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Sex-Dependent Effects Of Cannabis-Induced Analgesia

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Abstract

Background—Preclinical studies demonstrate that cannabinoid-mediated antinociceptive effects vary according to sex; it is unknown if these findings extend to humans.

Methods—This retrospective analysis compared the analgesic, subjective and physiological effects of active cannabis (3.56 - 5.60% THC) and inactive cannabis (0.00% THC) in male (N = 21) and female (N = 21) cannabis smokers under double-blind, placebo-controlled conditions. Pain response was measured using the Cold-Pressor Test (CPT). Participants immersed their hand in cold water (4°C); times to report pain (pain sensitivity) and withdraw the hand (pain tolerance) were recorded. Subjective drug ratings were also measured.

Results—Among men, active cannabis significantly decreased pain sensitivity relative to inactive cannabis ($p < 0.01$). In women, active cannabis failed to decrease pain sensitivity relative to inactive. Active cannabis increased pain tolerance in both men women immediately after smoking ($p < 0.001$); a trend was observed for differences between men and women ($p < 0.10$). Active cannabis also increased subjective ratings of cannabis associated with abuse liability ('Take again,' 'Liking,' 'Good drug effect'), drug strength, and 'High' relative to inactive in both men and women ($p < 0.01$).

Conclusions—These results indicate that in cannabis smokers, men exhibit greater cannabis-induced analgesia relative to women. These sex-dependent differences are independent of cannabis-elicited subjective effects associated with abuse-liability, which were consistent between men and women. As such, sex-dependent differences in cannabis's analgesic effects are an important consideration that warrants further investigation when considering the potential therapeutic effects of cannabinoids for pain relief.

Keywords

Cannabinoids; Analgesia; Sex-differences; Abuse liability; Subjective effects

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1. Introduction

Cannabis is the most widely used illicit drug worldwide (United Nations Office in Drugs and Crime, 2013) and has the highest rates of abuse in the United States relative to other illicit drugs, with 18.9 million people over the age of 12 reporting use in the previous month, a number that has increased by over 25% since 2007 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2013). While epidemiological reports consistently demonstrate that men use cannabis more frequently than women (SAMHSA, 2013), seek treatment for cannabis use more often than women (TEDS, 2012) and are at a higher risk for developing Cannabis Use Disorder (CUD; Stinson et al., 2006), a trend is emerging with a growing number of women reporting cannabis use for medical purposes (McConnell et al., 2014; Finseth et al., 2015; Ryan-Ibarra et al., 2015). Given this emerging trend, identifying potential sex-differences in the therapeutic effects and risks associated with cannabis is a public health imperative that has not yet been explored.

Although being male is a risk factor for developing CUD, women show an accelerated progression from first use to CUD relative to men, providing evidence for a ‘telescoping effect’ (Hernandez-Avila, 2004; Ehlers et al., 2010; Khan et al., 2013). Recent controlled studies in male and female cannabis users matched for current use demonstrated that while both men and women showed similar levels of intoxication following cannabis administration; women report higher ratings associated with abuse liability, such as liking the drug and willingness to take again (Cooper and Haney, 2014). The increased sensitivity observed in that clinical study corresponds to preclinical findings demonstrating that female laboratory animals are more sensitive to a range of behavioral and physiological effects of cannabinoids (for review, see Craft et al., 2013). Relative to male rats, females are more sensitive to the reinforcing effects of cannabinoids with faster acquisition of cannabinoid self-administration, higher rates of responding for cannabinoids (Fattore et al., 2007), and higher rates of cue and drug-induced reinstatement (Fattore et al., 2010). However, in addition to the increased susceptibility to the negative effects of cannabinoids, female rats are also more sensitive to cannabinoid-induced antinociception relative to males in both acute and chronic models of pain (Tseng et al., 2001; Craft et al., 2012, 2013). These preclinical findings suggest that while women may be more sensitive to the abuse-related effects of cannabis, cannabis may also be more effective as an analgesic in women relative to men; similar sex differences in analgesia have been shown with opioids (for review, see Campesi et al., 2012). Given that pain is one of the primary indications for which medical cannabis is used (Ilgen et al., 2013; Bonn-Miller et al., 2014), understanding if these preclinical findings translate to humans is critical to predicting clinical risks and outcomes associated with medical cannabis use in women, a growing population of users.

This retrospective analysis was designed to investigate if there are sex-dependent differences in cannabis' analgesic effects in humans. Apart from one study in healthy, non-cannabis using participants that identified nabilone-induced decreases in hyperalgesia in women but not men (Redmond et al., 2008), most studies of cannabinoid-induced analgesia have tested only one sex (Hill et al., 1974; Buggy et al., 2003; Greenwald and Stitzer, 2000; Kraft et al., 2008; Ellis et al., 2009; Lee et al., 2013) or have not included sex as a factor in the data

analysis (Noyes et al., 1975; Karst et al., 2003; Naef et al., 2003; Svendsen et al., 2004; Abrams et al., 2007; Nurmikko et al., 2007; Rog et al., 2007; Wilsey et al., 2008 and 2013; Ware et al., 2010; Issa et al., 2014; Wallace et al., 2015). We published a study designed to compare the dose-dependent analgesic effects of THC administered orally (dronabinol) versus smoked cannabis with delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, in 15 men and 15 women. Included in the overall analysis was an exploratory assessment of potential sex-dependent analgesia across all the doses; 10 and 20 mg dronabinol, 1.98 and 3.56% THC cannabis, and a placebo dronabinol and inactive cannabis (0.0% THC) condition. While this overall analysis did not yield significant differences in pain responses between men and women (Cooper et al., 2013), differences in the analgesic effects of cannabis between men and women emerged upon a more in-depth investigation of separate dose conditions. This retrospective analysis was designed to further examine sex-dependent effects of specifically cannabis-induced analgesia and draws from a larger pool of participants (N = 21 men and N = 21 women). Using double-blind, placebo-controlled methods, the analgesic effects of active cannabis was compared to inactive cannabis. Pain response was assessed using the Cold Pressor Test (CPT), a laboratory model of pain that has predictive validity for clinical efficacy of opioid analgesics in non-pain populations (Zacny et al., 1996a; Conley et al., 1997) and has been used to demonstrate the analgesic effects of smoked cannabis and oral THC (Cooper et al., 2013). In addition to analgesia, cannabis' subjective and cardiovascular effects in men and women were also compared to determine generalizability of cannabis' sex-dependent effects.

2. Methods

Data from two outpatient studies carried out at New York State Psychiatric Institute were used for this analysis (total N = 49). These double-blind, within-subject studies, designed to assess the analgesic effects of cannabinoids in non-treatment seeking, recreational (non-medical) cannabis smokers, measured the subjective ratings of drug quality, drug effect, mood, and physiological effects of a single strength of active cannabis (3.56-5.60% THC, active strength varied according to study) relative to inactive cannabis (0.00% THC). All participants were included from the first study (N = 15 women and 15 men; Cooper et al., 2013). For the second study (N = 6 women and 13 men), data from 6 men that best matched the women for frequency of cannabis use (days/week) and amount smoked per day (joints/day) were used. This matching was done to account for tolerance to cannabis' effects that occur with repeated use (Haney et al., 1997; Hart et al., 2002). Subjective and cardiovascular effects of cannabis smoked according to a controlled smoking procedure were analyzed according to cannabis condition (active and inactive) and sex for each endpoint.

2.1. Participants

Volunteers ages 21-50 were recruited through newspaper advertisements for a study on the effects of cannabis on pain response, mood, and physiology. Those who met inclusion/exclusion criteria after an initial telephone screen were invited to the laboratory for further screening. Prior to enrollment, participants gave written informed consent, received a psychiatric and medical evaluation, and provided a detailed drug use and medical history. All eligible participants currently smoked > 3 cannabis cigarettes at least four times a week

for the previous four weeks before screening, based on self-report and clinical interviews, and tested positive on a cannabis urine toxicology screen. Participants were accepted into the study if they were healthy, as determined by a physical examination, electrocardiogram, and urine and blood chemistries. Participants were excluded if they had current pain, repeatedly used other illicit drugs as determined by urine toxicology and self-report, or met criteria for alcohol dependence. Urine toxicology screens were performed during every screening visit and before each session. Exclusion criteria included Axis I psychopathology (DSM-IVth edition) as assessed by clinical interview, current use of over-the-counter or prescription medications, with the exception of oral contraceptives, pregnancy or nursing. Volunteers were told that during each session they would smoke a portion of a cannabis cigarette, but that the strength of the cannabis would vary. Participants were admitted into the studies only after written informed consent to participate was given and eligibility criteria were verified. All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute and were in accord with the Declaration of Helsinki.

2.2. Design and procedures

The studies included 5-8 outpatient sessions over the course of 2-8 weeks at the New York State Psychiatric Institute. Sessions began around 9 AM, and were 6-7 hours in duration. Before study onset, participants were familiarized with computerized tasks, study procedures, and the CPT with 1 or 2 training sessions. Data obtained from 21 men and 21 women were used for the present analysis. Of these, 15 men and 15 women participated in a study investigating the analgesic effects of cannabis (0.00, 1.98, or 3.56% THC relative to dronabinol (Cooper et al., 2013) and 6 men and 6 women participated in a study assessing the effects of cannabis (0.00 or 5.60% THC) combined with an FDA-approved medication (findings not yet published). During each session, a capsule containing placebo or medication was administered followed by cannabis (active or inactive) smoking. A within-subject design was used for these two studies in which all participants received active and inactive cannabis and medication strengths; the order of drug conditions was randomized. For this analysis, data obtained from the placebo session (placebo oral medication and inactive cannabis) were compared to data obtained from the session when only active cannabis was administered (placebo oral medication and active cannabis); thus, results only reflect outcomes from the placebo medication sessions.

2.2.1 Experimental session—Participants were told not to smoke cannabis or cigarettes after midnight the night before each session and not to eat breakfast the morning of the session. Before each session, carbon monoxide levels were measured to confirm no recent cannabis smoking, breath alcohol levels were assessed, and the use of illicit drugs other than cannabis was determined by a urine toxicology screen. Sessions were rescheduled if carbon monoxide levels indicated that the participant had smoked cannabis or a cigarette prior to arrival (> 8 ppm). A standardized breakfast was provided to all participants prior to baseline measurements.

Before drug administration, baseline subjective-effects questionnaires were completed and heart rate and blood pressure were measured using a Sentry II vital signs monitor (Model 6100; NBS Medical Services, Costa Mesa CA). Participants smoked a cannabis cigarette

according to a cued-smoking procedure shown to produce reliable increases in heart rate and plasma THC levels (Foltin et al., 1987): Investigators instructed participants to ‘inhale’ (5s), ‘hold smoke in lungs’ (10s) and ‘exhale’. Participants smoked according to this procedure with a 40-second interval between puffs until 70% of the cigarette was pyrolyzed. Pain response using the CPT, subjective ratings of drug effect and mood, heart rate, and blood pressure were assessed at set time-points throughout the session. Cigarette smokers were permitted to smoke at predetermined intervals throughout the session in order to minimize nicotine withdrawal symptoms. At the end of each session, participants passed a field sobriety tasks and were free to leave the laboratory.

2.2.2 Cold Pressor Test—The cold pressor apparatus consisted of two water coolers; one cooler was filled with warm water (37°C) and the other was filled with cold water (4°C). Each cooler was fitted with a wire cradle and an aquarium pump for water circulation. Participants removed jewelry from the left hand and forearm at the beginning of the session; during the test, participants were instructed to rest his/her hand with fingers spread apart on the wire cradle with their hand fully immersed. Each CPT began with an immersion of the left hand into the warm-water bath for three minutes, during which time blood pressure and heart rate were measured. Skin temperature of the thumbpad was recorded when the hand was removed from the warm-water bath and participants listened to a standardized script describing the procedures for the CPT. Participants then immersed the left hand into the cold-water bath and were instructed to report the first painful sensation. They were asked to tolerate the stimulus as long as possible, but were permitted to withdraw their hand from the cold water at any point. Maximum immersion time did not exceed 2 minutes. Latency to first feel pain (pain sensitivity) and latency to withdraw the hand from the water (pain tolerance) were recorded. Blood pressure and heart rate were measured before and after each immersion using the arm that was not immersed in the water bath. The experimenter administering the CPT was of the same sex as the volunteer. The Cold Pressor Test was performed 5 times after cannabis administration; 15, 45, 75, 135, and 225 minutes after smoking for the first study and 30, 60, 90, 120, and 180 minutes after smoking for the second study.

2.2.3 Subjective Effects—Subjective ratings of pain and drug effect were measured throughout the session.

2.2.4 Pain Intensity and Bothersomeness Scales—Immediately after removing the hand from the cold water, participants were asked to rate the how painful and bothersome the stimulus was on a scale from 0 to 10, 0 being ‘not painful/bothersome at all’ and 10 being ‘most painful/bothersome feeling imaginable’ (Black et al., 1999).

2.2.5 McGill Pain Questionnaire (MPQ)—A 15-item shortened form of the McGill Pain Questionnaire (Melzack, 1987) was used to assess the sensory and affective dimensions of the pain experience immediately following the CPT. Participants described their experience of pain by choosing among a series of possible answers (None [score=1], Mild [score=2], Moderate [score=3], or Severe [score=4]). They were asked to describe the pain as “Throbbing,” “Shooting,” “Stabbing,” “Sharp,” “Cramping,” “Gnawing,” “Hot-Burning,”

“Aching,” “Heavy,” “Tender,” “Splitting,” “Tired-Exhausting,” “Sickening,” “Fearful,” and “Punishing-Cruel.” Scores were added across all 15 items to generate a sum score, which ranged between 15 and 60. This questionnaire was completed immediately after participants withdrew their hand from the cold water.

2.2.6 Subjective Drug-effects—Subjective drug effects were measured using the visual analog scales described below. A series of 100-mm lines anchored with ‘not at all’ (0 mm) and ‘extremely’ (100 mm). Participants were instructed to indicate on the line how they felt at that moment 6 times after cannabis smoking (15, 45, 75, 105, 135, and 225 min after smoking for the 1st study and 15, 30, 60, 90, 120, and 180 min after smoking for the 2nd study).

Subjective Effect-Visual Analog Scale (VAS): Participants were asked to rate their mood and physical symptoms on a modified 44-item VAS intended to measure affective and physical subjective drug effects (see Haney et al., 1999 for description of the original 50-question version).

Cannabis Rating Form: Subjective cannabis-related drug effects were assessed using a 5-item VAS asking participants to rate the strength of the drug effect, good effect, bad effect, drug liking, and willingness to take the drug again. Participants were also asked to indicate whether they thought the cannabis was ‘placebo’ or ‘active’ (Haney et al., 2005).

2.3. Drugs

Cannabis cigarettes (0.00, 3.56 - 5.60% THC; ca. 800 mg) were provided by the National Institute on Drug Abuse. Cigarettes were stored frozen in an airtight container and humidified at room temperature for 24 hours prior to the session. For medication studies, capsules (size 00 opaque capsules with lactose filler) containing placebo or the test medication were prepared by the New York State Psychiatric Institute Research Pharmacy.

2.4. Data Analysis

To account for differences in baseline sensitivity to the CPT among participants, post-smoking values for pain sensitivity and tolerance were calculated as percent of the baseline pre-smoking CPT response for each participant. Similarly, post-smoking values for subjective ratings of “Painfulness” and “Bothersomeness,” participant ratings of pain as assessed by the MPQ, and heart rate were calculated as the difference from baseline pre-smoking values for each participant. Differences in demographics and cannabis use between men and women were determined by independent t-tests. Baseline differences between the inactive and active cannabis sessions for pain sensitivity, pain tolerance, subjective ratings of “Bothersomeness” and “Painfulness,” participant ratings of pain as assessed by the MPQ, and heart rate were determined with repeated measures analysis of variance (ANOVA) with between-subject analysis for sex. Repeated measures ANOVA with between-subject analyses were also used to determine sex differences in analgesic, subjective, and cardiovascular effects of active cannabis compared to inactive cannabis across post-smoking time-points; 5 time-points for pain response and heart rate and 6 time-points for subjective-drug effects (time-points were averaged between the two studies). Separate repeated

measures ANOVAs comparing active and inactive cannabis conditions according to each sex were performed only if the between-groups analysis yielded a significant interaction between sex and dose or sex, dose, and session time-point. Results were considered statistically significant when p values were equal to or less than 0.05 using Huynh-Feldt corrections. Statistical analyses were performed with SPSS (IBM® SPSS® Statistics Version 20, IBM Corp.).

3. Results

3.1. Demographics

Table 1 portrays the demographic information of the participants according to sex. Men and women did not differ in age, number of days per week cannabis was smoked, or number of cannabis cigarettes smoked per day. Men and women did not differ in number of tobacco cigarette smokers, or weekly alcohol drinkers. Although men and women did not differ in BMI, men weighed significantly more than women.

3.2. Analgesic Effects

3.2.1 CPT: Pain Sensitivity and Tolerance—Figure 1 portrays the effects for inactive and active cannabis on pain sensitivity defined as latency to report pain (left panel) and pain tolerance defined as latency to withdraw the hand from the cold water (right panel) in men and women. Baseline pain sensitivity did not differ as a function of cannabis condition or sex. Between-groups analysis revealed a significant interaction between cannabis strength and time-point ($p = 0.0001$), an effect that varied as a function of sex ($p = 0.05$). Separate analyses according to sex demonstrated that for men, active cannabis decreased pain sensitivity relative to inactive cannabis ($p = 0.05$) an effect that varied across the session time-points ($p = 0.01$). Peak differences in pain sensitivity between active and inactive cannabis occurred at the first post-smoking time-point (active cannabis, $200.0 \pm 32.8\%$ vs inactive cannabis, $91.5 \pm 4.5\%$) and returned to inactive cannabis values by the last post-smoking time-point. In women, cannabis did not significantly change pain sensitivity. Pain sensitivity did, however, vary over the course of the session, regardless of cannabis strength ($p = 0.01$).

Baseline pain tolerance did not differ as a function of session, but a trend for women exhibiting shorter latencies to withdraw their hand from the cold water relative to men was observed ($p = 0.10$). Between-groups analysis for pain tolerance after cannabis smoking indicated that active cannabis increased pain tolerance relative to inactive cannabis as a function of session time ($p < 0.001$). A trend for active cannabis to increase pain tolerance as a function of sex was observed ($p = 0.10$); for men, active cannabis increased pain at the first post-smoking time-point relative to inactive cannabis and returned to inactive cannabis values 2 hours post-smoking. Among women, active cannabis first increased pain tolerance followed by a decrease later in the session relative to inactive cannabis.

3.2.2 Subjective Pain Ratings—Figure 2 portrays the subjective ‘Bothersomeness’ ratings of the CPT as a function of cannabis strength between men and women. Baseline ratings of ‘Bothersomeness’ did not differ as a function of session or sex. These ratings

varied after cannabis smoking as a function of the interaction between session time and cannabis strength ($p = 0.001$), with active cannabis decreasing ratings relative to inactive cannabis early in the session; differences as a function of sex were not observed. Baseline ratings of 'Painful' did not vary as a function of session, yet a trend was observed for higher baseline ratings among women relative to men ($p < 0.10$) (data not shown). These ratings also did not vary after cannabis smoking between men and women as a function of cannabis strength or session time-point. Baseline pain ratings as measured by the MPQ did not vary as a function of session or sex (data not shown). These ratings varied as a function of session time ($p = 0.01$) with ratings increasing over the course of the session, but did not differ between men or women or as a function of cannabis strength.

3.3. Subjective Drug Effects

Figure 3 illustrates subjective ratings of active and inactive cannabis according to sex and session time-point as assessed by the MRF and VAS. For men and women, ratings of cannabis associated with abuse liability, 'Drug liking,' 'Good,' 'Take Again,' were higher for active cannabis relative to inactive ($p = 0.0001$). Ratings for 'Drug liking' remained elevated throughout the session for active cannabis, and peak ratings occurred immediately after smoking and decreased over the course of the session for 'Good drug effect' ($p = 0.0001$) and 'Take again' ($p = 0.05$) independent of cannabis strength. No differences were observed between men and women for these endpoints. Similarly, subjective ratings of cannabis 'Strength' were significantly higher under active cannabis smoking relative to inactive cannabis ($p = 0.0001$; data not shown) and decreased over the session ($p = 0.05$). No differences were observed between men and women. Analysis for subjective ratings of cannabis 'High' revealed a significant interaction between cannabis strength and session time ($p = 0.0001$), with active cannabis producing higher ratings relative to inactive cannabis, an effect that peaked after cannabis smoking and decreased over the course of the session; this effect did not vary according to sex. However, independent of cannabis strength, ratings of 'High' varied across session time-point as a function of sex ($p < 0.05$), with men exhibiting elevated rating throughout the session relative to women.

3.4. Cardiovascular Effects

Figure 4 portrays changes in heart rate over the session as a function of sex and cannabis condition. Baseline heart rate did not vary as a function of session, but was significantly higher in women relative to men ($p = 0.01$). Between groups analysis for post-smoking time-points demonstrated that overall, active cannabis increased heart rate relative to inactive cannabis above baseline values ($p < 0.0001$), an effect that peaked after smoking and decreased over the course of the sessions ($p < 0.0001$). A trend emerged for an interaction between cannabis strength and session time as a function of sex ($p < 0.10$) with men exhibiting greater increases in heart rate after smoking active cannabis relative to women.

4. Discussion

The results from this retrospective analysis demonstrate that among cannabis smokers, men exhibit greater cannabis-induced analgesia relative to women as measured by the CPT. Active cannabis decreased pain sensitivity and increased pain tolerance among men. In

women, active cannabis did not significantly decrease pain sensitivity. Although active cannabis produced a small increase in pain tolerance in women shortly after smoking, pain tolerance decreased relative to inactive cannabis later in the session. This modest response to the CPT observed among women late in the session after active cannabis administration relative to inactive cannabis is suggestive of reports of opioid-induced hyperalgesia (Lenz et al., 2011), and may indicate that women are more susceptible to the potential hyperalgesic effects of cannabinoids. Of note, cannabis affected only one of three subjective measures of pain assessed, bothersomeness, an effect that did not differ between men and women. Despite the differences in cannabis-induced analgesia, men and women reported comparable ratings of active cannabis' subjective effects associated with abuse liability, drug strength, and intoxication. As medical cannabis becomes increasingly more available and accepted as a viable therapeutic option for a wide range of indications, these findings underscore the necessity of double-blind, placebo-controlled studies to understand both its risks and potential therapeutic effects. Additionally, these results exemplify the importance of not only including both men and women in cannabinoid-related investigations, but also analyzing the data for sex-dependent effects.

The present findings diverge from preclinical reports demonstrating that female laboratory animals are consistently more sensitive to both reward-related and antinociceptive effects of cannabinoids relative to males (Craft et al., 2013). Therefore, the absence of a sex-dependent difference for cannabis' subjective effects, coupled with the sex-dependent effect for cannabis-induced analgesia that is the reverse of what is observed in the preclinical literature appears unexpected, but may in fact reflect important differences in cannabis exposure in rodent and human studies. Recent preclinical studies revealed that although females are more sensitive to cannabinoid-induced antinociception, this effect is restricted to the acute administration of cannabinoids. Under conditions of repeated THC administration, both male and female rats develop tolerance to THC's antinociceptive effects and females develop significantly greater tolerance relative to males (Wakley et al., 2014, 2015). For instance, after repeated daily THC administration, female rats demonstrated a 4.2-fold increase in ED50 values for THC's antinociceptive effects, whereas males demonstrated only a 2.8 fold increase in ED50 values (Wakley et al., 2014). A proposed mechanism for this sex-dependent tolerance relates to estradiol-dependent increases in β -arrestin2 recruitment to the cell membrane (Sandén et al., 2011). Because β -arrestin2 plays a role in CB1 receptor internalization and desensitization (Raehal and Bohn, 2014), estradiol-dependent increases of this protein are hypothesized to contribute to the increased tolerance observed in female rats relative to male rats (Wakley et al., 2014). Based upon these preclinical findings, it is conceivable that in the current sample of daily cannabis smokers, the sex-dependent differences observed for cannabis-induced analgesia, with men exhibiting an analgesic response and a lack of response in women, is due to differential tolerance between men and women. Another potential indication of differential tolerance was a trend for smaller increases in cannabis-elicited increases in heart rate in women relative to men. If cannabis-elicited analgesia in the current study was indeed constrained because of tolerance, an enhanced analgesic response would be expected in less frequent or non-cannabis users, with women exhibiting greater sensitivity to this effect relative to men, as observed in preclinical studies. As such, determining this effect in populations that are lighter users or who do not

currently use cannabis is directly relevant to understanding the effects of cannabis in nonrecreational using populations that explore medical cannabis for pain relief.

Another implication of the preclinical evidence of tolerance to cannabinoid-induced analgesia is that using higher strengths of cannabis than those used in the current study would likely produce an analgesic effect in women and perhaps a greater response in men. Although higher strengths of cannabis are expected to produce greater analgesia, it is expected that the subjective ratings related to abuse-liability and intoxication would increase as well, a clear limitation of the potential therapeutic effects of cannabis for pain relief. Oral THC (dronabinol) has been shown to elicit longer lasting analgesia with significantly attenuated positive subjective drug effect ratings relative to smoked cannabis (Cooper et al., 2013), suggesting the potential of alternative methods to utilize the therapeutic effects of THC while decreasing its negative effects.

The lack of a significant sex-dependent effect for abuse-related subjective ratings of cannabis effects in the current study was unexpected given our recent human laboratory report demonstrating that female daily cannabis smokers show enhanced subjective effects related to abuse liability relative to male daily cannabis smokers (Cooper and Haney, 2014), an analysis that utilized subjective effects data from 11 men and 11 women from the current study. A possibility for the lack of sex-dependent effects for positive subjective drug effect ratings in the current analysis is the potential sex-dependent interaction of the CPT on subjective drug responses. The CPT has been shown to alter subjective drug effects, an effect that is observed during exposure to the painful stimulus, including ratings of 'High' and 'Elated' (Conley et al., 1997; Zacny et al., 1996a, b). In one study, pain-induced modulation of opioid subjective effects were specifically observed among women and not men (Zacny and Beckman, 2004). Although participants in the current study completed the drug effect scales after, rather than during, the CPT, it is conceivable that the repeated exposure to the painful stimulus attenuated the overall subjective effects of cannabis in a sex-dependent manner. An important aspect in the intersection between an effective analgesic agent and its abuse potential extends beyond subjective drug effect ratings to the drug's reinforcing effects. Preclinical and clinical studies investigating the interaction between the reinforcing effects of opiates and pain demonstrate that opiate self-administration is positively associated with pain (Gil et al., 1990; Zacny et al., 1996a; Colpaert et al., 2001; Comer et al., 2010). In the current analysis, men and women did not differ in subjective drug effect responses, but the reinforcing effects of cannabis as a function of sex were not explored. As such, exploring the extent to which the reinforcing effects of cannabis can change as a function of pain and if the effect varies according to sex is an important consideration for future studies investigating cannabinoid-induced analgesia.

Sex-dependent effects of several classes of psychoactive drugs are mediated by fluctuations in reproductive hormones in humans and laboratory animals. For cocaine (Sofuoglu et al., 1999, 2002; Evans et al., 2002; Evans and Foltin, 2006; Mello et al., 2007; Lynch, 2008), opioids (see Craft, 2003 for review), and cannabinoids (Craft et al., 2013). Relative to males, females are more sensitive to drug effects during the follicular / estrus phase when progesterone is low and estradiol is high. For cannabinoids, sex-dependent differences mediated by gonadal hormones have been most thoroughly characterized in laboratory

animals, with minimal data available from human studies. These preclinical studies have found that when estradiol levels are high, female rats exhibit greater sensitivity to the antinociceptive (Craft and Leidl, 2008; Wakley and Craft, 2011), reinforcing (Fattore et al., 2010; Castelli et al., 2014), and dependence-producing (Marusich et al., 2015) effects of cannabinoid agonists relative to males, whereas progesterone decreases the sensitivity to cannabinoid's antinociceptive effects (Wakley et al., 2015). Despite the modulatory role of ovarian hormones on sex-dependent cannabinoid effects, they do not seem to play a role in the development of tolerance between males and females (Wakley et al., 2015). While it is possible that cycling reproductive hormones contribute to differences between men and women in cannabis-induced analgesia and subjective drug responses, the effects observed in the current study were likely independent of these hormonal fluctuations; sessions were run weekly over a 2-8 week period, and drug conditions were randomized across session. Similar to the current study, sex-dependent opioid-induced analgesia has also been observed using the CPT with women exhibiting a decreased response to the opioid agonist butorphanol relative to men, an effect that was independent of menstrual cycle phase (Zacny and Beckman, 2004). However, investigating potential hormone-dependent effects of cannabinoids would elucidate the extent to which the preclinical findings translate to humans, and would be valuable in assessing the role of cannabinoids in both the therapeutic practice and in predicting the relative risks associated with their use (i.e., increases in abuse liability).

Assessing the sex-dependent analgesic effects of cannabis in volunteers without pain provided a degree of control that would not have been afforded in a chronic-pain population. The fluctuations of day-to-day baseline pain measures in a chronic pain population and the use of over-the-counter or prescription analgesics outside of the laboratory are two examples of issues that could have significantly affected the findings. Nevertheless, performing a well-controlled study with a clinical population is optimal to further understand the therapeutic utility of cannabinoids as analgesics. The opioid literature provides ample evidence that the presence of pain produces neuroadaptations that alter the behavioral and physiological effects of opioid agonists (Niikura et al., 2010). Similarly, preclinical studies show parallel changes to the endocannabinoid system in response to pain (Miller and Devi, 2011). As such, there is a need to further understand the efficacy of cannabinoid agonists in chronic-pain population as a function of sex. Given that responses to only one nociceptive stimulus was assessed in the current analysis, with little effect on subjective pain ratings, future studies assessing sex dependent analgesic effects of cannabinoids should also explore additional laboratory models of pain that utilize various nociceptive stimuli including mechanical-, thermal-, and chemical-induced pain.

In the present analysis, male cannabis smokers exhibited greater cannabis-induced analgesia relative to females despite comparable ratings of active cannabis' subjective effects associated with abuse liability. These findings underscore the importance of including sex as a primary variable when designing studies investigating cannabinoid effects and should be replicated in a larger sample size with diverse populations (infrequent cannabis users, patient populations, etc) to ascertain the generalizability of this effect. While legalization of medical cannabis is occurring rapidly, it is clear that the negative effects are a significant limitation to their therapeutic use. It is imperative that both the therapeutic potential and negative effects

of cannabinoids be studied under double-blind placebo-controlled conditions, taking into account the variables that impact their effects like sex, as explored in the current analysis, current cannabis or cannabinoid use, and disease state.

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Highlights

- Sex-dependent analgesic and subjective effects of cannabis were assessed.
- Men and women were matched according to current cannabis use
- Cannabis significantly decreased pain sensitivity in men but not women.
- Subjective effects of cannabis did not differ between men and women.
- Sex is an important variable to address when investigating cannabis analgesia.

Figure 1.

Pain sensitivity (left panel) and tolerance (right panel) as calculated by percent baseline latency (seconds) to report pain and withdraw the hand from the cold water. Data are presented as mean values ($\pm$ SEM) for men and women according to cannabis strength (inactive and active) and time-point. Baseline, pre-smoking latencies are portrayed in seconds and post-smoking values are portrayed as percent of the baseline values. For pain sensitivity, significant interactions between cannabis strength and time-point observed among men are indicated by ** = $p < 0.01$. For pain tolerance, significant differences between active and inactive cannabis as a function of session time, independent of sex, are indicated by ** = $p < 0.001$.

Figure 2.

Subjective ratings of cold water 'Bothersomeness' (left panel) calculated by difference from baseline ratings on a scale of 0-10. Data are presented as mean values ($\pm$ SEM) for men and women according to cannabis strength (inactive and active) and time-point. Baseline, pre-smoking ratings are portrayed as the raw score and post-smoking ratings are portrayed as differences from the baseline ratings. Ratings varied after cannabis smoking as a function of the interaction between session time-point and cannabis strength (** = $p < 0.001$), but not as a function of sex.

Figure 3.

Subjective ratings of cannabis quality ('Take Again,' 'Drug Liking,' 'Good Effect') and 'High' as measured by the MRF and VAS on a scale of 0-100 mm. Data are presented as mean ($\pm$ SEM) ratings for men and women as a function of cannabis strength (inactive and active) and time-point. Significant differences between active and inactive cannabis, independent of sex, are indicated by *** = $p < 0.0001$.

Figure 4.

Cardiovascular effects of active and inactive cannabis as calculated by difference from baseline heart rate (BPM). Data are presented as mean values ($\pm$ SEM) for men and women according to cannabis strength (inactive and active) and time-point. Baseline, pre-smoking heart rate is portrayed as BPM and post-smoking heart rate is portrayed as the difference from baseline BPM. A significant difference in baseline heart rate between men and women is indicated by ## = $p < 0.01$; significant differences between active and inactive cannabis, independent of sex, are indicated by *** = $p < 0.0001$.

Table 1

Demographic Characteristics of Study Participants.

	Men (N = 21)	Women (N = 21)
Age (years old)	28 ± 6	28 ± 6
Race (B/W/M/A)	14 / 6 / 1 / 0	12 / 5 / 3 / 1
Body Weight (kg) Body Mass Index	75.6 ± 11.9* 24.5 ± 2.5	66.7 ± 11.3 26.2 ± 5.0
Cannabis Use		
Days/Wk	6.6 ± 0.8	6.3 ± 1.3
MJ Cigarettes/Day	7.2 ± 5.6	9.8 ± 7.3
\$/Wk	69.1 ± 56.1	74.1 ± 74.9
Tobacco Smokers		
# Daily Smokers	9/21	11/21
Cigs/Day	8.5 ± 7.1	7.8 ± 6.7
Alcohol		
# Weekly Drinkers	15/21	10/21
Days/Wk	2.1 ± 1.1	1.5 ± 0.6
Drinks/occasion	2.7 ± 2.4	2.3 ± 0.8

Note: Data are presented as means (± SD) or as frequency.

Race is indicated as Black or African American (B), White (W), Mixed (M), or Asian (A).

Significant differences between men and women are indicated by a

* = p < 0.01.