



Commentary

# New Challenges: Developing Gendered and Equitable Responses to Involuntary Exposures to Electronic Nicotine Delivery Systems (ENDS) and Cannabis Vaping

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**Abstract:** Recreational cannabis use is in the process of being legalized in Canada, and new products and devices for both nicotine and cannabis vaping are being introduced. Yet, research on the harms of involuntary exposure to electronic nicotine delivery systems (ENDSs) and cannabis vaping is in its infancy, and there is a lack of investigation on sex-specific health effects and gendered patterns of exposure and use. We argue that responses to ENDS and cannabis vaping exposures should align with policy and progress on restricting exposure to tobacco secondhand smoke (SHS). Furthermore, we argue that sex, gender, and equity considerations should be integrated in both research and policy to benefit all Canadians.

**Keywords:** electronic nicotine delivery systems (ENDSs); cannabis; vaping; involuntary exposure; sex; gender

## 1. Background

Progress on reducing secondhand smoke (SHS) exposure in Canada is facing new challenges. National data from Canada reveal that 16.1% of males and 10.5% of females have tried electronic cigarettes, and 14.9% of males and 9.7% of females have reported cannabis use in the past year [1]. Of those who reported cannabis use in the past year, 28% reported using a vaporizer to consume cannabis [2]. With the introduction and expansion of electronic nicotine delivery systems (ENDSs), combined with the legalization of recreational cannabis use in Canada, there is a need to consider the health effects of involuntary SHS exposure to these substances and review the existing policy and public health responses to SHS messaging and smoke-free legislation. In the following commentary we argue that in order to support the development of regulations and policies that benefit all, sex, gender, and equity considerations must be integrated in research and policy from the outset. Moreover, we argue that the development of regulations must be in alignment with policy, and that progress on restricting exposure to tobacco SHS should be supported.

Legislation on tobacco smoking location restrictions in indoor public places and workplaces exists both in Canada and in many other countries. In Canada, the federal *Non-Smoker's Health Act* restricts smoking and the use of ENDSs in workplaces and on public transportation. Further provincial, territorial, and municipal laws restrict smoking and ENDS use in public places. Smoking location restrictions have been associated with improved cardiovascular health outcomes, as well as reductions in mortality for smoking-related illnesses [3], preterm births, and hospital admissions for asthma [4]. In Canada, there is a federal commitment to apply gender-based analysis when developing and evaluating policies, programs, and initiatives. However, smoke-free policies have typically been gender-blind or applied a “one-size-fits-all” approach to reduce exposure to SHS [5,6]. Yet, there

is clear evidence that sex-, gender-, and diversity- based factors impact tobacco use in general, and in particular, SHS exposure and its health effects [7]. For example, a systematic review revealed a significant association between combustible SHS and heart disease, chronic obstructive pulmonary disease (COPD), and stroke, with a greater risk for women than men for all three health outcomes [8]. Women and men tend to be exposed to SHS in different locations—men in the workplace and women in the home [9,10]. For these reasons, it is essential to apply a sex and gender lens to research on patterns of exposure and health effects to inform more nuanced policy and public health responses, especially as new products and substances are being regulated.

While there is currently less evidence on the health effects of exposure to secondhand cannabis smoke, cannabis smoke is similar in chemical composition to tobacco smoke (although in varying concentrations) [11]. A systematic review found that exposure to secondhand cannabis smoke results in the presence of cannabinoids in bodily fluids and psychoactive effects for those exposed [11]. There is evidence from some animal studies on the potential harms of secondhand cannabis smoke exposure. For example, a study with rats found that secondhand cannabis exposure produced negative cardiovascular health effects [12]. However, there is a lack of research on the long-term human health effects of secondhand cannabis smoke exposure [11], and no studies are available on the sex-specific effects of exposure.

As cannabis legalization is introduced in Canada (17 October 2018), it is expected that cannabis smoking will be included in tobacco smoking restriction by-laws. However, this will ultimately be the responsibility of individual provinces and territories [13]. As research on cannabis use patterns continues to emerge and policies and regulations regarding location restrictions of smoking cannabis are introduced, it is important that sex and gender differences and implications are investigated, analysed, and reported.

Compared to smoking tobacco, ENDSs and non-combustible forms of cannabis may be associated with lower relative harm both for users and for those who are exposed to the aerosol vapor. Currently, ENDSs are being investigated and debated regarding their potential as a harm reduction method, and as a tool to support smoking cessation [14]. Furthermore, the Lower Risk Cannabis Use Guidelines for Canada suggest people avoid using combustible cannabis, and use non-smoking methods such as vaping [15], as vaping natural cannabis has been associated with fewer respiratory effects compared to smoking cannabis [16].

In the current Canadian context of forthcoming legalization of cannabis and the regulation and expansion of the use of ENDS, further research is required to: (1) investigate the sex-specific health effects of involuntary exposure to ENDS and cannabis vaping products; (2) examine the health effects, including sex-specific effects, of exposure to new nicotine and cannabis vaping products and devices; and (3) examine how ENDS and cannabis vaping impact existing smoke-free legislation and patterns of involuntary exposure, all with particular attention to the implications for gender and health equity.

## 2. Health Effects of Involuntary Exposure to Vaping

Electronic nicotine delivery systems aerosolize a liquid that includes nicotine, a carrier ingredient (typically either propylene glycol or vegetable glycerine), and flavours, in varying concentrations [17]. There is evidence that exposure to aerosol vapour from ENDS may be less harmful than exposure to SHS [18]. Cigarette smoking is associated with higher airborne markers of nicotine [19]. However, non-smokers who are exposed to traditional cigarette smoke and e-cigarette vapour in the home demonstrate statistically similar levels of nicotine absorption [19]. A systematic review examining the health effects of passive exposure to e-cigarette vapour reported that while the health risk is not as pronounced as exposure to combustible cigarette smoke, bystanders may be exposed to a variety of harmful chemicals, including formaldehyde, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) [18]. For example, measurements of air quality in indoor spaces following e-cigarette use have demonstrated an increase in ultrafine particles, including a 20% increase in carcinogenic PAHs [20]. A study in Greece reported an increase in the irritation of, and inflammatory markers of, the airways

following 30 min of exposure to ENDS vapour [21]. Some authors have noted that the toxicants produced by ENDSs may be a greater risk for populations who are more vulnerable, including children and pregnant women [20]. Overall, there is a dearth of research examining the sex- or gender-specific health effects of exposure to ENDS vapour.

Cannabis vaping products are available that heat oil or liquid containing cannabis extracts or raw plant material to release aerosolized water vapour [22]. However, there is a lack of research examining the health effects of exposure to vapour from cannabis products, and no available studies examining sex-specific health effects. Reproductive aged and pregnant women have been identified as potentially vulnerable to the health effects of being exposed to toxicants from both ENDS and SHS from cannabis [23]. One study reported that health care providers are not asking pregnant women about their exposure to cannabis smoke or ENDS vapour [23]. Again, there is a dearth of evidence on sex and/or gender and the effects of exposure to ENDS and cannabis vapour.

More nuanced research is clearly needed on the health effects of involuntary exposure to ENDS and cannabis vaping. Meanwhile, however, products are rapidly evolving, while the harms associated with involuntary exposure to new products are largely unknown. There are “heat not burn” (HNB) products that do not use an electronic heat source (e.g., Eclipse), that have been granted substantial equivalence status by the United States Food and Drug Administration, and are now approved for test marketing in the USA [24]. There are also HNB products such as IQOS [25], and higher nicotine containing ENDS products and brands such as Juul [26], which may be associated with greater health harms than standard nicotine vaping products. There is evidence that non-users who are exposed to e-cigarette products with higher nicotine content may absorb more nicotine [27]. The level of nicotine exposure may also be affected by the type of delivery device, the materials and battery used (specifically the voltage), and nicotine form (free-base or nicotine salts) [28]. Testing of the vapour released from a variety of commercially available e-cigarette products in the USA found that the majority of the nicotine was in the free-base form, and the measured nicotine concentration was higher than the labelled concentration [29]. In another study, among a group of non-smokers exposed to e-cigarette vapour, cotinine levels were higher following exposure to aerosol from tank-style e-cigarettes compared to disposable e-cigarettes [30].

Similar to e-cigarettes, cannabis vaping devices vary widely and the by-products and resulting health effects of exposure may differ depending on the carrier compounds, product materials, and heating capacity [22]. For example, along with cannabis smoking, Russell et al. identified “dabbing” as having the greatest potential for harm [16]. This route of administration involves the use of a modified water pipe in which a nail is heated with a blowtorch to vaporize cannabis concentrates (e.g., wax, shatter, budder). While the health effects of involuntary exposure to dabbing requires further investigation, there are numerous potential health risks for the user, including burns and explosions, and greater addiction due to the high potency of the concentrates used [16]. Again, further research is needed, particularly on the sex-specific health effects and gendered usage patterns, of both novel nicotine delivery products and cannabis vaping products.

### 3. Vaping in Smoke-Free Spaces

In Canada, restrictions on the use of e-cigarettes and vaping products tend to align with smoke-free by-laws. However, there is evidence that vaping products are commonly used in smoke-free locations [31], and that involuntary exposure to vaping products is likely to increase. E-cigarette use is common in smoke-free locations, particularly among young adults. In a US study, 74% of young adults used e-cigarettes in a smoke-free location [32]. Similarly, there is evidence that cannabis vaporizers are often used to “stealth vape” [31] in locations where smoking is prohibited (e.g., while at work) [13]. A study with older cannabis users in San Francisco found that some participants prefer using a vapour pen in public spaces because it is more discreet than smoking [33]. Similarly, a survey conducted with Canadians revealed that some people reported using e-cigarettes in locations where they were unable to smoke cigarettes [34].

Clearly, after legalization, the prevalence of cannabis vaping is likely to increase in Canada, similar to the experiences of US states that have legalized recreational cannabis [35], further exacerbating regulation and enforcement issues. Budney et al. have argued that the normalization of vaping nicotine and cannabis may increase frequency and misuse of cannabis among youth, particularly as the “positive features” of vaping will likely be used by the growing cannabis industry to encourage greater use and uptake [22]. Researchers have argued that implementing similar restrictions on cannabis smoking in public spaces is an important measure to prevent potential health harms and to support the gains made to denormalize smoking [11,36]. This concern is echoed in recommendations regarding the provincial regulation of cannabis in Canada. For example, the Health Officers Council of British Columbia recommend that the smoking and vaping of cannabis must align with tobacco smoking and nicotine vaping regulations, in order to avoid youth modelling [37].

However, it is important to avoid the errors of historical approaches to tobacco use and SHS exposure. Based on decades of research on tobacco exposure and policy impacts [5,38], it is very clear that patterns of use, involuntary exposure, and responses to policies are gendered. An Australian study found that women, young people, and people living on a low income are more often exposed to SHS in the home [9]. Similarly, a cross-European study reported that women were more often exposed in the home, while men and people with challenges in paying bills were more likely to be exposed to SHS in workplaces, restaurants, and bars [39]. It is to be expected that patterns of use and involuntary exposure to cannabis and vaping will also be gendered. Further research is needed on gendered patterns of use and sex-specific health effects of cannabis and nicotine vaping, to understand the implications of substituting ENDS and cannabis vaping for combustible tobacco and cannabis products, as well as the consequences of restricting vaping locations. For example, there could be a reduction in health-related harms for women and children living with combustible cigarette or cannabis smokers who substitute with/switch to ENDS or cannabis vaping. However, there is evidence that smoke-free legislation may not have equal benefits for all. Low-income women and men, and those who are renting a home (rather than owning) are more likely to be exposed to SHS, and may have limited capacity to reduce exposure to tobacco smoke in the home and workplace [40]. If there are significant health risks associated with indoor exposure to aerosol vapour, women and men who are experiencing social and economic disadvantage may be less likely to benefit from location restrictions on ENDS and nicotine vaping. Hence, comprehensive approaches to research that include sex-, gender-, and diversity-related factors that will inform equitable policies and regulations are urgently required. Investigation into both gender and SES differences in how vaping restrictions in public spaces impact involuntary exposure in private spaces are warranted to inform and improve policy responses to nicotine and cannabis vaping.

#### 4. Conclusions

ENDS and cannabis vaping products pose significant challenges for researchers, decision-makers, and regulators, who must work quickly to keep pace with new products and a rapidly changing product, policy, and regulatory landscape such as Canada. To date, research on the health effects of involuntary exposure to ENDS and cannabis vaping products has been sex- and gender-blind, as was early tobacco research.

As new ENDS and cannabis vaping products continue to be introduced, and recreational cannabis is legalized in more jurisdictions, it is imperative that researchers and policy-makers reflect on the knowledge gained from tobacco policy implementation, smoking location restrictions, and denormalization policies, and consider sex- and gender-related factors in all research on the health effects of involuntary exposure to vaping products and cannabis policies. Specifically, researchers and policy-makers should explore how regulation and messaging efforts on cannabis smoking and vaping could reflect sex, gender, and equity concerns, and align with that of tobacco and nicotine vaping. This should be considered given overlapping issues such as location restrictions, SHS messaging, and related public health concerns. This way, the relevant science will be improved and

the development of policy responses that are informed by sex, gender, and equity will be accelerated and enhanced.

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Review

# Sex and Gender Interactions on the Use and Impact of Recreational Cannabis

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**Abstract:** Cannabis is the second most frequently used substance in the world and regulated or legalized for recreational use in Canada and fourteen US states and territories. As with all substances, a wide range of sex and gender related factors have an influence on how substances are consumed, their physical, mental and social impacts, and how men and women respond to treatment, health promotion, and policies. Given the widespread use of cannabis, and in the context of its increasing regulation, it is important to better understand the sex and gender related factors associated with recreational cannabis use in order to make more precise clinical, programming, and policy decisions. However, sex and gender related factors include a wide variety of processes, features and influences that are rarely fully considered in research. This article explores myriad features of both sex and gender as concepts, illustrates their impact on cannabis use, and focuses on the interactions of sex and gender that affect three main areas of public interest: the development of cannabis use dependence, the impact on various routes of administration (ROA), and the impact on impaired driving. We draw on two separate scoping reviews to examine available evidence in regard to these issues. These three examples are described and illustrate the need for more comprehensive and precise integration of sex and gender in substance use research, as well as serious consideration of the results of doing so, when addressing a major public health issue such as recreational cannabis use.

**Keywords:** sex; gender; cannabis

## 1. Introduction

Cannabis is the second most frequently used substance in the world, after alcohol [1]. It is an illegal substance in most countries, but increasingly becoming regarded as a controlled substance in various states in the USA and, as of 2018, all of Canada [2]. In 2018, recreational cannabis was legalized in Canada, 17 years after the regulation of medical use. Recreational cannabis use is also legal in Uruguay—for personal use since 1974, and for cultivation and sale since 2013 [3]. Eleven US states plus Washington, D.C. and two US territories (Guam, Northern Mariana Islands) have also introduced legal recreational cannabis use among adults and fifteen US states have decriminalized cannabis. Cannabis is semi-legal in several other countries. For example, Argentina, South Africa, and Mexico have identified punishment for possession of cannabis for personal consumption as unconstitutional; the Netherlands tolerates public consumption and sale of cannabis in licensed coffee-shops; and in Spain personal consumption and cultivation of cannabis is tolerated [3].

When legalization of recreational cannabis occurred in Canada in October 2018, efforts to research the impacts of legalization and use were accelerated and numerous key clinical and public policy issues emerged. In Canada, 17.1% of the population report using recreational cannabis in the past three months, with 20.3% of males and 14% of females reporting such use [4].



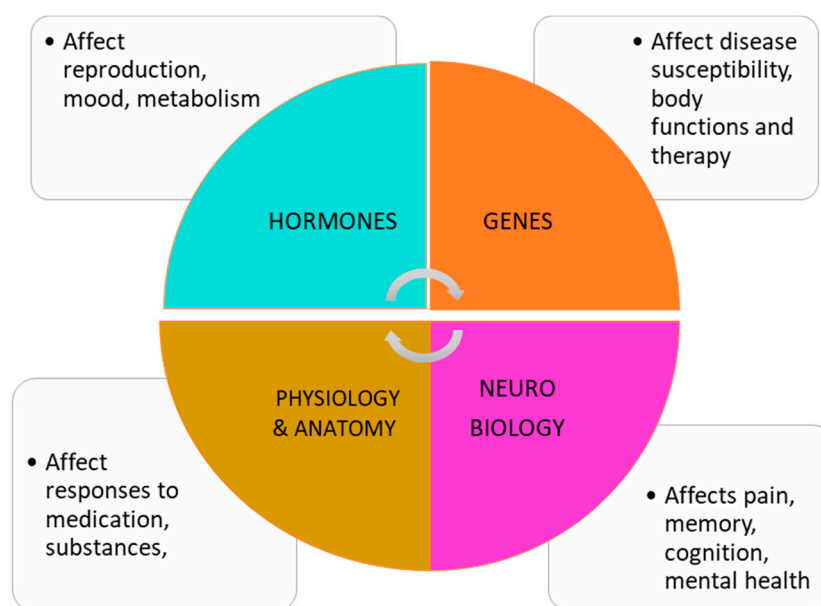
While it is unclear how cannabis policies will evolve in other countries, there will undoubtedly be a rapidly evolving legal and social environment in various countries and jurisdictions, as cannabis use increasingly comes to the attention of regulators. However, its widespread use globally indicates that developing evidence of its impacts is already a critical global health issue. Hence, it is important to actively monitor recreational cannabis use patterns and trends, in particular in Canada and other jurisdictions where legalization has occurred, in order to understand the implications of such regulation and legalization.

It is clear from the wider substance use research field that sex- and gender-related factors (fully defined below) have a profound effect on substance use, the effects of use, and the response to interventions, approaches to treatment and overall policies [5]. As cannabis use trends evolve, it is therefore essential to collect and analyze evidence on sex and gender related factors and the effects on the benefits and risks of cannabis use. In the past, however, the integration of sex and gender concepts in substance use research and policy has often been overlooked [5], thereby preventing the building of evidence for effective programming for all sub populations and individuals. Integrating sex and gender in a disciplined manner within all future cannabis research will inform tailored harm reduction messaging, health information, and prevention and treatment responses for all genders.

### *1.1. How Do Sex and Gender Matter in Substance Use?*

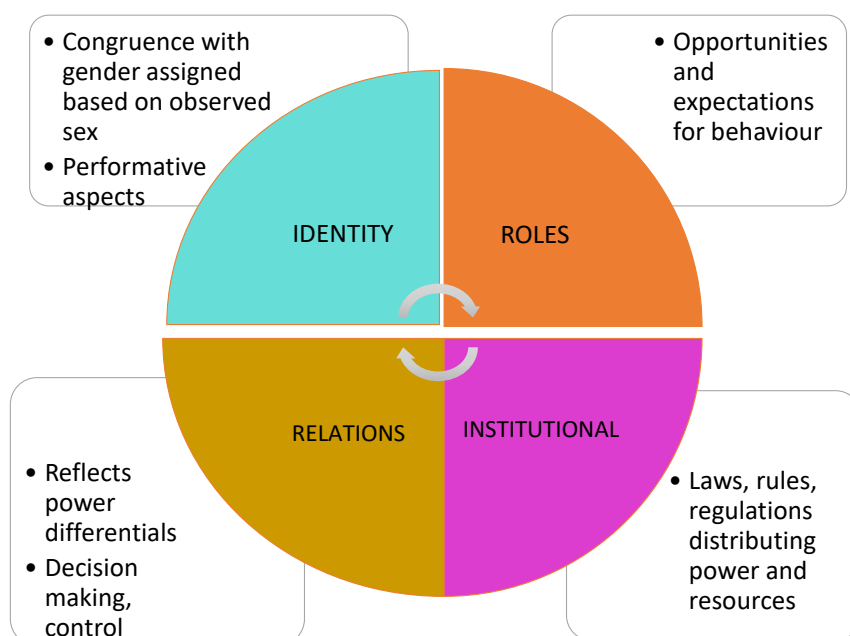
Sex related factors include the biological factors and mechanisms that are affected by, or affect, substance use in male and female bodies, while gender related factors include the effects on all people of gender norms, relations, identity and gendered institutional factors including customs, laws and regulations. Further, sex and gender related factors interact to influence patterns of substance use, effects of use, and responses to treatment. For example, Becker et al. argue that “gender and sex differences in addiction are a complicated interaction between sociocultural factors and neurobiological sex differences” [6]. It is also essential to take a transdisciplinary approach to addictions research in order to capture the myriad conceptual and theoretical perspectives that impact use and responses to substance use [7], including both sex and gender [8]. More specifically, investigating and analyzing interactions between aspects of sex and gender in cannabis research is an important step in understanding the full impact of cannabis use and legalization, as well as developing the required evidence for effective policy, programming, messaging and treatment.

Sex related factors include a number of aspects of human biology, physiology, anatomy and genetics (see Figure 1). Bodily characteristics at birth are either male or female, with a small percentage of individuals who are labelled as intersex due to ambiguous characteristics [9]. These male or female characteristics contribute to a lifetime of developmental milestones, processes and stages, and determine reproductive capacity. In addition, a range of processes are affected by sex-based factors such as rates of metabolism, production of sex hormones, organ function, and development and distribution of adipose tissue, among others. These factors affect the ingestion of substances, including cannabis, and their rate of absorption, effects and impacts on the body and brain. These sex-based factors can also affect the response to therapeutic and treatment regimes, such as pharmaceutical treatments.



**Figure 1.** Sex related factors. These factors include reproductive characteristics, physiological processes, susceptibility to substances, and impacts on all body systems.

Gender is often assumed or ascribed, based on our sex. Gender related factors are those connected to the gender relations we experience, the gender roles and norms to which we are exposed and influenced by, our gender identities (such as feminine, masculine, or gender diverse) and the gendered regulations and rules embedded in institutions such as education, politics and religion (see Figure 2). These factors are often temporal and culturally dependent and can change over time.



**Figure 2.** Gender related factors. These factors include culturally driven influences on relationships, opportunities, access to power, resources, decision making, autonomy, and identity.

For example, substance use initiation patterns can be influenced by gendered relationships with partners or household members or friends, affecting our access and usage of cannabis. These influences can heighten dominant understandings of masculinity or femininity, and be expressed in intimate

partnerships, peer groups, friendships, or families. Gendered roles such as mothering or fathering are often impacted by substance use, in that caregiving is often seen as anathema to substance use, particularly for mothers for whom the stigma associated with substance use is acute. Gender identities and the ‘performance’ of our identities; whether feminine, masculine, or gender diverse (transgender, non-binary, or queer) have an impact on how and why substances such as cannabis are used, ingested, and in what contexts, not to mention how they are marketed and advertised when legal. Finally, large institutions affect substance use by imposing standards, moral teachings, or public education that implies restrictions, rules or opportunities based on gender, all of which can restrict or encourage substance use in gendered ways.

This wide range of gender related factors combine to create social and cultural contexts for substance use that in turn interact and intersect with the sex-based factors, along with a range of other characteristics such as sexual orientation, age, income, ethno/racial characteristics, Indigenous status, ability, rural and remote life, occupation, etc., to create both clinical and public health impacts.

In short, both sex and gender are of relevance and importance to any researcher or clinician investigating any substance use, including recreational cannabis. If such concepts are introduced (in disciplined and precise ways) into research designs, measured, analyzed, and reported, the resulting evidence will contribute to improved public education and health information for the population. This will enable the promotion of safe cannabis use, which is especially important in a rapidly changing policy environment. Further, including sex and gender in the analysis of the impact of policy can lead to more tailored and sharpened regulations, standards and public policy.

### 1.2. Gendered Trends of Use

Similar to most substances, more men than women use cannabis. According to data from the 2019 National Cannabis Survey in Canada, more men than women reported cannabis use in the past three months (20.3% vs. 14%). Further, men are more likely to report greater frequency of use and are twice as likely as women to report daily or almost daily use (8% of men vs. 4% of women). Indeed, after alcohol, cannabis is the most commonly used substance in Canada. These national statistics on cannabis use in Canada mirror evidence from the US and Europe where boys and men also report greater prevalence of cannabis use. Indeed, the prevalence of cannabis use among boys and men is higher compared to girls and women for past year [10–12], lifetime [13,14], and past 90 day use [15]. However, again, similar to historical trends of other substances there is evidence of a narrowing in the gender gap [14,16]. Some researchers suggest that the diffusion of cannabis use and experimentation appears similar to that observed with tobacco, with use beginning among men and more educated and higher income groups first, with later diffusion to women and lower socioeconomic status groups [16]. While population based data on prevalence of cannabis use among transgender populations are limited, a study conducted in the USA with  $n = 1210$  transgender adults identified cannabis use among 24.4% of the sample; and cannabis use was significantly greater among transgender men compared to transgender women [17].

The majority of available studies and surveys have focused on gendered patterns and preferences for cannabis use. These forms of data are instrumental in offering insight into modes of use and trends of use. For example, there is evidence of gendered preferences for cannabis routes of administration [18], and that dominant gender norms may be reinforced or resisted through cannabis use behaviors [19]. With respect to sex related factors, some recent reviews have examined preclinical and clinical research on sex differences in the therapeutic effects of cannabis and potential for abuse [20] and on the sex-specific neurobiological mechanisms of cannabis use and dependence and associations with psychiatric symptoms [21]. Early evidence of sex differences from animal studies and (to a lesser extent) human studies suggests that females may be more sensitive to cannabis or cannabinoids in general [21], may transition to problematic cannabis use faster than males, and exhibit more intense withdrawal symptoms during abstinence [20].

Clearly, sex and gender related factors both matter in the context of cannabis use and there is much yet to explore in research and clinical practice. Overall, evidence on either sex or gender and cannabis use is lacking and nascent [22]. However, there is also a clear lack of research examining the interactions of sex and gender based factors on cannabis use and its effects. Hence, this paper draws on evidence from two scoping reviews to explore sex and gender based factors, and the potential interactions of these factors in the context of three key and current cannabis use practice and policy issues: cannabis use dependence, cannabis routes of administration (ROA), and driving under the influence of cannabis. These three exemplars comprise: a key clinical issue, a key health promotion/harm reduction issue, and key public policy issue. These are all important issues in early phases of legalized cannabis regimes, and all currently under scrutiny in Canada.

## 2. Materials and Methods

This article draws on evidence from two scoping reviews examining sex and gender related factors in the context of cannabis use, including: (1) a scoping review on sex, gender and substance use which identified  $n = 784$  papers on cannabis; and (2) a more specific scoping review on sex, gender and cannabis routes of administration. The methods for the former are described in full in Hemsing and Greaves [23]. The methods for the latter review are described below.

### *Scoping Review on Routes of Administration*

We conducted a second scoping review of the academic and grey literature to identify literature on cannabis routes of administration (ROA). Specifically, we searched the literature for evidence on sex, gender and cannabis smoking or cannabis vaping, and health promotion, harm reduction and policy approaches to ROA.

The research questions were:

(Q1) How do sex and gender related factors impact:

- (a) The mode of cannabis or tobacco/nicotine use (ROA)?
- (b) The health effects of various cannabis routes of administration?

(Q2) What existing health promotion, harm reduction and policy approaches to cannabis ROA are available? Do these approaches include a sex/gender/equity lens?

The following academic databases were searched:

Medline, Embase (including Ovid), Cochrane; CINAHL, PsycINFO, Social Work Abstracts, Women's Studies International, and Social Science Citation Index via Clarivate Analytics

The search covered studies published in the past 10 years (2009 to 2019) combining the following search terms on sex/gender and ROAs:

women; man; women; men; girl; boy; girls; boys; trans; transgender; female; male; sex; gender AND cigar\*; e-cigar\*; tobacco; nicotine; smoking; vaping; "heat not burn"; marijuana; cannabis; cannabinoid.

In total,  $n = 2332$  studies were identified after duplicates were removed. One researcher screened abstracts and full papers, including studies that measured and analyzed some aspect of sex or gender, and that examined cannabis or tobacco routes of administration. Following abstract screening and full paper screening,  $n = 122$  studies were included. In addition, we conducted a targeted search on the co-use of cannabis and tobacco and identified an additional 80 studies; after abstract and full paper screening, 19 of these studies were identified as relevant. In total,  $n = 131$  papers were included in the scoping review.

This paper draws on some of the key findings from these two scoping reviews to consider the interplay of sex and gender in the context of cannabis use on three topic areas: cannabis use dependence,

driving under the influence and cannabis routes of administration. Given the paucity of evidence on the interaction of sex and gender in cannabis use, relevant findings on sex, gender and substance use are included to explore biological and social interactions.

### 3. Results

#### 3.1. Cannabis Use Dependence

Cannabis use disorder (CUD) affects approximately 10% of cannabis users [1]. It results in a range of symptoms, such as using cannabis in larger amounts or greater frequency than intended, challenges with cutting down, and withdrawal symptoms including anxiety and insomnia [24]. Despite the minority of users developing CUD, it is a high priority public health issue as dependency can interfere with social and economic activities, as well as negatively impact health and wellbeing. Monitoring the potential CUD effects post cannabis legalization is a key aspect of assessing the clinical impact of such legislation.

Sex and gender related factors both affect the development and impact of cannabis use disorder. Similar to other substance use, there is emerging evidence that females transition more quickly to cannabis use dependence compared to males, a process often called “telescoping” [25,26]. Cross-sectional studies analyzing US national data reported no differences between females and males in the age at first or heavy cannabis use, age at onset of CUD, total number of episodes of cannabis abuse or dependence, or in the number of criteria met for cannabis dependence [25]. However, the time from age at first use of cannabis to the age at onset of the CUD was longer among males (mean = 2.64 years vs. 2.24 years,  $F = 5.20$ ,  $p < 0.05$ ), providing support for telescoping among females who use cannabis [25].

Similarly, a second study found that while prevalence of CUD was greater among males, females reported a shorter duration from onset of cannabis use to onset of CUD compared to men (mean of 5.8 vs. 4.7 years) [26]. Clinical research also indicates greater abuse liability among females, such that females reported greater subjective effects at lower doses of oral THC (5 mg), while males reported greater subjective effects at higher doses (15 mg) [27]. The authors suggest these sex differences in subjective effects may contribute to the more rapid progression to dependence (telescoping) observed in females [27]. Clearly, more robust research on cannabis telescoping is needed to inform tailored prevention and harm reduction approaches for women and girls, in particular.

There is also emerging evidence that females may experience greater severity of cannabis dependence. In animal studies (mostly rodents) females have demonstrated slightly greater withdrawal symptoms compared to males, which is one component of dependence [28,29]. However, there are clear challenges in translating findings from animal to human studies including: more controlled experimental conditions, different methods of administration, the tendency to use synthetic forms of cannabinoids, and translational challenges due to the differences between animal and human bodies. Unfortunately, females tend to be underrepresented in human studies despite evidence of a telescoping effect [30].

However, there is some evidence based on self-reports of more severe CUD symptoms among women. Analysis of the US National Epidemiological Survey of Alcohol and Related Conditions ( $n = 43,093$ ) found that both women and men who used cannabis reported a lower quality of life compared to those who did not use cannabis, and women and men with CUD reported a lower quality of life compared to those without CUD [31]. However, the negative effect of cannabis use on mental quality of life scores was more pronounced for women. Each daily joint smoked was associated with a greater decrease in mental quality of life summary scores in women compared to men [31]. This effect does not appear to be due to higher prevalence of depression among women who used cannabis, as there was no difference in the prevalence of mood and anxiety disorders between women and men in the sample who used cannabis. In our review, another study also reported greater CUD severity in women. In a sample of treatment-seeking adults with CUD, women reported greater



withdrawal intensity, more co-occurring mental health issues (including lifetime panic disorder and current agoraphobia), and more days of poor physical health [32].

Both the telescoping effect and differences between women and men in the severity of CUD, may reflect the influence of sex hormones, the endocannabinoid system, and pharmacodynamics and pharmacokinetics. Neurobiological differences have been identified in the endogenous cannabinoid system of females and males. Studies examining the neural regions of rats have reported greater CB1 receptor desensitization and downregulation in females, which may in part explain cannabis telescoping among females [33]. In addition, sex hormones may modulate cannabinoid sensitivity [34–36]. However, studies on the influence of sex hormones on responses to cannabinoids in humans are lacking [21]. Cannabis pharmacodynamics and pharmacokinetics may also be implicated in the development of dependence. While sex differences in the metabolism of cannabinoids have been demonstrated in animal studies, these findings have not, to date, been found in human studies. For example, female rats metabolize THC more quickly than males [37,38], although this effect was reversed when CBD was provided to the rats before injection with THC [38]. Female rats also produce more 11-OH- $\Delta^9$ -THC, the primary active metabolite of THC, while males metabolize THC to 11-OH- $\Delta^9$ -THC and other inactive metabolites [21]. Further research is required to investigate the biological mechanisms underpinning sex differences in the progression to cannabis use dependence and the severity of cannabis use dependence.

While it has not yet been investigated, there may also be a gendered dimension to the greater severity of CUD reported by women. Women experience greater stigma and discrimination when they use substances of any kind, and this may partially explain the greater severity of CUD observed among women in some observational studies. For example, women may experience and report more shame and blame regarding their substance use, particularly if they are pregnant or parenting [39]. In general, women with substance use issues tend to experience more isolation and less social support compared to men [6]. The experience of stigma creates additional barriers to accessing substance use services and supports for substance use dependence and related health and social services, which may exacerbate the negative effects of women's cannabis use dependence. Identifying the specific sex and gender factors associated with greater CUD severity among women, and tailoring treatment responses to ameliorate these risks is an important consideration for intervention development.

However, despite evidence of a telescoping effect and greater severity of CUD for females, males are more likely to be diagnosed with CUD [13] and tend to report a younger age of onset of CUD [40]. If there is evidence of a more rapid progression to dependence among females, and emerging evidence that females with CUD may be more severely impacted, why are men more likely to be diagnosed with CUD? As argued by Becker and colleagues, biological vulnerability does not equate to greater prevalence of dependence [6]. While biological factors impact the reinforcing effects of cannabis, social and environmental factors also influence the development of CUD [41]. Specifically, gender roles and norms may impact the risk of developing CUD. Men and boys tend to have greater prevalence of cannabis use, initiate earlier and use cannabis more frequently; and being male has been identified as one of the greatest risk factors for developing CUD [41].

Gender differences in the prevalence of substance use are in part due to men's greater access to substances relative to women [42]. Substance use is more socially acceptable among boys and men relative to girls and women, and therefore men tend to have greater opportunities and access to substances in their social environments. In addition, adherence to dominant masculine norms boys has been associated with increased risk taking and substance use behaviors in general [43]. This is also reflected in the cannabis research literature suggesting that men tend to engage in riskier patterns of use, thereby increasing their risk of cannabis use dependence. For example, boys and men tend to report using a greater variety of cannabis routes of administration [18], and use higher potency cannabis products including cannabis concentrates [44] both of which increase the risk of dependence. With expanding cannabis legalization and increasing normalization of use, it will be crucial to monitor changes in gendered patterns of use and risks of dependence, particularly given the emerging evidence on greater biological vulnerability to dependence among females.

### 3.2. Routes of Administration

Routes of administration (ROA) refer to the various methods of using, inhaling or ingesting cannabis. These include: smoking, vaporizing, heating, ingesting oils or edibles, or using topical versions of cannabis such as creams. It is often assumed that smoking cannabis is the standard approach, both in popular culture and often implicitly, in policy and health promotion. However, examining and comparing the effects of ROAs using sex and gender related factors is essential to creating more precise and harm reducing health information and advice. The majority of the studies on cannabis ROAs that include an analysis of sex or gender have simply described prevalence and patterns of use. Men and boys tend to report higher rates of inhalation ROAs (smoking and vaping), including: joints, blunts, vaporizers, and concentrates [15,45], and water pipes/bongs [46]. There is some evidence that young women [47] and girls [48] may prefer edible cannabis products.

Several human studies have examined the pharmacokinetics of smoked cannabis. Some have demonstrated higher concentrations of THC and THC-COOH levels among females compared to males after administration of smoked [49,50] or vaporized cannabis [50], and greater subjective ratings of cannabis intoxication among females [49]. In contrast, a study with young adults aged 19–25 years who regularly used cannabis (1–4 days per week) found that females smoked less of the cannabis cigarette compared to males to reach their desired effect, but that blood THC and THC-COOH (a metabolite of THC) levels were lower among females compared to males even after adjusting for differences in the dose of THC inhaled [51]. The authors suggest that the similar subjective effects experienced by females at lower doses may reflect sex differences in the endocannabinoid system, as some animal studies have demonstrated greater cannabinoid type-1 (CB1) receptor availability and binding affinity with cannabinoids in females [51]. Ovarian hormones may also influence the subjective effects of cannabis in females; studies with other substances have revealed differences in subjective effects depending on menstrual cycle phase, though similar research on cannabis is currently lacking [51].

Further, Matheson et al. (2019) suggest that there may be sex differences in cannabis smoking topography [51]. In their experiment, females and males smoked for the same duration yet females smoked less of the cannabis cigarette suggesting they took smaller puffs, inhaled less deeply or held the smoke in the lungs for a shorter duration [51]. This finding may be influenced by neuro-biological factors, such as greater cannabinoid sensitivity among females [21], causing females to titrate their dose via their smoking behaviors. There could also be gender related influences; for example, a qualitative study with cannabis using women and men found that women often reported only smoking part of a joint, and typically avoided more “intense” ROAs such as water pipes/bongs, instead preferring a more gradual high [52]. The authors suggest these patterns of cannabis use align with feminine norms regarding the avoidance of excessive substance use and intoxication [52].

Recently, the emergence of e-cigarette or vaping associated lung injury (EVALI), highlights how gendered cannabis ROA preferences may shape health risks. EVALI has primarily affected young men (70%) in the USA and the majority of the reported cases have involved vaping THC products [53]. In the context of an unregulated market, young men may be more likely to access counterfeit cannabis vaping cartridges that are contaminated, increasing their risk of EVALI. Combined with broad improvements in the regulation of vaping products, tailored prevention and harm reduction responses are needed.

The preferences of women and girls for edible cannabis may reflect gender roles and norms regarding the social acceptability of substance use. Inhalation methods are more visible, while edible use can be easily concealed. This may be a more desirable option for girls and women, to avoid experiencing discrimination and stigma related to their cannabis use. This was reflected in a focus group study which found that girls reported a preference for edible cannabis because these products are more discreet [54]. However, given the challenges of titrating edible cannabis dosage, these trends and preferences signal the need for gender informed harm reduction messaging.

There is also evidence of differences in preferred ROA within groups of women and men. For example, women who are pregnant may prefer inhalation methods, because of the difficulty

ingesting due to nausea [55]. This is an example of how biological factors—hormonal changes and/or pregnancy-related nausea, may underpin preferences for cannabis ROAs.

Culture can also intersect with gender roles to influence preferred routes of administration. Mixing cannabis with tobacco, often called “spliffs” is a common practice in some countries, particularly in the UK, European countries, and Australia [56]. In a qualitative study with Australian men who “mulled” (smoked a mixture of cannabis and tobacco), men described the effects of mixing tobacco and cannabis as producing a milder, more manageable “high” [56]. They described feeling more “grounded” than if they smoked only cannabis, and they preferred this effect as they were able to continue to participate in family and work responsibilities. In addition, blunt use—hollowed out cigars filled with cannabis, have been promoted through hip-hop culture [57], and are particularly popular among young Black males in the USA [58–62]. However, cannabis use ROAs that combine cannabis and tobacco, such as spliff and blunt use, confer greater risk of dependence [57] as well as adverse respiratory health effects. Gendered and/or culturally sensitive harm reduction messaging that addresses the risks associated with co-use of cannabis and tobacco is warranted.

In short, the sex and gender interactivity affecting ROA choices and effects should be areas of key concern to clinicians, researchers, and health promotion and harm reduction specialists. Currently precise and gendered health information aimed at the general public about ROA choices is lacking, along with tailored information that includes basic evidence on sex and gender.

### 3.3. *Driving Under the Influence of Cannabis*

Driving under the influence of cannabis is a key public policy issue in jurisdictions that have legalized recreational cannabis. Discussions about legalization of cannabis often focus on estimating risks associated with possible impaired driving. Not surprisingly, after the legalization of cannabis in Canada in 2018 there has been increased interest in understanding cannabis related impairment and preventing and responding to driving under the influence of cannabis. This emphasis formed one of the key focal areas of health promotion and messaging campaigns aimed at young people in particular [63].

Impaired driving is a gendered activity, with the prevalence of driving after cannabis use higher among men. In a Swedish study, a greater proportion of men were apprehended with THC concentrations detected in their blood (94% vs. 6%), and among those with detected THC, blood concentrations were higher in men than in women (mean 2.1 ng/mL vs. mean 1.4 ng/mL) when cannabis was the only substance detected [64]. In a US study, among college students who reported past month cannabis use, 43.9% of males and 8.7% of females reported driving after cannabis use [65]. In addition, males were more likely to report riding as a passenger with someone who had recently used cannabis (51.2% vs. 34.8%). O'Malley and colleagues' analysis of US high school seniors also found that male students were more likely to report driving after smoking cannabis; however, there was no gender difference in riding as a passenger after cannabis use [66].

Gendered patterns of cannabis use likely influence the risk of driving under the influence of cannabis. In one study, males were more likely to both vape and use cannabis edibles; and more frequent vaping was associated with driving under the influence [67]. As discussed above, in general, boys and young men tend to engage in riskier substance use behaviors. Boys and men are also more likely to co-use cannabis and alcohol, which significantly increases impairment, driving errors and accidents [68]. Further, compared to women, men tend to perceive lower harm with driving under the influence of cannabis, are less likely to believe that cannabis negatively affects their driving ability, are more likely to perceive their friends as approving of driving under the influence of cannabis, and are more likely to report an intention to drive after cannabis use in the future [69]. These gendered patterns of cannabis use and beliefs and perceptions are clear and critically important targets for gender specific harm reduction and health promotion efforts. Specifically, gender informed harm reduction messaging is needed that addresses both driving after cannabis use and riding as a passenger with a driver who has recently consumed cannabis.

Sex differences in the subjective effects of cannabis may impact impairment. As noted above, the greater subjective effects that females tend to experience at lower doses and with a lower blood level of THC may suggest the potential for greater impairment with a lower dose of cannabis among females [51]. It is possible that females may require more time to achieve sobriety before driving, though further research is required to investigate sex differences in the metabolism of cannabinoids and the effects on intoxication and impaired driving. This evidence can be used to inform more precise and refined harm reduction and health promotion responses, messages, and recommendations. Sex specific measures of impairment are lacking; further research is needed to understand sex differences in cannabis impairment and effects on attention and driving to inform measures of impairment and enforcement of impaired driving laws.

It is clear that more research is needed to examine sex differences in driving related impairment. In simulated studies by Anderson et al., they found no evidence of any sex differences. They studied the effects of inhaled THC on attention impairment among people who used cannabis occasionally (participants reported using cannabis at least once per month, but no more than 10 times per month), while driving in a simulator [70], and found no sex differences in the impact of cannabis use. In another study, participants reduced their overall driving speed and performed more poorly on a neuropsychological test following the driving simulation, but no sex differences were observed [71]. In short, this vital area of public policy is still lacking in research that would enable health promoters and enforcement officials to better target their messaging and policy using comprehensive sex and gender related evidence.

#### 4. Discussion

Research on sex and gender related factors and cannabis use and its effects is in its infancy. This area needs considerable attention and growth in light of the high level of cannabis use globally, as well as the legalization of cannabis in various jurisdictions. We have reported elsewhere on known sex and gender related factors that appear to affect use, impact and effect of cannabis use [22]. In this article we have elucidated the various components of sex and gender that are relevant to the study of recreational cannabis use (and other substances) and illustrated how sex and gender interact and combine their effects. We illustrated these interactions in three examples relevant to health outcomes, health promotion and public policy: the development of CUD, the differential choices and impacts of ROA, and cannabis impaired driving.

Aside from one review that acknowledges the influence of both social and biological factors on cannabis use [41], most of the literature we found in our searches for sex and gender influences on cannabis use and ROA has examined either sex related or gender related factors. Going forward, a framework may be useful for examining the interactions of sex and gender, along with other social dimensions of health and equity. There have been calls for understanding intersectional factors affecting health, including the intersection of sex and gender [72]. While intersectional frameworks have been criticized for not adequately attending to biological factors, some proponents have identified opportunities for integrating biological and social dimensions of health within this framework, and begun to consider how biological factors intersect with other factors including gender, class, and ethnicity to address health inequities [73].

Physiological aspects of sex are increasingly understood as being influenced by gender-related social dynamics [74]. Yet, most of the evidence on gender and cannabis to date has focused on noting simple differences between women and men and boys and girls in patterns and prevalence of use. The evidence on sex differences in cannabis use is largely confined to animal studies, and studies on humans have not consistently included female participants and/or integrated a full sex-based analysis. More research is needed to understand how male and female bodies respond to cannabis use and the respective health consequences of use, and the influence of social factors on biological mechanisms. This evidence can then be used to inform more precise harm reduction and health promotion messaging, similar to the sex specific Canadian Lower Risk Drinking Guidelines [75]. Overall, the development of

precise, sex, and gender tailored responses to cannabis use are needed to reduce harms, maximize benefits, and improve clinical treatment and health promotion.

Despite these current limitations and insufficiencies, these early findings on cannabis use dependence, cannabis routes of administration, and driving while under the influence have important implications for prevention, health literacy, public education, and treatment. For example, tailored messaging is needed to address risky patterns and consequences of use among boys and men, including greater and more frequent cannabis use, inhaling high potency/high THC products, co-use with alcohol and tobacco, and driving or riding with drivers under the influence of cannabis. For women, emerging evidence on female vulnerabilities to developing dependence and severity of CUD could inform prevention and treatment responses. If telescoping occurs more quickly in females, compounded by increased social stigma directed at women, treatment options should be more readily available for women at the earliest stage possible.

In addition, gender specific efforts can be made to address and reduce discrimination and stigma for all groups, via public education and in the design and delivery of substance use services. Further, considering sex and gender together in cannabis use, can pave the way for gender transformative initiatives in health promotion and messaging. Such approaches simultaneously reduce risky use and work toward gender and health equity in cannabis prevention, harm reduction and treatment responses, thereby alleviating inequities associated with cannabis use [76,77].

It will be critical to continue to monitor and collect data on gendered cannabis use patterns. Patterns of use may change as recreational cannabis becomes increasingly normalized, and producers and advertisers tailor product promotions to target specific groups. As discussed, the gender gap appears to be narrowing [16] and there are indications that cannabis vapour product producers are marketing specific devices to girls and women [78]. If the gender gap in cannabis use continues to narrow, and girls and women begin to use different cannabis ROAs, this will likely affect their health and social consequences of cannabis use including cannabis dependence and driving under its influence.

## 5. Conclusions

While research on recreational cannabis use is rapidly expanding in response to a shifting policy landscape, research specifically focussed on the impact of sex and gender on its use is in its infancy. More adherence and precision is required in applying sex and gender related concepts to the study of substance use in general, and cannabis use in particular. Robust studies are needed to investigate a full spectrum of sex related factors in the effects of cannabis use; and to explore how gender norms, roles, relations and identities all impact cannabis use and health and social consequences. Further, as illustrated using the examples of CUD, ROA and impaired driving, research is needed that examines the interactions of sex with gender related factors and other social determinants of health including class, age, income, and ethnicity to address and prevent inequities in health related to cannabis use. Advancing knowledge on the interaction of sex, gender and equity based factors will inform more responsive health promotion, effective harm reduction, and precise treatment approaches for all genders.

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Review

# Sex- and Gender-Based Analysis in Cannabis Treatment Outcomes: A Systematic Review

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**Abstract:** There is evidence that sex- and gender-related factors are involved in cannabis patterns of use, health effects and biological mechanisms. Women and men report different cannabis use disorder (CUD) symptoms, with women reporting worse withdrawal symptoms than men. The objective of this systematic review was to examine the effectiveness of cannabis pharmacological interventions for women and men and the uptake of sex- and gender-based analysis in the included studies. Two reviewers performed the full-paper screening, and data was extracted by one researcher. The search yielded 6098 unique records—of which, 68 were full-paper screened. Four articles met the eligibility criteria for inclusion. From the randomized clinical studies of pharmacological interventions, few studies report sex-disaggregated outcomes for women and men. Despite emergent evidence showing the influence of sex and gender factors in cannabis research, sex-disaggregated outcomes in pharmacological interventions is lacking. Sex- and gender-based analysis is incipient in the included articles. Future research should explore more comprehensive inclusion of sex- and gender-related aspects in pharmacological treatments for CUD.

**Keywords:** sex- and gender-based analysis; SGBA; cannabis use disorder; randomized controlled trial

## 1. Introduction

Growing evidence related to the importance of sex- and gender-based factors within health research has led to increased interest among researchers, funding agencies, scientific journals and database creators to find innovative ways of examining these factors in previously unexplored areas [1–3]. The integration of sex- and gender-related factors into research, policy, or health programs revisits or identifies the influence of components such as anatomy, physiology, genetics and other bodily characteristics biological (sex-based) and the social and cultural milieu affecting humans socio-cultural (gender-based) is known as sex- and gender-based analysis (SGBA) [4]. Sex and gender are not independent of other social characteristics and they might interact with each other and other characteristics to influence health outcomes [5].

Randomized controlled trials (RCT) provide the strongest research evidence and are often used to test the efficacy of new pharmacological interventions. However, sex- and gender-based analysis in RCTs is very scarce. For example, in a study that analyzed 100 Canadian-led or funded RCTs, Welch et al. found that 98% of studies included sex in the description of sociodemographic characteristics of the participants, while only 6% conducted a subgroup analysis across sex, and only 4% reported sex-disaggregated data. None of the examined articles included a definition of “sex” or “gender” nor a comprehensive sex- and gender-based analysis [6]. Failing to include a sex- and gender-based analysis of the outcomes might have important and serious clinical consequences for individuals or subgroups of patients.



There are differences between women and men in referrals and pathways to substance use treatment in general. For example, women are less likely to be referred to residential treatment than men [7]; women are more likely to be referred to outpatient treatment vs. residential treatment [7,8]. Women tend to access substance use services via primary health care or mental health services vs. specialty substance use treatment services [8,9], while men are more likely to enter treatment via the criminal justice system [10]. Lack of awareness of options, stigma, confrontational treatment models, and lack of childcare are some of the common barriers encountered by women when accessing treatments for substance use [9]. Women tend to enter treatment with a more severe clinical profile and more problems related to mental health, family, interpersonal relationships, and physical health [9–12]; while men have more legal, criminal, and financial problems [13].

There are also differences in response to treatment for other substance use. For example, evidence derived using a sex- and gender-based analysis reveals that women have additional difficulties in tobacco smoking cessation. Women have poorer smoking cessation outcomes with some pharmacological supports, including nicotine replacement therapy, regardless of whether combined with counselling [14]; and bupropion [15]. In contrast, treatment with varenicline has shown similar, or better, outcomes for women compared to men [16–18]. Women tend to require more smoking quit attempts before achieving cessation. While women report lower quit rates, the use of any medication increases women's likelihood of cessation [19].

Women and men receiving treatment for alcohol use disorder (AUD) report similar rates in reductions and/or abstinence from alcohol, including medical management and behavioral counselling for AUD [20]; treatment with the medication acamprosate (based on a meta-analysis) [21]; and residential treatment [22]. Studies on the effectiveness of naltrexone treatment for AUD treatment are mixed, with some studies reporting similar outcomes for women and men [22,23], and others reporting a greater reduction in craving scores for women [24], or greater reductions in alcohol use (and other substance use) in men [25]. The limited evidence examining sex differences in treatment outcomes for opioid use disorder (OUD) have reported similar improvements in opioid use outcomes for women and men following a medical management intervention (tapering with buprenorphine–naloxone) either alone or combined with counselling [26].

## 2. Sex- and Gender-Based Analysis in Cannabis Research

There is growing evidence that sex- and gender-related factors are involved in cannabis patterns of use, health effects and biological mechanisms. Men and boys are more likely to initiate cannabis use earlier, and use more frequently and in greater quantities, compared to women and girls. However, the gender gap has been narrowing over time [27,28]. For example, an analysis of US trends in adolescent cannabis use from 1999 to 2009 revealed that in 1999, 51% of boys and 43.4% of girls reported lifetime cannabis use, while in 2013, this decreased to 42.1% for boys and 39.2% for girls [27]. Furthermore, sex and gender factors also intersect with factors such as education and cultural context. Evidence suggests that the diffusion of cannabis experimentation among men appears similar to that observed with tobacco, with use beginning among men and the most educated groups first, in countries such as USA and Germany. In France, cannabis experimentation continues to be more prevalent among women with higher education [28].

Not everyone who uses cannabis transitions to cannabis use disorder (CUD). It is estimated that approximately 9% of those who initiate cannabis use will meet the criteria for cannabis use dependence. Those who initiate during adolescence have an increased likelihood (16.6%) of developing CUD [29,30]. Multiple factors have been associated with cannabis use disorder in women and men. Specifically, both frequency of use and form of cannabis used have been associated with CUD. Among females, cannabis use with strangers was more strongly related to being diagnosed with CUD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) compared to males [31]. Compared to women, men have a younger age of onset for CUD [32]. Polysubstance use, trauma and violence may also be risk factors for CUD. In a US study, sexual abuse and history of alcohol use disorder were more

strongly associated with 12 month CUD among females, compared to males [33]. Men with lifetime CUD were more likely than women to be diagnosed with any psychiatric disorder, any substance use disorder and antisocial personality disorder, whereas women with CUD had more mood and anxiety disorders [34].

Similar to other substance use, there is some evidence that females transition more quickly to cannabis use dependence compared to males. Studies found that women demonstrate a “telescoping effect”, meaning a shorter duration from onset of cannabis use to onset of CUD [34–36]. In a nationally representative sample of the U.S. population, there were no gender differences in the age at first or heavy cannabis use, age at onset of CUD, total number of episodes of cannabis abuse or dependence, or in the number of criteria met for cannabis dependence. However, the time from age at first use of cannabis to the age at onset of the CUD was shorter among women [34].

The results of studies on the subjective effects of cannabis are mixed, and seem to depend on the dose, route of administration (oral vs. smoked) and population (e.g., user vs. non user) [37]. After inhaling tetrahydrocannabinol (THC), women rated themselves as “higher” than men [38]; and reported higher ratings of cannabis as “good” and desire to “take again” compared to men [39]. Another study demonstrated women were more likely to describe cannabis as “good” at low doses, while men more likely to report the same at high doses [40]. In animal studies, female rats exhibit greater drug seeking behavior. In one study that primed rats for drug use and cues before a period of absence, females exhibited higher baseline cannabis intake during training, and reinstate responding for the cannabinoid at higher levels than males [41].

Finally, women and men report different CUD symptoms. For example, several studies report that women have worse withdrawal symptoms compared to men mostly related to gastrointestinal and mood symptoms [42–45]. Men are more likely than women to report experiencing insomnia and vivid dreams as withdrawal symptoms [45]. These findings have important implications since withdrawal symptoms correlate with relapse [46]. Moreover, in a sample of treatment-seeking adults with cannabis use disorder, women reported more co-occurring mental health issues (including lifetime panic disorder and current agoraphobia), and more days of poor physical health [45]. Although CUD is associated with poorer mental health and quality of life in both women and men, this pattern is more pronounced in women with CUD [47]. Animal studies also illustrate the impact of sex-related factors on withdrawal symptoms. Several studies show that females have slightly greater withdrawal symptoms than males [48]. After a week of daily THC treatment in Sprague–Dawley rats, Harte-Hargrove et al. observed the presence of locomotor depression in females but not males during the abstinence period [49].

### 3. Objective of the Present Study

This systematic review draws on a much broader scoping review on sex- and gender-related factors in substance use (initiation/uptake, patterns of use), effects, and prevention, treatment or harm reduction outcomes for four substances (opioids, alcohol, tobacco/nicotine and cannabis use). It also examined harm reduction, health promotion/prevention and treatment interventions and programs that include sex, gender and gender transformative elements to address each of the four substances. The methodology of the scoping review is described in full elsewhere [50].

Despite the evidence regarding sex and gender differences in, and impacts of cannabis use, little is known about sex- and gender-related factors in pharmacological interventions for cannabis dependence. Pharmacological interventions for cannabis dependence have been recently reviewed [51,52], but sex and gender factors have not been closely examined. Therefore, the purpose of this systematic review was to evaluate the effects of sex and gender factors in cannabis pharmacological interventions.

Our initial research question was:

What cannabis pharmacological interventions are available that include sex, gender and gender transformative elements and how effective are these in addressing cannabis use?

After examining the results of the original scoping review and realizing that there is a lack of examination of sex and gender factors in substance use interventions, and more specifically in cannabis pharmacological interventions, we decided to analyze the studies on cannabis pharmacological interventions that included women and men and sex-disaggregated the outcomes of the interventions for both sexes. In addition, we assessed the role of sex- and gender-based analysis in the included studies.

The research question was then updated to:

What cannabis pharmacological interventions are available that include both sexes and how effective are these in addressing cannabis use for women and men?

#### 4. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [53].

##### 4.1. Search Strategy

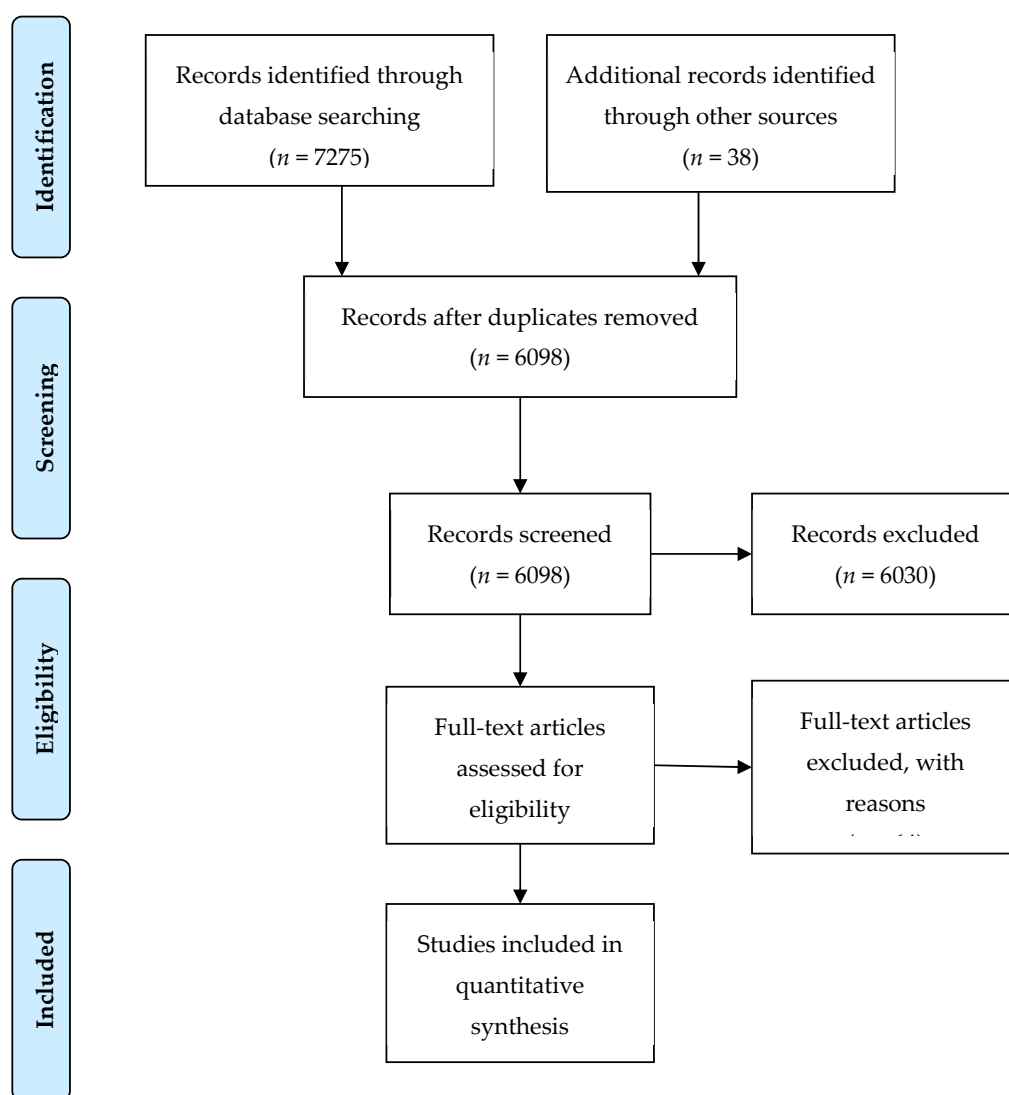
A systematic search of the literature was undertaken to identify relevant studies published in English between 2007 and 2019 (up to fourth week of October). The following databases were used: PubMed, CINAHL, PsycINFO, and Embase. The search strategy was developed based on keywords and Medical Subject Headings (MeSH) terms. We based our search strategy on the search strategy developed for the scoping review [50] and, in addition, we also included more keywords relevant to pharmacological interventions such as “drug therapy”, “pharmacotherapy”, “pharmacology”, “cessation”, “addiction treatment” that were not included in the previous scoping review. An additional search was also completed from a recent systematic review on cannabis pharmacological interventions. Thirty-eight articles were included for the screening in this systematic review.

##### 4.2. Literature Screening

Searches in four databases resulted in  $n = 6098$  unique returns. Firstly, titles and abstracts were screened by a single reviewer for relevance. Then, the full-text of the articles were obtained and reviewed by two reviewers according to the inclusion criteria. These inclusion criteria were: (a) English language articles from a selection of Organization for Economic Cooperation and Development (OECD) member countries such as Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, United States; (b) the population of interest included: women, girls, men, boys of all ages and sociodemographic characteristics; (c) studies including pharmacotherapies that targeted cannabis use (in addition to other comorbid conditions) and presented sex-disaggregated data; (d) studies that analyzed outcomes such as cannabis abstinence or cannabis reduction; (e) randomized clinical trials. Articles were excluded if: (a) although both women and men were included in the study, outcomes of the interventions were not sex-disaggregated; (b) the study did not examine a pharmacological intervention aiming to modify cannabis use; (c) studies were conducted in a non-OECD country; (d) studies analyzed baseline characteristics of the population but the analyses are not done in relationship to the pharmacological treatment. Figure 1 provides an overview of the literature search returns, the number of articles included and excluded at each level of screening, and the final number of included articles.

##### 4.3. Study Selection

The abstract screening was conducted by a single reviewer. Full papers of the included studies at this stage ( $n = 68$ ) were then retrieved and assessed by two independent reviewers. Inter-rater reliability was calculated, and the overall kappa was 0.78. Differences between the reviewers in the inclusion of articles were resolved through discussion and consensus was reached.



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of study selection.

#### 4.4. Data Extraction

Data regarding the following information was extracted by one reviewer from the four papers included in this systematic review: (1) study details (authors and year of publication); (2) aim of the study; (3) study design; (4) country of study; (5) setting of the study; (6) details on recruitment; (7) inclusion and exclusion criteria; (8) method of allocation to intervention/control; (9) details regarding the intervention; (10) sample size and demographics; (11) baseline comparisons; (12) outcomes; (13) details on the sex, gender or diversity analysis; (14) follow up periods; (15) methods of analysis; (16) results; (17) results regarding the sex, gender or diversity based factors in findings; (18) attrition details; (19) study limitations; (20) evidence gaps and/or recommendations for future research.

#### 4.5. Sex- and Gender-Based Analysis in the Included Studies

Research can incorporate sex- and gender-based analysis in several ways. Hammarström presented a tool that researchers might use when developing gender research [54]. Although Hammarström [54] does not employ the term “sex- and gender-based analysis”, in this paper we used the concept sex- and gender-based analysis as in the scoping review conducted by McCarthy et al. [55]. The authors reviewed 458 articles on pharmacy practice research and found that only six studies

mention any information related to sex and gender considerations and only three were classified as SGBA according to Hammarström's model [55]. Table 1 presents the classification based on Hammarström's typology [54]. For the sex- and gender-based analysis of the included articles, we examined the following characteristics:

1. *Use of sex and gender in the aim and research questions:* were sex and gender included in the aim of the study or explicitly mentioned in the research question and the study design?
2. *Study design and reporting results:* how were the outcomes analyzed and reported in relation to sex and gender?
3. *Interpretation of sex/gender findings:* how were findings related to sex and gender included in the interpretation of the data?
4. *Intentional and accurate use of language:* were the terms sex and gender used intentionally and appropriately by the authors of the study?

**Table 1.** Sex- and gender-based analysis in health research.

Research Phase	Model 1: Sex/Gender Differences	Model 2: Sex and Gender-Based Analysis (SGBA)	Model 2(a): SGBA+	Model 3: Intersectional Approach
Research question	Sex/gender included, but not primary focus of study. Sex/gender included in the study design or the reporting but are not specifically stated in the research question or aim of the study.	Specific questions related to sex/gender. Looking for sex/gender differences, or the impact of sex/gender an explicit aim of the study or stated research question.	Specific questions related to sex/gender, and additional subgroups/identities included. Research question includes sex/gender and other factors such as race, age, sexual orientation, etc.	Specific questions related to sex/gender, and additional subgroups/identities included. Research question includes sex/gender and other factors such as race, age, sexual orientation, etc.
Data analysis and reporting of findings	Disaggregation by sex/gender; sex as confounder/controlled for (e.g., included in a model). Data related to the outcomes is reported for different sex/gender groups or sex/gender is controlled for in the analysis.	Sex/gender as analysis category Beyond reporting results by different sex/gender group, there is testing of significance between gender groups in relation to the outcomes of the study.	Sex/gender as analysis category; other factors included (e.g., race, SES). There is testing of significance between sex/gender groups in relation to the outcomes of the study and related to other factors such as race, ethnicity, age, etc. But as sperate analysis, not combined into one analysis. Must be beyond reporting demographic characteristics of a sample.	Multi-faceted analysis of multiple factors. More than one factor is included in the same analysis (e.g., comparing young and old white and Hispanic men, to the same 4 groups of women).
Interpretation of sex/gender findings	Findings related to sex and gender are not necessarily included in the interpretation of the data. Differences reported are not necessarily explained.	Findings related to sex and/or gender are reported in the discussion/conclusion. The differences reported in the results section are interpreted and explained.	Findings related to sex and/or gender are reported in the discussion/conclusion in relationship to at least another factor.	Findings related to sex and/or gender are reported in the discussion/conclusion in relationship to other factors such as race, age, etc. The differences reported in the results section are interpreted and explained.
Use of language	Not dependent on specific aim, design/results and interpretation.	Not dependent on specific interpretation and use of language.	Not dependent on specific interpretation and use of language.	Not dependent on specific interpretation and use of language.

Adapted from: Hammarstrom (2007) [54]; McCarthy et al. (2017) [55].

## 5. Results

### 5.1. Included Studies

Four randomized controlled trials involving 623 participants met the inclusion criteria for this review [56–59]. Characteristics of the studies are described in Table 2. In total, 316 participants received the intervention while 307 participants received placebo. The number of women included in the studies oscillated between 16 [58] and 86 [57]. Disaggregating by sex, 170 women and 453 men were included in the randomized controlled trials and 82 women and 234 men received the pharmacological intervention.



In the placebo group there were 88 women and 219 men. In addition to the pharmacological intervention and placebo, some form of psychological intervention was offered in all included studies.

**Table 2.** Characteristics and findings of included studies.

Cornelius et al. (2010) [56]	
Study design	Randomized controlled trial
Participants	<p>Recruitment: Through referrals from the Western Psychiatric Institute and Clinic (WPIC) treatment programs and by responding to newspaper, radio, and bus advertisements.</p> <p>Setting: Outpatient clinic, Pittsburgh, USA. Scheduled for 12 weeks.</p> <p>Participants: In total, 70 participants between 14 and 25 years of age at baseline and comorbid presence of both a current CUD (using DSM-IV) and a current major depressive disorder (MDD).</p> <p>Exclusion criteria: Diagnosis of bipolar disorder, schizoaffective disorder, or schizophrenia; subjects with hyper- or hypothyroidism, significant cardiac, neurological, or renal impairment, and significant liver disease; substance abuse or dependence other than alcohol abuse or dependence, nicotine dependence, or cannabis abuse; any history of intravenous drug use; pregnancy, inability or unwillingness to use contraceptive methods, and an inability to read or understand study forms.</p> <p>Sample size: Intervention, 34; placebo: 36.</p> <p>Demographics: Mean age 21.1 years <math>\pm</math> 2.4 years; 61% male; 56% Caucasian, 37% African-American.</p> <p>In total, 94% cannabis dependent, using on average of 76% of days in prior month; 20 participants met diagnostic criteria for alcohol dependence; seven for alcohol abuse and 16 reported a history of an antidepressant medication in the month prior to recruitment.</p>
Interventions	<p>Intervention: In total, one capsule of 10 mg of fluoxetine for 2 weeks and increased to two capsules of 10 mg of fluoxetine.</p> <p>Placebo: In total, one capsule of 10 mg of placebo and after 2 weeks, two capsules of 10 mg of placebo. The low dose was used to maximize the safety and minimize the risk of medication side effects.</p> <p>In total, nine sessions of cognitive behavior therapy (CBT) for depression and CUD, and motivation enhancement therapy (MET) for CUD.</p>
Outcomes	<p>Severity of abuse or dependence (cannabis and alcohol), number of days of cannabis use, quantity and frequency, number completing the treatment</p> <p>Timeline follow-back method (TLFB) for the cannabis use behaviors and other substance use behaviors;</p> <p>Hamilton Rating Scale for Depression (HAM-D-27) for observer-rated depressive symptoms;</p> <p>Beck Depression Inventory (BDI) for participant-rated depressive symptoms;</p> <p>Number of drinks per drinking day, the number of drinking days, number of heavy drinking days (defined as greater than or equal to four drinks per day for women and five for men);</p> <p>Side Effects Questionnaire for Children and Adolescent for the side effects during each assessment throughout the course of the clinical trial.</p>
Findings	<p>The group that received fluoxetine did not have better cannabis or depressive than the group that received placebo.</p> <p>The improvement of the depressive symptoms and decrease of number of days of cannabis use may have resulted either from the psychosocial therapy or the natural course of the disorders.</p>
Gray et al. (2017) [57]	
Study design	Randomized controlled trial
Participants	<p>Recruitment: Community media advertisements.</p> <p>Setting: Outpatient, six sites within the National Drug Abuse Treatment Clinical Trials Network, USA. Scheduled duration 12 weeks.</p> <p>Participants: In total, 302 treatment-seeking adults ages 18–50 with CUD and submitting a positive Urine cannabinoid testing UCT during the initial screening visit.</p> <p>Exclusion criteria: Individuals with acutely unstable medical or psychiatric disorders, DSM-IV-TR substance dependence aside from cannabis or tobacco, contraindications for N-acetylcysteine (NAC) treatment, or recent synthetic cannabinoid use.</p> <p>Sample size: Intervention, 153; placebo, 149.</p> <p>Demographics: Mean age 29.8 years <math>\pm</math> 8.74 years; 71.5% male; 58.3% White; 27.8% Black or African-American. Mean cannabis use 26.0/30 days at baseline.</p>
Interventions	<p>Intervention: In total, two capsules of 600 mg of United States Pharmacopeia grade NAC powder (twice-daily dose).</p> <p>Placebo: In total, two capsules of 600 mg of placebo (twice per day).</p> <p>Riboflavin 25 mg was added to all capsules (100 mg/day total) as a biomarker for medication adherence.</p> <p>All participants received contingency management twice weekly during treatment. Medical management.</p>
Outcomes	<p>Urine specimens were collected at baseline, twice weekly throughout treatment, at end-of-treatment. UCT at post-treatment follow-up.</p> <p>Medication adherence included taking <math>\geq</math>80% of prescribed study medication per study week, confirmed by urine riboflavin level <math>&gt;</math>1500 ng/mL.</p> <p>Adverse effects at each study visit.</p>
Findings	<p>No statistically significant differences between the NAC and placebo groups in cannabis abstinence.</p> <p>In the NAC group, 22.3% of urine cannabinoid tests were negative compared to 22.4% in the placebo group.</p> <p>Exploratory analysis within medication-adherent subgroups revealed no significant differential abstinence outcomes by treatment group.</p>

Table 2. Cont.

McRae-Clark et al. (2015) [59]	
Study design	Randomized controlled trial.
Participants	Recruitment: Media and internet advertisements. Setting: Outpatient. Scheduled duration 12 weeks.
	Participants: In total, 175 participants between 18 and 65 years of age and met DSM-IV criteria for current cannabis dependence.
	Exclusion criteria: current dependence on any other substance (with the exception of caffeine and nicotine), history of psychotic, bipolar or eating disorder, current suicidal or homicidal risk, current major depression, current treatment with psychoactive medication (with the exception of stimulants and non-benzodiazepine sedative/hypnotics), major medical illness or disease, significant cognitive impairment, hypersensitivity to bupirone or other product component, current consumption of substances that inhibit or induce CYP3A4, and pregnancy, lactation or inadequate birth control. Sample size: intervention, 88; placebo, 87. Demographics: Mean age 24.00 years (23.1–25 years); 76.6% male; 64% Caucasian.
Interventions	Intervention: Dosage initiated at 5 mg bupirone or placebo twice daily and increased by 5–10 mg every three to four days as tolerated, to a maximum dose of 60 mg daily for 12 weeks.
	Placebo: Up to 60 mg of placebo. Adjunctive motivational enhancement therapy sessions (MET) during the first four weeks of the treatment period.
Outcomes	Semi-quantitative urine cannabinoid tests (UCTs) for cannabinoids administered at screening and weekly throughout the study. Proportion of negative urine test during treatment. Point prevalence of abstinence by urine test at the end of the treatment Number of reporting adverse events.
Findings	No differences of UCTs and the weekly creatinine adjusted cannabinoid levels between the two groups. Although participants in both groups reduced their cannabis craving over the course of the study, there were no differences between the bupirone and placebo groups. However, participants who attained abstinence from cannabis reported less cannabis craving.
McRae-Clark et al. (2016) [58]	
Study design	Randomized controlled trial
Participants	Recruitment: Media and internet advertisements. Setting: Outpatient, 8 weeks.
	Participants: In total, 76 participants between 18 and 65 years of age and CUD.
	Exclusion criteria: current dependence on any other substance (exception caffeine and nicotine), history of psychotic, bipolar, or eating disorder, current suicidal or homicidal risk, current treatment with psychoactive medication (exception stimulants and non-benzodiazepine sedative/hypnotics) or CYP3A4 inhibitors, major medical illness or disease, pregnancy, lactation, or inadequate birth control, patients that would be unable to comply with study procedures or assessments. Sample size: Intervention, 41; placebo, 35. Demographics: Mean age 22.2 (21.3–23.1) years; 79% male; 54.8% Caucasian.
Interventions	Intervention: In total, 10 mg daily dose of Vilazodone tablets provided by Forest Pharmaceuticals for 7 days, increased to 20 mg daily for 7 days, followed by 40 mg daily as tolerated.
	Placebo: In total, 10 mg daily dose of placebo tablets for 7 days, increased to 20 mg daily for 7 days, followed by 40 mg daily. Both groups received three adjunctive motivational enhancement therapy sessions (MET). First session, prior to medication initiation. Second session, approximately 1 week later. Third session, week 4.
Outcomes	Quantitative urine cannabinoid tests (UCTs) for cannabinoids administered at screening and weekly throughout the study. Self-report cannabis use measured by TLFB (Time-Line Follow-Back). Marijuana Craving Questionnaire (MCQ) for levels of cannabis craving. Adverse effects assessed weekly. Medication compliance by weekly patient report. Proportion of scheduled visits attended.
Findings	The vilazodone group did not show greater efficacy when compared to the placebo group on cannabis use outcomes. Participants in both groups reported lower cannabis use with no differences between the two groups.

Several medications with different mechanisms of action were applied in the studies included in this review. Cornelius et al. [57] examined the role of fluoxetine while McRae-Clark et al. [58] used vilazodone. Both medications are selective serotonin reuptake inhibitors. The effect of bupirone, a serotonin 5-HT<sub>1A</sub> partial agonist, was explored by McRae-Clark et al. [59]. Lastly, Gray et al. [57] examined the effect of N-acetylcysteine, a supplement promoting glutamate release and modulating N-methyl-D-aspartate (NMDA).

All studies were undertaken in outpatient settings. In one study, the scheduled duration for the clinical trial was 8 weeks [58] while in the three other studies, it was 12 weeks [56,57,59]. The four selected studies were all conducted in the USA. The mean age of participants was between 16.64 [56] and 29.8 years [57]. Three studies included young adults [57–59] and one study targeted adolescents [56]. In one study, participants had comorbid major depression and cannabis use disorders [56]. The other three studies excluded people with psychiatric conditions.

### 5.2. Sex-Disaggregated Outcomes

In one of the included articles, sex was not a significant predictor of cannabis abstinence, and there was no sex-by-treatment interaction [57]. Females showed a greater improvement with time on depressive symptoms ( $F = 5.01$ ,  $p = 0.028$ ) and DSM cannabis abuse criteria count than males ( $F = 4.22$ ,  $p = 0.044$ ) [56]. In a study using buspirone McRae-Clark et al. (2015) [59] found that UCTs were negative in 8.7% of buspirone and 4.5% of placebo of male participants. In females, 2.4% of buspirone participant UCTs were negative and 12.9% of placebo; although the difference was not statistically significant ( $p = 0.007$ ). Regarding the creatinine adjusted cannabinoid levels, there was a sex by treatment interaction indicating that for males, those randomized to buspirone treatment had significantly lower creatinine adjusted cannabinoid levels as compared to those randomized to placebo. For females, those randomized to placebo had lower creatinine adjusted cannabinoid levels compared to those randomized to buspirone [59]. Examining the effect of vilazodone, McRae-Clark (2016) found that males had significantly lower creatinine-adjusted cannabinoid levels and a trend for increased negative urine cannabinoid tests compared to females [58].

### 5.3. Sex- and Gender-Based Analysis of the Included Studies

The assessments of the role of sex- and gender-based analysis in the included studies is presented in Table 3. While Cornelius et al. and Gray et al.'s studies were classified in the sex/gender differences category, McRae-Clark et al. (2015) [59] and McRae-Clark et al. (2016) [58] were categorized as SGBA (see Table 3). Based on the categories that were analyzed, the results are as follows:

1. *Aim and research questions:* The four studies included sex/gender in the study design or the reporting. However, none of the studies included sex or gender in their major research question.
2. *Reporting sex/gender in the results:* In Cornelius et al.'s study [56] on the effects of fluoxetine in adolescents and young adults with comorbid depression and cannabis use dependence, sex by time was analyzed for the outcomes of the study (number of days participants used cannabis in past month; DSM cannabis dependence count; DSM CUD total count - DSM dependence + abuse symptoms). The authors also examined whether abstinence rates differed across sex [56]. Although Gray et al. did not find statistically significant results, they examined whether sex was a predictor of cannabis abstinence, and whether there was a sex-by-treatment interaction [57]. McRae-Clark (2016) used sex as one of the randomization variables in addition to the presence or absence of anxiety or depressive disorders [58]. Sex and sex by treatment group interactions were added to examine the effect of gender on the primary and secondary efficacy outcomes in a randomized clinical trial that tested the efficacy of vilazodone, a selective serotonin receptor inhibitor and partial 5-HT<sub>1A</sub> agonist, for treatment of cannabis dependence [58]. McRae-Clark et al. also conducted a sex- and gender-based analysis since they used sex as a stratified randomization variable [59]. Sex was analyzed in relationship to the negative UCTs and cannabinoid levels in this study that examined the efficacy of buspirone for participants with cannabis use dependence [59].
3. *Interpretation of Sex/Gender findings:* Cornelius et al. did not report their findings related to sex and/or gender in the discussion section [56]. Gray et al. did not discuss any aspects of sex or gender, likely because their results were not statistically significant [57]. The differences reported in the results section are interpreted and explained in McRae-Clark et al. (2015) [59] and McRae-Clark et al. (2016) [58]. McRae-Clark et al.'s study, which featured sex or gender in their research question, provided a comprehensive discussion of their interpretation of the impact of sex and gender in their findings [59].

In this study, the authors acknowledged that this is the first study to demonstrate a sex difference in response to a pharmacological treatment for cannabis dependence. The authors highlighted the importance of including gender in the development and evaluation of new treatments for addictive disorders [59]. However, they did not specify what sex or gender-related factors could be considered for the development and evaluation of new treatments for addictive disorders. McRae-Clark et al.'s (2016) study suggests that women with CUD might have more problems in achieving cannabis cessation compared to men with CUD [58]. Their findings are related to sex and gender in the discussion. They also note that their analyses of sex differences might have been underpowered, and they mention that women are underrepresented in pharmacological trials calling for higher representativity of women in future studies.

4. *Intentional and accurate use of terminology:* None of the included studies define sex and gender. Cornelius et al. use only the term sex and they do not mention gender [56], while Gray et al. used sex and gender interchangeably [57]. For example, in the sociodemographic table the authors use "gender" and throughout the paper they mentioned "sex". McRae-Clark et al. and McRae-Clark et al. used "gender" throughout the article though the study is in fact measuring sex although they also employ the terms females and males and women and men at the same time [58,59]. All four articles included in this systematic review lacked accuracy in the application of the concepts of sex and gender. Not even the articles that were categorized as applying a sex- and gender-based analysis in their studies used intentional and accurate terminology throughout the articles.

**Table 3.** SGBA applied to cannabis pharmacological interventions.

Authors	Publication Date	SGBA Categorization	Sex/Gender in the Research Question	Results	Interpretation of Sex/Gender Findings	Use of Terminology	Findings Related to Sex and Gender
[56]	2010	Sex/Gender Differences	No	Sex by time was analyzed in relation to the outcomes.	No	Use only sex	Females showed a greater improvement with time on the depressive symptoms and DSM cannabis abuse criteria count than males.
[57]	2017	Sex/Gender Differences	No	Examined whether sex was a predictor of cannabis abstinence, and whether there was a sex-by-treatment interaction.	No	Sex and gender used interchangeably	Sex was not a significant predictor of cannabis abstinence, and there was no sex-by-treatment interaction.
[59]	2015	SGBA	No	Sex was used as a randomized stratification variable. Sex was analyzed in relationship to the negative UCTs and cannabinoid levels.	Yes	Sex and gender used interchangeably	In males, 8.7% of buspirone participant UCTs were negative and 4.5% of placebo UCTs were negative. In females, 2.4% of buspirone participant UCTs were negative and 12.9% of placebo; although the difference was not statistically significant ( $p = 0.007$ ). There was a sex by treatment interaction for the creatinine adjusted cannabinoid levels: for males, those randomized to buspirone treatment had significantly lower creatinine adjusted cannabinoid levels as compared to those randomized to placebo; for females, those randomized to placebo had lower creatinine adjusted cannabinoid levels compared to those randomized to buspirone.
[58]	2016	SGBA	No	Sex was used as a variable for randomization. Sex and sex by treatment group interactions were analyzed.	Yes	Sex and gender used interchangeably	Men had significantly lower creatinine-adjusted cannabinoid levels and a trend for increased negative urine cannabinoid tests than women. There were no sex differences regarding the self-reported frequency and amount of cannabis use; nor significant interactions between sex and treatment. Male participants randomized to vilazodone showed a reduction in the Purposefulness subscale of the MCQ; it did not happen for females.



## 6. Discussion

In this systematic review on sex- and gender-related factors in cannabis pharmacological interventions, there was a paucity of studies that sex-disaggregated outcomes for women and men or analyzed the sex- or gender-related factors in the interventions. Although overall the findings showed that the pharmacological interventions analyzed in the studies (fluoxetine, vilazodone, buspirone, N-acetylcysteine) are not effective for treating CUD, three of the four included studies found different results for women and men. Of the three studies, one showed that females demonstrated a greater improvement with time on the depressive symptoms and DSM cannabis abuse criteria count than males [56]. The other two studies suggest that women have worse results than men in cannabis pharmacological interventions [58,59].

The lack of reported sex-disaggregated results does not mean that there are no differences or similarities between women and men. However, it is not possible to accurately interpret these results. Given the emergent evidence of sex- and gender-related factors in cannabis research [42,43], sex- and gender-related factors may intervene in the efficacy of cannabis pharmacological interventions. As in the case of smoking cessation treatment, demonstrating that women have more difficulty maintaining long-term abstinence than men [60], two of the four included studies showed that women have worse outcomes when examining the efficacy of buspirone [59] and vilazodone [58].

Even though the included studies did not find a greater efficacy of the pharmacological intervention, two of the four studies found that women had better results in the placebo group while men had better results in the pharmacological intervention group [58,59]. The different mechanisms generating the placebo effect between women and men are not well understood. However, preliminary findings suggest that sex- and gender-related factors might also be intervening in the placebo effect [61].

Although two of the included studies described the integration of aspects of sex into research questions, analysis, reporting of findings and discussion, there is an overall lack of comprehensive integration and analysis of sex and gender in these randomized controlled trials. These findings are consistent with those found by Welch et al. (2017) examining the use of sex and gender considerations in 100 Canadian-led or funded RCTs [6]. This study showed that 98% of studies included sex in the description of sociodemographic characteristics of the participants and only 6% conducted a subgroup analysis across sex and 4% reported sex-disaggregated data. Even in those RCTs that included females, most of the studies did not sex-disaggregate the outcomes [6].

Studying the effect of sex- and gender-related factors in cannabis pharmacological interventions is challenging and there is still an overall lack of research on sex, gender and cannabis. To determine sex- and gender-related factors in pharmacological interventions for cannabis use, researchers urgently need to fill this void. The preliminary findings show that women might not benefit from certain pharmacological interventions. Including and reporting sex- and gender-related factors might contribute to better determine the effectiveness of pharmacological interventions for both women and men and tailor treatment for all individuals.

In the included studies, the terms “sex” and “gender” were used in an inconsistent way and there were no definitions provided for these terms. Three of the included studies used “sex” and “gender” interchangeably. Throughout the studies, authors used “male/female” and “women/men” and the use of “gender” was inaccurate. These findings are consistent with results from a study on Campbell and Cochrane systematic reviews [62]. Petkovic et al. (2018) found that reporting in systematic reviews is inadequate [62]. None of the studies in our systematic review included gender diverse populations or other gender considerations. Findings from a scoping review on how gender norms, roles and relations impact cannabis use patterns showed that there is a complex relationship between substance use and gender norms. While certain feminine and masculine norms might be protective, there are others that might be linked with greater risk of developing cannabis use dependence [50].

This systematic review has limitations. Since sex and gender are not often examined in pharmacological interventions for cannabis use, our results are limited. This is reflected in the small number of studies that met the inclusion criteria, and therefore, what we could draw from for

interpretation. Our search strategy was designed taking into account that there is a growing body of literature that focuses on sex- and gender-related factors and we conducted searches using sex- and gender-related keywords [63]. However, since the use of sex and gender terms are not used in pharmacological interventions for cannabis use, we reviewed references from a recent systematic review [52] and screened those that were not captured by our search strategy. Sex and gender factors might have been tested in many other studies but not reported. We did not contact authors for further details on sex- and gender-based analysis, methods or results. Although we intended to apply the Feminist Quality Appraisal Tool [64] to analyze the ways in which gender is addressed in the included studies, the lack of deeper gender analysis did not support it. We did not perform a quality assessment of the studies since our aim was to examine the role of sex- and gender-related factors and the uptake of sex- and gender-based analysis. The included articles were assessed in two previous systematic reviews that examined the effectiveness of pharmacotherapies for cannabis dependence [51,52].

## 7. Conclusions

This systematic review aimed to examine the treatment outcomes in cannabis pharmacological interventions for women and men. In addition, it analyzed the uptake of sex- and gender-based analysis in pharmacological interventions for cannabis use. Despite the increasing evidence showing that sex and gender factors intervene in patterns of cannabis use, health effects and biological mechanisms, we found only four articles that sex-disaggregated the outcomes for both sexes on CUD treatment. Taking into account the poor uptake of sex- and gender-based analysis, future research should consider more consistent and disciplined integration of sex and gender in cannabis pharmacological interventions in order to improve outcomes for all individuals experiencing CUD.

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Review

# Gender Norms, Roles and Relations and Cannabis-Use Patterns: A Scoping Review

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**Abstract:** Currently, boys and men use cannabis at higher rates than girls and women, but the gender gap is narrowing. With the legalization of recreational cannabis use in Canada and in multiple US states, these trends call for urgent attention to the need to consider how gender norms, roles and relations influence patterns of cannabis use to inform health promotion and prevention responses. Based on a scoping review on sex, gender and cannabis use, this article consolidates existing evidence from the academic literature on how gender norms, roles and relations impact cannabis-use patterns. Evidence is reviewed on: adherence to dominant masculine and feminine norms and cannabis-use patterns among adolescents and young adults, and how prevailing norms can be both reinstated or reimagined through cannabis use; gendered social dynamics in cannabis-use settings; and the impact of gender roles and relations on cannabis use among young adults of diverse sexual orientations and gender identities. Findings from the review are compared and contrasted with evidence on gender norms, roles and relations in the context of alcohol and tobacco use. Recommendations for integrating gender transformative principles in health promotion and prevention responses to cannabis use are provided.

**Keywords:** cannabis; gender norms; gender roles; gender relations

## 1. Introduction

Similar to other substances, men and boys have higher rates and frequency of cannabis use [1–6]. Boys and men also report using a greater variety of routes of administration of cannabis use compared to women and girls [7] and are more likely to use high-potency products and cannabis concentrates. These patterns of use have been linked with greater risk of developing cannabis-use dependence [8]. Young men who use cannabis are also more likely to report using alcohol and other substances, which increases the risk of adverse health and social consequences [9]. Researchers have often examined substance use from the purview of men, perceived as primarily an activity of men [10]. While the current cannabis-use patterns and trends might immediately suggest that policy and practice responses should prioritize the needs of boys and men, emerging evidence reveals the gap in cannabis-use prevalence between women and men is narrowing [11], and similar to other substances, trans and gender-diverse individuals report higher prevalence of cannabis use [12,13].

These patterns and trends in cannabis use highlight the need to attend to a range of gender-related factors. Not to be confused or conflated with sex, which refers to a range of biologically based characteristics that are linked to being male or female, gender refers to the socially constructed norms, relations, roles, expressions, behaviours and identities of girls, women, boys, men, and gender diverse people [14]. Gender is often conceptualized as a binary (e.g., woman/man). For example, masculinity and femininity have often been conceptualized in opposition to one another “as a relation of complementary difference” [15]. Yet how people understand, experience, and express gender is far more

complex and varied [14]. Furthermore, as argued by Budgeon, the “gender binary which traditionally established gender hierarchy has become more multi-dimensional and complex,” (p. 318) as social norms and gender ideologies continue to change and evolve [15]. Gender norms are dynamic and embedded in the social, cultural and political context of social groups. Gender is socially constructed and individually enacted and experienced, but influenced by institutionalized power and the social, political and economic advantages and disadvantages afforded to different genders. It also intersects with other social determinants of health including social class, race, and ethnicity [16]. Therefore, studying gender in the context of cannabis use, or any other substance use, is complex, temporal and culturally specific. For further details on the features of both sex and gender as concepts, and the interaction of sex and gender in the context of cannabis use see the article published in this special issue by Greaves and Hemsing [17].

### *Gender Norms, Roles and Relations*

Of these multiple dimensions of gender that can be examined in the context of substance use, in this paper we focus on gender norms, roles and relations. *Gender norms* refer to societal rules and expectations that dictate the behaviors considered appropriate or desirable for people based on their gender [14]. Men and women often experience different social pressures to engage in behaviours that are reflective of traditional masculine or feminine norms. Traditional masculine norms are also sometimes referred to as hegemonic masculinity, or dominant masculinity. In some cases, extreme or strong versions of hegemonic masculinity are identifiable such as: dominance, aggression, competition, invulnerability, risk taking, stoicism, and physical and emotional control [18]. These expressions of ‘hypermasculinity’ enacted through substance use may include frequent using, bingeing and combining substances, all patterns which may increase the risk of negative health and social consequences. In contrast, traditional or hegemonic feminine norms include values and characteristics such as: nurturance, beauty, virtuousness and expressing emotions [19]. Dominant feminine norms tend to “emphasize risk aversion” and are typically negatively associated with substance-use behaviours in various studies [20]. The greater prevalence of substance use among boys and men may reflect differences in access to substances, with social norms affording greater permissibility for boys and men to experiment with, use substances and engage in riskier patterns of use [21].

While these dominant femininities and masculinities are archetypes, and individuals and sub-populations will deviate from them, adherence to these can be measured. The majority of research on gender norms and substance use has examined adherence to hegemonic gender norms, and particularly masculine norms. For example, the dominant masculine norms from the Conformity to Masculine Norms Inventory (CMNI) of “risk taking” and “playboy” have been strongly associated with heavy alcohol use [22,23]. Having said this, Everitt-Penhale and Ratele critique the notion of a single traditional masculinity, arguing that “traditional masculinity” varies by class, race, ethnicity and geographic context. Furthermore, they suggest that “competing traditional masculinities” are likely to exist within a single group or context [24]. In addition, Wilkinson et al. critique narrow conceptualizations of gender as either a trait (e.g., masculine personality traits) or ideology (e.g., beliefs and attitudes regarding the roles of women and men) [25]. They argue that focusing on traits lacks attention to the social construction of gender, while ideological conceptualizations narrowly focus on beliefs—one dimension of gender which does not always align with behaviors.

*Gender roles* include the expected roles and behaviours attached to the genders. Expectations about gender roles often affects and determines the opportunities available to different genders, based on culture, place and time. For example, there may be different expectations regarding substance use among girls and boys, or mothers and fathers, in different social contexts and among different cultures.

*Gender relations* refer to the interactions between genders that reflect gendered norms and affect health, behaviours and roles [14]. Femininity and masculinity can be defined both individually and relationally; for example, one’s own gender ideology may restrain substance use, while the gender norms of friends or partners, or those embedded in media may promote, or deter, substance-use

behaviours [20]. Due to the social, relational and performative nature of gender and its different contexts, qualitative research is instrumental for understanding how gender norms are expressed in gender roles and relations. Therefore, investigating the relational aspects of gender is a critical area of inquiry to understand the relationship between gender and cannabis use.

While there are many cross-sectional studies and surveys analyzing gender ‘differences’ in cannabis prevalence and consumption patterns, there is limited research exploring the social factors underpinning these patterns of use. Indeed, no reviews are available on the impact of gender related factors on cannabis use. In response to this gap, we conducted a scoping review to explore the available literature on gender and cannabis use, focusing on three dimensions of gender: gender norms (societal norms regarding gender and cannabis use), gender roles (who uses cannabis and in which contexts) and gender relations (how gendered interactions influence cannabis use). In the discussion, we consider this nascent and emerging literature on gender and cannabis in light of evidence from the fields of alcohol and tobacco research and discuss opportunities for responding to various gendered aspects of cannabis use in prevention and harm reduction programming.

## 2. Methods

This scoping review on gender and cannabis is part of, and based on, a larger scoping review conducted on sex, gender and four substances: cannabis, alcohol, tobacco/nicotine and opioids.

We conducted a scoping review of the academic literature to identify, analyze and synthesize current research in: sex and gender related factors in substance use (initiation/uptake, patterns of use), effects, and prevention, treatment or harm reduction outcomes for four substances (opioids, alcohol, tobacco/nicotine and cannabis); and harm reduction, health promotion/ prevention and treatment interventions and programs that include sex, gender and gender transformative elements to address each of the four substances. A scoping review methodology was used to identify the extent of existing research on sex, gender and the four substances, and existing gaps [26]. Scoping reviews are exploratory, and unlike systematic reviews, have broad inclusion criteria and do not typically assess the quality of individual studies [27]. The scoping review was based on two broad questions:

- (1) How do sex and gender related factors impact:
  - (a) patterns of use;
  - (b) health effects of;
  - (c) and prevention/treatment/or harm reduction outcomes for opioid, alcohol, tobacco/nicotine and cannabis use?
- (2) What harm reduction, health-promotion/prevention and treatment interventions and programs are available *that include sex, gender and gender transformative elements* and how effective are these in addressing opioid, alcohol, tobacco/ nicotine and cannabis use?

We engaged in an iterative academic literature search to identify relevant peer-reviewed studies. The searches were conducted in health-related academic databases with international coverage, including: Medline, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials via Ovid; The Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, Social Work Abstracts, Women’s Studies International, and Lesbian, Gay, Bisexual and Transgender (LGBT) Life via EbscoHost; and Social Science Citation Index via Clarivate Analytics.

An information specialist worked with the research team to design, implement and amend the search strategy. The searches were complex, given the multiple substances and levels of intervention of interest, and various components of the concepts sex and gender. The search strategy was amended and refined based on team discussion and analysis of the search returns, articles missed by the searches, and consultation with the information specialist. The initial search covered studies published from January 2007 to August 2017, combining keywords for: sex and gender; substance use and

substance-use disorders for each of the four substances (opioids, alcohol, cannabis, tobacco/nicotine); and the three levels of intervention (harm reduction, health promotion and prevention, and treatment).

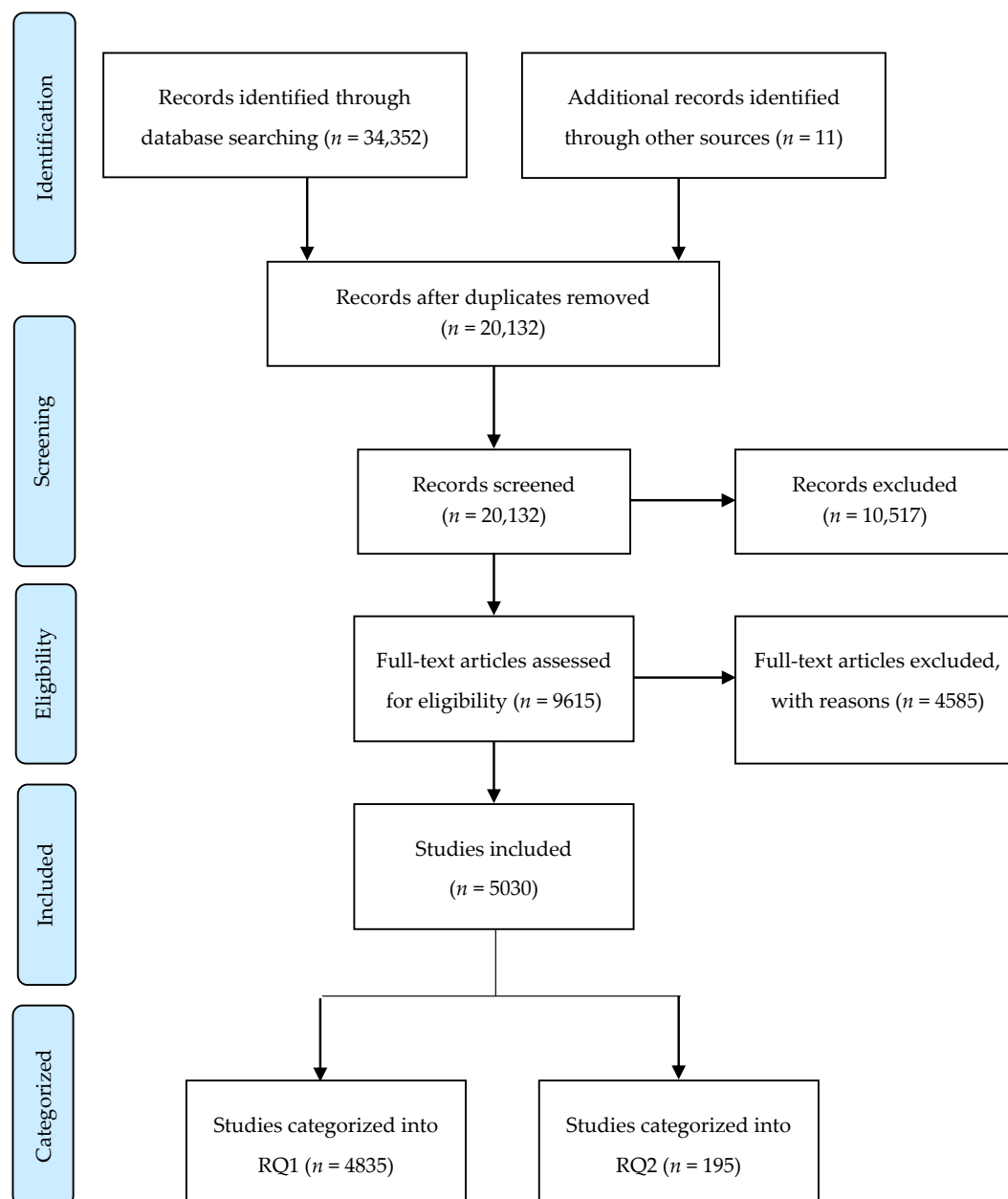
After reviewing the search returns and consulting with the information specialist, the research team determined that the searches were missing key literature on the health effects of substance use (research question 1b). Therefore, the search was amended in September 2017 to include terms for health effects, and to apply additional sex and gender terms and substance-specific terms. During the process of screening returns from the second search, the research team identified multiple substance-use intervention studies relevant to the review that were not being captured by the first two searches. The information specialist analyzed the keywords used in each of the missed articles, and in April 2018 performed a third literature search with additional sex/gender terms to locate relevant studies and extend the search to cover January 2007 to April 2018. Details on the search terms used in each of these three searches are provided in Appendix A.

The three database searches resulted in  $n = 20,121$  unique articles; an additional  $n = 11$  records were identified through other sources. The  $n = 20,132$  records were first screened by title, then by abstract and finally the full text of remaining papers was retrieved and screened a final time for inclusion. In accordance with the UK National Institute for Health and Care Excellence (NICE) manual *Methods for the Development of NICE Public Health Guidance*, abstract and full paper screening was conducted independently by two reviewers, and inter-rater reliability was compared, recorded and maintained [28]. A screening tool was used by the two reviewers to independently code the inclusion/exclusion of each study screened and the reason for exclusion. The coding decisions of the two reviewers were then compared; they participated in weekly meetings with a third researcher for the duration of abstract and full paper screening to review disagreements over the inclusion or exclusion of articles, and to resolve discrepancies by discussion and consensus.

In alignment with scoping review methods, inclusion criteria were amended post-hoc [26]. Based on increasing familiarity with the literature we used an iterative team approach to select relevant studies. The team had weekly web meetings between March 2018 and April 2019 to discuss the progress and to resolve any coding discrepancies. At the beginning of screening (February 2018) and near the end (April 2019) the team met face to face for full day meetings to discuss the scope of included literature and to further refine the inclusion and exclusion criteria. The final set of inclusion criteria, including the PICO (Population, Intervention, Comparator, Outcomes) details for framing each research question, are provided in Appendix B. Included studies were English language articles from a selection of Organization for Economic Cooperation and Development (OECD) member countries (see Appendix B for this list). The population of interest included: women, girls, men, boys, trans and gender diverse people of all ages and demographics. However, studies conducted primarily with pregnant girls and women were excluded as the research team has conducted multiple evidence reviews on substance use among this population. Studies were included that assessed: patterns of use, beliefs and perceptions regarding substance use, and health effects; and intervention studies that analyzed the impact of sex and gender or described or evaluated sex or gender informed interventions. With regard to the four specific substances of interest: tobacco and nicotine included electronic nicotine delivery systems (ENDS); alcohol use included all use and not just problematic use; opioid use included illicit and prescription opioids; and cannabis included both therapeutic and recreational use.

Before acquiring papers for assessment, the  $n = 20,132$  titles were initially scanned by one reviewer who removed the clearly irrelevant studies. Title screening reduced the number of included papers to  $n = 11,842$ . Initially, a random sample of 10% of these abstracts were independently scrutinized by two reviewers in relation to the inclusion criteria. The two reviewers achieved agreement on 83.19% of the sample of abstracts reviewed; the remaining abstracts were then divided and assessed by a single reviewer. Full papers of the remaining included studies ( $n = 9615$ ) were then retrieved and assessed by two independent reviewers. Inter-rater reliability was monitored quarterly (each quarter of the retrieved papers) throughout the full paper screening stage to ensure the reliability score (Cohen's kappa) remained above  $\kappa = 0.6$ . The final overall kappa was 0.73. After the full paper review,  $n = 5030$

papers were still included ( $n = 4835$  were categorized into Research Question 1 (RQ1), and  $n = 195$  were categorized into Research Question 2 (RQ2)). Figure 1 provides an overview of the literature search returns, the number of papers included and excluded at each level of screening, and the final number of included papers identified.



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) flow diagram. From Moher D. et al. [29].

Included studies were categorized by one researcher, who coded details on: research question (question one or two); the substance(s) addressed (cannabis, alcohol, opioids, tobacco/nicotine); primary and secondary topic (prevalence/patterns of use; beliefs/perceptions; mechanisms/biological responses; health effects or consequences; prevention intervention; brief intervention; treatment intervention; harm reduction intervention); and whether the study was a quantitative or qualitative design or a systematic review. Because the inclusion criteria were developed iteratively, and amended during screening, a second researcher checked the coding to ensure alignment with the finalized set of inclusion



criteria. Once the categories were checked by a second researcher, a final searchable database of included studies was produced, with each included study categorized by substance and topic.

In total,  $n = 784$  papers on cannabis were identified in the search. The majority of these papers focused on prevalence and patterns of use ( $n = 445$ ). Additional categories included:  $n = 57$  studies on interventions to address cannabis use (including prevention, harm reduction and treatment);  $n = 18$  studies on beliefs and perceptions regarding cannabis use;  $n = 78$  papers on biological mechanisms; and  $n = 186$  studies on the health effects of cannabis use.

Of these, we identified  $n = 15$  studies on cannabis and gender roles, norms and relations. We reviewed the reference lists of these included studies, identifying an additional  $n = 6$  relevant studies. In total, we included  $n = 21$  studies. Some studies were included that were conducted with one gender group if the authors explored gendered dimensions of cannabis use. While studies were excluded from the original search if they were conducted in Mexico, we chose to include these studies in this scoping review on gender and cannabis use because there were relatively few studies available examining feminine norms and cannabis use.

### 3. Findings

Details on the  $n = 21$  included studies are provided in Table 1, including information on: country, study design, aims, the dimensions of gender included in the study, and key findings regarding cannabis and gender. The 21 studies included were conducted in a range of countries including: Canada, USA, Mexico, Ireland, Norway and the UK. The majority of studies were either qualitative or cross-sectional. The majority of cross sectional studies examined conformity to gender norms (e.g., based on measures of gender typicality), and qualitative studies tended to explore gender roles and relations in the context of cannabis use. A total of  $n = 8$  studies included adolescents,  $n = 2$  included a longitudinal design and examined cannabis use from adolescence to adulthood; and  $n = 11$  included adults. See table for further details.

Findings from the studies on gender norms and cannabis use are summarized narratively in the three sections: *male typicality and cannabis use*; *conformity to feminine norms*; and *conformity to gender norms, culture and acculturation*. Findings from research on gender roles and relations are summarized in five sections: *reinstating and resisting dominant gender norms*; *cannabis and gender relations in social networks*; *cannabis use in intimate relationships*; *stigma and discrimination*; and *stigma among mothers and fathers who use cannabis*.

**Table 1.** Study details.

Author/Year	Country	Study Design	Study Aim	Population	Assessment of Cannabis Use	Dimension of Gender Addressed	Gender and Cannabis Findings
Arnall and Ryder 2019	UK and USA	qualitative comparative study	To prioritize the voices of justice-involved girls in the UK and USA regarding their reasons for substance use	age 13–18 adjudicated girls who had been sentenced for a violent offense; $n = 24$ girls in USA (primarily identified as “women of color”), $n = 35$ in UK (primarily White British)	Participants were assessed for eligibility based on self-reported “ever use” of cannabis and alcohol	Gender relations; explored use of alcohol and cannabis, within justice involved girls’ social groups.	Girls described pleasure related to their cannabis use with other girls. Within their friend groups they managed physical and sexual risks when using substances.
Belackova and Vaccaro 2013	USA	qualitative	To explore the role of cannabis in friendship groups	$n = 44$ adult cannabis users and retailers in Florida; $n = 32$ men and $n = 12$ women; primarily White	Participants were assessed for eligibility based on self-reported use of cannabis in past 12 months	Gender relations in the context of reasons for/functions of cannabis use.	Some men described opportunities for pursuing intimate interactions with women when using cannabis.
Brady et al. 2016	USA	systematic review	To examine feminine norms and substance use outcomes among women	only $n = 2$ studies included cannabis use (Kulis 2008; and Kulis 2010, see below)	Not reported	Gender norms; studies were eligible for inclusion if examined feminine norms/ideology or feminine role conflict.	Majority of studies reported that adherence to feminine norms increased substance use, but only two studies included cannabis (included below).
Dahl and Sandberg 2014	Norway	qualitative	To examine how women navigate a gendered cannabis-use culture in Norway	Analyzed data from 2 studies: one with $n = 100$ cannabis using adults; and one with $n = 25$ experienced cannabis users ( $n = 7$ women; $n = 18$ men)	Participants were assessed for eligibility based on self-reported long term cannabis use; included sporadic to heavy use (not quantified)	How adults “do gender” through cannabis use; examined women and men’s roles and positions in social networks using cannabis, and their concerns about use.	Dominant femininities and masculinities are both reinstated and reimaged through cannabis use.
Dahl 2015	Norway	qualitative	To examine the change in identity among experienced cannabis users who had quit or reduced their use	$n = 7$ women, $n = 18$ men; Age = 23–40 years; former daily cannabis users who had reduced or quit using cannabis without formal drug and alcohol treatment	Participants were assessed for eligibility based on self-reported former daily cannabis use	Gender roles and gender relations in the context of reducing and quitting cannabis se.	New fathers discussed the cannabis user identity as incompatible with their role as father; men discussed changing their use in the context of intimate relationships.

Table 1. Cont.

Author/Year	Country	Study Design	Study Aim	Population	Assessment of Cannabis Use	Dimension of Gender Addressed	Gender and Cannabis Findings
Darcy 2019	Ireland	qualitative	To explore how men's illicit substance use patterns and intoxication converge with masculinities	<i>n</i> = 20 Irish men who used illicit substances ( <i>n</i> = 17 heterosexual; 2 homosexual; 1 undeclared)	Participants identified as "recreational illicit drug users"	Gender relations; gender norms; applies a gender lens to examine Irish men's illicit substance using practices in the context of masculinities, and within the context of use with other men.	Men use illicit substances as a way to navigate traditional masculinity in paradoxical ways: both for closeness in friendships, and in competition.
Darcy 2018	Ireland	qualitative	To explore men's substance use as a friendship practice	Same as above	Participants identified as "recreational illicit drug users"	Gender roles and relations; how cannabis is used in friendships and social settings, and in relation to conventional masculine stereotypes.	Cannabis use provided opportunities to "contravene conventional masculine stereotypes" (e.g., by offering a space for bonding with male friends, being more emotionally expressive), as well as reinforced masculine stereotypes (e.g., expressing dominance by obtaining and supplying substances, including cannabis).
Gonzalez, Gallego, and Bockting 2017	USA	cross-sectional	To examine the relationship between gender minority stress and substance use among transgender adults	<i>n</i> = 1210 transgender adults ( <i>n</i> = 680 transgender women; <i>n</i> = 530 transgender men)	Participants were asked: "In the last three months, how many days did you use marijuana or hashish (weed, grass, reefers)?"	Gender roles (non-conformity, gender minority stress), gender dysphoria and cannabis use.	Gender dysphoria was associated with cannabis use among both transgender women and men; among transgender women, gender minority stress was associated with cannabis use.
Haines-Saah et al. 2019	Canada	qualitative	To highlight the perspectives of parents on preventing problematic adolescent cannabis use, and critique notion of 'parents as the best prevention'	<i>n</i> = 16 parents of children (over age 13) who used cannabis; mostly women ( <i>n</i> = 12)	Participants were eligible to participate if they were a parent of a child over age 13 who had experience with cannabis use	Discusses gender roles: expectations of mothers.	Mothers described feeling like failures if they had challenges regarding their child's substance use, and experienced a lack of social support due to judgement and stigma.

Table 1. Cont.

Author/Year	Country	Study Design	Study Aim	Population	Assessment of Cannabis Use	Dimension of Gender Addressed	Gender and Cannabis Findings
Haines et al. 2009	Canada	qualitative	To explore how adolescents perceive cannabis-use experiences as influenced by gender	$n = 45$ adolescents, 13–18 years; $n = 26$ boys, $n = 19$ girls	Participants included frequent cannabis users (minimum of past week use)	Gender norms, roles and relations; gender was coded into several sub-themes: styles of use by boys and girls; sex differences in use; gender and access; use in the context of relationships; issues of safety when smoking or “partying”. Analysis focused on how students spoke about gender.	Girls and boys described gendered social dynamics in cannabis-use settings and patterns of use.
Hathaway et al. 2011	Canada	qualitative	To examine extra- legal forms of stigma based on interviews with cannabis users	$n = 92$ (mean age 39) who had used cannabis on 25 or more occasions	Eligibility screening survey identified participants with personal experience with cannabis i (lifetime prevalence)	Gender roles; examines stigma in the context of cannabis use and the disadvantages and benefits of using.	Women described experiencing stigma when using cannabis during pregnancy and as mothers; conflict with the role of “good mother.”
Hathaway et al. 2018	Canada	qualitative	To examine patterns of supply of cannabis among students at Canadian universities	$n = 130$ social sciences students in universities in Ontario and Alberta (55% female; 47% reported ever using cannabis)	Eligibility screening survey identified “regular” or “occasional” cannabis users (not quantified)	Gender relations in the context of cannabis supply.	Buying and maintaining a supply of cannabis was typically a male activity.
Ilan 2012	Ireland	qualitative	To explore the experience of street culture among socio-economically disadvantaged young men in Ireland	$n = 7$ adolescents and young men engaged in street culture in Dublin	Not reported	Gender relations in the context of male friendships.	Cannabis was used to facilitate male friendships, social bonding.
Kulis et al. 2008	Mexico	cross-sectional	To examine the relationship of femininity and masculinity constructs developed for Mexican-American youth with a range of substance use outcomes	$n = 327$ adolescents in Mexico	Self-report past 30 day use of cannabis (Likert scale)	Gender norms; assessed four constructs based on Mexican concepts of <i>marianismo</i> and <i>machismo</i> including: aggressive masculinity, assertive masculinity, affective femininity and submissive femininity.	Aggressive masculinity was associated with greater risk of substance use for most outcome measures, while affective femininity was generally associated with lower risks including less recent use of cannabis.

Table 1. Cont.

Author/Year	Country	Study Design	Study Aim	Population	Assessment of Cannabis Use	Dimension of Gender Addressed	Gender and Cannabis Findings
Kulis et al. 2010	USA	cross-sectional	To examine the relationship of femininity and masculinity constructs with substance use among Mexican-American youth	$n = 151$ Mexican-American adolescents	Self-report past 30 day use of cannabis (Likert scale)	Same as Kulis et al. 2008.	Submissive femininity was significantly associated with alcohol use; no significant association was found for gender role and cannabis use.
Kulis et al. 2012	USA	cross-sectional	To examine the relationship between adaptive and maladaptive constructs of masculinity and femininity, substance misuse and acculturation among Mexican-American youth	$n = 1466$ Mexican-American adolescents	Self-report past 30 day use of cannabis (Likert scale)	Same as Kulis et al. 2008.	Highly acculturated girls who reported high maladaptive masculinity (aggressive, controlling) reported the highest cannabis use.
Mahalik et al. 2015	USA	cross sectional longitudinal	To examine the relationship between gender, male-typicality, and social norms on longitudinal patterns of alcohol intoxication and cannabis use in US youth	$n = 10,588$ youth (48% male; 52% female)	Self-report days per month cannabis use (Likert scale)	Gender norms; adherence to male typical behaviours and attitudes among females and males from adolescence to adulthood (based on measure of male typicality from Add Health data).	Greater male typicality among both females and males was associated with substance use including cannabis use; however, the effect was greater for males.
Palamar et al. 2018	USA	qualitative	To examine and compare cannabis users' psychosocial and physical sexual experiences and sexual risk behavior	$n = 24$ adults ( $n = 12$ women; $n = 12$ men); all heterosexual	Participants were eligible to participate if they self-reported sexual intercourse while high on cannabis in the past 3 months	Gender relations; cannabis use in the context of heterosexual sexual relations.	Young women reported being more selective regarding sexual partners when they were using cannabis. Participants (female and male) reported feeling more in control on cannabis than alcohol, but also quieter and less social.



Table 1. Cont.

Author/Year	Country	Study Design	Study Aim	Population	Assessment of Cannabis Use	Dimension of Gender Addressed	Gender and Cannabis Findings
Robinson 2015	Canada	mixed methods	To examine the impact of anxiety on cannabis use among bisexual women	$n = 92$ bisexual women ages 18–54	Self-report cannabis use in the past year (Likert scale) using the Drug Use Disorders Identification Test-Extended Version (DUDIT- E)	Non-conformity to gender roles and impact on stress and substance use.	Cannabis may be used as a way to cope with “female gender roles”, and discrimination based on gender and sexual orientation.
Robinson, Sanches, and MacLeod 2016	Canada	correlational	To examine the prevalence and mental health correlates of illicit cannabis use among bisexual women	$n = 262$ bisexual adult women	Self-report cannabis use in the past year (Likert scale) using the Drug Use Disorders Identification Test-Extended Version (DUDIT- E)	Gender relations; non conformity to gender roles and social exclusion.	Cannabis use correlated with social support; bisexual women who often face social exclusion may use cannabis as a tool for social connection.
Wilkinson et al. 2018	USA	cross-sectional longitudinal	To examine the associations between adherence to gender-typical behavior and substance use from adolescence to adulthood	$n = 4617$ males; $n = 5660$ females	Self-report number of occurrences (Waves 1 and 3) and days of cannabis use (Wave 4) in the past 30 days	Gender norms; gender typicality based on adherence to gender typical behaviours; behaviours included a range from individual actions (e.g., exercising) to states of being (e.g., getting sad) that correlated with being female or male.	Greater male typicality at wave one was associated with greater odds of high frequency cannabis and cigarette use and increased risk of use of one or more substances at Wave three (during emerging adulthood). Among females, there was a lower change in high frequency use and polysubstance use over time.

## 4. Gender Norms

### 4.1. Male Typicality and Cannabis Use

Several studies were identified measuring adherence to “male typicality” in the context of substance use, including cannabis use. Based on the theory that some boys and young men may use substances to support the development of a “male-typical or masculine” identity, Mahalik et al. explored the relationship between gender, male typicality and social norms in regards to alcohol and cannabis use, following a sample of youth from adolescence to adulthood [30]. The gender typicality measure includes 16 items assessing attitudes and behaviours demonstrated to have moderate to strong gender differences among adolescents (e.g., frequency of crying; frequency of being in serious fights) based on data from the National Longitudinal Study of Adolescent Health (Add Health). This measure identified the gender of females and males with 81.7% accuracy. Mahalik et al. applied these measures to predict the probability of each participant being male and analyzed the correlation with substance use. They hypothesized that females and males, but particularly males, who report greater conformity to male-typical behaviours and attitudes would demonstrate greater substance use during adolescence and into adulthood. Confirming their hypothesis, they found males reported greater cannabis use over time. Greater male typicality among both females and males was associated with substance use including cannabis use; however, the effect was greater for males.

Wilkinson and colleagues applied the same Add Health gender diagnostic measures, in relation to substance use from adolescence to young adulthood. However, in contrast to the study by Mahalik et al., they used multiple waves of data collection to assess gender typicality, and they assessed females and males on their adherence to female and male typicality. Similar to Mahalik et al., they also found a stronger relationship between substance use and traditional masculine gender norms for boys. Greater male typicality at wave one was associated with greater odds of high frequency cannabis and cigarette use and increased risk of use of one or more substances at wave three (during emerging adulthood). Among females, there was less change in high frequency use and polysubstance use over time. However, they caution when interpreting these findings that there is individual variability in how masculinity and femininity are understood and enacted.

### 4.2. Conformity to Feminine Norms

A systematic review examined the role of feminine norms on substance use among women. The authors were interested in individual conformity to traditional feminine norms and the relationship with substance use. The majority of studies used the Bem Sex Role Inventory (BSRI) which measures feminine traits based on societal norms, or the Conformity to Feminine Norms Inventory (CFNI) which assesses conformity to the following eight dominant feminine norms: nice in relationships, thinness, modesty, domestic, care for children, romantic relationship, sexual fidelity, and invest in appearance [19]. Their review found that 74% of studies identified a relationship between feminine norms and substance use. However, while they included search terms for cannabis/marijuana, of the  $n = 23$  studies included in their review, only  $n = 2$  studies included cannabis use in relation to feminine norms. All authored by Kulis et al., these studies are described in the following section.

### 4.3. Conformity to Gender Norms, Culture and Acculturation

Kulis and colleagues conducted several studies with Mexican and Mexican-American adolescents examining the impact of gender norms on cannabis use. They developed four gender constructs based on “marianismo” and “machismo”—conceptualizations of femininity and masculinity in Mexico that they argue include both positive and negative dimensions. Accordingly, the authors developed the following four constructs: *assertive masculinity* (self-confidence, personal valor and assertiveness); *affective femininity* (empathy, emotional expression, nurturing); *negative masculinity or aggressive masculinity* (a tendency to control and seek domination in relationships); and *negative femininity or submissive femininity* (dependence and submissiveness). They used 19 items to measure these four

dimensions of gender identity, asking students to indicate how often they thought they exhibited gender typical traits and behaviours.

In their 2008 study, Kulis et al. surveyed adolescents in Mexico, and found that affective femininity tended to be associated with lower risks including less recent use of cannabis, while submissive femininity was not related to substance use [31]. Aggressive masculinity was associated with greater substance use including cannabis use, while assertive masculinity was only associated with perceptions of substance use among friends and receiving substance use offers. However, as the study was cross-sectional it is not possible to determine the direction of these relationships. The authors suggest that for youth identifying with aggressive masculinity, substance use may be a tool for demonstrating “toughness.” In contrast, they suggest that affective femininity may be associated with lower risk of substance use because using substances may be incompatible with aspects of this construct, such as gentleness and showing attention to others. Furthermore, they suggest that the lack of relationship of assertive masculinity and submissive femininity with substance use may reflect cultural differences between the USA and Mexico. While the USA has a more individualistic culture, in which substance use may relate to measures of assertiveness, Mexico tends to be a more collectivistic society. Similarly, they explain that submissive femininity is more strongly valued and prescribed in Mexico than the USA, and therefore boys and girls who conform to submissive femininity may not experience the same pressures to use some substances (as has been observed in studies conducted in the USA).

Two additional studies led by Kulis et al. used the same measures but with samples of Mexican-American adolescents. In one study, submissive femininity was significantly associated with alcohol use, but no significant association was found for cannabis use [32]. In a second study, they reported the following correlations regarding gender and cannabis use: assertive masculinity (assertive, self-confident, problem-solving) was associated with higher cannabis amount and frequency in girls; while assertive femininity was associated with lower levels of cannabis use in boys. Furthermore, acculturation was largely unrelated to substance use, except for cannabis use in girls [33]; highly acculturated girls who reported high aggressive masculinity (aggressive, controlling) reported the highest cannabis use. They suggest that as adolescent girls became acculturated, they may adopt certain dominant masculine norms that confer greater risk for substance use. According to the authors, *marianismo* (a Mexican conceptualization of traditional femininity) may be protective by limiting social interactions outside controlled family settings, but this protective effect may decrease with acculturation. Another explanation they offer is that as girls become more acculturated, they may be more vulnerable to using cannabis to cope with stress.

## 5. Gender Roles, Norms and Relations

### 5.1. Reinstating and Resisting Dominant Gender Norms

Several qualitative studies have explored gender roles, norms and gender relations in the context of cannabis. The performative aspect of gender expresses itself in norms of use, and through the adoption of gendered roles in relation to substance use. There is evidence that adolescents and adults “do gender” through cannabis use, and dominant femininities and masculinities can be both reinstated or resisted through cannabis use [34]. For example, in a Canadian qualitative study, adolescents were hesitant to discuss their cannabis-use behaviours as shaped by gender even though the narratives of adolescents revealed gendered social dynamics in cannabis-use settings and patterns of use [35]. For example, habitual use by girls was described as inappropriate, and girls who did smoke cannabis were often perceived as acting too “silly” and “giggly” when high, while boys who used cannabis regularly were seen as cool and relaxed. Similarly, in the qualitative study by Dahl et al., female cannabis users “did gender” in multiple ways. Predominantly, they “did traditional femininity” by not buying cannabis, remaining in control when using, smoking less and admitting when they felt anxious or too high [34]. However, some participants “did masculinity” by supplying cannabis, rolling joints, being able to consume large amounts, and enjoying being high. In contrast, men were more engaged

with dealers and cultivators, often used cannabis with other men, were more likely to maximize their intoxication (e.g., by method or quantity of use) and were more open with their use.

Cannabis may also be used in ways contrary to dominant gender norms as a “way to revise or undermine gender norms” [35] (p. 2035). In the study with Canadian adolescents, boys suggested cannabis use may be associated with more androgynous values, and may represent an alternative and gentler way of “doing masculinity,” in comparison to other substance use [35]. For example, some boys described their preference for using cannabis over alcohol because it is a “happy drug” and allowed them to talk honestly and be open with their emotions; in contrast, boys explained that alcohol use among groups of boys often resulted in aggressive behavior and fights. Similarly, in a study conducted in Norway, Dahl and colleagues suggest that the “masculinity embedding cannabis use” combined two ideologies. One is a form of traditional masculinity, which tends to foster substance use, violence and sexism, and the other is a form of masculinity that “combines an ideology of gender equality with relaxation, play, fun and not taking things too seriously” [34] (p. 708). For example, men were accepting and often applauding of women who engaged in cannabis-use patterns perceived as masculine (e.g., using frequently, enjoying the high), yet they also described these behaviours as “manly” or unfeminine.

These studies from Canada [35] and Norway [34] both reveal how female cannabis users can resist dominant feminine ideals, positioning themselves as “one of the boys” by engaging in cannabis-use activities traditionally identified as more masculine. Similarly, a qualitative study by Arnall and Ryder described alcohol and cannabis use among a sample of justice-involved girls in the UK and USA as a way of “doing gender control” by resisting “hegemonic norms [framing] ... [alcohol or drug] use as unusual, unfeminine or non-agentic” [36] (p. 1365). By sharing the girls’ narratives, they argue that substance use among girls is both a “pleasurable and bounded” activity for girls. The authors stress the role of girls as agents in making decisions regarding their alcohol and cannabis use, rather than framing girls’ substance use as deviant, “unfeminine” or caused by trauma.

## 5.2. Cannabis and Gender Relations in Social Networks

Qualitative research reveals gendered social dynamics in accessing cannabis. Hathaway et al. conducted interviews with social sciences students attending universities in Ontario and Alberta regarding their substance use [37]. Young women who used cannabis discussed the benefits of gaining access to cannabis via their male friends. As one young woman said:

*“I have never really bought it. I always sort of smoke other people’s weed. Like I have this friend of mine. He is a really nice guy, and I usually smoke with him and his friends. They never let me pay, because they say I don’t smoke much ... but I really think it’s because I am a girl and they are trying to be nice (laughs) (Female, 18).” [37] (p. 1675).*

The authors suggest that buying and maintaining a supply of cannabis is typically a male activity, but that some women may access cannabis for free through their relationships with men. Similarly, a qualitative study with Canadian adolescents found that among some participants, girls were perceived (by both girls and boys) as more easily accessing cannabis [35]. While men are usually the dealers or suppliers, girls were described as flirting and using their beauty or “sexuality as a tool” to access cannabis for free. As one male participant explained:

*“Because a lot of the dealers are men and women have a lot of power of persuasion over men, especially if they are beautiful women. It’s easy for them to get what they want out of men, so there’s a bit of manipulation that goes on there” (p. 2034).*

There are also gendered social dynamics regarding cannabis use among male friend groups. A qualitative study explored men’s greater prevalence of illicit psychoactive substance use in Ireland in relation to masculinities [38]. Darcy argues that men use illicit substances to navigate masculinities in “paradoxical ways.” They found that some of the men’s substance-using behaviours aligned with

hegemonic masculine ideals—including notions of “toughness,” competition and endurance of physical and emotional strain. For example, they described “competitive drug taking” scenarios in which experienced cannabis users would consume cannabis using a combination of methods (e.g., bucket bong, gravity bong), with the purpose of “*seeing, how high, how far, how fast. Last man standing, whatever it might be*” [38] (p. 11).

Certain ways of consuming cannabis, including the methods used, the intensity, and the combination with other substances may provide opportunities for men to demonstrate their masculinity by showing the control they have over their bodies. The authors argue this is a form of gender performance. However, other ways of performing masculinity, or resisting dominant masculine norms, emerged. For example, men described how using cannabis facilitated closeness and allowed men to express their emotions; in particular, among heterosexual men, cannabis allowed opportunities for men to “contravene conventional gender expectations” regarding expressing emotions and openness between male friends [38].

In a second paper based on qualitative data collected with the same sample of men, the offering and sharing of cannabis with other men was perceived as a sign of friendship [39]. While using cannabis together was described as a “social leveler,” possessing and providing cannabis to other men was identified as facilitating an elevated social position and changing the social dynamic. In addition to providing a space where men could perform traditional masculinity via cannabis use (achieving dominance by obtaining and supplying substances including cannabis), cannabis use provided opportunities for bonding with male friends and being more emotionally expressive. Similarly, in an ethnographic study with low income, criminally involved young men living in Ireland, buying, maintaining and consuming cannabis strengthened social bonds with other men, with them consuming cannabis together in “a regularity that approached ritual” [40] (p. 8).

One study explored substance use, including cannabis use, in the context of girls’ friendships. Arnall and Ryder argue that public health approaches have focused narrowly on the risks of substance use, avoiding both the pleasurable functions of substance use, and the efforts of people who use substances to manage and minimize risks. By sharing the voices of a group of justice-involved girls, they describe how girls negotiate risks and use substances for social bonding and pleasure. Girls reported having fun with friends while using substances and experiencing pleasure from intoxication. They also described how they relied on their friend group to prevent or reduce physical and sexual risks of alcohol and cannabis use. For example, girls discussed remaining with their girlfriends when they went out partying, ensuring their friends arrived home safe or staying in each other’s homes if they were too intoxicated.

### 5.3. Cannabis Use in Intimate Relationships

There is evidence from qualitative research on cannabis use and gender relations in intimate heterosexual relationships. In a Norwegian study conducted with people who had reduced or quit using cannabis, some participants discussed changing their cannabis-use patterns to please a partner. This theme was central in interviews with young men, but only one woman discussed stopping her daily cannabis use when she began a new relationship with a man who did not use cannabis [41]. Some men described engaging in arguments and conflicts with their partners regarding reducing or quitting cannabis use, while others described their change in use as unproblematic. For example, one man in the study described quitting cannabis when he moved in with his non cannabis-using partner, explaining: “*it would be sort of excluding if I was to be on a different mental level*” (p. 180). Men negotiated the frequency, occasion and context of their cannabis use to please their partners, and several described this shift as a natural progression from youth to adulthood. However, the authors caution that the findings from this study may have limited generalizability as participants were relatively socially advantaged with 19 of the 25 men having a higher education. These findings may not be translatable to cannabis users who are experiencing social disadvantage.

In one qualitative study examining substance use and sexual experiences among young adults, alcohol was commonly used by young men for pursuing potential sexual partners, and young women reported being more accepting of sexual offers from men when using alcohol [42]. In contrast, when using cannabis, young women reported being more selective regarding sexual partners. Both young women and men reported feeling more in control on cannabis than alcohol, but also quieter and less social. Women and men who used cannabis prior to a sexual experience reported greater post-sexual satisfaction compared to those who used alcohol before sex, while participants who drank alcohol reported greater regret following sex. Some participants reported that the illegal nature of cannabis occasionally meant more private use that sometimes facilitated sexual encounters [42].

Similarly, in a qualitative study with cannabis users and retailers in Florida, some men discussed the role of cannabis for facilitating private moments with women they were attracted to [43]:

*‘Kara is the one that I’m quite fond of, she smokes in my bathroom at all the parties . . . So being able to steal Kara was very easy to do with just [saying to her] “Hey why don’t you come and have a conversation with me in my bathroom?” (Matthew, age 30) (p. 761).*

While these gender relations have been observed in the context of illegal cannabis markets, the hidden nature of use and opportunities for privacy may diminish as cannabis use becomes legal, openly consumed, and socially normalized [42]. Nonetheless, it seems clear that the role of cannabis in intimate heterosexual relationships may be somewhat different than that of alcohol.

#### 5.4. Stigma and Discrimination

There is a lack of research examining the impact of gender roles and relations on cannabis use among people with a range of sexual orientations or diverse gender identities. Yet, several studies suggest cannabis may be used to cope with experiences of stigma and discrimination related to not conforming to predominant gender norms and roles. In a qualitative study on the impact of anxiety on cannabis use among bisexual women in Canada [44], some women described experiencing a lack of belonging, and how this contributed to using cannabis to manage anxiety. The authors suggest that cannabis may be used as a way to cope with not conforming to gender roles, or the stress related to experiencing multiple forms of oppression and discrimination related to being a bisexual woman, including sexism and biphobia. For women who experience these social disadvantages, cannabis may be used as a way to facilitate social belonging. This is also elucidated in their findings from an earlier study in which cannabis use was correlated with higher levels of social support among bisexual women, and described during focus groups as a tool for social connection [45].

Gender identity has also been examined in a study examining the relationship between gender minority stress and substance use among transgender women and men in the USA where the authors found that transgender men reported higher rates of cannabis use compared to transgender women. The authors note that this is similar to findings among general populations of women and men who do not identify as transgender, suggesting that gender socialization may also influence cannabis use among transgender people. Gender dysphoria, defined as the conflict between one’s sex assigned at birth and gender identity, was associated with cannabis use among both transgender women and men. Additionally, among transgender women gender minority stress was associated with cannabis use [46]. The authors conclude that transgender individuals may use cannabis to “validate and affirm their gender identities” and identify the need for more research to explore the differences in cannabis use among transgender men and women.

#### 5.5. Stigma among Mothers and Fathers Who Use Cannabis

Substance use tends to be perceived as more socially acceptable for men than women. In particular, gender norms that position women as mothers and caretakers are defined in opposition to substance use. Women who are mothers have identified stigma associated with cannabis use [34]. Women often



report stopping cannabis use when they transition to motherhood because of this stigma, and those who do not report experiencing social disapproval [47]. Dahl argues that women experience more social controls at an earlier age compared to men [41]. In a qualitative analysis of cannabis use and stigma among a sample of cannabis users in Canada, Hathaway and colleagues discuss how stopping substance use during pregnancy was expected among women [47]. Women who smoked cannabis during pregnancy reported experiencing social disapproval [47]; as one woman remarked:

*“When I was pregnant, I had morning sickness all day, every day for nine months, but I smoked only a few times. There was a strong social stigma against me. People told me not to smoke. (Paralegal, 41)”* (p. 462).

Women who were parents of adolescents described being afraid of child welfare involvement and feeling hypocritical if they were using and hiding their cannabis use from their children. In order to manage this, women limited where and when they used cannabis to avoid having their children and others knowing about it. The authors describe the women as internalizing stigma regarding their cannabis use and engaging in practices of “moral regulation” to maintain their mothering role, as well as others’ perception of them as a “good mother.”

Similarly, in a qualitative study with parents of children who had used cannabis, participants revealed normative gender roles and the expectations that women experience [48]. Mothers described feeling like failures if they had experienced challenges regarding their child’s substance use, and often encountered a lack of social support due to the judgement and stigma. While this appeared to be more salient for women, one father also expressed feeling judgement and stigma regarding asking for help with parenting challenges related to substance use. Furthermore, the authors argue that focusing on the parent-child unit as the site for preventing and responding to substance use is problematic because it individualizes substance use and decontextualizes it from the influence of social factors.

One study found that men also perceived cannabis use as incompatible to their role as fathers. In a qualitative study conducted with people who had reduced or quit using cannabis in Norway, participants who were parents or who were expecting a child discussed cannabis use as being incompatible with parenting, particularly due to fear over the consequences of using an illicit substance [41]. One father said it would be “out of the question” to keep cannabis in the home, and multiple men spoke of the dangers of buying and using cannabis in the context of fatherhood. As one man explained:

*“Smoking hash isn’t that dangerous, but being caught and stigmatized as a criminal—a criminal parent of young children; is that what I am? That is quite a poor starting point for being a family man, as you’re supposed to be”* (p. 178).

Men who were expectant fathers also discussed reducing or stopping to support the transition in their role to fatherhood. Some men qualified that they do not perceive cannabis use during parenting as necessarily harmful, but with the new responsibility of caring for and protecting their child, they felt uncomfortable with the idea of using cannabis while parenting. However, some men did convey a sense of loss with the shift in identity from cannabis user to a non-using father.

## 6. Discussion

Based on limited, but emerging evidence, it is clear that gender norms, roles and relations impact patterns of cannabis use in a range of ways. Several correlational studies examined the relationship between adherence to gender norms and cannabis use, reporting an association between measures of masculinity (specifically, male typicality) and cannabis use [20,30]. Most research on adherence to dominant masculine norms or male typicality and health behaviours has reported a negative effect on measures of health, including higher rates of substance use and dependence [22]. However, the relationship between gender norms and behaviours, including those surrounding substance use, is complex. Some masculine norms may actually be associated with health promoting behaviours.

For example, the “winning” and “competition” subscales of the CMNI have been associated with protection from substance use and misuse, and may have application in promoting health among men [49].

Studies examining the relationship of adherence to feminine norms with cannabis use are lacking. However, similar to the research on masculine norms and substance use, there is evidence that some feminine norms may be protective of substance use while others may increase risk. For example, women who conformed to traditional feminine norms identified in the CFNI, including “sexual fidelity” and “modesty,” have reported lower likelihood to engage in binge drinking. However, the feminine norm “relational” was associated with increased binge drinking [50]. Adherence to some ‘masculine norms’ by young women is also associated with substance use [20]. For example, a study with college women in the US found that female adherence to certain masculine norms (as identified in the CMNI), including ‘risk-taking’ and “emotional control,” was associated with binge drinking [50]. Further research is needed to examine the relationship of specific traditional feminine or masculine norms with cannabis use and how they operate across genders.

Studies measuring adherence to gender norms have been critiqued for underestimating the complexity of the relationship of gender norms with various social factors including race, ethnicity, religious identity, and sexual orientation [22]. For example, cross-sectional study designs assessing measures of male typicality or adherence to masculine or feminine norms at specific time-points may erroneously imply that gender norms are fixed [19]. For example, the CMNI and CFNI do not recognize or integrate historical or developmental changes in gender norms or the influence of culture and social and political contexts [20]. Additionally, Wilkinson et al. argue that gender ideologies and the expression of gender norms changes with age, especially during transitional periods from adolescence to adulthood that involve changing relationships, roles, employment, social settings and responsibilities [20]. Recently, there has been much greater understanding of gender as fluid and socially constructed.

Indeed, gender is both socially constructed and individually enacted, and traditional masculinities and femininities can be both reinstated and reimagined through cannabis use. In addition to discussing how adherence to traditional gender norms influences substance use, findings from several qualitative studies show how substances may be used to challenge or disrupt societal gender norms. As described by Robertson and colleagues, masculinities are complex, dynamic, and can be expressed in diverse ways [51].

Research on alcohol use and tobacco use among girls and young women has also explored how substances may be used to transcend and contest certain femininities. For example, a study conducted in Spain describes how female adolescents use alcohol in public spaces as a way of challenging social expectations regarding femininity that have typically restricted their use of public space and substances [52]. Similarly, qualitative research reveals that young women can frame their alcohol [53] and tobacco use [54] as a form of rebellion against traditional gender roles. These complex and sometimes contradictory ascribed meanings of tobacco use can persist into adulthood among women [55,56]. As social norms and gender ideologies continue to evolve [15], further research is needed to examine how gender norms are perceived, expressed and contested, how these meanings persist or change through the life cycle, how they may differ across cultures, and how this influences cannabis-use patterns.

While cannabis use is becoming more socially acceptable, findings from the review suggest that stigma remains high among pregnant women and mothers who use cannabis. This is also true for other forms of substance use. Among women, substance use is considered in conflict with traditional feminine norms and gender roles. Women who use substances during pregnancy and parenting are often perceived as selfish and uncaring, and in opposition to the traditional role of the “good mother” [57]. Applying a feminist embodiment approach to substance use, Ettorre discusses how substance use among women tends to focus narrowly on the health effects for the fetus, with women’s bodies reduced to “fetal containers” [58]. Women who use substances are perceived as “unfit to

reproduce”, and pregnant women who use substances are perceived as “lethal fetal containers” [58]. She stresses the importance of addressing stigma and discrimination and maintaining the basic human right of reproductive choices regardless of substance use. Indeed, it is important to see women’s health and substance use as in itself worthy of harm reduction-oriented support, whether during pregnancy or motherhood, or in general. Service approaches that consider three clients as important: the mother, the child, and the mother-child unit are increasingly being advocated [59].

The Norwegian study conducted with women and men who had recently reduced or stopped smoking cannabis found that men described fatherhood as incompatible with cannabis use, although this was discussed largely in the context of fear of legal consequences (in Norway, where cannabis is an illegal substance) rather than social disapproval [41]. Men also described reducing or quitting using cannabis if their partner disapproved of their use, although some men did cite arguments and conflicts. Similarly, researchers in Canada have explored the experiences of fathers who smoke [60] and developed and evaluated gender-sensitive resources for men [61]. In a qualitative study on men’s experiences of quitting during the transition to fathering, they found that men often experienced disapproval from their partners and sought to maintain their autonomy while experiencing pressures to stop smoking [49]. Further research is needed to identify opportunities for addressing gender norms in cannabis use in harm reduction and health promotion efforts.

There is a general lack of research on gender norms, roles, relations and cannabis use among non-heterosexual people and people with diverse gender identities. Yet trans and gender-diverse youth report high rates of substance use, mental health issues and violence and trauma, and transgender women and non-binary assigned male at birth youth tend to report greater substance use [62]. Similarly, among young adults, high rates of tobacco use have been reported among both sexual minority females and gender minorities [63]. Further research is needed to understand how substance use among trans and gender diverse people, and cannabis use in particular, is shaped by gender norms, roles and relations. In addition, qualitative research on the experiences related to gender and cannabis use among people of diverse sexual orientations is needed to explore the complex relationships between sexual minority status, heterosexuality and gender roles and norms. Existing evidence highlights the need for integrating social supports in responses to prevent and address cannabis use among both groups: people of non-heterosexual orientations and diverse gender identities.

More research is also required to explore how gender intersects with other social determinants of health to influence cannabis use. In our review, we found several studies exploring the relationship between gender and culture or acculturation and substance use [31]. Some qualitative studies included sub-groups of males or females experiencing social disadvantage, including: low income men [40], and justice involved girls [36]; however, these studies did not analyze the intersection of gender and social disadvantage in relation to cannabis use. Yet evidence from the wider substance use field suggests that other social dimensions of health influence how we act, respond to, or “do gender.” For example, in an intersectional analysis of women’s smoking, the authors contend that the ability to challenge traditional social constructions of femininity is typically a privilege reserved for women belonging to higher social class [54]. More nuanced research is required to explore how other social determinants of health intersect with gender to shape cannabis-use experiences.

In summary, addressing gender norms, roles and relations in health-promotion messaging regarding cannabis use is critically important. Evidence from the review suggests that these dimensions of gender can have an effect on harms, risk and exposure. As more evidence emerges on gender and cannabis use, it is critical to avoid approaches to either prevention or health promotion that are gender exploitive and reinforce negative gender stereotypes. For example, an analysis of substance use education in Australia describes how school-based substance-use education reproduces harmful feminine and masculine norms by framing young women’s substance use as more problematic than men’s and blaming women for the physical and sexual victimization they are at risk of while intoxicated [64].

But advancing beyond approaches that merely avoid harmful gender stereotypes, health-promotion responses are needed that actively integrate gender transformative principles. Rather than just reflecting gender-based factors and concerns in messaging, gender transformative health promotion is aimed at improving gender equity *at the same time* as improving health [65]. Evidence from this review suggests there may be substantial opportunities for both gender-responsive and gender-transformative responses to cannabis use. For example, messaging might address shared responsibility for abstinence from cannabis use during pregnancy and parenting, and resources and supports could be developed for men to reduce or quit cannabis use during pregnancy and parenting, emphasizing the role of men as providers and protectors, similar to smoking cessation resources that have been developed for men [61]. In addition, messaging could address gendered risky patterns of use, including: cannabis and alcohol use, competitive use among men, and driving and riding as a passenger after cannabis use. Finally, there is a need for stigma reduction among pregnant women and mothers and fathers who use cannabis. One way stigma can be reduced is by providing accurate information regarding the health effects of cannabis use during pregnancy and parenting, while avoiding language that is judgmental and shaming.

## 7. Conclusions

While research on gender and cannabis is in its infancy, the available literature indicates that, similar to other substance use, gender norms, roles and relations have the potential to strongly influence patterns of cannabis use. How gender is expressed through cannabis use is complex, culturally specific, multi-faceted, and ever-evolving. As gender norms, roles and relations are constantly in flux, ongoing research is needed to explore the relationship between gender and cannabis use that is situated in the social, cultural and political context. Further research is also needed to understand how people belonging to diverse gender identities perceive and express gender through cannabis use; and that investigates how gender intersects with other social determinants of health including: sexual orientation, class, race and ethnicity. Harm-reduction, health-promotion and prevention messaging approaches are needed that address substance use and gender norms, as well as structural and institutional factors that specifically support harmful gender norms and behaviours. Specifically, gender transformative principles can be integrated in prevention, harm-reduction and health-promotion messaging to advance gender and health equity simultaneously, and erode the impact of negative gender stereotypes and stigmas. All of these gender-related issues need to be visited as cannabis use becomes more regulated, decriminalized or legalized in various jurisdictions around the world.

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## Appendix A. Database Search Strategies

Search (1) August 2017

1	"gender transformative". ti,ab.
2	("gender informed" or "gender integrated" or "gender responsive"). ti,ab.
3	("sex informed" or "sex integrated" or "sex responsive"). ti,ab.
4	("gender equalit*" or "gender equit*" or "gender inequality*" or "gender inequit*"). ti,ab.
5	("sex equalit*" or "sex equit*" or "sex inequality*" or "sex inequit*"). ti,ab.
6	("gender related" or "gender difference*" or "gender disparit*"). ti,ab.
7	("sex related" or "sex difference*" or "sex disparit*").ti,ab.
8	"gender comparison*". ti,ab.
9	"sex comparison*". ti,ab.
10	"compar* gender*". ti,ab.
11	"compar * sex*". ti,ab.
12	"gender based".ti,ab.
13	"sex based".ti,ab.
14	("gender divers*" or "gender minorit*"). ti,ab.
15	"gender analys*". ti,ab.
16	"sex analys*". ti,ab.
17	(transgender * or "trans gender*" or LGBTQ or LGBTQ or LGBT or LGB or lesbian * or gay or bisexual * or queer *). ti,ab.
18	("transsexual*" or "trans sexual*").ti,ab.
19	17 or 18
20	(transgender * or "trans gender*" or LGBTQ or LGBTQ or LGBT or LGB or lesbian * or gay or bisexual * or queer * or "transsexual*" or "trans sexual*"). ti,ab.
21	("non binary*" or nonbinar *). ti,ab.
22	Homosex *. ti,ab.
23	("woman focused" or "woman focussed" or "girl focused" or "girl focussed" or "woman centred" or "girl centred" or "woman centered" or "girl centered" or "female focused" or "female focussed" or "female centred" or "female centered"). ti,ab.
24	("man focused" or "man focussed" or "boy focused" or "boy focussed" or "man centred" or "boy centred" or "man centered" or "boy centered" or "male focused" or "male focussed" or "male centred" or "male centered"). ti,ab.
25	Transgender Persons/
26	Sexual Minorities/
27	Transsexualism/
28	Bisexuality/
29	exp Homosexuality/
30	Gender Identity/
31	(bigender * or "bi gender*"). ti,ab.
32	("gender identit*" or "gender incongru*"). ti,ab.
33	"differently gendered". ti,ab.
34	or/1–33 [GENDER]
35	exp Opioid-Related Disorders/
36	exp Analgesics, Opioid/
37	(opiod * or opiate *). ti,ab.
38	(fentanyl or phentanyl or Fentanest or Sublimaze or Duragesic or Durogesic or Fentora or "R 4263" or R4263). ti,ab.
39	(oxycontin or oxycodone or oxycodan or percocet or percodan). ti,ab.
40	(heroin or morphine). ti,ab.
41	or/36–40 [OPIOIDS]
42	Prescription Drug Misuse/ or Prescription Drug Overuse/
43	((("prescription drug" or "prescription drugs" or "prescribed drug" or "prescribed drugs") and (dependen * or misuse * or mis-use * or abuse * or overuse * or over-use * or addict *)). ti,ab.
44	exp Substance-Related Disorders/

45	("substance disorder *" or "substance related disorder *" or "substance use disorder *" or "drug use disorder *" or "drug related disorder *"). ti,ab.
46	("over prescription" or "over prescribed"). ti,ab.
47	Drug Overdose/ or (overdose* or over-dose *).ti,ab.
48	or/42–47
49	35 or (41 and 48)
50	exp Alcohol-Related Disorders/
51	exp Alcohol Drinking/
52	(binge drink * or underage drink * or under-age drink * or problem drink * or heavy drink * or harmful drink * or alcoholi* or inebriat * or intoxicat *). ti,ab.
53	("alcohol dependen *" or "alcohol misuse *" or "alcohol mis-use *" or "alcohol abuse *" or "alcohol overuse *" or "alcohol over-use *" or "alcohol addict *"). ti,ab.
54	alcohol. ti,ab. and (44 or 45)
55	Alcohol Abstinence/
56	or/50–55
57	"Tobacco Use Disorder"/
58	Tobacco/
59	Nicotine/
60	exp Tobacco Products/
61	exp "Tobacco Use"/
62	((cigar * or e-cigar * or tobacco or nicotine or smoking or vaping) and (dependenc * or misuse * or mis-use * or abuse * or overuse * or over-use * or addiction *)). ti,ab.
63	(58 or 59 or 60 or 61) and (44 or 45)
64	exp "Tobacco Use Cessation"/
65	exp "Tobacco Use Cessation Products"/
66	((tobacco or smoking) and cessation). ti,ab.
67	or/57,62–66
68	Marijuana Abuse/
69	Cannabis/
70	Marijuana Smoking/
71	exp Cannabinoids/
72	(marijuana or marihuana or hashish or ganja or bhang or hemp or cannabis or cannabinoid * or cannabidiol or tetrahydrocannabinol). ti,ab.
73	(69 or 70 or 71 or 72) and (43 or 44 or 45)
74	or/68,73
75	or/49,56,67,74
76	Harm Reduction/
77	("harm reduction" or "reducing harm" or "reducing harmful" or "harm minimization" or "minimizing harm" or "minimizing harmful" or "harm minimisation" or "minimising harm" or "minimising harmful"). ti,ab.
78	exp Risk Reduction Behavior/
79	("risk reduction" or "reducing risk" or "reducing risks" or "risk minimization" or "minimizing risk" or "minimizing risks" or "risk minimisation" or "minimising risk" or "minimising risks"). ti,ab.
80	or/76–79
81	exp Health Promotion/
82	("health promotion" or "promoting health" or "promoting healthy" or "promoting wellness" or "patient education" or "consumer education" or "client education" or outreach or "wellness program" or "wellness programs" or "wellness programme" or "wellness programmes"). ti,ab.
83	81 or 82
84	Preventive Health Services/
85	Consumer Health Information/ or Health Literacy/
86	Secondary Prevention/
87	(prevention or "preventive health" or "preventive healthcare"). ti,ab.
88	or/84-87
89	(prevention or preventive). ti,ab.
90	88 or 89



91	Rehabilitation/
92	(abstain * or abstinence or detox * or rehab * or sobriety or sober or temperance or intervention * or cessation or recovery). ti,ab.
93	Methadone/tu [Therapeutic Use]
94	"methadone maintenance". ti,ab.
95	Opiate Substitution Treatment/
96	("opiate substitution" or "opioid substitution" or "withdrawal management" or "managing withdrawal"). ti,ab.
97	(treatment* or treating or therapy or therapies). ti,ab.
98	Intervention *. ti,ab.
99	or/91–98
100	or/80,83,88,99
101	or/80,83,90,99
102	34 and 75 and 101
103	limit 102 to (english language and yr = "2007–2017") [Limit not valid in Cochrane Database of Systematic Reviews (CDSR); records were retained]
104	(Animals/ or Animal Experimentation/ or "Models, Animal"/ or (animal * or nonhuman * or non human * or rat or rats or mouse or mice or rabbit or rabbit or pig or pigs or porcine or dog or dogs or hamster or hamsters or fish or chicken or chickens or sheep or cat or cats or raccoon or raccoons or rodent * or horse or horses or racehorse or racehorses or beagle *). ti,ab.) not (Humans/ or (human * or participant * or patient or patients or child * or seniors or adult or adults). ti,ab.)
105	103 not 104
106	(editorial or comment or letter or newspaper article). pt.
107	105 not 106
108	(conference or conference abstract or conference paper or "conference review" or congresses). pt.
109	107 not 108EBM Reviews- Cochrane Database of Systematic Reviews < 2005 to 2 August 2017 >Embase < 1980 to 3 August 2017 >Ovid MEDLINE(R) Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) < 1946 to Present >EBM Reviews- Cochrane Central Register of Controlled Trials < July 2017 >
110	remove duplicates from 109EBM Reviews- Cochrane Database of Systematic Reviews < 2005 to 2 August 2017 >Embase < 1980 to 3 August 2017 >Ovid MEDLINE(R) Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) < 1946 to Present >EBM Reviews- Cochrane Central Register of Controlled Trials < July 2017 >
111	110 use ppez [MEDLINE]
112	110 use emezd [EMBASE]
113	110 not (111 or 112) [selected 2 only as 13 were conference abstracts]

## Search 2: September 2017

After reviewing the returns from the original search in August 2017, we amended the search in September 2017 to identify studies on the health effects of substance use (for cannabis, alcohol, opioids, tobacco/nicotine). In addition, we added sex/gender terms and substance-specific terms. The search was amended as follows:

### 1. Health effects terms were added to the search terms.

("health effect" or "heath effects" or "effect on health" or "effects on health" or "affect \* health" or "affect \* the health" or "heath impact \*" or "impact \* on health" or "impact \* health"). ti,ab. [HEALTH EFFECTS]

These terms were searched in combination with the gender terms and substance terms as follows:

Concept 1—Gender/sex

AND

Concept 2—Substances (opioids, alcohol, tobacco, cannabis)

AND

Concept 3—health effects

1. “gender determinant\*” or “gender specific” were added to the gender/sex terms (see lines 1–33 in original search strategy)
2. “alcohol use” or “use of alcohol” and “risky drink” were added to the alcohol terms

### Search 3: April 2018

After identifying multiple papers relevant to our review that were not being captured by the original searches, we conducted a third search in April 2018. Based on analysis of the keywords in the articles that were missed, we amended the search as follows:

1. The following terms were added to the gender/sex terms:  
(woman or man or women or men or girl or boy or girls or boys or trans or transgender or transgendered or female or male or sex or gender). ti. [GENDER IN TI]  
  
A search was then conducted of the article titles only, combining the following concepts:  
  
Search strategy:  
  
Concept 1—Gender/sex terms  
  
AND  
  
Concept 2—Substances (opioids, alcohol, tobacco, cannabis) terms  
  
AND  
  
Concept 3—Harm reduction, health promotion, prevention, treatment, health effects terms
2. “heat not burn” was added to the tobacco terms.
3. The search included studies published up until April 2018

## **Appendix B. Final Inclusion Criteria**

### *Study Design:*

- randomised-controlled trials (RCTs) (not already covered in an included systematic review)
- case-control studies
- interrupted time series
- cohort studies
- cross sectional studies
- observational studies
- systematic reviews
- qualitative studies
- grey literature sources
- case series

### *Note:*

- Narrative reviews will not be included but saved as context.
- Case studies will be excluded.

The following types of literature will be included in the grey literature review:

- book chapters
- reports
- practice guidelines
- health policy documents
- unpublished research, theses

Note: magazines and books will be excluded from the grey literature.

*Countries of studies:*

- Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, United States
- Studies published in all other countries will be excluded, including animal studies.
- Studies including data from multiple countries, that include an out of scope country, will be excluded if the data is not disaggregated.
- Systematic reviews which include studies from multiple countries will be included if reporting on one or more studies published in an eligible country.

*Date of publication:*

- The literature search will cover studies published between 2007 to 2017

*Language:*

- Only studies published in the English language will be included.

**Research Q1: PICO (Population, Intervention, Comparator, Outcome)**

Q(1) *How* do sex- and gender-related factors impact:

- (a) patterns of use;
- (b) health effects of;
- (c) and prevention/treatment/or harm reduction outcomes for opioid, alcohol, tobacco and cannabis use?

*Population:*

- Women, girls, men, boys, trans people/ gender diverse people
  - All ages, demographics within the defined populations
- Studies that are conducted primarily with pregnant girls and women will be excluded.
- Studies addressing the fetal health effects of maternal/ paternal substance use will be excluded.
- Studies addressing the health effects of substance use on the infant among women who are breastfeeding will be excluded.
- Studies comparing heterosexual populations to LGBT populations, without sex or gender disaggregation will be excluded.

*Intervention:*

Q1 (a) and (b) includes non-intervention studies (e.g., patterns of use, health effects):

- Inclusive of tobacco in general (include e-cigarettes)
- Inclusive of all alcohol use (not just binge drinking)
- Inclusive of all opioid use issues (include illicit use/heroin, prescription opioids, etc.)

■ Opioid use for cancer pain management will be excluded

- Inclusive of all purposes (therapeutic and recreational), forms and modes of ingestion of cannabis (e.g., smoking, vaping, edibles, extracts, etc.).
- Studies that report on “substance use” but do not disaggregate results by one or more of the four substances in our review will be excluded.

Q1 (c) Harm reduction, health promotion, prevention, treatment (including brief intervention) responses to opioids, alcohol, cannabis, tobacco/e-cigarettes

- Studies that report on “substance use” but do not disaggregate results by one or more of the four substances in our review will be excluded.
- Opioid substitution therapy for substances other than opioids (e.g., cocaine, methamphetamine) will be excluded

*Comparator:*

- Many Q1 (a) and (b) studies will be descriptive/ prevalence studies (not intervention studies) and may not include a comparator.
- Many qualitative and grey literature sources will likely not include comparators
- Q1 (c) studies *must* include a comparison between gender groups e.g., women vs. men; sub-groups of women/ men OR if sex- or gender- based factors are described or discussed in the study (e.g., masculinity norms, hormones etc.). Q1c studies that do not compare gender groups or describe sex- or gender-based factors will be excluded.

*Outcome:*

- For non-intervention studies: prevalence/patterns of use (frequency of use, form and method of ingestion, etc.);
- For intervention studies (Q1c): outcomes reported in the reviews will be the outcomes that are reported in the individual papers that are reviewed. Relevant outcomes from the included studies might include:
  - Changes in substance use (uptake/initiation, harms associated with use cessation, reduction)
  - Changes in client perceptions/attitudinal change
  - Changes in service provider perceptions
  - Changes in retention/treatment completion
  - Increased use of services
  - improved health and quality of life outcomes

Note: Studies that report on one or more of the four substances in relation to sex/gender *only* in the baseline characteristics of the sample will be excluded, even if statistical significance is reported.

**Research Q2: PICO (Population, Intervention, Comparator, Outcome)**

(Q2) *What* harm reduction, health promotion/prevention and treatment interventions and programs are available *that include sex, gender and gender transformative elements* and how effective are these in addressing opioid, alcohol, tobacco and cannabis use?

*Population:*

- Women, girls, men, boys, trans people/gender-diverse people
  - All ages, demographics within the defined populations
- Studies that are conducted primarily with pregnant girls and women will be excluded.
- Studies addressing the fetal health effects of maternal/paternal substance use will be excluded.
- Studies addressing the health effects of substance use on the infant among women who are breastfeeding will be excluded.

*Intervention:*

- Harm reduction, health promotion, prevention, treatment (including brief intervention) responses to opioids, alcohol, cannabis, tobacco/e-cigarettes including some *sex, gender and/or gender transformative elements*

- Studies that report on 'substance use' will be included if they potentially contain one of the four substances. However, if substance use is defined, and does not contain alcohol, tobacco, opioids or cannabis it will be excluded.
- Opioid substitution therapy for substances other than opioids (e.g., cocaine, methamphetamine) will be excluded.
- Examples of sex specific elements (address biological differences in substance use and dependence):
  - administering different types or quantities of pharmacotherapies based on evidence of biological differences in drug metabolism/effectiveness
  - timing tobacco-cessation intervention for young women based on the menstrual cycle (hormonal fluctuations impact withdrawal)
- Examples of possible gender/gender-transformative elements:
  - address gender-based violence
  - provide social support
  - address caregiving
  - address poverty
  - address negative gender stereotypes
  - include education or messaging on gender norms/relations
  - address employment issues/work-related stress
  - address discrimination and violence related to gender identity

Interventions to address these four substances are:

- Inclusive of tobacco in general (include e-cigarettes)
- Inclusive of all alcohol use (not just binge drinking)
- Inclusive of all opioid use issues (include illicit use/heroin, prescription opioids, etc.)
- Opioid use for cancer pain management will be excluded
- Inclusive of all purposes (therapeutic and recreational), forms and modes of ingestion of cannabis (e.g., smoking, vaping, edibles, extracts, etc).

Note: Methadone maintenance therapy will only be included if it is provided to opioid users (i.e., exclude if provided to treat substances outside of scope such as cocaine).

*Comparator:*

- No intervention or usual practice (i.e., interventions that are not gender-informed/gender-transformative, sex-specific), or the comparison of two intervention types.
- Many qualitative and grey literature sources will likely not include comparators.

*Outcome:*

- Outcomes reported in the reviews will be the outcomes that are reported in the individual papers that are reviewed. Relevant outcomes from the included studies might include:
  - Changes in substance use (uptake/initiation, harms associated with use, cessation, reduction)
  - Changes in client perceptions/attitudinal change
  - Changes in service provider perceptions
  - Changes in retention/treatment completion

- Increased use of services
- improved health and quality of life outcomes
- changes in health and gender equity

Note: Studies that report on one or more of the four substances in relation to sex/gender *only* in the baseline characteristics of the sample will be excluded, even if statistical significance is reported.

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