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Review

A review of the additive health risk of cannabis and tobacco co-use

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ABSTRACT

Introduction: Cannabis and tobacco are the most widely used substances, and are often used together. The present review examines the toxicant exposure associated with co-use (e.g., carbon monoxide, carcinogens), co-use via electronic nicotine delivery systems (ENDS), and problematic methodological issues present across co-use studies.
Method: An extensive literature search through PubMed was conducted and studies utilizing human subjects and in vitro methods were included. Keywords included tobacco, cigarette, e-cigarette, ENDS, smoking, or nicotine AND marijuana OR cannabis OR THC.
Results: Co-use may pose additive risk for toxicant exposure as certain co-users (e.g., blunt users) tend to have higher breath carbon monoxide levels and cannabis smoke can have higher levels of some carcinogens than tobacco smoke. Cannabis use via ENDS is low and occurs primarily among established tobacco or cannabis users, but its incidence may be increasing and expanding to tobacco/cannabis naïve individuals. There are several methodological issues across co-use research including varying definitions of co-use, sample sizes, lack of control for important covariates (e.g., time since last cigarette), and inconsistent measurement of outcome variables.
Conclusions: There are some known additive risks for toxicant exposure as a result of co-use. Research utilizing consistent methodologies is needed to further establish the additive risk of co-use. Future research should also be aware of novel technologies (e.g., ENDS) as they likely alter some toxicant exposure when used alone and with cannabis.

1. Introduction

Nearly 16 million Americans are living with a smoking-related disease(s) and tobacco use remains the leading cause of preventable death (CDC, 2015). Cigarettes contain at least 69 chemicals known to cause cancer (Hoffmann et al., 2001). Despite the known health risks of smoking, 16.8% of U.S. adults continue to smoke (CDC, 2015).

Cannabis is the most commonly used illicit substance (WHO, 2016). A recent national survey found that 5.2% of adults used cannabis and tobacco within the past month (Schauer et al., 2015); however, 90% of individuals who have smoked cannabis have also smoked tobacco cigarettes (Agrawal et al., 2012). Co-users are more likely to have mental health problems compared to exclusive users of either substance (Peters et al., 2014). Additionally, co-users have poorer cannabis cessation outcomes compared to exclusive cannabis users (Haney et al., 2013; Peters et al., 2012, 2014); however, co-users and exclusive tobacco users have similar tobacco cessation outcomes (Peters et al., 2012). Several group, individual, and web-based treatments for co-use have been effective at decreasing tobacco and cannabis use (see Becker et al., 2014; Lee et al., 2014, 2015; Becker et al., 2015; Hill et al., 2013); however, research examining treatments for co-use are limited. Given the high co-occurrence of tobacco and cannabis use, the known physical and mental health risks of each substance, and poor cannabis cessation outcomes among co-users, understanding the additive effects of co-use (compared to exclusive use of either substance) on health and toxicant exposure is critical.

Previous reviews on co-use summarized additive health risks and theories of co-use. One review concluded that co-use does not appear to lead to an additive disease risk among adolescents and young adults; however, co-users experience greater respiratory symptoms and have an increased likelihood of developing mental health problems compared to exclusive tobacco smokers (Ramo et al., 2012). Although this review begins to examine health effects of co-use, important toxicological and exposure variables (e.g., exposure to harmful constituents) were not extensively discussed.

Two reviews discussed several mechanisms of initiation or continued co-use (Agrawal et al., 2012; Rabin and George, 2015).

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Briefly, self-administration animal studies and human laboratory studies have suggested co-use creates *synergistic effects* via primed endocannabinoid systems that facilitate greater potential for nicotine use (Valjent et al., 2002). Secondly, clinical studies have shown that *combined withdrawal symptoms* of tobacco and cannabis may promote continued use; these combined withdrawal symptoms are more severe than the sum of independent tobacco and cannabis withdrawal symptoms (Vandrey et al., 2008). Third, a clinical study on adolescents showed that co-users have greater cognitive functioning declines when experiencing nicotine withdrawal compared to exclusive tobacco smokers, potentially negatively reinforcing co-use behaviors (Jacobsen et al., 2007). Fourth, genetic studies supporting the *addiction vulnerability hypothesis* have found common genes related to tobacco initiation and cannabis-related problems suggesting that specific neurobiological pathways may make some individuals predisposed to addiction (Agrawal et al., 2009; Chen et al., 2008). Fifth, clinical and pre-clinical research supporting the *gateway hypothesis* suggests that trying cigarettes may prime users to the pharmacological effects of other substances such as cannabis (Levine et al., 2011; Panlilio et al., 2013). Sixth, *environmental factors* such as peer influence, availability and exposure to drug use opportunities, and social norms around smoking, may make it easier for some to initiate and maintain co-use (Agrawal et al., 2012). Finally, smoking one substance may increase an individual's willingness to try the other, given their *common routes of administration* (Agrawal and Lynskey, 2009). Multiple mechanisms likely influence the development and maintenance of co-use.

One area that has not been synthesized in the literature is the toxicant exposure experienced by co-users compared to exclusive users of either substance. Although this research comprises of a small number of studies that vary considerably in methodology, summarizing the current literature is the first step in informing future studies. We first aim to extend on current published reviews by making a strong emphasis on toxicological and exposure effects. Second, given the recent introduction of electronic nicotine delivery systems (ENDS) and the potential exposure to toxicants from co-use via these systems, we aim to summarize articles discussing co-use via ENDS. Finally, our review process revealed several methodological issues prevalent across studies (e.g., small sample sizes, varying operational definitions of co-use) that create difficulty in making generalizations about many of our variables of interest. Therefore, our final aim is to discuss the implications such various method and design flaws have in drawing conclusions from the current literature and implications for future research. We also discuss ways of refining current definitions of co-use throughout the literature. Summarizing the current literature addressing these topics is not only timely, but necessary given the rapid changes in both tobacco and cannabis research.

2. Methods

An extensive literature search through PubMed was conducted. Articles published from January 1985 to February 2016 examining the co-use of cannabis and cigarettes/ENDS were identified. Those utilizing human subjects and in vitro studies (e.g., examining sidestream smoke produced by a machine) were included. Keywords included tobacco; cigarette; e-cigarette; smoking; ENDS; OR nicotine AND cannabis; marijuana; OR THC. This search revealed 7615 articles. Because of the scarcity of articles targeting co-use; no inclusion or exclusion criteria were implemented. Backward and forward searches were conducted to identify further relevant articles. Selected articles ($n = 13$) included empirical studies examining (a) exposure to toxicants as a result of co-use; (b) topography among co-users; and (c) tobacco and cannabis co-use via ENDS.

3. Results

3.1. Toxicology and exposure

While we know that tobacco and cannabis use exposes users to harmful constituents (e.g., carbon monoxide, known carcinogens), whether using both has an additive harm is less clear. Relevant studies are discussed below by the following outcome variables: carbon monoxide, THC and nicotine exposure, topography, cellular alterations, and exposure to other constituents. Due to inconsistent overlap in outcomes measured across studies, some studies are mentioned multiple times throughout subtopics. Studies to be discussed are summarized in Table 1.

3.1.1. Carbon monoxide. Four studies examined moderators of co-use and their effect on exhaled carbon monoxide (CO). Two of these studies examined cannabis smoked in blunts (e.g., cigar papers), one examined the effects of smoking cannabis before a tobacco cigarette, and one analyzed the effects of order of first use/initiation (e.g., first tried cannabis vs. tobacco vs. simultaneous initiation) on CO.

In the first study examining blunts, a subgroup of co-using adolescents enrolled in a cigarette smoking cessation study were examined. Researchers measured exhaled CO after each time participants reported both (a) seven days of tobacco cigarette abstinence and (b) any cannabis smoking during that seven day period (Moolchan et al., 2005). Those who reportedly smoked cannabis from a blunt produced CO levels greater than 6 ppm (study's suggested adolescent-specific cut off) more frequently than those who smoked cannabis via some other route (e.g., pipe; 52% vs. 5%); however, this difference was only marginally significant after accounting for outliers (i.e., removal of someone who had smoked a blunt immediately prior to their visit with a CO = 140 ppm). Additionally, these differences became non-significant when a CO cut-off of 8 ppm was tested. In the second study examining blunts, researchers conducted a lab-based within-subjects design in adult co-users. Participants smoked three THC doses (0%, 1.8%, and 3.6% THC) according to standardized smoking instructions in cigar papers, and again in joint papers (Cooper and Haney, 2009). Average CO of four post-smoking measurements was analyzed. Compared to cannabis joints, cannabis blunts produced higher average CO levels at all THC strengths. Although quantity smoked was not statistically accounted for in CO analyses, separate analyses of post-smoking weight of the joint/blunt were conducted. Participants smoked similar amounts of cannabis in joints and blunts at lower THC strengths, but greater proportions of cannabis in blunts at higher THC strengths.

These two studies suggest that smoking cannabis blunts may increase CO more than smoking cannabis via other routes of administrations (e.g., joints or bowls); however, neither study statistically controlled for important variables that affect CO, such as cannabis or tobacco quantity smoked. Furthermore, Cooper and Haney (2009) note that certain procedures may have interfered with ease of puffing on the cannabis blunts, causing participants to puff harder, potentially inflating CO measurements. Additionally, Moolchan et al. (2005) assessed self-reported cannabis use, did not control for time to last cannabis use, utilized a discreet cut-off for CO (above or below 6 ppm) rather than a continuous measure of CO, and some groups comprised only 20 observations. The limited number of studies examining blunts' vs. joints' effects on CO, with methodological issues, obscure interpretations of results from the current literature.

Alternatively, in a randomized crossover trial, adult co-users completed a standardized cannabis smoking procedure (placebo vs. active) followed by ad libitum tobacco smoking (Nemeth-Coslett et al., 1986). CO was measured pre- and post-

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