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A Review of Co-Morbid Tobacco and Cannabis Use Disorders: Possible Mechanisms to Explain High Rates of Co-Use

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Background: Tobacco and cannabis are among the most commonly used psychoactive substances worldwide, and are often used in combination. Evidence suggests that tobacco use contributes to an increased likelihood of becoming cannabis dependent and similarly cannabis use promotes transition to more intensive tobacco use. Further, tobacco use threatens cannabis cessation attempts leading to increased and accelerated relapse rates among cigarette smokers. Given that treatment outcomes are far from satisfactory among individuals engaged in both tobacco and cannabis use highlights the need for further exploration of this highly prevalent co-morbidity.
Objective: Therefore, this review will elucidate putative neurobiological mechanisms responsible for facilitating the link between co-morbid tobacco and cannabis use.
Method: We performed an extensive literature search identifying published studies that examined co-morbid tobacco and cannabis use.
Results: Evidence of both synergistic and compensatory effects of co-morbid tobacco and cannabis use have been identified. Following, co-morbid use of these substances will be discussed within the context of two popular theories of addiction: the addiction vulnerability hypothesis and the gateway hypothesis. Lastly, common route of administration is proposed as a facilitator for co-morbid use.
Conclusions & Scientific Significance: While, only a paucity of treatment studies addressing co-morbid tobacco and cannabis use have been conducted, emerging evidence suggests that simultaneously quitting both tobacco and cannabis may yield benefits at both the psychological and neurobiological level. More research is needed to confirm this intervention strategy and future studies should consider employing prospective systematic designs. (Am J Addict 2015;24:105–116)

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INTRODUCTION

Drug addiction continues to be an important public health problem. Tobacco and cannabis (marijuana) are among the most common psychoactive substances used worldwide[1] and are often used in combination. Cannabis is the most frequently used drug among tobacco users,[2] and similarly, tobacco use often co-occurs among active cannabis users.[3]

While the preference to use multiples substances over a single substance alone is not a novel phenomenon, the neurobiological investigation of drugs that are used concurrently remains a relatively unexplored area in the addiction literature. If certain drugs are used together more frequently than others, it may speak to underlying neurobiological mechanisms that render them more appealing to use in combination versus alone.

Studies report that up to 90% of cannabis users are also tobacco smokers, while rates for co-use of other substances such as alcohol (33.3–45.7%), cocaine (37.5–42.9%), stimulants (30.0–51.7%), and hallucinogens (35.6–41.7%)[4–6] occur at much reduced rates.

This suggests that tobacco and cannabis may possess unique properties that render them more likely to be used together than co-use of other substances, in general.[6,7]

Epidemiological data indicate that co-morbid use has increased throughout the 1990s in Western countries, with an estimated 9.5 million Americans smoking both substances.[8] Chronic tobacco and cannabis use are associated with symptoms of dependence,[9,10] withdrawal,[11,12] and high rates of relapse among those who attempt to quit.[13,14] Furthermore, the use of one substance may hamper the success of quitting the other.[3] Tobacco use has been demonstrated to contribute to an increased number of cannabis dependence symptoms[15,16] and precipitates cannabis relapse.[17] Similarly, cannabis use is associated with tobacco use[18] and nicotine dependence[19] and decreases the likelihood of tobacco cessation.[3,20]

Tobacco smoking is a worldwide epidemic and is the leading cause of preventable morbidity and mortality in the Western world.[21] Its use has been linked to respiratory problems, lung cancer, and heart disease.[22] While research associating chronic cannabis use with these adverse health risks are less clear.[23,24] The full breadth of cannabis' health-related effects are far from clear and remain under investigation.[23] Chronic cannabis consumption may also lead to unfavorable effects on academic performance, employment, interpersonal relationships, and mental health.[25–27] Taken together, further research targeted at treatment development is critical as tobacco and cannabis use are serious threats to current and future world health.

In this review we aim to first discuss patterns of tobacco and cannabis use, followed by their neurobiological profiles. Potential theories and mechanisms to explain the robust relatedness of tobacco and cannabis co-use are then proposed. This includes synergistic and compensatory effects of co-use, as well as theories such as the addiction vulnerability hypothesis (AVH) and the gateway theory. A common route of administration (ROA) is then proposed as a facilitator of continued co-morbid use.

Second, we review treatment studies addressing co-morbid tobacco and cannabis use in an attempt to corroborate and support the theories presented. Lastly, we integrate current available research and evidence in order to provide clinicians with a more concrete treatment approach of how to treat individuals misusing tobacco and cannabis.

While previous reviews in this area have been published,[6,28] here we approach the topic with a strong emphasis on neurobiological factors that facilitate the relationship between tobacco and cannabis co-use. Little scientific information exists on how to best treat co-morbid tobacco and cannabis misuse, and a better neurobiological understanding of this co-morbidity can provide a forum in which to explore unique and efficacious treatment interventions.

METHOD

An extensive literature search through several online databases, including PsychInfo, PubMed, Google Scholar was conducted to identify studies that examined tobacco and cannabis co-use. The key words used were cannabis, marijuana or marihuana or tetra-hydrocannabinol or THC with tobacco or nicotine. The reference lists of these articles were checked for relevant studies in the field that may have been overlooked by the initial literature search. The search included both animal and human/clinical studies.

PATTERNS OF CO-MORBID USE

Simultaneous use of tobacco and cannabis refers to the use of these substances at the same time.[29] The main route of simultaneous administration of tobacco and cannabis is through smoking. Cannabis is most often loosely rolled into cigarettes known as joints. Tobacco is commonly added to joints, a process referred to as mulling.[30] Up to one half of a cigarette can be added to a joint to aid in burning efficiency. Akre et al.[30] conducted a qualitative study that examined how young users consume cannabis and the beliefs that accompany such use. They reported that 15–24 year olds combine tobacco along with their cannabis, as pure cannabis joints are too strong and expensive. Recently, blunts have been gaining popularity, especially among urban youth in the United States.[31] Blunts are hollowed out cigars, in which the majority of tobacco has been replaced with cannabis. The precise ratio of cannabis to tobacco varies with the preparation. One blunt is the equivalent of up to five cannabis joints in quantity[32,33] and is typically shared by a small group of users. The emergent blunts subculture promotes a "chasing" ritual, that is, smoking tobacco (cigarillos, cigarettes, or cigars) immediately following cannabis.[34]

Simultaneous use is in contrast to *concurrent* use, which implies that one uses both tobacco and cannabis, but not necessarily on the same occasion. Homotypic co-morbidity refers to the co-occurrence of mental disorders within a diagnostic grouping,[35] thus the term *co-morbid* will be used throughout this review as an umbrella term that encompasses both simultaneous and concurrent use. Research suggests that simultaneous users consume greater quantities of cannabis,[36] and experience more severe psychosocial consequences compared to single drug users.[37]

NEUROBIOLOGY OF TOBACCO AND CANNABIS ADDICTION

Neurobiology of Tobacco Addiction

Nicotine is the active ingredient that facilitates the addictive process in tobacco[38] and binds to ubiquitously distributed nicotinic acetylcholine receptors (nAChRs). There are two families of nAChRs: high-affinity receptors (which contain the β2 subunit) and low-affinity receptors (which contain the α7 subunit). nAChRs are situated on presynaptic and postsynaptic[39] terminals and act as a modulator of neurotransmitter release.[40]

Nicotine is one of the most potent stimulants of the midbrain dopamine reward pathway. Nicotine produces its rewarding effects, both directly and indirectly, by activating nAChRs on neurons in the mesolimbic dopaminergic system.[41,42] Dopamine release is facilitated by nicotine-mediated increases in glutamate release and by inhibition of GABA release. Effects of nicotine are amplified by its short half-life duration of about one to two hours,[43] resulting in continued consumption of nicotine at high frequency intervals.

Neurobiology of Cannabis Addiction

δ-9-tetrahydrocannabinol (THC) is the main psychoactive constituent of cannabis and acts as a partial agonist at

cannabinoid Type-1 receptors (CB1Rs).[44,45] One important role of the CB1R is to modulate neurotransmitter release in a manner that maintains homeostasis by preventing excessive neuronal activity in the central nervous system.[46] CB1Rs are highly concentrated in brain regions implicated in cognition, namely the hippocampus, prefrontal cortex (PFC), anterior cingulate cortex (ACC), basal ganglia, cerebellum, and cortex.

Psychoactive cannabinoids increase the activity of mesolimbic dopaminergic neurons that terminate in the striatum and PFC via CB1R activation,[47–50] which mediates the rewarding and motivational properties of cannabis.[51,52] Given that CB1Rs are not expressed on DA neurons, this effect is not a result of direct activation of DA neurons, but due to GABAergic interneuron activity.[53,54]

MECHANISMS UNDERLYING CANNABIS AND TOBACCO CO-MORBIDITY

In the following sections, we review evidence on the putative mechanisms underlying co-morbid use of tobacco and cannabis. Studies examining associations between THC and nicotine are increasingly being evaluated in preclinical studies, while research in human populations remains limited. See Table 1 for a description of clinical studies examining the tobacco-cannabis link.

Synergistic Effects

Research suggests that there is a relationship between nicotine and CB1Rs and between cannabis and nAChRs. For example, the CB1R antagonist rimonabant (SR141716) and AM251 dose-dependently attenuate nicotine self-administration[55–57] and block nicotine conditioned place preference (CPP) in rats.[58] In line with these results, CB1R knockout mice failed to develop CPP to nicotine as compared to wild-type mice suggesting an attenuation of the reinforcing effects of nicotine.[59] Contrasting findings have also been reported showing no difference in nicotine self-administration as a function of CB1R knockouts.[60] Conflicting findings may be a result of different mechanisms that subserve self-administration versus CPP behaviours.[61] Taken together, these studies demonstrate a role of the endocannabinoid system in mediating nicotine's rewarding properties.[62]

There seems to be fewer such studies addressing the involvement of the nicotinic system in the reinforcing properties of THC. One such study reported that rats with prior exposure to THC were more likely to self-administer nicotine (94%) versus rats exposed to vehicle only (65%). Another such preclinical study demonstrated that nAChRs modulate the discriminative effects of THC, and that elevations in anandamide levels may be responsible.[63]

There is a paucity of clinical data examining functional interactions between tobacco and cannabis. One theory proposed is that tobacco is added to cannabis to prolong and increase the rewarding effects of cannabis.[64] This tenet was confirmed in a laboratory study by Penetar et al.[65] who demonstrated that pre-treatment with transdermal nicotine increased subjective cannabis ratings of "stimulated" and "high" on a visual analog scale. Moreover, effects were even more pronounced among males.[65] This sex-effect was replicated in another study that showed that men with prior cannabis use experienced greater nicotine reward and nicotine reinforcement.[66] This may in part help to explain higher rates of cannabis use among males than females.

In contrast, other studies have failed to find enhanced reinforcing effects of cannabis mediated by tobacco. Haney et al.[17] observed no additive effect of tobacco on cannabis intoxication relative to those who were only exposed to cannabis. This sample consisted mainly of male participants, so sex was unlikely to explain this effect. In line with these results, a comparison of blunt versus joint smoking on subjective, pharmacokinetic, and physiological effects demonstrated that joints produced greater subjective ratings of cannabis intoxication, strength, and quality compared to blunt smoking.[67] However, methodological issues likely confounded this study, as THC plasma levels were higher among joint users, and are most likely responsible for augmented effects.

This body of research provides preliminary evidence that a primed endocannabinoid system may contribute to higher addictive potential of nicotine. However, support for this mainly comes from animal studies; continued research in clinical samples is clearly needed to iron out between-study inconsistencies. If future studies can support the mediating effects of CB1R in the rewarding effects of nicotine, then CB1R antagonists may offer hope as potential agents for managing nicotine addiction.

Compensatory Effects

Attenuating Adverse Effects

It has been proposed that nicotine and cannabis may be used in combination to attenuate each other's undesirable and/or aversive effects. Withdrawal symptoms, in particular, may be driving the co-morbid use of tobacco and cannabis.

First, the endocannabinoid system has been implicated in the physical dependence syndrome associated with nicotine. For example, acute THC administration in mice lessened somatic symptoms and dysphoria associated with nicotine withdrawal.[68] In another study, rimonabant was shown to abolish anxiolytic effects in mice, but only at low-doses of nicotine. At higher doses of nicotine, rimonabant potentiated anxiety.[69] The latter result was replicated in a similar study that co-treated mice with nicotine and THC in the presence of rimonabant.[62]

Clinical studies further support the involvement of the endocannabinoid and nicotinic systems in the withdrawal syndromes of these agents. Vandrey and colleagues[70] demonstrated that cannabis withdrawal was of equal magnitude and had similar consequences as nicotine withdrawal, but when both substances were ceased simultaneously, withdrawal

TABLE 1. Description of clinical studies examining tobacco-cannabis link

Authors	Objective	Design	Sample	Synergism & Dependence	Withdrawal	Relapse	Cognition
Moore & Budney, 2001	To compare cannabis dependent outpatients who currently smoke tobacco with ex- and never smokers on cannabis indices response to a 14-week treatment program.	Cannabis treatment trial.	Treatment-seeking cannabis dependent adults N = 174	No group differences in severity of cannabis dependence.		Cannabis and tobacco smokers provided about half as many cannabis-negative urines and had fewer weeks of abstinence than former smokers.	
Tullis et al., 2003	To examine whether recent increases in tobacco use among college students are associated with cannabis use.	Self-report survey.	Random sample of university students N = 233	Co-use of tobacco and cannabis increased and prolonged reinforcing effects of cannabis.			Tobacco was used to reverse cannabis' anti-performance effects on cognition.
Penetar et al., 2005	To investigate effects of nicotine, on cannabis-induced intoxication.	Double blind, cross-over study.	Current tobacco and cannabis users N = 20	Pretreatment with nicotine increased cannabis ratings of "stimulated" and "high".			
Agrawal et al., 2008	To examine whether cannabis use prior to age17 is associated with increased likelihood of nicotine dependence.	Population-based cohort.	24–36-year-old twins N = 6257	Early-onset cannabis users are at increased risk for nicotine dependence.			
Vandrey et al., 2008	To compare cannabis, tobacco, and combined cannabis and tobacco withdrawal among users of both substances.	Within-subject, randomized study.	Non-treatment seeking cannabis and tobacco users N = 15		Severity of withdrawal increases when tobacco and cannabis are ceased simultaneously as compared to each substance alone.		
de Dios et al., 2009	To determine the relationship between cigarette smoking status and 12-month and cannabis treatment outcomes.	Community based longitudinal study.	Treatment-seeking adolescents for substance abuse N = 1779			Cigarette smoker had greater rate of cannabis relapse compared to non cigarette smokers and those who quit cigarettes during the study.	
Agrawal et al., 2009	To examine whether regular cigarette smoking is associated with greater cannabis involvement and whether simultaneous use of cannabis and cigarettes is associated with greater negative cannabis-related outcomes.	Data from a larger longitudinal cohort survey analyzed cross-sectionally.	Women N = 3427	Co-users were twice as likely to meet criteria for DSM-IV cannabis abuse. Simultaneous users were 1.6 times more likely to meet criteria for DSM-IV cannabis abuse than co-users.			

(*Continued*)

TABLE 1. Continued

Authors	Objective	Design	Sample	Synergism & Dependence	Withdrawal	Relapse	Cognition
Agrawal, & Lynskey, 2009	To examine whether cannabis use and abuse/dependence were associated with smoked versus smokeless forms of tobacco.	Cross-sectional	epidemiological survey.	Adults who participated in the National Epidemiological Study on Alcohol Related Conditions N = 43 093	Tobacco smoking was associated with a 3.3 and 4.5 times increased risk for cannabis use and abuse/dependence respectively.		
Cooper & Haney, 2009	To directly compare effects of cannabis smoked as blunts (cannabis + tobacco and joints (cannabis alone).	Within-subject, randomized, double-blind, placebo-controlled study.	Cannabis blunt smokers N = 24	Joint users reported greater subjective intoxicating effects of cannabis versus blunt users.			
Perkins et al., 2009	To determine what factors influence initial sensitivity to acute nicotine administration (using different doses of nicotine).	Within-subject design	Young adult nonsmokers N = 131	Prior cannabis use increased sensitivity to the effects of nicotine, in that it was rated more satisfying.			
Levin et al., 2010	To assess cannabis withdrawal and its relationship to relapse.	Cross-scctional retrospective study.	Non- treatment-seeking cannabis-using adults N = 469		48.2% of sample reported using cannabis to relieve cannabis withdrawal. 37.7% increased tobacco use and 10.2% decreased tobacco use.		
Haney et al., 2013 Study 1	To assess factors predicting likelihood and severity of relapse among cannabis users	Data from 5 inpatient lab studies.	Non-treatment-seeking cannabis smokers N = 51		Withdrawal symptoms did not predict the likelihood of relapse.	Cigarette-smoking status was the factor to best predict cannabis relapse.	
Haney et al., 2013 Study 2	To test effects of tobacco cigarette smoking on cannabis relapse using 2 conditions: while smoking tobacco cigarettes as usual and after ≥5 days without cigarettes	Within-subject, counter-balanced design.	Daily cannabis and cigarette smokers N = 15	Tobacco had no effect on cannabis intoxication.	tobacco cigarette smoking did not alter most symptoms of marijuana withdrawal relative to tobacco cessation.	Cigarette smoking did not alter cannabis relapse rates relative to tobacco cessation.	
Hill et al., 2013	To assess the feasibility of a cognitive behavioral therapy (CBT) and transdermal patch nicotine replacement therapy (NRT) to treat co-occurring nicotine and cannabis dependence.	Treatment period of 10 weeks.	Nicotine and cannabis dependent individuals N = 7	While use of cigarettes decreased, no changes in cannabis use were reported.			

was more severe than the additive effect of each substance alone. However, this effect was not very robust and there was great between-subject variability in discomfort ratings across the three abstinence conditions (cigarettes vs. cannabis vs. cigarettes and cannabis). Interestingly, for a subset of participants the dual abstinence condition was associated with less withdrawal and rated as less difficult.[70] The authors proposed that this finding may be a result of smoking-related cues given that both substances are delivered via a common route of administration (ROA). Exposure to drug cues may elicit craving[71] and can lead to more rapid relapse rates;[72] therefore in the absence of such cues, withdrawal may be attenuated. Further exploration of this subset is of interest. Perhaps with a bigger sample size, further characterization of such individuals, including clinical and genetic profiling, may lead to new insights that can be applied to treatment initiatives.

Haney et al.[17] compared non-treatment seeking daily cannabis and cigarette smokers under two conditions: while smoking tobacco cigarettes as usual, and after at least five days of tobacco abstinence. Regardless of state, 87% of their sample relapsed to cannabis. While assessing the phenomenon of cannabis withdrawal and its relationship to cannabis relapse in non-treatment-seeking adults, Levin et al.[73] observed that in a minority of participants (37.7%), tobacco use was increased during quit attempts, often to relieve specific withdrawal symptoms, such as cannabis cravings, sleep problems, and irritability.[73] These studies provide preliminary evidence for the use of tobacco to mitigate symptoms of cannabis withdrawal and cannabis use to attenuate withdrawal associated with tobacco, although findings from clinical studies are equivocal. Future studies should employ laboratory-controlled designs using clinical samples in order to determine the particular withdrawal symptom being targeted by these substances; in turn this will help facilitate treatment options aimed to reverse these specific aversive states.

Cognitive Function

Brain regions involved in the pathophysiology of substance abuse overlap extensively with those involved in cognitive processes, such as the striatum, prefrontal cortex, amygdala, and hippocampus,[74–76] thus circuits within the brain mediating cognitive processes are likely to be involved in the development and progression of addictive disorders.

In general, acute nicotine and cannabis appear to exert opposite effects on cognition in non-psychiatric populations. While nicotine exposure increases arousal and improves attentiveness and cognition,[77] cannabis induces difficulties in concentration and impairs performance on learning and memory tasks.[78,79] To date, only a handful of studies have investigated the effects of both tobacco and cannabis collectively on cognition.

A preclinical study investigated the effects of pre-treating mice with the cannabinoid receptor antagonist AM 251, or the cannabinoid receptor agonist, WIN55 212–2 and evaluated behavior on an elevated maze task.[80] The study revealed that both cannabinoid ligands administered prior to injections of nicotine significantly prevented nicotine-induced memory improvement as compared to nicotine alone.

Jacobsen and colleagues[81] examined the interaction between cannabis use and nicotine withdrawal in a sample of adolescents. The authors found that among cannabis users, nicotine withdrawal elicited poorer verbal delayed recall and greater activation of a network of brain regions, including frontoparietal cortical regions, compared to smokers who only used tobacco. They postulated that cannabis use during adolescence leads to developmental changes in neurocircuitry responsible for cognitive processes, and nicotine use may mask these impairments.

Cannabis users may use tobacco to attenuate cognitive impairment. Perhaps cannabis users use tobacco as a means to neutralize cognitive function to a state of equilibrium. While it is clear that both nicotine and cannabis influence cognition, it remains unclear if these two drugs interact to render some differential effect on cognition than a simple addictive effect of both drugs. Future research in this area is clearly needed.

Addiction Vulnerability Hypothesis (AVH)

The AVH postulates that pre-existing neurobiological factors predispose individuals experimenting with abusive substances to move from recreational use to more chronic consumption.[82,83] Genes encoding neurotransmitters likely play a critical role in addictive behaviours including tobacco and cannabis use disorders. For example, polymorphisms associated with GABA (GABAR2) and dopamine (DRD2, DRD4, and DAT) have been associated with multiple drugs of addiction.[84–87] Such genetic effects may contribute to the phenomenon of co-substance misuse in general.

There is some genetic evidence that exists that pertains specifically to co-morbid tobacco and cannabis use. Early-onset cannabis users have been demonstrated to be at increased risk for nicotine dependence, attributed largely to common genetic vulnerability.[88] Genes coding for the CB1R have been associated with tobacco initiation, as well as dependence and cannabis-related problems.[89,90] Allelic variation within the M5 muscarinic receptor gene has been implicated in the maintenance of tobacco and cannabis misuse.[91]

Further, progression of use to abuse may be a result of an underlying pattern of disinhibitory psychopathology rather than a direct risk.[92] Koob and Volkow[41] attribute addiction to cycles of impulsivity and compulsivity and thus genes influencing these personality traits will likely have a general effect on multiple addictions.[41] Impulsivity has been identified in association with substance use disorders, in that individuals engage in goal-directed behaviors characterized by poor judgment and loss of self-regulation in attempt to attain rewards, despite growing awareness of the associated negative consequences.[93,94] Poor impulse control patterns and addictive behaviors in general share common neurobiological mechanisms that involve motivational neurocircuitry;[95] these traits also contribute to early onset of tobacco and cannabis use.[96] While there are studies that provide evidence for these

associations in tobacco and cannabis users,[97,98] research examining their combined effects is minimal.

Gateway Hypothesis

The gateway hypothesis, first introduced by Denise Kandel in Columbia in 1975 posits that there is a systematic sequencing in the use of psychoactive substances, which begins with alcohol and cigarettes, and then progresses to cannabis and other "harder" drugs such as cocaine, heroin, and LSD. Cigarette smoking in particular is a "gateway" to "harder" drugs.[99] For example, studies demonstrate that compared with nonsmokers, early smokers, such as those between the ages of 12.5 and 16, were 2–3 times more likely to engage in future regular use of cannabis.[100,101] While it is difficult to disprove this theory, there is an extensive body of literature that suggests alternate explanations for tobacco and cannabis co-use, such as the reverse gateway theory. The reverse gateway hypothesis posits that "harder" drug use precedes "softer" drug use, and given that cannabis use is increasing and tobacco use decreasing, cannabis now appears to be a strong predictor of tobacco smoking.[15,102] Research demonstrates that cannabis use in one's teen years and early adulthood is associated with an increased subsequent risk of initiation of tobacco use as well as progression to nicotine dependence.[3,103] Given that this review focuses on neurobiological factors, we choose to conceptualize these gateway theories from a biological perspective. Both clinical and preclinical studies suggest that pharmacological effects of nicotine exposure may predispose one to the use of other drugs by triggering changes in the brain that sensitize or prime users to the effects of other substances.[104–106] Epigenetic modifications have been suggested at the molecular mechanism involved in the trajectory from nicotine use to cocaine.[107] Whether similar processes are responsible for the transition between tobacco and cannabis or cannabis use to tobacco use have yet to be examined.

Route of Administration (ROA)

Inhalation is the most common ROA for both tobacco and cannabis, and is also the most effective means of delivering a psychoactive substance to the brain, with respect to addiction liability.[108] In fact, the method of mixing tobacco and cannabis has been demonstrated to increase the amount of THC inhaled per gram of cannabis by as much as 45 per cent.[109] In support of this, Agrawal and Lynskey[16] demonstrated that tobacco smokers are more likely to report a cannabis use disorder than individuals who consume smokeless tobacco. Additionally, a shared ROA may compel individuals who have experimented with smoking tobacco to be more willing to experiment with other smoked substances.[16] However, another study showed that adolescents with early onset tobacco use were just as likely to initiate cannabis use as those with early onset alcohol use.[110] Shared ROA may also act as a behavioral cue for other substances, triggering and/or exacerbating symptoms of cravings.[111]

TREATMENT OF TOBACCO AND CANNABIS USE DISORDERS

It is critical to determine and understand how cannabis use may impact tobacco cessation, and how tobacco use influences cannabis cessation when conceptualizing and developing effective treatment strategies. For example, Moore and colleagues[112] found that among individuals seeking treatment for cannabis dependence, those with concurrent tobacco use reported a significantly lower percentage of cannabis-negative urine screens and relapsed more quickly compared to former tobacco users.[112] Consistent with this, other studies found that tobacco smokers have significantly greater odds of cannabis relapse as compared to tobacco non-smokers.[113] Further research suggests that cannabis use not only impedes tobacco cessation attempts,[3,114,115] but can also be associated with increases in tobacco use.[116] Such research demonstrates how co-morbid substance use may thwart successful treatment outcomes and highlights the need for specialized treatment approaches.

Drug cues can stimulate the mesolimbic pathway triggering a hyper-attentive state towards drug-related stimuli that ultimately promote increased withdrawal, manifested as strong cravings and more rapid relapse in those trying to quit.[117–119] Given shared ROA between tobacco and cannabis, the use of one substance may act as a cue, activating incentive-system structures resulting in craving for the other drug.[70]

Further, research suggests that it is the ability of being able to quit one drug that is the best predictor in determining one's ability to be successful in abstaining from other substances.[17,112] Thus, perhaps cigarette smokers who are unable to achieve abstinence are less likely to abstain from drug use in general. Factors such as genetics, personality traits, environmental influences, and/or cue exposure may be responsible for an individual's overall lack of ability to facilitate successful cessation of substance use as a whole. As observed in the study by Vandrey and colleagues,[70] individual characteristics may contribute to the severity of withdrawal symptoms. There is other data that supports that quitting behaviors may cluster across substances, in that cessation of one substance increases the likelihood of abstinence from the second drug.[120,121] Evidence on how to treat co-morbid tobacco and cannabis misuse guided by clinical trials is very limited. This may be because, while three pharmacotherapy options are available for tobacco cessation (nicotine replacement therapies, sustained-release bupropion, and varenicline[122]), to date there are no approved pharmacological treatment interventions for cannabis use disorders.[123]

Withdrawal symptoms have long been considered to be a hallmark of drug addiction, and can serve as negative reinforcers propelling individuals towards relapse.[124] Minimizing such symptoms may lead to more favorable treatment outcomes. Clinical trials aimed at treating tobacco and cannabis co-morbidity are scarce. Interestingly, some investigators have examined the effects of approved tobacco pharmacotherapies for treating cannabis dependence.

Bupropion, a noradrenergic, and dopaminergic reuptake inhibitor, effectively reduces negative mood symptoms associated with nicotine withdrawal,[125] therefore it has been evaluated to target withdrawal symptoms associated with cannabis abstinence. However, two studies showed that this medication did not attenuate cannabis use or withdrawal symptoms in cannabis dependent participants.[126,127] More promising, but still contentious, results were observed by Penetar et al.[128] who demonstrated that self-reported symptoms of craving and withdrawal increased for individuals treated with placebo but remained constant for those treated with bupropion. Further and paradoxically, Haney et al.[127] reported that the combination of bupropion and active cannabis resulted in an increase in tobacco cigarette smoking among individuals who were also tobacco users.

To our knowledge Hill et al.[129] from Harvard is the only group to conduct a (small pilot) study to treat co-morbid tobacco and cannabis dependence. They examined the feasibility of cognitive behavioral therapy plus transdermal patch nicotine replacement therapy (NRT). After ten weeks participants had lower nicotine dependence scores and significantly reduced tobacco smoking. Cannabis use remained unchanged.

CONCLUSIONS, RECOMMENDATIONS AND FUTURE DIRECTIONS

Undoubtedly tobacco and cannabis use are linked. To date, only one study has evaluated treating co-morbid tobacco and cannabis use, thus whether these substances should be treated simultaneously or sequentially remains to be determined.

Simultaneous treatment of nicotine misuse and co-occurring substance use disorders has been debated in the past.[121,130] Current cessation programs typically focus on treating one substance while addressing the other either marginally or not at all. However, cessation programs that exclusively address tobacco consumption appear to be less effective for individuals who also consume cannabis.[115] In fact, evidence is accumulating that suggests that simultaneous tobacco and cannabis abstinence predicts better treatment outcomes.[6,131,132]

Neurobiological evidence reviewed here is in support of a dual cessation intervention program. The nicotinic and endocannabinoid system interact to enhance the reinforcing properties of tobacco and cannabis which may strengthen behaviours for using both substances as well as increase the risk for ongoing use. Further, cannabis users frequently engage in concurrent and simultaneous use of both substances, either by smoking a mixture of tobacco and cannabis in a blunt or by closely following cannabis use with tobacco smoking. Common ROA may also contribute to this effect. Smoking behavior can act as a cue, eliciting strong feelings of craving. Craving alone is sufficient to activate neuroanatomical networks such as the mesocortico–limbic dopamine pathway[41] thus triggering substance-seeking behaviors and motivation to use the drug, not presently being administered.[6,16,106,109] Further, the practice of combining tobacco and cannabis may be an attempt to counterbalance negative and aversive states induced by the other substance. Accordingly, removing one substance may eliminate the need to alleviate aversive effects with the other substance.

In summary, quitting the two substances simultaneously may bring forth benefits at both the psychological and neurobiological level. Such an integrated approach is already being incorporated into other co-morbid substance use disorders, such as tobacco and alcohol, and proving to have successful outcomes.[133] Simultaneous approach may also be beneficial from a financial and resource perspective given that both drugs can be targeted during a single treatment program.[134]

This preliminary body of research provides theoretical and empirical evidence suggesting an integrated treatment approach targeting both tobacco and cannabis misuse concurrently (Fig. 1).

Treating co-morbid addictions is challenging and perhaps such a feat requires scientists to think outside the box. Neuromodulation techniques may be a promising avenue to pursue. Repetitive transcranial magnetic stimulation (rTMS) delivers repeated magnetic pulses to the cortex to induce changes in cortical function and behavior. Recent studies demonstrate that rTMS applied to the dorsolateral prefrontal cortex can reduce cigarette craving and consumption in otherwise healthy smokers.[135,136] The effectiveness of rTMS may lie in its ability to enhance dopamine release in mesocorticolimbic pathways, alter neuroadaptation induced by chronic drug use and influence inhibitory control–a trait common to those vulnerable to substance use disorders. Given that similar mechanisms underlie cannabis addictions, it follows that effects of rTMS on co-morbid tobacco and cannabis use disorders should be investigated. To date, no studies have explored how rTMS may play a role in treating cannabis use disorders and data examining this would be a welcome addition to the literature.

Other nonpharmacological treatments should be also considered such as contingency management (CM). Contingency management is an approach that provides a structured incentive contingent upon changes in a participant's behavior. These incentives are often in the form of a voucher or monetary reward for achieving a pre-specified therapeutic target behavior. Several studies have demonstrated moderate efficacy in improving tobacco and cannabis cessation rates with CM.[137–139] Moreover, combining CM with other behavioral interventions may prove to be more effective that CM alone.[140]

With respect to medication approaches both cannabinoid agonists and antagonists may prove to be effective in treating co-morbid tobacco and cannabis dependence by suppressing withdrawal symptoms. Dronabinol, synthetic THC, has already shown some promise in treating cannabis dependence alone. In a randomized, double-blind, placebo-controlled 12-week trial, dronabinol was well-tolerated, improved treatment

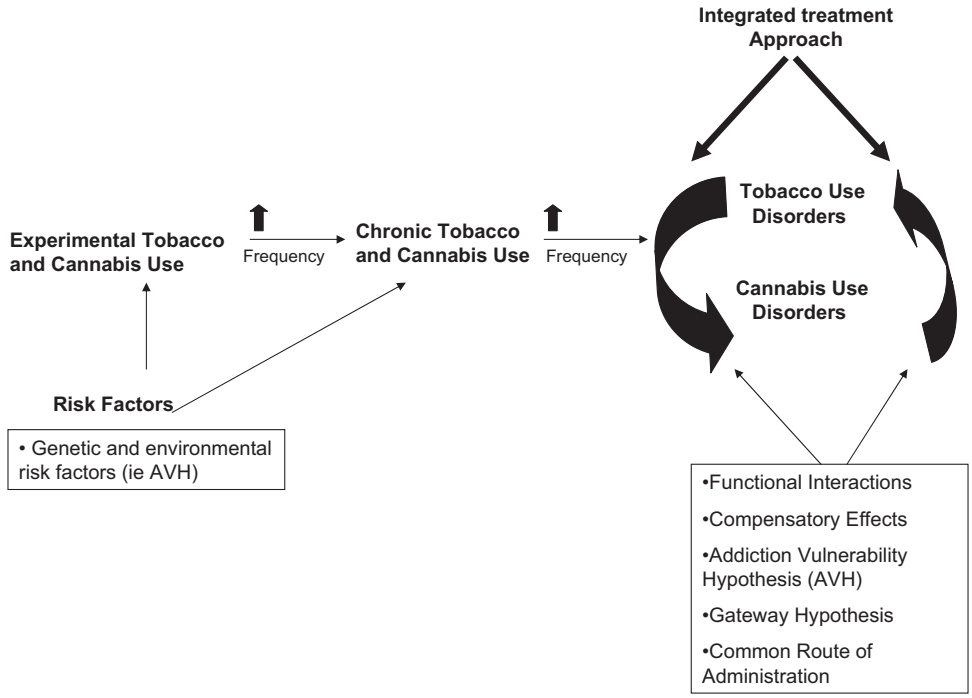

FIGURE 1. Contributors to co-morbidity of tobacco and cannabis use disorders.

retention and withdrawal symptoms,[123] however, it had no effect on cannabis use.

As a scientific and clinical community we need to gain insights into and determine to what extent the presence of cannabis use increases tobacco use and vice versa. Thus, understanding the reasons fueling high rates of co-morbid tobacco and cannabis consumption can then allow us to address the complexities implicated in treating individuals with these polysubstance use disorders.

Declaration of Interest

Ms. Rabin has no conflicts to report. Dr. George reports that in the past 12 months he has been a consultant to Pfizer on smoking cessation medications, and recipient of grant support for multi-center and investigator-initiated studies from Pfizer, as well as a member of a Data Monitoring Committee (DMC) for Novartis. The authors alone are responsible for the content and writing of this paper.

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