



Sex and Gender Differences in Simultaneous Alcohol and Cannabis Use: a Narrative Review

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Abstract

Purpose of Review The aim is to review recent literature on sex and gender differences in patterns of use, motives, pharmacological effects, and consequences of simultaneous alcohol and cannabis use (SAC).

Recent Findings Men engage in SAC more frequently than women. Women may have more substance-specific motives for use, while men tend to consistently endorse social/enhancement motives for both alcohol and cannabis. Regarding pharmacological effects, women experience the same subjective effects as men do at lower levels of use, with some evidence that women modulate cannabis use during simultaneous use episodes to avoid greater subjective intoxication. Finally, women appear more vulnerable to experiencing a range of positive and negative consequences from SAC relative to men.

Summary Research has identified several important sex/gender differences in SAC and its correlates and consequences. However, research has primarily focused on white and cisgender populations, with a need for more research among racial/ethnic and gender minorities.

Keywords Cannabis use disorder · Alcohol use disorder · Δ^9 -Tetrahydrocannabinol · Co-use · Co-administration · Polysubstance use

Introduction

The co-use of cannabis and alcohol is highly prevalent; over 75% of people who report cannabis use also report use of alcohol [1–3] and cannabis is the most commonly used drug among individuals who drink alcohol [4]. Many people who use both alcohol and cannabis report doing so simultaneously [5]. Simultaneous use of alcohol and cannabis (SAC), colloquially termed “cross-fading” [6••, 7], is the use of cannabis and alcohol at the same time so that the effects overlap. SAC is particularly prevalent among adolescents and

young adults [8–10, 11•]. In fact, approximately 20–30% of drinking episodes among adolescents and young adults are accompanied by simultaneous cannabis use [1, 3, 4, 12]. Though estimates for cannabis use are more variable, 40–80% of cannabis use episodes are associated with simultaneous drinking among adolescents and young adults [1, 3]. Furthermore, SAC is increasing among young adults [12] and potentially among older adults in states where recreational cannabis is legalized [13]. In contrast, SAC appears to be decreasing among high school seniors in the USA; however, this decrease is more pronounced among adolescent boys versus adolescent girls [11•], highlighting an emerging sex/gender-related trend that warrants additional attention in the literature.

Historically, SAC has been substantially more prevalent among men compared to women [2, 12, 14–19; c.f., 5, 20]. Despite higher prevalence among men, women may be particularly susceptible to the negative effects of SAC [7, 21–23]. Collectively, this underscores the importance of understanding sex/gender-related risk factors for SAC and related consequences.

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The goal of this paper is to review recent literature on sex/gender differences in SAC (1) patterns, (2) motives, (3) pharmacological effects, and (4) consequences. To provide a recent update on this topic, we searched PubMed, Google Scholar, and Scopus databases for articles published between January 2018 and April 2023. We focused on articles that defined SAC as (1) overlapping effects of alcohol and cannabis use, (2) use at the same time or within the same occasion, or (3) use of both substances within a specified time frame (e.g., within 3 h), consistent with a recent review [6••]. Earlier publications and/or those that focused on co-use more broadly defined were included when recent articles were lacking or when needed to convey the foundation for this line of work.

Of note, sex and gender are distinct constructs, and are defined in this review consistent with the SAGER guidelines [24]. Sex is typically categorized as male or female and is defined by biological attributes. In contrast, gender is non-binary and refers to socially influenced identities, roles, and behaviors. Sex and gender can interact in complex ways to influence health and behavior, including SAC. Given that reporting guidelines for sex and gender are relatively new, much of the extant research on SAC has not defined sex or gender with enough precision to allow us to parse out their unique effects in this review [see 10, 25 for recent exceptions]. Thus, we use sex-related terms to refer to physiological or pharmacological drug effects and gender-related terms for prevalence and patterns of SAC, motives, and consequences. It is also important to note that the existing research, and therefore this review, largely pertains to cisgender individuals. At least one study [10] found that prevalence of past year SAC was numerically lower among individuals who identified as non-binary relative to cisgender individuals; however, the small sample of individuals identifying as non-binary ($n=29$) limits conclusions that can be drawn and highlights the need to include gender minorities in future work.

Patterns of Alcohol and Cannabis Co-use

Recent research has examined individual differences in alcohol and cannabis use among young adults (ages 18–25) with at least one episode of binge drinking and one episode of past month SAC [26]. Using a latent profile analysis, four profiles were derived that were characterized by low alcohol and cannabis use (49% of sample), average alcohol and cannabis use (38% of the sample), average alcohol use, but high peak levels of alcohol and cannabis (5% of sample), and heavy alcohol and cannabis use (8% of the sample). The groups did not significantly differ by sex/gender [26].

A significant limitation of a large portion of the literature focusing on sex/gender differences in SAC prevalence has

been the reliance on use of epidemiologic and cross-sectional datasets that do not include fine-grained data regarding patterns of alcohol and cannabis use (i.e., whether they are used simultaneously). Data collection methods with increased temporal precision (i.e., intensive longitudinal methods) have been used to characterize SAC episodes more precisely. Furthermore, when used, these methods often identify important gender differences in patterns or correlates of SAC.

Intensive longitudinal methods, such as experience sampling methods or ecological momentary assessment, consist of sequential, repeated assessments designed to characterize an event, process, or behavior for a specific individual [27]. These methods often occur in real-time in participants' naturalistic environments and allow researchers to identify how close in time alcohol and cannabis were used, as well as examine fluctuations in SAC within-person over time. For example, using intensive longitudinal methods, researchers have found that approximately 42% of simultaneous use days may be considered "unplanned," meaning that the individual had planned to use neither alcohol nor cannabis, to use alcohol but not cannabis, or to use cannabis but not alcohol [21]. Planned simultaneous use days may be associated with higher risk relative to unplanned simultaneous use days as the latter were associated with consuming fewer drinks, fewer hours high from cannabis, and lower subjective intoxication/high, and were not associated with either positive or negative consequences of use [21].

Although relatively few intensive longitudinal studies of SAC patterns have examined sex/gender differences, those available tend to demonstrate consistent differences. Specifically, relative to young adult women, young adult men report consuming a greater number of drinks, using more grams of cannabis, and experiencing more hours high on simultaneous use days [7, 21]. Intensive longitudinal data also suggest that there may be gender differences in preferred substance and/or order of substance administration. A sample of college students (ages 18–24) who endorsed past year alcohol and cannabis use participated in an intensive longitudinal study in two 4-week bursts [28•]. A latent class analysis found evidence for 5 unique classes [28•]. Young adult men (ages 18–24) were more likely than young adult women to fall in two specific classes. The first class (63% men) was characterized by frequent cannabis use, with multiple different cannabis methods (e.g., leaf, concentrate, edible) endorsed, and cannabis use on non-SAC days. Additionally, this class was more likely than all other classes to begin a SAC episode with cannabis use rather than alcohol use. The second class that included a higher prevalence of men (63% men) was also characterized by cannabis use on non-SAC days, but more moderate consumption overall relative to the first class. They were unlikely to achieve a very high peak blood alcohol content. They were equally likely to

start a SAC day with alcohol or cannabis. In contrast, young adult women were overrepresented in two different classes. Women made up approximately 74% of a class characterized by heavy drinking, with a high peak blood alcohol content, and infrequent SAC (1–2 times in approximately 2 months). They were more likely to consume alcohol first, followed by cannabis (when cannabis was used at all). Additionally, women were overrepresented in a class (62% women) characterized by heavy drinking, frequent SAC (3 or more times in ~2 months), as well as frequent independent use of both alcohol and cannabis on non-SAC days. This class was also likely to use alcohol prior to cannabis use on SAC days. The authors concluded that young adult women may benefit from more alcohol-focused content when addressing SAC, whereas young adult men may benefit from more cannabis-focused content [28•].

Motives for SAC

Research on motives for cannabis and alcohol separately each support motivational models in which substances are used for approach (*enhancement*, to enhance positive mood; *social*, to obtain positive social rewards) or avoidance (*coping*, or to reduce/regulate negative emotions; *conformity*, to avoid social rejection) reasons [29, 30], with the addition of *expansion* (to expand awareness/understanding) motives for cannabis [31]. Motives for SAC are similarly characterized (conformity, positive effects, calm/coping, social) and have demonstrated moderate correlations with motives for alcohol and cannabis use [20]. Recent ecological momentary assessment (EMA) studies have shown evidence for enhancement, followed by social, motives predicting SAC days [32, 33], wherein enhancement motives were associated with a higher likelihood of simultaneous use on days in which either alcohol or cannabis was used, relative to days when only alcohol or cannabis was used. Social motives were associated with simultaneous use on days in which cannabis was used, whereas coping motives were associated with simultaneous use on days in which alcohol was used. These results suggest that alcohol may contribute social facilitation effects on days when cannabis is used, whereas cannabis may contribute to reducing or coping with negative affect on days when alcohol is used.

Sex/gender differences in motives for cannabis use and alcohol use have been observed separately (see Table 1 for a summary of findings); however, no studies to date have examined sex/gender differences in SAC motives. A recent latent profile analysis of cannabis use motives found that men and women college students differed in their motives profiles [34]. Women were more likely to be in profiles characterized by low use motives (i.e., few and infrequent reasons of any kind to use cannabis) or high use motives (i.e.,

more and frequent reasons of any kind to use cannabis), as well as high enhancement and coping use motives only (i.e., more and frequent reasons to use cannabis associated with improving mood and managing negative affect). Alternatively, men were more likely to belong to profiles characterized by high enhancement motives only or high enhancement and social motives + moderate expansion motives (i.e., more and frequent reasons to use associated with improving mood and facilitating social situations and some reasons/occasions to use associated with trying to understand things differently). Whereas only one profile was characterized, in part, by coping use motives among students who used cannabis [34], another study observed multiple profiles characterized by coping in a sample of undergraduate students who drink heavily [35]. The sample was majority men (62%), and, although not evaluated statistically, classes characterized by high positive reinforcement (i.e., enhancement or social reasons) and extreme (72.2% men) or moderate coping (70.7% men) consisted of proportionally more students who were men than in the full sample [35]. Together, these studies suggest that young adult men most frequently use alcohol or cannabis for the positive effects (i.e., enhancement, social reasons) associated with use and that this pattern may be true for SAC as well. Patterns among young adult women appear less consistent across alcohol and cannabis separately, suggesting that young adult women may seek substance-specific effects. If this is the case, then we may expect to see pronounced sex/gender differences in motives for SAC that reflect the desire for these substance-specific effects. Further research is necessary and could have an important impact on tailoring prevention and treatment interventions.

Pharmacological Effects of SAC

Previous studies have shown sex differences in the pharmacological effects of alcohol and cannabis when consumed separately. Pharmacokinetic studies have shown that female participants metabolize and absorb alcohol differently than male participants, due to factors including body size/composition and lower activity of the gastric and hepatic enzyme alcohol dehydrogenase, resulting in higher blood alcohol concentration and greater vulnerability to organ injury after consuming the same amount of alcohol [36, 37]. These pharmacokinetic differences are associated with subjective differences, where female participants report higher levels of subjective intoxication and impairment after controlling for body weight [38, 39••]. However, these findings are dependent on the limb of the blood alcohol curve, task demands, and individual drinking histories, and some studies have not replicated sex/gender differences in metabolism or subjective effects [40].

Table 1 Summary of sex/gender differences in alcohol and cannabis use motives

Motives for use	Definition	Sex/gender-related differences in alcohol motives [35]	Sex/gender-related differences in cannabis motives [34]
Enhancement	To enhance positive mood	<ul style="list-style-type: none"> Men overrepresented in profiles characterized by high positively reinforcing motives profiles (i.e., enhancement motives) 	<ul style="list-style-type: none"> Men and women both likely to be in profiles characterized by high enhancement motives
Social	To obtain positive social rewards	<ul style="list-style-type: none"> Men overrepresented in profiles characterized by high positively reinforcing motives (i.e., social motives) 	<ul style="list-style-type: none"> Men more likely to be in profiles characterized by high social motives
Coping	To regulate distressing emotions	<ul style="list-style-type: none"> Men overrepresented in some profiles characterized by moderate to extreme coping motives 	<ul style="list-style-type: none"> Women more likely to be in profiles characterized by high coping motives
Conformity	To avoid social rejection (<i>typically the least frequently endorsed motive across substances</i>)	<p>(<i>Study did not include in the analysis due to inconsistent relations with alcohol-related outcomes in the literature</i>)</p>	<p>(<i>Study did not include items to reduce the length of the survey</i>)</p>
Expansion	To expand awareness/understanding	<p>(<i>not a typical motive for alcohol use</i>)</p>	<ul style="list-style-type: none"> Men more likely to be in a profile characterized by moderate expansion motives
All motives		<ul style="list-style-type: none"> No clear differences by sex/gender 	<ul style="list-style-type: none"> Women more likely to be in profiles characterized by overall high motives (endorsing most or all motives at high frequencies), or characterized by overall low motives (endorsing few or any motives at low frequencies)

The men and women referenced throughout the table were undergraduate students between age 18 and 24 from just two studies that have evaluated patterns of motives endorsed ($N = 1213$ [34]; $N = 648$ [35]). Both studies used latent class analysis to empirically derive patterns of motives

Regarding cannabis, sex differences in $\Delta 9$ -tetrahydrocannabinol (THC) metabolism have been observed in both clinical and preclinical studies, with females more efficiently converting THC to the metabolite 11-hydroxy- $\Delta 9$ -tetrahydrocannabinol (11-OH-THC), which is also psychoactive [41–46; c.f., 47, 48]. However, it is important to note that sex differences in pharmacokinetics may vary based on route of administration [e.g., 48, 49]. There are mixed findings in controlled administration studies regarding sex differences in subjective intoxication, though there is some evidence that relative to male adults, female adults report “liking” THC more [50], rate THC as “stronger” [50], report a greater “high” [51]), and report increased adverse effects [42]. Other studies find that female participants require lower levels of plasma THC to experience equivalent subjective effects as male participants [43, 52]. Sex differences in subjective effects may be dose dependent. For example, one study found that female participants reported stronger subjective effects at lower doses of THC (5 mg) while male participants reported stronger effects at higher doses (15 mg [53]).

Laboratory administration studies have examined the combined effects of alcohol and THC (i.e., SAC). When alcohol is administered before THC, most studies have not found any effect of THC administration on blood/breath alcohol content (BAC/BrAC; see [54] for a review); however, two studies have suggested that THC may slow alcohol absorption in male young adults (ages 20–35 [55, 56]). In contrast, the co-administration of alcohol and THC may increase peak THC and/or 11-OH-THC [57–59]. These studies consisted predominantly of young adult, white male participants or did not examine sex differences, so it is unclear the extent to which results generalize to female adults or other age groups.

One within-subjects study examined the unique and combined effects of a standardized dose of alcohol (~0.08% BrAC) and a self-titrated dose of THC, up to 12.5% THC [39••]. Thirty ($N=30$; 12 female, 16 male) young adults (ages 19–29; mean age = 23) who regularly used cannabis and had at least one heavy drinking episode in the past 6 months received each of 4 conditions: (1) combined alcohol + THC, (2) active alcohol + placebo THC, (3) placebo alcohol + active THC, (4) or both placebos [39••]. Alcohol was consumed first, and ad libitum cannabis smoking occurred 15 min after completion of alcohol consumption. Female participants self-titrated THC more than male participants in the combined alcohol + THC condition, but not in any other condition. Though not statistically significant, numerically, male participants averaged more mg of THC smoked in the combined condition relative to the cannabis only condition. The reverse was true for female participants—numerically, female participants averaged lower mg of THC in the combined condition versus the cannabis only

condition. Even though female participants smoked less in the combined condition relative to male participants, their blood levels of THC and 11-OH-THC did not differ from male participants. These findings suggest that, under the pharmacological influence of alcohol, female young adults may modify their THC intake, while still experiencing comparable effects as when not under the influence of alcohol.

Another alcohol administration study examined individuals (17 female, 20 male; mean age = 27) who engaged in heavy drinking and cannabis use at least once in the past 6 months [60]. THC was not co-administered in this study, but cannabis craving was assessed after participants received alcohol or placebo. As BrAC increased for male participants, so did their cannabis craving. In contrast, there was a trend for female participants to report decreasing cannabis craving as BrAC increased [60]. This suggests that alcohol use and/or intoxication may serve as a stronger cue for cannabis use among male young adults relative to female young adults, potentially due to more frequent pairing of the two substances among men, who show higher rates of SAC.

Consequences of SAC

Individuals who engage in SAC experience more negative consequences and substance-related problems compared to those who do not combine substances [9, 14, 61]. In addition, a growing body of research at the within-person level suggests that SAC episodes are associated with the experience of more negative consequences compared to episodes involving the use of alcohol or cannabis alone [8, 22, 62]. However, relatively little research has explored potential sex/gender differences in these effects. Given that women may be more sensitive to the effects of alcohol and cannabis [39••, 52, 63]) and that SAC has been associated with higher levels of subjective intoxication compared to single substance use [64], it might reasonably be anticipated that women would experience greater negative consequences resulting from SAC. Despite relatively sparse research on the topic, there is some evidence to support this possibility.

Research among emerging adults has found potential gender differences in the overall number of consequences and in the experience of negative consequences following SAC. Women have been found to experience greater negative alcohol and cannabis consequences on SAC days than do men [7, 21]. Consistent with this, one study found that SAC days were associated with greater negative consequences relative to cannabis-only use days for women, but not men [22]. Gender has also been found to moderate the association between SAC compared to cannabis-only use days on the experience of positive consequences (e.g., expressing feelings more easily, increased sociability, and feeling buzzed) [22], suggesting that women may be more vulnerable to experiencing a

broad range of SAC consequences. Other research among young adults has found that SAC was more strongly associated with next day negative affect among women who were higher in trait anxiety levels compared to men and those lower in trait anxiety [23]. Therefore, women with elevated anxiety may represent an important subgroup whose SAC is likely to exacerbate existing mental health vulnerabilities. Taken together, these studies suggest that women may be more vulnerable than men to experiencing greater harms resulting from SAC.

Other research has examined SAC as a risk factor for intimate partner violence, sexual assault, and risky sexual behaviors. In a recent study of adults ($N=496$), participants who reported regular SAC also perpetrated physical and psychological partner violence more frequently compared to those who used only alcohol, after controlling for gender [65]. Other research has examined gender differences in sexual risk-taking and gender-specific risk for victimization. Within a young adult sample (ages 18–25), days on which participants used both cannabis and alcohol were associated with a higher likelihood of having condomless sex, but this association was stronger among women than men [66]. A study among women found indirect effects of SAC on risk for experiencing sexual assault, with these effects being mediated by intoxication levels and the presence of likely offenders (assessed by asking about the presence of men who attempted to isolate them, showed negative attitudes towards women, were known to be “players,” or were behaving in sexually aggressive ways [67]). However, given that men were not included in this sample, gender differences could not be formally assessed.

Although there is currently only a small body of research examining potential gender differences in the experience of consequences following SAC, this work points to unique vulnerabilities for women that warrant further exploration. Future work should aim to assess consequences for which sex or gender differences have not yet been examined, such as physiological consequences (e.g., blackouts, passing out, and hangover) and academic consequences.

Summary/Interpretation

The existing literature suggests that SAC is more common among men and that men are at-risk for greater consumption on days that they use both substances [e.g., 5, 11•, 14, 21, 32]. Men may increase their self-administration of THC when under the influence of alcohol, while women show the opposite pattern [39••]. Men also show clearer enhancement motives and may seek to intentionally use both substances together to enhance the effects of either substance.

We posit that while men engage in more SAC, women may exhibit an alternative pattern of co-use, known as “substitution.” As substitutes, one may be used in place of the other if cost or availability restricts use of one but not the other. As complements, use of one serves to enhance the effects of the other; SAC is therefore considered a form of complementary use. Broadly, evidence exists for both substitution and complementary use, though when and for whom they occur is nuanced [68, 69]. The hypothesis that women may show greater rates of substitution relative to men is partially supported by a study in Washington state that found women exhibited greater decreases in alcohol-related problems compared to men after recreational cannabis legalization [13]. Furthermore, our review points to additional evidence that women may show greater substitution. First, women reported more substance-specific motives than men, suggesting that they may use alcohol and cannabis in separate contexts in anticipation of different effects. Second, a trend-level decrease in cannabis craving observed in females following alcohol administration [60] may be evidence of a tendency for women to engage in substitution; however, this finding did not reach statistical significance. Third, females appear to self-titrate within an episode, self-administering lower doses of THC when under the influence of alcohol [39••]. Finally, our review suggests that women may be more susceptible to both negative and positive consequences of SAC, suggesting potential heightened sensitivity of the combined effects of alcohol plus THC.

Limitations

A pervasive limitation of the literature focusing on sex/gender differences in SAC to-date is that most studies reported sex or gender, but not both. Additionally, gender was often treated as binary, when reported. Research studying SAC among gender minorities is lacking, and future research should explore the prevalence and consequences of SAC among gender-diverse individuals. Although discussion of the literature on sexual minority identities was outside of the scope of this review, it is important to note that sex/gender differences in prevalence of SAC may be reduced among sexual minority populations [25, 70]. In fact, one study suggested that sex/gender identity and sexual orientation may interact to predict risk for polysubstance use and people who identify as a woman and as a sexual minority are at increased risk of polysubstance use, relative to heterosexual women [70]. Thus, future research should also consider sexual orientation.

The current literature is also limited by its reliance on samples that are predominantly white, and some emerging literature points to interactions between sex/gender and race/ethnicity as being relevant to alcohol and cannabis co-use [e.g., 71, 72]. Therefore, research is needed in racially/ethnically diverse samples. Finally, most literature focused on adolescents and young adults; considering that recent research suggests significantly increased rates of simultaneous use among those 50 years of age or older [13], research is needed to examine potential sex and gender differences in temporal patterns, motives, pharmacological effects, and consequences of SAC across this and other developmental periods.

More research is needed to directly test the hypothesized sex/gender difference in “substitution” versus “complementary” use, as it has important implications for interventions. For example, interventions for both alcohol use and cannabis use among men may need to directly address SAC, particularly if use of one substance increases desire to use the other. In contrast, interventions targeting one substance may inadvertently increase use of the other among women, if women are shown to be more susceptible to substitution effects. Further research is needed to better understand the complex relationship between sex, gender, and SAC and to inform the development of evidence-based interventions that consider these factors.

Conclusions

The literature on sex/gender differences in SAC is limited, but existing data demonstrates that SAC is increasingly prevalent, particularly among men. Furthermore, men and women show differences in titration of cannabis when already under the influence of alcohol. Sex and gender differences in patterns of SAC have significant implications for sex and gender-informed interventions.

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Declarations

Human and Animal Rights and Informed Consent This article is a review and therefore did not include any studies with human or animal subjects.

Conflict of Interest Rachel Tomko has provided consultation to the American Society of Addiction Medicine, Kevin Gray has provided consultation to Jazz Pharmaceuticals and has received research support from Aelis Farma, and Aimee McRae-Clark has received research support from Pleo Pharma. The other authors have no relationships to disclose.

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