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The Impact of Cigarette Smoking on Stimulant Addiction

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Abstract

Objectives—Stimulant users smoke cigarettes at high rates however, little is known about the relationship between tobacco and stimulants.

Methods—Our goal in this paper is to synthesize a growing literature on the role of cigarette smoking in stimulant addiction.

Results—Early nicotine exposure may influence the development of stimulant addiction. Preclinical and clinical studies suggest a faciliatory role of nicotinic agonists for stimulant addiction. Smoking appears to be associated with more severe stimulant use and poorer treatment outcomes.

Conclusions—It is important to assess smoking and smoking-related variables within stimulant research studies to more fully understand the co-morbidity. Integrating smoking cessation into stimulant treatment may improve both nicotine and stimulant treatment outcomes.

Keywords

Stimulant related-disorders; cocaine; amphetamine; methamphetamine; smoking; cigarettes; nicotine; treatment

Introduction

Currently in the United States, 2.4 million people ages 12 and up use cocaine and 1.1 million use other stimulants including 512,000 who use methamphetamine (1,2). Compared to the general population, cocaine users report extremely high rates of cigarette smoking (~70–80% versus 22%) (3–8) and nicotine dependence (~50% versus 13%) (9). Methamphetamine users report even higher rates of smoking [87–92% (10–14)]. Little is known about the nature of this high co-morbidity or its implications for treatment outcomes.

Cigarette smoking has been implicated as a “gateway” to other drugs of abuse. The mechanism of gateway effects of smoking has been assumed to involve psychosocial processes (15–18). However, more recent studies are uncovering the neurobiological mechanisms by which smoking may facilitate initiation of stimulant addiction (19–22). A clearer understanding of the mechanisms linking smoking and stimulant use may lead to better insight into the development of stimulant addiction and new treatment approaches.

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Our goal in this paper is to synthesize a growing literature on the role of cigarette smoking in stimulant addiction. We will briefly overview neurobiological processes mediating the rewarding effects of cigarette smoking and stimulant use, examine the literature on the impact of smoking and nicotine exposure on stimulant addiction, and review treatment approaches for stimulant and nicotine dependence

2. Neurobiology

2.1. Stimulant Effects

The main components of the brain reward circuit are thought to include the mesocorticolimbic dopamine system which originates from the ventral tegmental area (VTA) of the midbrain and targets a number of limbic and cortical structures, including the nucleus accumbens (NAc) and prefrontal cortex (23). Dopamine release, especially in the NAc, mediates the rewarding effects of stimulants which either facilitate release (e.g., amphetamines) or block uptake (e.g., cocaine) of dopamine (24).

2.2. Nicotine's Effects

Nicotine is the main addictive chemical in tobacco smoke. Nicotine's effects are mediated by the nicotinic type acetylcholine receptors (nAChR). nAChR receptors are ligand-gated ion channels (25,26) and are pentameric combinations of 12 subunits (α2-α10 and β2-β4). Most nicotinic receptors contain α4, β2 or α7 subunits (25). Beta2 containing receptors are critical for addictive as well as cognitive performance enhancing properties of nicotine (27,28).

Within the brain reward circuit, nicotinic cholinergic and mesolimbic dopaminergic systems interact closely especially in the VTA and NAc. In the VTA, β2 nicotinic receptors increase the activity of dopaminergic cells and increase dopamine release in terminal regions including NAc and prefrontal cortex (27). In addition, activation of α7-nicotinic receptors, by increasing glutamate release on dopamine neurons in the VTA, may also induce dopamine release in the NAc (29). The resultant dopamine release in NAc is critical for the rewarding and addictive effects of nicotine.

To summarize, the final common pathway for nicotine and stimulant reward is dopamine release in NAc. While stimulants enhance synaptic dopamine levels by inhibiting its reuptake or increasing release, nicotine stimulates nAChR in the VTA which increases dopaminergic activity.

3. Clinical Characteristics of Smoking and Non-Smoking Stimulant Uses

3.1. Demographic and Drug Use Variable Differences

Cocaine users who smoke are younger, less educated (5), and have more legal problems (30) than nonsmokers. Co-morbid smoking is related to earlier onset (30,31), more frequent use (30), and greater quantity use (5) of cocaine. Smokers spend more money on cocaine (30) and report more frequent drug-related problems (32). Although differences have not been observed using the Addiction Severity Index (ASI, (33)) (6,30), most studies suggest that co-morbid nicotine and cocaine use is associated with more severe drug use and drug-related problems.

Studies examining the relationship between stimulant use and nicotine dependence have been mixed. Meier et al (32) found a moderate positive correlation between nicotine dependence and ASI Drug Severity in crack cocaine patients. Conversely, Patkar et al (34) found that nicotine dependence was only associated with the ASI Medical Composite scores for cocaine-dependent adults. Moreover, this study (34) found that higher levels of nicotine dependence were associated with more positive cocaine drug screens in patients who were abstinent from

cocaine at the start of treatment suggesting that co-morbid nicotine dependence may increase risk of relapse to cocaine.

A review of cocaine treatment outcomes found that several demographic and drug use variables are related to poorer outcomes (35). Cocaine users who smoke cigarettes report longer duration and more frequent use of cocaine, variables that have been linked to poorer treatment outcomes (36), so nicotine dependent cocaine users may be a more treatment-resistant group than nonsmoking cocaine users.

3.2. Cognitive effects of smoking in stimulant users

Cocaine and amphetamine users show cognitive deficits in a variety of domains including decision-making and response inhibition (37–40) and greater cognitive impairment may predict cocaine treatment drop-out rates (41,42). A recent review suggested that impairments caused by cocaine (e.g., short-term memory, attention) may be accentuated by use of other drugs like alcohol (43); however, there is no information about the effects of concurrent nicotine use. Nicotine use has been associated with greater severity of cocaine use which is associated with greater neuropsychological impairments (43). However, unlike most drugs of abuse, nicotine may improve some aspects of cognitive functioning like memory and attention (44). It is unclear whether nicotine would have a harmful or a protective effect on the cognition of stimulant users as there has been little empirical research examining this question.

A recent study found that methadone-maintained smokers did more poorly than control smokers and nonsmokers on a gambling task (45). Thirty to forty percent of the sample reported current cocaine use and cocaine use had no significant effect on gambling task performance. Although this study provided evidence only for increased deficits for co-morbid methadone and nicotine use, more research is needed to examine the impact of smoking on cognitive functioning of cocaine and amphetamine users.

3.3. Health impact of smoking in stimulant users

Approximately 440,000 people in the United States and 4 million people worldwide die each year from smoking-attributable medical illnesses (e.g., lung cancer, cardiovascular disease) (46). Stimulant addiction is also associated with significant morbidity and mortality rates (47–49) and heavier use of stimulants has been associated with greater health problems (50). Adults who use both cocaine and tobacco report more medical symptoms including respiratory and nose-throat symptoms (6,51) and more general systems problems (6) than non-smoking cocaine users. In addition, substance abuse smoker are more likely than other smokers to die of cigarette smoking-related illnesses (52,53). The additional medical problems experienced by smoking stimulant users could be a result of the additive effect of using two harmful substances or a result of greater stimulant use, a variable associated with co-morbid stimulant and nicotine use. Improving treatments for smoking stimulant users may improve their quality and length of life and reduce the health costs faced by individuals and society.

Overall, stimulant users who smoke appear to have more severe substance use disorders and drug-related health problems. The impact of cigarette smoking on the cognitive function of stimulant users is unclear as it has not been examined.

4. Role of cigarette smoking in development of cocaine addiction

Cigarette smoking generally precedes and may be a “gateway” to stimulant use. In a series of studies, Slotkin et al have shown that exposure of adolescent rats to nicotine levels (~25 ng/ml) that produce plasma nicotine levels similar to those in human smokers produced nAChR upregulation accompanied by decreased cholinergic synaptic function (54–56). These changes were much greater and persistent in adolescent rats, compared to adult rats supporting greater

vulnerability to nicotine effects during adolescence (57). In other studies, nicotine exposure during adolescence enhanced stimulant-induced locomotor activity but attenuated sensitivity to stimulants in conditioned place preference and drug discrimination paradigms (21,22,58). In a recent study, McQuown and colleagues demonstrated that adolescent rat exposure to low dose nicotine treatment facilitated acquisition of cocaine self-administration (59,60). These adolescent nicotine studies demonstrated that exposure to nicotine during adolescence may lead to long-term changes in cholinergic function. Cholinergic interneurons, especially those in the NAc, integrate the cortical and subcortical information related to reward and complement the dopaminergic system in reward processing (61). Thus, changes in cholinergic function may affect the reward pathways more susceptible for stimulant addiction.

Recently, 202 people who had tried cocaine on at least one occasion were studied prospectively from childhood into adulthood (61). After controlling for covariates like attention deficit-hyperactivity disorder (ADHD), cigarette smoking as a teenager was strongly correlated with becoming addicted to cocaine following an initial exposure to cocaine. Those who smoked reported greater “wanting” and “liking” of cocaine following first cocaine use. These findings complement studies supporting the gateway effects of nicotine (15–18) and suggest that early nicotine exposure may increase vulnerability to become addicted to stimulants.

To summarize, the adolescent nicotine studies in rodents demonstrated that exposure to nicotine during adolescence may lead to long-term changes in cholinergic function. Both preclinical and clinical studies suggest that these changes may affect the reward pathways more susceptible for stimulant addiction.

5. Nicotine and Stimulant Interactions

5.1. Preclinical Studies

Many preclinical studies have demonstrated that the cholinergic system modulates the rewarding effects of stimulants. Mice with ablated cholinergic neurons in the NAc as a result of immune toxin against the cholinergic neurons, show greater sensitivity and preference to cocaine (62). In contrast, enhancement of the cholinergic transmission by treatment with cholinesterase inhibitor donepezil reduced locomotor sensitivity and preference to cocaine in mice (63). In rats, donezepil, as well as nicotine, treatment also reduced methamphetamine-seeking behavior in rats (64). In a recent study, Crespo et al (65) have shown that both nicotinic and muscarinic receptor activation in the NAc are needed for rats to acquire cocaine self-administration.

In rats, treatment with repeated nicotine administration enhanced cocaine self-administration behavior (66). Interestingly, the nicotinic antagonist mecamylamine reduced, but did not eliminate, the increase in cocaine self-administration behavior after nicotine administration during 6 hour access in rats (67). These findings suggest that nicotinic cholinergic receptors play an important role in the enhancement of cocaine’s reinforcing effects and suggest one potential mechanism related to cocaine addiction for humans.

5.2. Human laboratory findings

Human studies examining the effect of administered nicotine on cocaine variables have suggested that nicotine may increase cravings for cocaine. For example, participants exposed to cocaine-related cues experienced significantly enhanced craving for cocaine when receiving transdermal nicotine patch (TNP) (68). Studies of the subjective effects of cocaine after nicotine administration have been mixed. Occasional users of cocaine (~1.7 days/month, n=7) reported a decrease in the subjective effects (feeling “high” or “stimulated”) of an acute dose of cocaine (0.9 mg/kg) after pretreatment with 14 mg TNP (69). Conversely, heavier users of cocaine (~19 days/month, n=9) did not report a change in the subjective effects of cocaine (15 and 30

mg/kg) after pretreatment with 21 mg TNP (70). Differences in the participants sample and methodology (e.g., cocaine dose) may have contributed to the contrasting results.

To summarize, preclinical and clinical studies generally support a faciliatory role of nicotinic agonists for stimulant addiction, although findings have not been consistent.

6. Treatment Implications and Future Directions

6.1. Treatment of nicotine dependence in stimulant dependent smokers

Although many smokers with substance use disorders report motivation to quit smoking (71, 72), smoking cessation rates are very low (~12%) for smokers in early recovery. Several studies have reported no spontaneous change in smoking or level of nicotine dependence during cocaine treatment (8,73,74) and few treatment programs offer combined stimulant and nicotine treatment. One report found that substance abuse patients can quit at rates comparable to the general population when enrolled in smoking cessation programs (75). There is a great deal of concern that smoking cessation may increase risk of relapse to other substances of abuse (71, 76) although concurrent treatment has not been associated with increased use of drugs (77–82). It should be noted that one large well-controlled study (83) has reported that drinking outcomes may be worse for patients in concurrent alcohol and nicotine treatment.

To summarize, few smokers quit smoking in treatment focused only on use of other drugs. Though mixed, research suggests that concurrent treatment for smoking and other drugs will not harm drug use outcomes. Integrating smoking-specific treatment into treatment for stimulant use may improve both nicotine and stimulant treatment outcomes and reduce relapse rates.

6.2. Conclusions and Future directions

Early exposure to nicotine influences the development of stimulant addiction and smokers with co-morbid drug use have more severe stimulant use and may be more treatment resistant. There are still many unanswered questions regarding the impact of smoking on the course of addiction and treatment of cocaine dependence. Very little research has been conducted on amphetamine use and smoking although the near universality of smoking suggests that this area should receive attention in future research.

Research is being conducted currently on a variety of pharmacological [e.g., (84,85)] and behavioral [e.g., (86,87)] treatments for stimulant addiction. Assessing smoking variables in stimulant research will provide more information about their relationship. In addition, some treatments for stimulant addiction improve smoking cessation outcomes [e.g., contingency management, (88)] and may play an important role in the concurrent treatment of stimulant and nicotine dependence to maximize the efficacy of interventions for this difficult-to-treat population.

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