhanced D-amphetamine self-administration in adulthood. This study by Stairs et al. (2017), however, only found enhanced D-amphetamine self-administration as a function of nicotine exposure in rats that were housed in isolation, but not in socially-housed rats. Notably, Cortright et al. utilized individually housed rats, akin to the isolation group of Stairs et al. The discrepancy in findings despite similar housing conditions might suggest that home cage nicotine exposure must occur in adolescence to exert effects on later D-amphetamine self-administration.

2.2. Reward-enhancement

As we mentioned earlier, psychostimulants such as nicotine and amphetamine, in addition to their primary reinforcing effects, can also enhance the rewarding effects of other environmental stimuli or outcomes (Barrett and Bevins, 2012; Winterbauer and Balleine, 2007). We have conducted two studies in our laboratory examining the chronic and acute interactions between nicotine and D-amphetamine on reward-enhancement. Both studies found that acutely co-administered nicotine and D-amphetamine interacted to additively enhance responding maintained by a visual stimulus reinforcer (McNealy et al., 2022, 2021). Our later study examined the impact of drug exposure orders. Nicotine-evoked increases in responding for a weak visual stimulus reinforcer were enhanced by prior amphetamine exposure. However, the opposite was not found – prior nicotine exposure did not change the reward-enhancing effects of D-amphetamine (McNealy et al., 2022). Following these exposure order manipulations, we found that the female rats that experienced nicotine exposure before amphetamine exposure exhibited greater interactive effects of nicotine and D-amphetamine on reward-enhancement than vice versa, while amphetamine before nicotine experience enhanced the interaction for males (McNealy et al., 2022).

2.3. Conditioned and general drug reward

The available research examining how nicotine and amphetamine interact in terms of conditioned drug reward is also sparse. One study

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Table 1
Table of experimental studies examining smoking behavior following acute or chronic amphetamine or methylphenidate administration.

Exposure Drug, Dose, and Type	Participants/ Subjects	Primary Question and Outcome (s)	Main Finding	Ref.
Acute pre-session D-amphetamine at 0, 5, 10, or 15 mg/kg	People who smoke N = 18; 7 M, 11F	Responding on PR schedule for cigarettes or money	D-Amphetamine increased breakpoints for smoking for 56% of subjects, breakpoint increases were dependent on reporting greater amphetamine subjective effects.	Sigmon et al. (2003)
Acute pre-session D-amphetamine at 25 mg	People who smoke, N = 6; 3M, 3F	Ad libitum smoking following drug administration	D-Amphetamine increased ad libitum smoking and decreased time between cigarettes.	Chait and Griffiths (1983)
Acute pre-session D-amphetamine at 10 or 20 mg.	People who smoke, N = 10 (6M, 4F)	Subjective ratings of craving and sensory aspects of smoking. Number of cigarettes during ad libitum smoking.	10 and 20 mg amphetamine increased smoking. Neither drug altered ratings of smoking craving.	Cousins et al. (2001)
Acute pre-session placebo or D-amphetamine at 5, 15, and 25 mg (within-subjects).	People who smoke, N = 8; 3M, 5F	Ad libitum smoking, smoking satisfaction post smoking session.	Dose-dependent increases in smoking, burned more grams of tobacco, and spent more time smoking. Participants reported cigarettes tasting better and greater smoking satisfaction.	Henningfield and Griffiths (1981)
Acute pre-session D-amphetamine at placebo 7.5 or 15 mg/70 kg.	People who smoke, N = 13; 9M, 4F	Choices during a discrete-trial choice procedure between cigarettes or money and smoking subjective effects.	Dose-dependent increases for smoking choices over money, such that higher doses increased smoking choices more.	Tidey et al. (2000)
One-week of chronic administration of placebo, 5 or 7.5 mg D-amphetamine (within-subjects).	People who smoke, N = 17; gender not reported. n = 17 smoked lightly, n = 6 smoked heavily.	Smoking enjoyment and tobacco smoked over one week period of drug treatment.	Chronic amphetamine treatment decreased smoking enjoyment across the sample. However, smoking was only reduced in people who smoked heavily but not those who smoked lightly.	Low et al., (1984)
Placebo (n = 15) chronic L-amphetamine at 30, 50, and 70 mg (7–14 days/dose within-subjects, n = 17) w/ NRT	People with ADHD who smoke, N = 32; 20M, 12F	Smoking cessation measured in cigarettes per day	NRT reduced smoking, but no smoking cessation outcomes were altered by L-amphetamine.	Kollins et al. (2014)
5 injections of saline or 0.4 mg/kg nicotine base injection, over 15 day period. Exposure either in home cage, IVSA chamber, explicitly paired with IVSA chamber, or explicitly unpaired.	Adult male Long Evans rats (N = 63).	Effects of nicotine exposure and type on 0.01 mg/kg/infusion amphetamine IVSA on PR Schedule, extinction, and amphetamine-primed reinstatement.	Nicotine enhanced amphetamine IVSA and reinstatement of amphetamine-seeking only when nicotine exposure occurred in IVSA chamber in IVSA chamber and paired rats, but not for unpaired rats or home cage rats. Regardless of exposure type, prior nicotine exposure halted extinction.	Cortright et al., (2012)
7-days of saline or 0.04 mg/kg nicotine during adolescence.	Male Sprague-Dawley rats (N = 24) raised in enriched (n =12) or isolated (n=12) conditions.	Interaction between environmental conditions and adolescent drug exposure on amphetamine IVSA.	Adolescent nicotine exposure only increased amphetamine IVSA in rats that were reared in socially isolated conditions.	Stairs et al. (2017)
Acute pre-session administration of placebo, 5, 10, 20, or 40 mg methylphenidate (within-subjects)	People who smoke (N = 10); 5M, 5F	Dose-dependent effects of methylphenidate on cigarettes smoked, number of puffs, and CO levels.	Methylphenidate dose-dependently increased all smoking-related outcomes, such that higher doses produced larger magnitude increases in smoking outcomes.	Rush et al. (2005)
Acute pre-session administration of placebo or 10, 20, or 40 mg methylphenidate (within-subjects).	People with ADHD who smoke (N=9); 4M, 5F	Dose-dependent effects of methylphenidate on cigarettes smoked, number of puffs, and CO levels.	Methylphenidate dose-dependently increased all smoking-related outcomes in people with ADHD who smoke, higher doses produced larger increases in smoking outcomes.	Vansickel et al. (2011)
Acute pre-session administration of placebo, immediate (7.5–30 mg), or sustained-release methylphenidate (18, 36, or 72 mg)	People who smoke (N = 8), 3M, 5F	Dose- and release rate-dependent effects of methylphenidate on cigarettes smoked, number of puffs, and CO levels.	Methylphenidate dose-dependently increased smoking-outcomes, but there was no effect of release formulation on smoking outcomes.	Vansickel et al. (2009)
Acute pre-session administration of placebo, methylphenidate (10, 20, 40 mg) within-subjects.	People who smoke (N=12); 6M, 6F.	Cigarettes smoked, number of puffs, and CO levels.	Methylphenidate dose-dependently increased all smoking variables.	Vansickel et al. (2007)
Acute pre-session methylphenidate (0, 10, 20, or 40 mg) within-subjects.	People who smoke (N = 11); 6M, 5F.	Dose-dependent effects of methylphenidate on number of choices made for smoking a cigarette versus $0.25.	Methylphenidate dose-dependently increased the number of cigarette choices over money.	Stoops et al. (2011)
11 weeks of Osmotic Release (OROS) methylphenidate or placebo (dose NS). Delivered with 21 mg nicotine patch starting Week 4.	People with ADHD who are trying to quit smoking (N = 253).	Effects of methylphenidate administration on smoking abstinence.	Methylphenidate increased smoking abstinence rates.	Covey et al. (2010)
Chronic placebo (n = 128) or OROS methylphenidate (n = 127) administration (dose NS) with 21 mg nicotine patch.	Secondary analysis of people who smoke (N = 255).	Smoking abstinence during one month methylphenidate discontinuation follow-up and interaction with ADHD symptom severity.	Individuals that previously took methylphenidate had greater abstinence even after methylphenidate was discontinued, but only for people high severity ADHD symptoms.	Luo et al. (2019)

(*continued on next page*)

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Table 1 (*continued*)

Exposure Drug, Dose, and Type	Participants/ Subjects	Primary Question and Outcome (s)	Main Finding	Ref.
Chronic placebo (n = 127) or 72 mg/day OROS methylphenidate (n = 128) with 21 mg nicotine patch for 11 weeks.	People trying to quit smoking (N = 255).	Prolonged smoking abstinence in response to drug treatment group and interaction with ADHD symptom severity.	70% of patients with higher severity ADHD who took OROS-methylphenidate had prolonged abstinence compared to 37% of placebo. Individuals with low severity ADHD taking methylphenidate exhibited 30% abstinence compared to 61% taking placebo.	Nunes et al. (2013)
Chronic placebo (n = 127) or 72 mg/day OROS methylphenidate (n = 128) with 21 mg nicotine patch for 11 weeks.	People trying to quit smoking (N = 255).	Prolonged smoking abstinence in response to drug treatment group.	No effect of methylphenidate on abstinence during methylphenidate treatment period, but methylphenidate group had higher abstinence post-treatment than placebo.	Winhusen et al. (2010)
Chronic placebo (n =40) or 54 mg/day OROS methylphenidate treatment for 8 weeks.	People trying to quit smoking (N = 80).	Nicotine withdrawal, point-prevalent smoking at end of medication phase.	No effect of methylphenidate on smoking abstinence or withdrawal symptom relief.	Hurt et al. (2011)
Chronic methylphenidate (30 mg) over 5 days following abrupt cessation	People who currently smoke that have previously attempted to quit (N = 19)	Tobacco withdrawal, ease of quit attempt	Tobacco withdrawal increased when methylphenidate was administered, but 76% of the sample said methylphenidate quit attempt was easier than prior quit attempts.	Robinson et al. (1995)
Exp 1: Acute pre-session methylphenidate at 0, 1.25, 2.5, 5, and 10 mg/kg (within-subjects) Exp 2: Chronic pre-session methylphenidate at 0 or 2.5 mg/kg (between-subjects)	Male Sprague-Dawley rats (N = 28; n = 14 per exp)	Exp 1: Effects of acute doses of methylphenidate on 0.01 (n = 7) or 0.03 (n =7) mg/kg/inf nicotine IVSA. Exp 2: Effects of repeated 0 (n = 6) or 2.5 mg/kg (n = 8) methylphenidate on 0.03 mg/kg/inf nicotine IVSA.	Methylphenidate increased nicotine IVSA in both experiments. 2.5 and 5 mg/kg increased 0.03 mg/kg/inf nicotine IVSA in Exp 1. Only 1.25 mg/kg methylphenidate increased 0.01 mg/kg/inf nicotine IVSA in Exp 1. Tolerance to the effects of 2.5 mg/kg methylphenidate on nicotine IVSA with repeated exposure (Exp 2) not observed.	Wooters et al. (2008)

exposed mice to nicotine or saline during adolescence and tested them for the presence of a place preference to an amphetamine-associated context in adulthood. Mice exposed to nicotine exhibited a larger magnitude preference for the amphetamine-associated context in adulthood (Alajaji et al., 2016). We could interpret this outcome as nicotine exposure strengthening amphetamine-context associations later in life. Drug-context associations in humans are powerful modulators of drug taking and seeking such that drug-associated contexts can instigate recurrence of substance use (Crombag et al., 2008). While further examination is needed with contingent drug experiments, nicotine enhancement of later amphetamine-context associations might lead to more tenacious and perseverant amphetamine-seeking.

Another study using adult rats found that an acute amphetamine-priming injection did not reinstate a previously established and extinguished nicotine-associated context preference (Biala and Budzynska, 2008). This finding may tell us that chronic drug exposure or exposure during adolescence is necessary to augment conditioned drug reward. Alternatively, this finding could tell us that while drug exposure augments place preference expression of other drugs, it cannot reinvigorate a previously extinguished conditioned place preference. As we mentioned earlier, ICSS measures more general drug rewards by determining the degree to which test injections modulate the reinforcement threshold of an electrical impulse into a brain reward center. One study using ICSS in rats found that a low dose of D-amphetamine (0.06 mg/kg) decreased ICSS thresholds relative to nicotine alone (Huston-Lyons et al., 1993). That is, acute D-amphetamine increased the rewarding effects of nicotine.

2.4. Stimulus effects

Drug discrimination studies examining nicotine substitution for the amphetamine stimulus by-in-large have found that nicotine partially substituted for amphetamine (Bardo et al., 1997; Cunningham et al., 2006; Li and McMillan, 2003; Palmatier et al., 2005; Quarta et al., 2009). Likewise, studies examining amphetamine substitution for a nicotine stimulus have largely found that amphetamine partially substituted for nicotine (Besheer et al., 2004; Chance et al., 1977; Chandler and Stolerman, 1997; Mansbach et al., 1998; Palmatier et al., 2005; Quarta et al., 2009; Varvel et al., 1999). Two studies found that nicotine and amphetamine fully substituted for each other (Stolerman, 1989). Although the minority, there are a few studies that have reported nicotine not having substituted for amphetamine (Ho and Huang, 1975; Schechter and Rosecrans, 1973).

Drug discrimination studies can also assess the degree to which a compound interacts with the training drug to enhance stimulus effects during the substitution testing phase. One such study trained rats to discriminate between 0.6 mg/kg amphetamine and saline. Co-administration of nicotine enhanced substitution by lower doses of amphetamine. While low dose amphetamine only partially substituted for the 0.6 mg/kg amphetamine dose, co-administration of these low doses with nicotine led to full substitution of the amphetamine stimulus (Reavill and Stolerman, 1987).

2.5. Aversive effects

Amphetamine or nicotine administration is generally found to produce anxiety-like effects in rodents (Biala and Kruk, 2008; Caldarone et al., 2008; Lin et al., 1999; Rauhut, 2019). Two studies with rats found that repeated exposure to amphetamine produced tolerance to the later anxiogenic effects of amphetamine or nicotine administration as measured by performance on an elevated plus-maze task (Biala et al., 2009; Biala and Kruk, 2008). Aversive experiences with nicotine may reduce the likelihood of people becoming dependent on nicotine (for a review, see Fowler and Kenny [2014]). Although this area of research is extremely limited, perhaps amphetamine exposure could mitigate the aversive effects of nicotine, thereby increasing the likelihood for persistent nicotine use. Indeed, amphetamine decreased alcohol withdrawal-like symptoms in a rodent model (Popkin et al., 2018). Of course, further preclinical and human research is required, but these findings may suggest careful consideration of amelioration of nicotine withdrawal symptoms by amphetamine as a potential co-use mechanism.

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2.6. Locomotor sensitization

Studies that exposed rats to nicotine in adolescence have generally observed locomotor cross-sensitization from nicotine to amphetamine under a variety of circumstances (Collins et al., 2004; Santos et al., 2009; Adams et al., 2013). Adams et al. (2013) identified that one week of 0.4 mg/kg nicotine exposure produced cross-sensitization to 0.5 and 1.0 mg/kg amphetamine in socially isolated rats. However, 0.4 mg/kg nicotine only produced cross-sensitization to 1.0 mg/kg amphetamine in environmentally enriched rats. These results follow the same pattern as those described in Section 2.1 identifying enhancement of amphetamine self-administration by prior nicotine exposure in isolated but not enriched rats (Stairs et al., 2017). Perhaps the protective effects of environmental enrichment on neurochemical sensitization by nicotine prevent enhancement of future amphetamine self-administration. Locomotor sensitization may also be sensitive to age and sex. For example, cross-sensitization to amphetamine was only observed in male rats that were exposed during the early adolescent period and not at all for adult males or any age of exposure group for females. These cross-sensitization findings were identical whether rats were tested in adolescence or adulthood (Collins et al., 2004).

Santos et al. (2009) were the only authors to examine both the effect of nicotine cross-sensitization to amphetamine and amphetamine cross-sensitization to nicotine. Interestingly, amphetamine pre-exposure in adolescence produced cross-sensitization to nicotine, whether rats were tested for nicotine-evoked locomotor activity in adolescence or adulthood. In contrast, adolescent nicotine pre-exposure produced cross-sensitization to amphetamine only when tested in adulthood (Santos et al., 2009).

Notably, a few studies have reported no effect of prior nicotine exposure on amphetamine-evoked locomotor activity (Biala and Weglinska, 2004; Bruijnzeel et al., 2011; Edwards et al., 2014). In each of these cases, the nicotine exposure protocol diverged from the previously mentioned studies. For two of these studies, the injected nicotine dose was much lower than previously shown to produce cross-sensitization (Biala and Weglinska, 2004; Edwards et al., 2014). Further, Edwards et al. (2014) implemented a two-day exposure protocol that was much shorter than other studies. Lastly, the blood levels of nicotine achieved in the experiment by Bruijnzeel et al. were far lower than in previous studies. This is likely attributed to the use of tobacco smoke exposure versus injected nicotine (Bruijnzeel et al., 2011). Notably, the inhalation route of exposure used by Bruijnzeel et al. also exposed animals to tobacco constituents that are not present when administering injected nicotine. Perhaps these constituents play an important role in modulating nicotine-amphetamine interactions. In summary, exposure dose, length of treatment, and route of administration appear important to consider when examining locomotor cross-sensitization to amphetamine. Ultimately, these factors may provide clues for how results relate to human co-use liability. For example, smoking or vaping may only increase vulnerability to amphetamine use via sensitization of addiction-related pathways later in life when nicotine exposure is frequent, in high concentrations, and/or over a long period of time.

2.7. Neurochemical interactions

Only a few studies have directly assessed the interaction between amphetamine and nicotine on neurochemical systems, largely focusing on acetylcholine and dopamine. The primary receptor systems of interest concerning nicotine and amphetamine are nicotinic acetylcholine (nAChRs) and dopamine receptors, respectively. Nicotine works as an agonist at nAChRs, binding to and activating these receptors to produce downstream dopamine release (Tiwari et al., 2020). In contrast, amphetamine works by targeting the dopamine transporter, thereby increasing dopamine levels by transporter-mediated exchange (Rudnick and Clark, 1993). Glutamatergic systems have also been implicated in nicotine and amphetamine use liability behaviors (Castillo-Rolón et al., 2021; D'Souza and Markou, 2013; Palmatier et al., 2008). Glutamate plays an important role in learning and memory more generally (Zhou and Danbolt, 2014), but also as it relates to drug use behaviors (D'Souza and Markou, 2013). Nicotinic, dopaminergic, and glutamatergic systems are all composed of multiple receptor subtypes that are potentially responsible for different behavioral outcomes.

These neurochemical systems can be probed through multiple neuroscientific methods. One study examining dopamine overflow (measure of dopamine levels) via microdialysis found that nicotine pre-exposure did not alter amphetamine-evoked dopamine overflow (Birrell and Balfour, 1998). Another study found that acute nicotine administered between two and four hours before D-amphetamine heightened amphetamine-evoked dopamine overflow. Acute amphetamine administration also heightened nicotine-evoked dopamine overflow (Jutkiewicz et al., 2008; Kim et al., 2011).

Much of the research examining nicotine-amphetamine interactions has used pharmacological antagonism. Dihydro-β-erythroidine hydrobromide (DHβE) is a nAChR antagonist with selectivity for α4 and β2 receptor subunits. Many use liability effects of nicotine are attributable to α4β2-containing nAChRs (Rahman, 2011). Thus, probing these receptor subtypes is of particular interest when examining mechanisms of co-use liability. MK-801 is a noncompetitive glutamatergic N-Methyl--D-aspartate (NMDA) receptor antagonist (Song et al., 2018). Pretreatment with either DHβE or MK-801 reduced the effect of acute nicotine on amphetamine-evoked dopamine overflow suggesting a role for α4β2-containing nAChRs and NMDA glutamate receptors (Kim et al., 2011). The role of glutamate receptors in nicotine-induced enhancement of amphetamine-evoked dopamine overflow is consistent with later work examining MK-801 interactions with mecamylamine. Mecamylamine is a general nicotinic receptor antagonist that does not necessarily favor any specific receptor subtype (Crooks et al., 2014). Mecamylamine blocked locomotor sensitization to amphetamine when co-administered with MK-801, but neither did so by themselves (Degoulet et al., 2013). Further, DHβE or varenicline, a partial agonist at α4β2-containing nAChRs that competes with activation of these receptors by nicotine, administered before nicotine blocked later locomotor sensitization evoked by an amphetamine challenge (Kim et al., 2011). The summarized research suggests that both nAChRs and glutamate receptor systems underlie behavioral sensitization to amphetamine.

One study in humans further supports nicotine and amphetamine interacting neurochemically. Participants that currently smoked at the time of study showed lower baseline dopamine availability on positron emission tomography (PET) scans than controls that did not currently smoke, and females that currently smoked exhibited lower amphetamine-induced dopamine release than males who smoked or female controls that did not smoke (Zakiniaeiz et al., 2019). This sex-specific alteration in the dopamine system by smoking may lead to greater quantities of dopamine-increasing drugs being required to produce positive drug effects in women. Considering that nicotine and D-amphetamine combined increase dopamine levels more so than either alone, this may lead to greater co-use of nicotine and D-amphetamine amongst women. As we mention in the closing sections of this review, we do not yet have enough data in women or female animals to assess this conclusion.

2.8. Conclusions

Synthesizing the findings in this section, we might conclude that D-amphetamine only increases nicotine intake or misuse liability when taken acutely, such as in the case of occasional or recreational amphetamine use. While more research is needed, the single study that used chronic administration of D-amphetamine found decreases in smoking, suggesting those who use amphetamines chronically, such as in the treatment of ADHD, may not be at a greater risk for increased nicotine use. A topic of great interest would be whether previously non-

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medicated ADHD patients are at greater risk after the start of pharmacotherapy with D-amphetamine.

It is difficult to synthesize self-administration findings from human and preclinical studies given that all preclinical studies examine the impact of nicotine pre-exposure on later amphetamine self-administration. The discrepant findings between the two preclinical studies suggest that neurochemical alterations by nicotine exposure alone play a larger role in increased amphetamine taking only during the sensitive developmental period of adolescence (for a review of developmental nicotine exposure effects, see Ren and Lotfipour (2019)). In contrast, learning or environmental factors may be more important for enhanced co-use vulnerability in adulthood. Taken together, the research described throughout this section supports the existence of acute and long-term interactions of nicotine and amphetamine on primary reinforcement and nicotine intake.

The finding that amphetamine exposure enhanced the reward-enhancing effects of nicotine, but not vice versa (McNealy et al., 2022), suggests that considering the variety of potential nicotine and D-amphetamine use patterns is of clear import when designing preclinical studies. While not a traditional reward-enhancement study, somewhat parallel findings in humans have found that D-amphetamine enhances the sensory aspects of smoking, specifically augmenting cigarette taste (Henningfield and Griffiths, 1981). That finding, and reward-enhancement findings more generally, suggest that consideration of how amphetamine impacts stimuli that commonly co-occur with nicotine (e.g., the smell, taste, or sight of cigarettes or vapes) may be beneficial for uncovering mechanisms of enhanced use liability. This consideration is especially urgent given the advent of vapes or electronic cigarettes that come in myriad flavors with an entirely new nicotine use experience.

Overlapping stimulus effects may be one explanation for intake enhancement. As mentioned earlier, we can think of drug discrimination studies in rodents as a preclinical analog to human studies examining the subjective effects of drugs (McMahon, 2015; Young, 2009). Considering the numerous studies we described that identified partial and full cross-substitution, nicotine and amphetamine clearly share some stimulus effects. Indeed, nicotine and amphetamine have been found to produce similar subjective effects in humans such as cognitive enhancement (Sofuoglu, 2010; Thornton et al., 1996). Indeed, some research suggests high rates of smoking among individuals with ADHD are due to the similar cognitive enhancement and ADHD symptom reduction produced by nicotine and prescription stimulants (otherwise termed as the "self-medication hypothesis"; Gehricke et al., 2006; van Amsterdam et al., 2018; Vansickel et al., 2007). From the reviewed literature, nicotine and D-amphetamine clearly share some stimulus effects that could promote amphetamine use following nicotine use or vice versa. Further, the findings suggest that subjective effect enhancement is a potential mechanism for high rates of acute co-use between nicotine and amphetamine that should be further explored.

The review of amphetamine and nicotine interaction research described herein illustrated several gaps in this literature. As noted earlier in Section 2.1 and discussed in detail later, there is a surprising lack of preclinical research empirically examining the effects of amphetamine pre-exposure on nicotine-related outcomes. In fact, only two of the above cited preclinical studies assess this pattern of drug administration. Further, given the divergent findings between adult and adolescent drug exposure observed in preclinical studies, and that prescription psychostimulants are prescribed as early as age 6, there is a great lack of research examining possible divergent impacts of adolescent or adult exposure to nicotine or amphetamine on later co-use liability outcomes. Research examining general and conditioned drug reward interactions between nicotine and D-amphetamine, and how they may alter each other's aversive drug effects is also sparse – with the limited research in each area pointing towards the import of these factors.

3. Methylphenidate and nicotine

3.1. Primary reinforcement

Like amphetamine, acutely administered methylphenidate before experimental sessions has consistently enhanced smoking-related outcomes (see Table 1). These outcome measures include increases in cigarette puffs per session, total cigarettes smoked, and choice for cigarette puffs over money (Rush et al., 2005; Vansickel et al., 2011, 2009, 2007; Stoops et al., 2011). Currently, the only preclinical study we could identify examining the effect of pre-session methylphenidate on nicotine self-administration mirrored these findings. That is, rats dose-dependently increased nicotine self-administration when acutely administered a range of methylphenidate doses (1.25–5 mg/kg; Wooters et al. (2008)).

Acute methylphenidate administration also enhanced the subjective effects of smoking in humans such as ratings of enjoyment, craving, pleasure, and stimulation (Rush et al., 2005; Vansickel et al., 2009, 2007). Acute methylphenidate administration at therapeutic doses also increased smoking in participants with ADHD that were previously not medicated for their ADHD (Vansickel et al., 2011). These findings suggest that acute methylphenidate can exacerbate nicotine use liability in both ADHD and non-ADHD individuals. In contrast to studies examining acute methylphenidate administration, studies examining the effect of chronic methylphenidate exposure on future nicotine consumption, and vice versa, in humans are mixed. On one hand, a longitudinal retrospective study conducted on individuals who were diagnosed with ADHD as children found no differences in smoking between methylphenidate-treated and non-methylphenidate treated groups (Huss et al., 2008). Similarly, in a general population sample, researchers found no relationship between smoking and methylphenidate misuse (Fleary et al., 2011).

On the other hand, several studies support methylphenidate enhancing smoking or vice versa. Students who smoked cigarettes or experimented with tobacco products were more likely to misuse methylphenidate (Shillington et al., 2006). In a study by Bron et al., researchers placed methylphenidate-naïve participants with ADHD that currently smoked at the time of the study, participants that had previously smoked, and participants that had never smoked on a three-month methylphenidate treatment regimen. Participants that reported currently smoking increased tobacco use by 40–50% and nearly 30% of participants that had previously smoked reinitiated smoking. Notably, none of the participants that had never smoked started smoking, nor did they report nicotine craving (Bron et al., 2013). These increased nicotine consumption findings are consistent with smoking self-administration studies with ADHD patients described earlier in this review (e.g., Vansickel et al., 2011). Notably, the study Bron et al. was a prospective cohort study and as such, there is no placebo control group. No comparable study with randomized control trial (RCT) has been conducted to our knowledge.

The findings we just described are discordant with research on the potential efficacy of methylphenidate as a smoking cessation aid. Double-blinded clinical trials examining methylphenidate as a cessation aid in individuals with ADHD that smoke found that methylphenidate increased smoking abstinence relative to placebo (Covey et al., 2010; Luo et al., 2019; Nunes et al., 2013; Winhusen et al., 2010). Interestingly, the magnitude of this reduction was greater in individuals with more severe ADHD symptoms (Nunes et al., 2013). Studies in individuals without ADHD that smoke have consistently found no differences in smoking abstinence rates following chronic methylphenidate treatment (Hurt et al., 2011; Robinson et al., 1995). Methylphenidate did provide enhanced withdrawal relief compared to previous quit attempts in people without ADHD that smoke. However, this withdrawal relief was not commensurate with improved abstinence rates (Robinson et al., 1995).

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3.2. Conditioned reward

Research examining methylphenidate-nicotine interactions on tasks other than self-administration is limited but may point to other potential mechanisms for enhanced co-use liability. In the single place conditioning study examining the interaction of methylphenidate and nicotine, adolescent nicotine exposure in rats decreased the later conditioned rewarding effects of methylphenidate in adulthood (Nolley and Kelley, 2007).

3.3. Stimulus effects

Research examining the degree to which methylphenidate and nicotine share stimulus effects is also sparse. In a drug discrimination experiment by Reichel et al. (2007), a moderate dose of methylphenidate (10 mg/kg) partially substituted for the 0.2 mg/kg training dose of nicotine. In contrast, a later study by Wooters et al. (2008) found that a wide range of methylphenidate doses (0, 1.25, 2.5, 5, and 10 mg/kg) did not substitute for a 0.3 mg/kg nicotine stimulus. Despite this lack of substitution, that same study found that methylphenidate co-administration with nicotine during substitution testing enhanced the degree to which 0.056 mg/kg nicotine substituted for the 0.3 mg/kg nicotine stimulus. Interestingly, neither methylphenidate nor that low dose of nicotine substituted for the training dose of nicotine when tested alone (Wooters et al., 2008).

3.4. Locomotor sensitization

Studies examining locomotor cross-sensitization between nicotine and methylphenidate have reported mixed results. When adult rats were exposed to nicotine or saline and tested for methylphenidate-evoked locomotor activity after a washout period, nicotine exposed rats exhibited higher methylphenidate-evoked locomotor activity than saline exposed controls (Wooters et al., 2008). In contrast, locomotor cross-sensitization to nicotine was not observed when adult rats were pre-exposed to methylphenidate (Justo et al., 2010). These findings are in line with findings earlier in this review (Section 3.1) indicating that previous nicotine exposure appears to exacerbate methylphenidate misuse-liability outcomes (Shillington et al., 2006).

3.5. Neurochemical interactions

Neurochemically, the interaction of nicotine and methylphenidate has only been explicitly examined in relation to dopaminergic systems. A study in rats found that acutely co-administered 0.4 mg/kg nicotine and high dose methylphenidate (10 mg/kg) interacted synergistically to increase synaptic dopamine concentrations in the nucleus accumbens (Gerasimov et al., 2000). Interestingly, in that same study, low dose methylphenidate (5 mg/kg) only additively enhanced dopamine concentrations when co-administered with nicotine. These findings were attributed to methylphenidate dose-dependent alterations in dopamine transporter occupancy augmenting nicotine-evoked dopamine transmission.

Wheeler et al. (2013) examined mRNA levels of dopamine receptor subtypes in the ventral striatum of the rat brain following adolescent exposure to 2 mg/kg/day nicotine, 3 mg/kg/day methylphenidate, or co-administered nicotine and methylphenidate at these doses. Rats that had combined nicotine and methylphenidate exposure during adolescence exhibited higher locomotor activity (and thus greater tolerance to initial locomotor suppressant effects of nicotine) during adulthood after a long period with no drug exposure. These behavioral effects were accompanied with higher dopamine D_3 receptor levels in the nucleus accumbens core and increased D_1 receptor sensitivity in the nucleus accumbens shell during adulthood. Different dopamine receptor subtypes are thought to be responsible for different stimulant actions, such that dopamine D_1 and D_2 receptors are likely responsible for locomotor or general activating effects of stimulants, while D_3 receptors may act to produce tolerance to the behavioral effects of stimulants (Richtand, 2006). Both subtypes represent key factors of import to stimulant use or co-use liability, such that the general activating effects of stimulants may promote their use while behavioral tolerance allows an organism to consume higher drug concentrations. Thus, upregulation of both receptor subtypes suggests enhanced stimulant efficacy and tolerance as potential neural mechanisms of nicotine-methylphenidate co-use liability.

3.6. Conclusions

Compared to amphetamine, the literature investigating nicotine and methylphenidate interactions is sparse. With these findings, we suggest that methylphenidate may not necessarily confer additional risk for onset of nicotine use. Rather, methylphenidate may increase or reinvigorate smoking if there was an established smoking history prior to methylphenidate treatment in individuals with or without ADHD. Consistent with this idea, based on drug discrimination studies, methylphenidate and nicotine share similar stimulus effects and can potentiate each other's stimulus effects. Perhaps experience with the stimulus effects of nicotine are required for the like-stimulus effects of methylphenidate to reinstate or enhance smoking.

In the same vein, the fact that methylphenidate pre-exposure did not alter nicotine-evoked locomotor activation, but nicotine pre-exposure did augment methylphenidate-evoked locomotor activity suggests that the order of drug exposure may be relevant for alteration of neurochemical pathways. Importantly, these locomotor findings come from separate empirical studies (Justo et al., 2010; Wooters et al., 2008). Further research examining patterns of drug exposure with methylphenidate and nicotine is important to corroborate this conclusion.

Another interesting emergence from this report is that methylphenidate only acts as a cessation aid in individuals with ADHD. This suggests that ADHD symptom relief underlies the observed efficacy of methylphenidate as a cessation aid and that nicotine serves to reduce ADHD symptoms (e.g., self-medication; van Amsterdam et al., 2018). This conclusion reconciles the above findings that when people who smoke do not have ADHD or when those treated with methylphenidate have never smoked, methylphenidate does not alter smoking behavior. However, why acute methylphenidate increases smoking in people who smoke both with and without ADHD is unclear. Perhaps the onset of pharmacotherapy, where acute drug effects are observed before chronic effects of long-term treatment, may confer additional nicotine use vulnerability in people with ADHD that smoke. This possibility should be carefully considered in future research.

The summarized neurochemical studies suggest that nicotine and methylphenidate have a combinatory effect on dopamine concentrations (Gerasimov et al., 2000) and receptors in the nucleus accumbens (Wheeler et al., 2013). Further that these neurochemical alterations have downstream influences on behavior that may be important for later co-use liability. A neglected but promising area of future research is the examination of nicotine and methylphenidate interactions as it relates to nicotinic receptors. Like amphetamine, methylphenidate behavioral sensitization is thought to be at least in part controlled by nAChRs. That is, treatment with various nAChR antagonists attenuates the development of behavioral sensitization to the locomotor activating and stereotypy-inducing effects of methylphenidate (Wooters and Bardo, 2009). Thus, methylphenidate-evoked behavioral and neurochemical sensitization would likely also be altered by nAChR agonists such as nicotine. Knowledge of receptor mechanisms involved in methylphenidate-nicotine co-use liability may provide insights into effective treatments for individuals exhibiting problematic poly-substance use involving these drugs.

Given the sparse methylphenidate and nicotine interaction research, there are numerous gaps that emerge from the present review in addition to those already mentioned in this section. First, there is a surprising

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lack of preclinical research examining how methylphenidate alters nicotine self-administration and vice versa, with only a single study (Wooters et al., 2008). Additional research examining chronic exposure paradigms consistent with treatment for ADHD may be of interest. While two studies examined conditioned drug reward interactions between methylphenidate and nicotine, no published study has examined drug reward or reward-enhancement interactions. Such a gap may prompt ICSS studies to determine how prior or acute methylphenidate exposure alters the reward threshold decreasing effects of nicotine and vice versa. Like nicotine, methylphenidate also decreases ICSS reward-thresholds (Ide et al., 2018), so nicotine and methylphenidate would likely interact to alter drug reward.

4. Bupropion and nicotine

Bupropion is also known as prescription psychostimulant Zyban™ and Wellbutrin™. In addition to bupropion's anti-depressant effects (Patel et al., 2016), bupropion is used for smoking cessation (Richmond and Zwar, 2003) and as an off-label ADHD medication (Paterson, 2009). Bupropion and its role in smoking cessation has been reviewed extensively elsewhere (for reviews, see Lindson et al., 2019; Mooney and Sofuoglu, 2006; Patel et al., 2016; Paterson, 2009; Richmond and Zwar, 2003; Wilkes, 2008). Thus, we point the reader to these reviews and will only discuss this literature here as it directly relates to the primary goal of this review.

4.1. Primary reinforcement

Briefly, cessation and abstinence studies in humans have found that bupropion acts as an effective smoking cessation aid in both individuals with or without ADHD (Hayford et al., 1999; Hurt et al., 1997; Durcan et al., 2002; Gonzales, 2002; Shiffman et al., 2000; Verbeeck et al., 2017). Bupropion appears to do so, at least in part, by mitigating adverse effects typically induced by nicotine abstinence. For example, bupropion has been found to reduce cigarette craving (Durcan et al., 2002), ameliorate abstinence-related cognitive deficits (Perkins et al., 2013), and blunt negative affect during abstinence and reported satisfaction of cigarettes during reinstigation of smoking after a period of abstinence (West et al., 2008). In preclinical studies, bupropion pre-treatment also attenuated a conditioned place aversion to a context associated with mecamylamine-induced nicotine withdrawal (Malin et al., 2006) suggesting that aversive effects of nicotine withdrawal were also reduced by bupropion in rats. Chronic bupropion also diminished nicotine withdrawal associated increases in ICSS reward thresholds in rats. Further, bupropion attenuated physical signs of nicotine withdrawal such as anhedonia, chewing behavior, and headshakes (Paterson et al., 2007).

Bupropion has also increased nicotine intake under some circumstances. One study found that acute bupropion increased the number of cigarettes smoked *ad libitum* compared to placebo (Cousins et al., 2001). Conflicting with the above described human findings, daily pre-session administration of 30 mg/kg bupropion in adult rats tends to increase nicotine self-administration (Shoaib et al., 2003; Stairs and Dworkin, 2008). Notably, Shoaib et al. (2003) found that while bupropion tended to increase overall self-administration at 0.01 and 0.09 mg/kg/infusion nicotine, the increase was only significant for rats in the high dose nicotine group. Additionally, low doses of acutely administered bupropion (9 and 15 mg/kg) have either increased (Rauhut et al., 2003) or left nicotine self-administration unchanged (10 mg/kg; Stairs and Dworkin, 2008).

In contrast, high doses (30–78 mg/kg) tended to decrease nicotine self-administration (Bruijnzeel and Markou, 2003; Kazan and Charntikov, 2019; Rauhut et al., 2003). Kazan and Charntikov (2019) found that if baseline nicotine consumption was higher, the magnitude of the bupropion-evoked decrease in nicotine self-administration was greater. In contrast to the prior studies, Stairs and Dworkin (2008) found that 56 mg/kg bupropion did not significantly decrease nicotine self-administration. However, this dose did produce a non-significant decrease in nicotine self-administration consistent with the aforementioned prior high dose bupropion studies. Interestingly, this study also found that bupropion decreased food-maintained responding in food-restricted rats (thus baseline response rates were high) but increased food-maintained responding in satiated rats where baseline response rates were lower and more comparable to nicotine-maintained responding (Stairs and Dworkin, 2008). Thus, the baseline-dependent effects of bupropion on nicotine self-administration reported in Kazan and Charntikov (2019) could be due to the general rate-dependent effects of bupropion on operant responding.

Conflicting results have also been identified with short versus long access self-administration tasks. While all self-administration studies we have reviewed so far were "short-access," or standard one to two-hour sessions, there are also "long-access" variations where sessions are six or more hours. Long-access sessions are thought to lead to faster development of dependence-like behaviors in rodents that may better simulate some aspects of human drug use (Allain and Samaha, 2019; Knackstedt et al., 2010). Unlike the short-access studies previously described, moderate to high doses of bupropion (30–60 mg/kg) increased nicotine self-administration in a long-access self--administration study (Kazan et al., 2020). Considering that long-access variations may be more commensurate with the human experience (e.g., having access to cigarettes or vapes during most or all of the day), exploring the root of the discrepancy between short and long-access paradigms may be of interest for determining mechanisms of potential nicotine-prescription psychostimulant co-use liability.

4.2. Drug reward

A moderate to high dose of bupropion alone (up to 60 mg/kg) decreased ICSS thresholds indicating an increase in nicotine reward. However, a low dose of bupropion (5 mg/kg) completely blocked nicotine's ability to reduce reward thresholds in rats – a pattern denoting reduction of nicotine reward (Cryan et al., 2003). Perhaps the reduced rewarding effects of nicotine drive enhanced nicotine taking by requiring more nicotine to achieve the same reinforcing effects. However, this finding is not in line with a study by Paterson et al. that examined the effects of 30 or 60 mg/kg/day bupropion administered via osmotic mini pump on nicotine self-administration and ICSS. Bupropion did not change nicotine self-administration in this study, but did attenuate the ICSS-threshold reducing effects of self-administered nicotine (Paterson et al., 2008). It appears that bupropion altered the rewarding effects of nicotine without producing comparable alterations in nicotine intake. This pattern of results suggests mechanisms other than bupropion-evoked alteration of nicotine reward are involved in changes in nicotine intake.

4.3. Stimulus effects

One study found that a range of bupropion doses (1, 3, 10, and 30 mg/kg) did not substitute for a low training dose of nicotine (0.2 mg/kg; Shoaib et al., 2003). In other studies, 20–30 mg/kg bupropion fully (Bevins et al., 2006; Charntikov et al., 2014; Wiley et al., 2002; Wilkinson et al., 2010) or partially substituted (Besheer et al., 2004; Wilkinson et al., 2010; Young and Glennon, 2002) for a 0.4–0.6 mg/kg nicotine stimulus, suggesting that higher doses of bupropion exhibited similar stimulus effects to more moderate-to-high nicotine doses. Indeed, in a study where a low dose of 10 mg/kg bupropion was used as the training drug, a high dose of 30 mg/kg bupropion produced less bupropion-appropriate conditioned behavior during substitution testing than the 10 mg/kg training dose (Wilkinson et al., 2009). Likewise, when rats were trained to discriminate 0.2 mg/kg nicotine from saline and later tested for nicotine substitution, 0.3 mg/kg reduced nicotine-appropriate responding relative to 0.2 mg/kg nicotine (Reichel et al., 2007). That is to say, a high dose of bupropion may have

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qualitatively different stimulus effects than lower doses, and likewise for high and low doses of nicotine. These qualitative differences in stimulus effects may explain the divergent patterns of cross-substitution at high versus low drug doses described earlier.

Few studies have examined nicotine substitution for bupropion in drug discrimination tasks. Wilkinson et al. trained rats to discriminate between saline and 10 mg/kg bupropion. During substitution testing, a very low nicotine dose (0.05 mg/kg) substituted fully for 10 mg/kg bupropion. That is, 0.05 mg/kg nicotine produced bupropion-appropriate responding similar to that produced by the original bupropion training dose (Wilkinson et al., 2009). In a recent drug-drug discrimination study in our laboratory, rats were trained to discriminate between 0.4 mg/kg nicotine and 10 or 20 mg/kg bupropion. This study by Moran et al. (2022) found that rats quickly and robustly discriminated between nicotine and 10 mg/kg bupropion. Rats also acquired the discrimination between nicotine and 20 mg/kg bupropion stimulus, but much more slowly and less robustly (Moran et al., 2022), which suggests that nicotine and 20 mg/kg bupropion exhibit more similar stimulus effects than nicotine and a lower 10 mg/kg bupropion dose.

When the interaction between bupropion and nicotine has been examined in substitution tests, low bupropion doses (0.1–10 mg/kg) consistently did not alter or block nicotine-appropriate responding (Shoaib et al., 2003; Wiley et al., 2002; Young and Glennon, 2002). Thus, the fact that bupropion increased nicotine self-administration in rodents under some circumstances may not be due to alteration of the stimulus effects of nicotine.

4.4. Locomotor studies

A study by Wilkinson et al. (2006) found that chronic pre-exposure to 0.4 mg/kg nicotine enhanced the locomotor stimulatory effects of 30 mg/kg, but not 20 mg/kg bupropion in locomotor chambers. Acute bupropion treatment also enhanced nicotine-evoked locomotor activity testing (Slemmer et al., 2000). In a later study, 0.4 mg/kg nicotine delivered 20 min following an acute 30 mg/kg bupropion injection enhanced bupropion-evoked locomotor activity (Sidhpura et al., 2007).

4.5. Neurochemical interactions

Neurochemically, a large body of research suggests that bupropion serves as a noncompetitive nAChR antagonist at α4β2, α3β2, and α7 subtypes, in addition to its action as a dopamine and norepinephrine reuptake inhibitor (Arias, 2009; Slemmer et al., 2000). $^{86}Rb^{+}$ efflux is an *in vitro* measure of activity through nAChR channels that can be used to identify substances acting at nAChRs; efflux was increased by nAChRs agonists and decreased by antagonists (Kassner et al., 2022). In one study, rats that were administered 30 mg/kg bupropion or vehicle were sacrificed and synaptosomes (isolated synaptic terminals) from the frontal cortex, hippocampus, striatum, and thalamus were isolated. Synaptosomes from rats that were administered bupropion showed greater *in vitro* nicotine-evoked $^{86}Rb^{+}$ efflux, suggesting an nAChR agonist effect of bupropion (Vann et al., 2006).

Bupropion treatment reduced nicotine-evoked dopamine release in *in-vitro* striatal brain slices, suggesting nAChR antagonist effects (Sidhpura et al., 2007). *In vivo*, acutely administered nicotine enhanced bupropion-evoked dopamine overflow in an additive fashion (Sidhpura et al., 2007). In rats that underwent abstinence-related nicotine withdrawal, bupropion enhanced dopamine overflow during the withdrawal period as measured via microdialysis in the nucleus accumbens shell. However, bupropion also did so in saline-exposed controls, so this effect of bupropion was unrelated to its interaction with nicotine (Paterson et al., 2007). Even non-specific enhancement of dopamine levels could potentially be responsible for the attenuating effects of bupropion on typical anhedonia and general adverse effects associated with nicotine withdrawal mentioned earlier in this review.

4.6. Conclusions

The research reviewed above (Section 4) suggests that the moderate efficacy of bupropion as a cessation aid may be rooted in amelioration of the adverse effects of nicotine withdrawal. This occurs in both human and animal models, such that bupropion blunts physical withdrawal symptoms during abstinence in rodents and cognitive deficits associated with nicotine abstinence. While chronic bupropion administration in humans appears to decrease nicotine intake consistent with its use as a smoking cessation drug, acute bupropion increased human smoking. This finding appears consistent with patterns observed in the Amphetamine and Nicotine and Methylphenidate and Nicotine sections of this report; thus, like other prescription psychostimulants reviewed here, bupropion appears to increase nicotine use liability under acute circumstances and mitigate nicotine use liability under chronic conditions. The root of this discrepancy, to our knowledge, has not been explored.

In preclinical studies, bupropion exhibits a different pattern of mixed effects on nicotine self-administration. Kazan et al. (2020) identified that high-dose bupropion increased nicotine self-administration in their long-access study, while short-access studies reviewed here consistently found high dose bupropion to decrease nicotine self-administration. To our knowledge, there is only one long-access study examining the impacts of prescription psychostimulants on nicotine self-administration. This gap may highlight an interesting area for future research, particularly considering our earlier point that long-access self-administration may better parallel the human condition (cf. Allain and Samaha, 2019; Knackstedt et al., 2010).

Bupropion impacts on nicotine self-administration are also mixed by dose, such that low bupropion doses appear to increase nicotine self-administration and vice versa for high doses. The cause of this bidirectional dose-dependency is unclear. One potential reason is the divergent impacts of high and low dose bupropion on nicotine reward, where one ICSS study found that high doses of bupropion heightened nicotine reward, whereas low doses reduced nicotine reward (Cryan et al., 2003). That reduction in nicotine reward could be responsible for increasing nicotine intake by requiring more drugs to produce the same rewarding effect. Notably, this was conflicting with one study examining continuous bupropion administration where 30–60 mg/kg/day blunted nicotine reward without altering nicotine intake (Paterson et al., 2008). Studies exploring the root of the discrepancy between continuously infused and acute bupropion may be informative for determining effective formulations for cessation.

Some research reviewed here may also suggest that the divergent stimulus effects of low and high dose bupropion may play a role in dose-dependent alterations in nicotine self-administration. That is, high doses of bupropion may better substitute for nicotine thus blunting nicotine intake, while low doses do not substitute as well.

The vast majority of research examining bupropion and nicotine interactions has focused on nicotine intake in the form of cessation or self-administration studies, stimulus effect substitution, and adverse effects of nicotine withdrawal. Some notable gaps that we have not yet mentioned exist in the exploration of how nicotine and bupropion interact to alter conditioned reward and the ability of nicotine and bupropion to alter the reinforcing efficacy of other non-drug rewards. For example, how bupropion alters the ability of nicotine to produce a preference to a nicotine-associated context might be of interest. Likewise, considering the import of reward-enhancement in nicotine self-administration, understanding how bupropion alters this important use liability effect of nicotine could be of import for understanding bupropion alterations in nicotine intake.

5. Putting it all together: concluding remarks and future research

While we have reflected on gaps and future directions in the previous sections, some themes that emerge throughout the body of this review

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warrant further discussion. Amphetamine and methylphenidate clearly impact nicotine use liability across an array of doses and use liability tasks. However, research with bupropion is mixed with low to moderate doses increasing nicotine use liability on a variety of tasks, and high doses not changing or decreasing use liability.

This review reveals a great lack of research examining female rats, such that only ~10% of the rodent studies reviewed here included females. An issue that is all-to-common with virtually every misused substance (Bevins and Charntikov, 2015; Killien et al., 2000). This gap in research leaves us knowing very little in how nicotine interacts with psychostimulants in women or female animals, which is particularly troubling given enhanced nicotine use vulnerability in women (Greaves and Hemsing, 2009; Ortner et al., 2002) and consistently higher rates of amphetamine and other psychostimulant addiction amongst women (Rungnirundorn et al., 2017). The human research in this report generally included men and women, but few were powered to robustly assess sex differences. Of the few preclinical studies that did examine sex as a biological variable, all examined amphetamine or bupropion. Highlighting our concern, each of the preclinical studies powered to assess sex differences found greater effects in women or female rodents (Collins et al., 2004; Íbias and Nazarian, 2020; McNealy et al., 2022, 2021; Zakiniaeiz et al., 2019). This work is consistent with females and human women being more sensitive to most behavioral effects of psychostimulants (Becker and Koob, 2016; Camp and Robinson, 1988; Milesi-Hallé et al., 2007). No preclinical study mentioned here examining methylphenidate utilized female rats. The literature being devoid of studies examining sex or gender differences leaves limitless possibilities for future research. For example, how nicotine might impact amphetamine self-administration or place conditioning differentially between the sexes would be of interest and of importance for ADHD-pharmacotherapy guidance.

Across all the prescription psychostimulants reviewed herein aside from methylphenidate, consideration of ADHD diagnosis or symptoms in relation to observed increases in smoking is lacking. In fact, most human research in this area lists any psychiatric diagnosis, including ADHD, as exclusionary criterion (e.g., Alsene et al., 2005; Henningfield and Griffiths, 1981). It is well documented that prescription stimulants evoke lower misuse liability and produce different drug effects in ADHD and non-ADHD individuals (Lakhan and Kirchgessner, 2012). Further, individuals with ADHD smoke at 2–3 times higher rates than individuals without ADHD suggesting altered nicotine use liability at baseline (van Amsterdam et al., 2018). Preclinical researchers examining nicotine-psychostimulant interactions could take advantage of robust animal models of ADHD such as the spontaneous hypertensive rat (Cho et al., 2014; Sanabria and Killeen, 2008). Using such models could account for ADHD-like symptoms in animal research to determine whether co-use liability effects of nicotine and prescription treatments for ADHD vary by the presence or severity of ADHD-like symptoms.

Another interesting discrepancy revealed by this review was the opposing findings regarding order of drug exposure between methylphenidate and amphetamine. Even with the limited research, interaction research with methylphenidate and nicotine are generally in accordance with "gateway" models of substance use suggesting that nicotine produces neurobiological alterations that enhance vulnerability for future substance use (Levine et al., 2011). That is, methylphenidate did not enhance smoking unless there was an established smoking history (Bron et al., 2013) – nicotine had to be experienced before methylphenidate. Further, on a number of preclinical behavioral tasks, nicotine-use liability measures were not increased with prior exposure to methylphenidate (e.g., Justo et al., 2010). In contrast, methylphenidate use liability measures were increased by prior exposure to nicotine (e.g., Wooters et al., 2008). The alignment of these findings with prior cocaine research (discussed in the Introduction) makes sense considering the foundational exposure pattern research with nicotine has largely focused on cocaine (Kandel and Kandel, 2014; Levine et al., 2011). Cocaine and methylphenidate share a mechanism of action as dopamine transporter inhibitors, which then causes an increase in extracellular dopamine (Rudnick and Clark, 1993). Thus, we may expect similar findings between methylphenidate and cocaine. For readers interested in making comparisons between illicit and prescription psychostimulants, we point them to the existing body of reviews describing the interaction of nicotine with illicit psychostimulants (Crummy et al., 2020; Cross et al., 2017; Kohut, 2017).

Future research may also consider exploring pharmacokinetic effects when examining nicotine interactions with psychostimulants. All animal research in the present report used injected/intravenous prescription psychostimulant compounds and all but one study used injected/intravenous nicotine (cf. Bruijnzeel et al., 2011). Further, all human research used oral formulations for psychostimulant administration. However, individuals who misuse amphetamine, methylphenidate, and bupropion also consume these drugs via insufflation or injection (Farquhar et al., 2002; Lewis et al., 2014). Pharmacokinetic changes as a result of these divergent routes of administration almost certainly influence subjective drug effects (e.g., Lile et al., 2011). Thus, perhaps results would diverge from those synthesized here with differing routes of administration.

The research with amphetamine discussed in this report suggests an opposite predominate tested pattern of exposure. Only two papers summarized in this review examined the effects of amphetamine exposure on nicotine-related outcomes, both of which found effects divergent from nicotine pre-exposure (McNealy et al., 2022; Santos et al., 2009). The original research characterizing drug use trajectories did not examine any type of amphetamine in neither pre-clinical or epidemiological studies examining patterns of drug use and concordant use liability effects (Degenhardt et al., 2010; Kandel and Kandel, 2015). Further, amphetamine's mechanism of action is disparate from that of cocaine and methylphenidate. Amphetamine works by binding to the dopamine transporter, thereby increasing dopamine by transporter-mediated exchange (Rudnick and Clark, 1993). We suggest that this review reveals that research design has been biased in the direction of nicotine pre-exposure, perhaps due to prior research supposing nicotine as an antecedent to other psychostimulant use. Thus, there is a lack of research assessing amphetamine pre-exposure effects. This bias is unfortunate given that amphetamine-containing drugs can be, and often are, prescribed as early as age six (Heal et al., 2013). Future research should focus on testing how amphetamine-containing drugs, and prescription psychostimulant drugs more generally, fit within current gateway models of substance use. This includes epidemiological studies examining progression of substance use, in addition to preclinical research varying order of drug exposure or correcting the current research bias by examining amphetamine or methylphenidate's effects on nicotine-related outcomes.

Future research may also consider exploring atomoxetine interactions with nicotine. Atomoxetine is the active component of Strattera™, a non-stimulant alternative to other ADHD pharmacotherapies typically prescribed to individuals with ADHD who have comorbid mental or physical health conditions that contraindicate stimulant use (e.g., insomnia, tic disorders; Yu et al., 2016). Unlike amphetamine and methylphenidate, atomoxetine administration does not increase smoking behavior (Vansickel et al., 2007). In fact, evidence from animal studies suggests that atomoxetine may attenuate the effects of nicotine (Reichel et al., 2007; Gould et al., 2005, Davis and Gould, 2007). Due to the contrasting effects of atomoxetine with bupropion, amphetamine, and methylphenidate, expanding the small literature examining nicotine and atomoxetine interactions may help in providing clinical guidance for treatment of ADHD in people who smoke and increase the understanding on the mechanisms of these differences between substances.

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CRediT authorship contribution statement

Kathleen R. McNealy: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Lucas Weyrich:** Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Rick A. Bevins:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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