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Journal

The American Journal of Drug and Alcohol Abuse, 45(6)

ISSN

0095-2990

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Publication Date

2019-11-02

DOI

10.1080/00952990.2019.1669628

Peer reviewed

HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2020 June 08.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2019 ; 45(6): 580–595. doi:10.1080/00952990.2019.1669628.

Considering abuse liability and neurocognitive effects of cannabis and cannabis-derived products when assessing analgesic efficacy: A comprehensive review of randomized-controlled studies

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Abstract

Background—Pain is the most frequent indication for which medical cannabis treatment is sought.

Objectives—The clinical potential of cannabis and cannabis-derived products (CDPs) relies on their efficacy to treat an indication and potential adverse effects that impact outcomes, including abuse liability and neurocognitive effects. To ascertain the extent to which these effects impact therapeutic utility, studies investigating cannabis and CDPs for pain were reviewed for analgesic efficacy and assessments of abuse liability and neurocognitive effects.

Methods—A comprehensive review of placebo-controlled studies investigating cannabis and CDP analgesia was performed. Methods and findings related to adverse effects, abuse liability, and neurocognitive effects were extracted.

Results—Thirty-eight studies were reviewed; 29 assessed cannabis and CDPs for chronic pain, 1 for acute pain, and 8 used experimental pain tests. Most studies ascertained adverse effects through self-report (N = 27). Fewer studies specifically probed abuse liability (N = 7) and cognitive and psychomotor effects (N = 12). Many studies related to chronic and experimental pain (N = 18 and N = 5 respectively) found cannabis and CDPs to reduce pain. Overall, adverse effects were mild to moderate, and dose-related. Studies investigating the impact of cannabis and CDPs of abuse liability and neurocognitive endpoints were mostly limited to inhaled administration and confirmed dose-related effects.

Conclusion—Few studies investigating cannabis and CDP analgesia assess abuse liability and cognitive endpoints, adverse effects that impact long-term clinical utility of these drugs. Future

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studies should include these measures to optimize research and clinical care related to cannabis-based therapeutics.

INTRODUCTION

Significant legislative changes in medical use of cannabis are occurring with a large number of adults in the United States (US) turning to cannabis to help alleviate a number of health conditions. As of November 2018, 33 states and the District of Columbia (DC) allow patients with qualifying medical conditions access to cannabis or cannabis-derived products (CDPs) based on state regulations [1]. A recent report estimates 2.3 million registered medical cannabis patients in the US [2] with many states seeing 30–100% increases in registered medical cannabis patients in the span of a year (Florida [3], Montana [4], Hawaii [5], New Jersey [6]). Repeatedly, pain has been reported to be the primary indication for which people use medical cannabis [7–9]. Chronic pain is also one of the few indications for which there is substantial evidence supporting the use of both cannabis and cannabinoids [10].

Several systematic reviews have addressed the strength of evidence for the utility of cannabis and CDPs for different types of pain (i.e.10–12). While recent reviews of cannabis and cannabinoids for pain have focused on the overall adverse effects of cannabis gleaned from the wider literature (i.e., cannabis' effects in the general adult population (i.e. 10,11), to date, few have systematically reported on the adverse effect assessments and outcomes within the context of rigorous double-blind studies of cannabis and CDPs for their therapeutic effects (see 13). This is an important distinction as the negative effects of cannabis and CDPs will vary significantly whether they are used recreationally or therapeutically, and based on the population studied (i.e., cannabis experienced versus non-cannabis experienced). In addition, since many reports investigating the negative effects of cannabis come from observational studies, there is a lack of standardization of cannabis product, dose, route of administration, and frequency of administration. As such, generalizability of these findings to studies of RCTs assessing standardized doses of cannabis and CDPs for therapeutic effects is limited. Given the increasing popularity of cannabis itself and CDPs for medicinal use, understanding the impact of these specific products in the medical context is especially relevant.

Two significant concerns arise when considering the short- and long-term therapeutic utility of cannabis and CDPs; potential abuse liability and neurocognitive effects. Abuse liability is defined as the potential of a drug to illicit positive subjective effects that contribute to non-medical use, which over time, could lead to chronic use despite negative consequences [14] and in this case, Cannabis Use Disorder (CUD). Over 80% of people who use cannabis for medical purposes also use it for recreational reasons [15] and approximately 25% of patients prescribed oral cannabinoid therapy demonstrated problematic medical cannabis use [16]. As such, understanding the abuse liability of cannabis and CDPs is critical to optimizing therapeutic benefit and preventing increases in rates of CUD among this population. Another issue that limits the therapeutic utility of cannabis and CDPs is their cognitive and psychomotor impact. These effects have been well described in the literature in recreational cannabis users and shown to vary according to drug dose, route of administration, and

frequency of cannabis use in the population tested (i.e.,17). However, these outcomes may vary considerably when cannabis and CDPs are used therapeutically, especially if they are alleviating conditions that interfere in cognitive processes. While considering cannabis and cannabinoids as therapeutics, assessing their abuse potential and neurocognitive effects is critical in identifying the magnitude of these effects and will help to guide strategies to minimize these outcomes, such as manipulating dose and route of administration. Through a systematic review of the literature, rigorous double-blind, placebo-controlled studies involving only cannabis and CDPs were assessed for both study outcome as they related to pain as well as rigor for assessing adverse events, with attention to abuse liability and neurocognitive effects.

METHODS

Data search and study selection

PubMed was used to identify unique randomized, placebo-controlled studies utilizing cannabis and CDPs for pain. To aid in this search, the most recently published (through September 1st, 2018) fair- to high-quality systematic reviews (i.e., those following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines) related to the analgesic effects of cannabis, CDPs, or cannabinoids were used to ensure all relevant studies were included. Primary literature was assessed and incorporated into this summary by searching with the keywords “cannabis OR cannabinoid AND placebo AND pain.” Peer-reviewed primary literature published in English after January 1980 and before September 1st, 2018 was considered. Studies published prior to January 1980 were unclear as to the source of the cannabinoids, blinding, pain assessments, or inaccessible. Article selections were restricted to studies that assessed cannabis or CDPs. For studies that used oral THC, if the source of the product (synthetic or plant-derived) was not clear in the manuscript or vendor website, the primary author of the article was contacted. The search yielded 208 articles, 37 of which met criteria; 1 study related to acute / postoperative pain, 8 studies related to experimental pain, and the remaining 28 involved chronic pain. One additional study involving chronic pain was included based on cross-reference with a recent PRISMA systematic review [11].

Data extraction

Each study was evaluated for elements related to the study design including 1) type of pain assessed, 2) drug studied (cannabis or CDP) and comparators (i.e, placebo), 3) dose, 4) route of administration, 5) study duration, 6) sample size, 7) inclusion of participants with history or current use of cannabis or cannabinoids, 8) study design (parallel group or crossover), and 9) adverse effect assessments. Outcomes for therapeutic endpoints were reported as positive, mixed, or negative based on results related to primary or secondary analyses of the study. Assessments related abuse liability, neurocognitive and psychomotor endpoints (Table 1), and adverse effects and events were obtained from the Methods section of each study; results related to treatment-related adverse effects and serious adverse events (SAEs) as defined by manuscript authors were documented.

RESULTS

CHRONIC PAIN

Table 2 describes all randomized clinical trials assessing the effects of cannabis and CDPs on chronic pain as a function of **1)** type of pain, **2)** therapeutic cannabinoid administered and route of administration, **3)** dose and duration of study drug administration, **4)** study design and samples size, and status of cannabis use in the sample, **5)** adverse effects assessments, **6)** outcomes for pain endpoint, and **7)** adverse effect outcome for cannabis / cannabis-based product relative to comparator.

From 29 studies evaluating the effectiveness of cannabis and CDPs for chronic pain, the most common condition assessed was neuropathy (N = 11 studies). Nine studies assessed pain associated with multiple sclerosis (MS), 4 assessed cancer-related pain, 4 studies enrolled patients with mixed chronic pain conditions, and 1 study investigated abdominal pain and another rheumatoid arthritis.

Of these studies, 17 utilized an oromucosal spray (nabiximols) with a 1:1 THC:CBD ratio and study duration spanning 1–14 weeks (5.7 ± 4.5 weeks) with a maximum THC dose per day ranging from 20 – 120 mg/day (71.6 ± 44.0 mg/day) (Table 2). Four studies assessed the effects of THC alone or THC plus CBD administered as an oral capsule over 4–10 weeks (7 ± 2.2 weeks) with a maximum THC dose per day ranging between 45–25 mg/day. The 8 studies that administered cannabis through inhalation only included THC without CBD with concentrations ranging from 1–9.4% (i.e., 18–21). Five of these studies investigated the impact of smoked or vaporized cannabis under acute administration conditions whereas 3 studies assessed the impact of cannabis administration over a period of 4–5 days.

Outcomes for therapeutic endpoints—From the 29 studies assessing the effects of cannabis and CDPs for chronic pain, 18 reported positive responses and 10 reported negative findings for the primary endpoint (5 of which reported positive findings for pain from secondary endpoints or analyses; Table 2). For one study, overall positive or negative findings were unclear [22].

For studies revealing significant reductions in pain, 8 of the 18 studies investigated neuropathy, 5 multiple sclerosis, 2 cancer, 2 mixed pain types, and 1 rheumatoid arthritis. The average duration of these 18 studies was 22.8 days (± 27.4 days), with 1 study lasting 14 weeks [23], 3 studies lasting less than a week, and 5 assessing the impact of acute administration, enrolling an average of 113.5 (± 148.6) participants Ten out of 18 of the positive studies used a parallel group design. Half of the studies (9/18) included two study arms comparing a single dose of cannabis or CDPs to placebo. Five studies included three study arms assessing the impact of dose [24–26] or THC alone or combined with CBD [27,28]. Four studies included 4 study arms to investigative the impact of dose [20,29–31] or THC and CBD alone or combined [32] on therapeutic endpoint. The majority of these studies (11/18) permitted recent cannabis use prior to enrollment, with abstinence required for 7–30 days prior to trial initiation. Five studies excluded past cannabis dependence or current cannabis use; previous or current cannabis use was unknown for two studies [28,33].

For studies with negative or mixed findings, 3 of the 10 investigated neuropathy, 4 multiple sclerosis, 2 cancer, and 1 abdominal pain (i.e.,34–36, Table 2). The average duration of these studies was 44.5 days (± 32.7 days), with all studies lasting more than a single week, and enrolling an average of 178.5 (± 166.1) participants. Seven out of the 10 studies used a parallel group design. Nearly all of the studies (9/10) studies included two study arms comparing a single dose of CDPs to placebo. A single study included three study arms assessing the impact THC alone or combined with CBD [37]. For 6 of these studies, previous cannabis use was unknown, 1 study required that participants be cannabis naïve [38], 3 studies allowed participants who had used cannabis previously but use was restricted before and during the study [32,37,39].

Overall adverse effect assessments—Apart from 3 studies that did not include details related to adverse effect assessments (i.e., 40), all studies (N = 26) included adverse effects assessment, many with clinical safety laboratory measurements (Table 2). Self-reported psychoactive drug effects, including intoxication, were assessed in 18 of the 29 studies. Nine studies included neurocognitive assessments, 3 self-reported measures of memory and cognitive impairments, 3 included assessments of abuse liability, and 2 assessed risk for suicidal ideation.

Overall, cannabis and CDPs were safe and well tolerated. No serious adverse events (SAEs) were reported for studies that were of acute or limited duration. For MS-related pain, SAEs related to agitation, tachycardia, hypertension (N = 1[41]) and paranoia (N = 1[41]), confusion (N = 1 [42]), urinary tract infection (N = 1 [42]) were reported with the THC:CBD oromucosal spray. Two instances of SAE's related to discontinuation of study medication with aggression, agitation, delusion, irritability, insomnia, and worsening depression were described in two participants [42]. In one study of oral CDPs for MS-related pain, three SAEs for UTIs were described; whether these instances were related to active or placebo medication is not clear [43]. For cancer-related pain, SAEs related to constipation and disorientation (N = 1 each [44]), and syncope (N = 1 [28]) were reported. For rheumatoid arthritis, oromucosal THC:CBD administration was associated with 1 SAE of constipation and malaise [33]. These SAEs did not seem to be related to high doses of study medication or cannabis experience since doses across studies reporting these SAEs ranged from 25–120 mg THC per day in a mixed-cannabis experienced population.

Relative to placebo, the most frequent adverse events reported included gastrointestinal complaints including constipation, nausea, vomiting, diarrhea, abdominal pain (N = 20 studies), fatigue and somnolence (N = 19 studies), dizziness (N = 18 studies), self-reported cognitive effects (N = 15), and intoxication (N = 12 studies). Many studies reported increased incidents of sedation (N = 6), dry mouth (N = 6), and disorientation (N = 5) (Table 2). Several studies described increased incidents of headache (N = 4), feeling drunk (N = 4), anxiety and mood disruptions (N = 4), and vasovagal syncope (N = 3). Only 3 of the 29 studies assessed abuse liability, all of which found an increase in positive subjective drug effects, which were reported to be dose-dependent [25]. For studies that incorporated neurocognitive testing (N = 9), decrements were apparent in learning, memory, attention, and psychomotor performance in all but two investigations [45,46]. There was an indication of a dose-dependent nature of these effects for attention, learning and memory, and

psychomotor speed [24,30]. Deficits in some domains (i.e., working memory) were considered not to be in the impaired range [30]. Most of the studies that tested for and found cognitive decrements utilized smoked or vaporized cannabis; in contrast, the two studies that did not find decrements utilized oromucosal THC:CBD spray (an average of 7.3 sprays [19.7 mg THC] / day; [45]) oral THC capsules at a relatively low dose of 15–24 mg per day [46]. The timing of the first neurocognitive testing relative to dose administration ranged from 5 minutes to 3 hours after administration [21,22,24–26,30]. However, timing of these assessments relative to dose administration was unclear in many studies [28,29,31,32,41,45,46].

ACUTE PAIN

Table 3 describes the single randomized clinical trial assessing the effects of a CDP on acute pain [47]. This study evaluated a single dose of cannabis-derived oral THC (5 mg) compared to placebo for postoperative pain using a parallel group design with a total of 40 patients. Oral THC was not found to be superior to placebo in alleviating pain or time to request rescue analgesics. This study assessed self-reported psychoactive drug effects, mood, memory, and general adverse events. No treatment-related SAEs were reported. The only adverse effect noted in the CDP group relative to placebo was increased awareness of surroundings.

EXPERIMENTAL PAIN

Table 4 describes all randomized clinical studies assessing the effects of cannabis and CDPs on experimental pain in a healthy population as a function of the variables enumerated for Table 2 under chronic pain. The effectiveness of cannabis and CDPs in experimental pain models enrolling volunteers without pain was investigated in 8 studies (Table 4). These analyses employed a range of pain tests including the Cold Pressor Test (N = 3), a model of pain that has predictive validity for analgesics used to treat chronic pain [48–51], sunburn and capsaicin-induced pain and hyperalgesia (N=3), stimulation of the trigeminal nocisensors (N = 1) and radiant heat stimulation (N = 1). All investigations utilized crossover designs and tested the impact of cannabis and cannabinoids after acute administration. Five of the 8 reports utilized smoked cannabis ranging from 1.98–8% THC, 2 administered cannabis-derived THC in an oral capsule (15 and 20 mg), and one studied oral administration of a THC / CBD combination (20 mg THC + 10 mg CBD). Four of the 8 studies enrolled current cannabis smokers, three excluded current cannabis smokers, and cannabis inclusion / exclusion was unknown for one study. Most studies compared a single dose (N = 4) or multiple active cannabis or cannabinoid doses (N = 2) to placebo. One study compared oral THC to diazepam and another assessed the effects of cannabis administration in combination with two doses of oxycodone (2.5 and 5.0 mg) or placebo [52].

Outcomes for analgesic endpoints—Overall, 3 of the 8 studies reported positive findings for analgesic endpoints for the cannabis / cannabinoid arms, 3 reported mixed findings with cannabis effect depending on strength [53], sex [54], or pain dimension (decreases in unpleasantness of pain but not perceived intensity [55]) (Table 4). Two studies with oral THC administration reported negative findings [56,57]. Of note, two studies reported an increase in pain with cannabis / cannabinoid administration; one demonstrated

increased pain response with a higher cannabis strength (8% THC [53]) and another detailed increased pain with oral THC administration (20 mg THC+ 10 mg CBD) relative to diazepam (5 mg [56]).

Overall adverse effect assessments—Self-reported psychoactive drug effects including intoxication were assessed in 7 of the 8 studies, 4 included assessments of abuse liability (1 of which measured cannabis self-administration), and 3 studies included neurocognitive or psychomotor assessments. The timing of the first neurocognitive testing relative to dose administration ranged from 5 minutes to 3.5 hours after administration [53,55,58]. No treatment-related SAEs were reported. Cannabis-induced intoxication was observed for all studies that included this measure as an endpoint; an effect that was dose-dependent (i.e.,53,59; Table 4). When assessed, abuse liability of smoked cannabis was also apparent (i.e., 58,59). Of note, these studies included current cannabis smokers. Psychomotor effects were observed in the two studies that included these assessments with 15 mg oral THC [55] and smoked cannabis (3.6% THC [58]); the former study was not comprised of current cannabis users whereas the latter was. One study that assessed neurocognitive effects did not find cannabis-induced impairments [53]. This study included cannabis-experienced participants but not current users. Other adverse effects including non-clinically significant increases in heart rate with cannabis smoking [54,59] and oral THC and CBD [56]. One incident of cannabinoid-induced psychosis was observed [56].

DISCUSSION

The primary objective of this review was to determine the extent to which abuse liability and neurocognitive effects were measured, detected, and impacted analgesic efficacy in randomized clinical studies of cannabis and CDPs. In general, randomized clinical studies of cannabis and CDPs demonstrate therapeutic promise for a range of chronic pain conditions. Only one study assessed a CDP for acute pain, which revealed negative outcomes. Studies with experimental pain in healthy participants reported mixed effects for cannabis and CDPs that varied according to dose, sex, and type of experimental pain. Overall, cannabis and CDPs were safe and well tolerated with few SAEs. This review found only 7 studies that assessed abuse liability and 12 studies that tested the psychomotor and neurocognitive effects of these products. This review found only 7 studies assessed abuse liability and 12 tested the psychomotor and neurocognitive effects of these products. All studies that measured abuse liability found that cannabis and CDPs do indeed produce prototypical subjective effects associated with intoxication and positive drug ratings, an effect that was dose-dependent. Neurocognitive and psychomotor impairment was revealed in the majority of studies that tested for them (9 of 12 studies). Of note, most investigations that included abuse liability and neurocognitive impairment as endpoints were those that assessed inhaled administration of cannabis, and many also included current or past cannabis smokers, which likely impacts outcomes. One study that compared the effects of smoked cannabis to oral THC (dronabinol) found that subjective effects related to abuse liability were comparatively lower with dronabinol compared to those elicited by smoked cannabis [59]. Additionally, cognitive decrements were not observed in two studies that assessed oral THC or oromucosal spray [45,46]. Together, these findings suggest that oral administration may be a

strategy to curb unwanted subjective ratings associated with neurocognitive effects and abuse.

An intention of this review was to understand the impact of various study design factors on both the efficacy and adverse effects of CDPs, with attention to abuse liability and neurocognitive effects. Understanding variables that contribute to both efficacy and adverse events across studies should provide an opportunity to direct strategies to help guide future studies and improve outcomes. It was hypothesized that lower doses, oral or oromucosal administration, and cannabis-experienced population with no history of adverse effects would exhibit improved outcomes. This hypothesis bore out under some instances. For instance, higher doses of THC/CBD oromucosal spray were not effective for cancer pain and increased adverse events [29] and higher cannabis strengths (8% THC) increased sensitivity to painful stimuli and intoxication [53].

Abuse liability and neurocognitive impairment were also shown to be related to cannabis strength in some studies with higher strengths eliciting greater effects [25,30]. These findings demonstrate that higher doses or strengths of cannabis are not necessarily the best therapeutic strategy for cannabinoid-related analgesic effects; in fact, higher doses and strengths may actually increase pain and / or increase incidence of adverse effects. These dose-dependent findings are important to consider in light of the high strength cannabis and CDPs available at medical dispensaries and highlight the need for clinical studies to include multiple study arms to assess dose-dependent effects. In fact, 5 of the 18 studies with a positive outcome from chronic pain assessed the impact of multiple doses, whereas none of the studies with negative outcomes assessed a range of doses. Positive findings were also reported for the two studies that investigated the dose-dependent effects of cannabis on experimental pain [53,59].

With the limited number of studies assessing abuse liability and cognitive impairment, conclusions regarding whether cannabis experience lessens or heightens these effects are tenuous. Since all studies that assessed these endpoints allowed for current or previous cannabis use, it is unknown to what extent cannabis or cannabinoid experience may impact these effects. Taking into account literature related to cognitive impairing effects of cannabis in heavy versus infrequent users, tolerance to these effects would be expected with more experience (i.e., 60). It may also be the case that medical use of cannabis and cannabinoids may improve overall functioning by treating the underlying disease state or symptoms, consequently improving cognitive abilities [61]. As such, it is abundantly clear that this endpoint be included when assessing therapeutic efficacy of cannabis and CDPs.

Another variable that is hypothesized to increase efficacy of cannabinoid-based therapeutics is the inclusion of CBD either in cannabis or CDPs. This is based on compelling preclinical literature that CBD may have analgesic effects on its own [62] and may also decrease the negative effects of THC, including cognitive impairment and anxiety [63–68]. Of the studies reviewed, only 5 assessed the impact of THC alone and in combination with CBD [22,27,28,32,37]. One study found that the combination improved pain outcomes [28], and another found that the combination decreased the analgesic effect relative to THC or CBD administered alone [32]. Reports related to CBD-elicited reductions in THC-induced adverse

effects were infrequent. Future studies investigating the effects of THC and CBD administered alone and in conjunction are necessary to determine the therapeutic impact of using CBD alone or in combination with THC.

CAVEATS AND LIMITATIONS

An important caveat to the findings summarized is that the doses, routes of administration, and drug preparations used in the RCTs reviewed do not reflect the products available in medical cannabis dispensaries today. Even the whole plant cannabis studied using smoked and vaporized methods of administration contained a fraction of the THC (1– 9% THC) that dispensary products offer currently (over 20% THC) [69]. That being said, the few studies that investigated smoked and vaporized cannabis did find significant decreases in pain scores relative to placebo, results that demonstrate lower strength cannabis products are adequate in treating pain. Cannabis dispensaries also provide a variety of products such as oils, suppositories, and topical preparations [69]. To date, there have been no published controlled studies investigating the therapeutic effects of these cannabinoid products for pain. Another important point that these findings raise is that the populations for many of these studies primarily consisted of pain patients who had little or no cannabis experience, or were required to abstain from cannabis for 1–4 weeks prior to the study. As such, pain patients who are current cannabis users may require higher doses or strengths of cannabis and cannabinoids for analgesia due to the potential effects of tolerance that can occur after repeated use. Furthermore, these studies did not assess the analgesic effects of cannabis and CDPs over the long term (study duration ranged from < 1 day to 15 weeks). Many patients with chronic pain will require an analgesic for long periods of time. Based on the current RCT literature, it is unknown if cannabis or cannabinoids can be helpful for pain beyond 4 months, or if patients will require higher doses over time to maintain pain relief.

One limitation of the findings from this review is that the adverse effect assessments and outcomes were extracted from the primary papers detailing the results from the RCT. However, some studies included follow-up reports related to endpoints of interest including an open-label extension to track the development of tolerance to the study medication over time [70]. Additional evidence for low risk of intoxication by oromucosal administration of THC and CBD (nabiximols) has been reported in an open-label study testing the medication for MS-related spasticity and other symptoms [71].

When determining the clinical potential of cannabis and CDPs, their relative abuse liability and neurocognitive effects compared to other prescribed analgesics should be considered. For example, widely used analgesics including opioids and gabapentin also elicit these effects [72–75]. With opioids, the severity of these adverse effects hinders their clinical use. This is especially relevant to abuse liability that can lead to the development of sometimes fatal opioid use disorder (OUD). While cannabis and CDPs have abuse potential, they do not carry the risk of fatal overdose, are safe and well tolerated. Comparative assessments related to efficacy and negative effects would determine whether cannabis and CDPs provide a more favorable clinical profile compared to other analgesics.

FUTURE DIRECTIONS AND RECOMMENDATIONS

While the current review highlights the paucity of assessments for abuse liability and cognitive impact, it should be noted that reports beyond the scope of this review published findings related to these effects. Frequently, assessments of abuse liability and cognitive function are performed during Phase I testing with control populations. For instance, independent of assessing a THC:CBD oromucosal spray (nabiximols) for a therapeutic endpoint, abuse liability testing revealed significant effects on positive subjective drug ratings, but minimal cognitive and psychomotor impact [76]. In this case, these assessments included current non-medical cannabis smokers who likely respond differently to abuse-related subjective ratings relative to non-cannabis experienced patients. Assessments that are sensitive to cannabis and CDP abuse liability, cognitive, and psychomotor effects should be included in a battery of adverse events testing such as **1)** visual analog scales detecting abuse-related subjective effects, **2)** the Divided Attention Task (DAT) to test attention, **3)** Digit Symbol Substitution Task (DSST), which assesses concentration, processing speed, and psychomotor effects and **4)** the Paced Auditory Serial Attention Test (PASAT) to measure working memory, attention, and information processing speed (Table 1; e.g., 17,77). If used routinely for RCTs of cannabis and CDPs for pain, these assessments will provide important data related to abuse and neurocognitive effects when these drugs are specifically used in a therapeutic capacity for given indications and specific patient populations. Instituting uniform procedures across RCTs for abuse liability and cognitive effect testing would allow for future meta-analyses from aggregate data across studies to identify trends and consistency of findings across investigations.

Follow-up analysis related to tolerance to the therapeutic effects and withdrawal symptoms after cessation of use should be tracked. In an observational study, approximately two-thirds of medical cannabis patients with pain endorse at least one moderate to severe withdrawal symptom [78]. This finding underscores the importance of measuring withdrawal symptoms among people who use cannabis for medical purposes as a function of medical indication, cannabis preparation, mode of administration and dose. Two reports in multiple sclerosis patients - one open-label study [79] and one blinded abrupt discontinuation study [80] - failed to find withdrawal symptoms after discontinuation of medication. Participants were maintained on approximately 20–25 mg THC and 17–23 mg CBD per day prior to discontinuation. Another study found that 46% of patients experienced at least one withdrawal symptom upon cessation of treatment; it is unknown what dose of THC / CBD these patients were using before discontinuation [71]. Understanding if withdrawal occurs at higher THC doses and in the absence of CBD is an important clinical endpoint to probe in future studies.

When designing RCTs for cannabis and cannabinoids it is recommended to 1) include endpoints related to abuse liability, cognitive impairment, tolerance, and withdrawal and 2) include these findings in the primary paper if possible. Adding these data to primary reports will provide practitioners and scientists with a holistic perspective of the study outcomes and improve accessibility of the much-needed data related to both safety and efficacy for a range of conditions. Reporting the timing of assessments relative to dosing, and the approximate total cannabinoid dose is critical in order to understand the impact of drug administration on

outcome measures. These two variables were not consistently reported across studies, which complicated data interpretation in the current review.

CONCLUSIONS

Synthesizing outcomes from controlled studies assessing the therapeutic effects of cannabis and CDPs, it is clear that there is encouraging evidence supporting their effectiveness for chronic pain. Investigations with positive findings frequently included more than two study arms (active versus placebo), taking into account the need to assess dose-related effects. This review also highlights the lack of systematic assessments of abuse liability, cognitive and psychomotor testing and across controlled studies of cannabis and CDPs. Given that these are two variables that can impact long-term therapeutic utility of cannabis and cannabinoids, it is recommended that future studies integrate these endpoints into trials. Understanding variables that can optimize therapeutic efficacy and mitigate adverse effects will be integral to developing strategic approaches to cannabis and CDPs studies that will advance the field. These include 1) pharmacological variables accounting for dose, route of administration, and the inclusion of CBD in the formulation, 2) demographic consideration such as cannabis experienced patients, geriatric and pediatric populations, and differences in response as a function of sex and 3) careful consideration for type of pain, comorbities, and concomitant medications. Understanding how these variables impact therapeutic outcomes in tandem with adverse effects will provide the necessary data to guide decisions related to the clinical potential of cannabis and CDPs.

ACKNOWLEDGEMENTS

The authors acknowledge and appreciate the exceptional assistance of Gina Johnson in data collection.

FUNDING AND DISCLOSURES

This research was supported by US National Institute on Drug Abuse Grant DA046614 and DA047296. ZDC and DA have no competing interests in relation to the work described. ZDC has received research funds and partial salary support from Insys Therapeutics. ZDC has served as a consultant to the following companies: GB Sciences and Beckley Canopy Therapeutics and has served on the scientific advisory board of FSD Pharma. DA is a scientific advisor to AXIM, Scriptyx, Tikun Olan and VIVO Cannabis and received speaker honorarium from Spectrum Cannabis.

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Table 1.

Assessments for abuse liability and cognitive effects

Abuse Liability Assessments	Neurocognitive / Psychomotor Assessments
1) Drug self-administration [52] 2) Modified Multiple Choice Procedure: Estimated monetary value of drug [58] 3) Visual Analog Scale for subjective drug effects: Good drug effect, drug liking, desire more of the drug [24–26; 52,54,59]	1) Adult Memory and Information Processing Battery: Speed of information processing adapted for patients with MS [22,32] 2) Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis (BRB-N): Range of tests for verbal learning and memory (Selective Reminding Test), Visuospatial memory (10/36 Spatial Recall Test), the Symbol Digit Modalities Test, attention, working memory, and information processing speed (Paced Auditory Serial Addition Test) and verbal fluency (Word List Generation Test) [41,45] 3) Digit Span (forward and reverse): Measure of short-term memory [58] 4) Digit Symbol Substitution Test: Concentration, psychomotor speed, and graphomotor abilities (24–26, 46, 58) 5) Divided Attention Task: Attend to two tasks performed simultaneously [58] 6) European Organization for Research and Treatment of Cancer, Cognitive functioning domain (EORTC QLQ-C30): Self-report memory and concentration [28,29] 7) Grooved Pegboard Test: Fine motor coordination and speed (24–26; 31,32) 8) Hopkins Verbal Learning Test Revised (HVLT): Verbal learning and memory [24–26] 9) Numerical Rating Scale for memory and concentration: Subjective assessment of memory and concentration [28] 10) Paced Auditory Serial Attention Test (PASAT): Attention, working memory, and information processing speed [21,26,30,53] 11) Short Orientation Memory-Concentration Test: Attention, working memory, problem solving [31,32] 12) Trail Making Task A and B: Psychomotor speed and attention (22,26,30,53)

Table 2.

Cannabis or cannabis-derived products for chronic pain (N = 29)

Pain	Drug/ Route	Dose / Duration	Design / Sample Size / Cannabis Use	Adverse Effect Assessment	Outcome (30% reduction in pain [responder analysis] or change in pain scores)	Adverse Effects (Related to Cannabis / Cannabinoid)
Neuropathic (HIV) [19]	**1)** Cannabis (0% THC) **2)** Cannabis (1–8% THC) *Smoked*	0.9 gram cigarette (~9 – 72 mg THC) 4 × day *4 days*	N = 28 *Crossover design* No history of cannabis dependence or current use	Self-report mood, intoxication, general AE monitoring. Vitals and clinical safety laboratory measures.	***Positive*** Significant reduction in pain in the C group C treated: 46% responded P treated: 18% responded	Concentration difficulties, fatigue, sedation, increased sleep, dry mouth, thirst. Cannabis-induced psychosis (N=1), intractable smoking-related cough (N =1). Non-clinically significant increases in heart rate. No SAEs.
Neuropathic (HIV) [18]	**1)** Cannabis (0% THC) **2)** Cannabis (4% THC) *Smoked*	0.9 gram cigarette (~36 mg THC) 3 × day *5 days*	N = 50 *Parallel group design* Cannabis experienced, current users discontinued use	Self-report mood, psychoactive drug effects, nausea, and general AE monitoring.	***Positive*** Significant reduction in pain in the C group C treated: 13/25 responded P treated: 6/25 responded	Anxiety, confusion, disorientation, dizziness, and sedation. Non-clinically significant increases in heart rate. No SAEs.
Neuropathic (brachial plexus avulsion) **[**37]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD), **2)** THC (2.7 mg) **3)**placebo *Oromucosal spray*	≤ 48 sprays (130 mg THC) / day *14 days*	N = 45 *Crossover design* ~50% used cannabis	Self-report intoxication, general AE monitoring and clinical safety laboratory measures.	***Negative*** Negative results for primary endpoints. C improved some pain rating.	Intoxication, dizziness, feeling drunk, nausea, somnolence. No SAEs.
Neuropathic (chemotherapy induced) **[**39]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD), **2)** Placebo *Oromucosal spray*	≤ 12 sprays (32.4 mg THC) / day *4 weeks*	N = 16 *Crossover design.* No current cannabis / cannabinoid use.	Not described	***Negative*** Negative results for primary endpoints. C administration improved some pain ratings	Dizziness, dry mouth, fatigue, and nausea. No SAEs.
Neuropathic (with allodynia) **[**45]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	≤ 48 sprays (130 mg THC) / day *5 weeks*	N = 125 *Parallel group design.* Abstinence from cannabis / cannabinoids for 7 days	Self-report psychoactive effects, including intoxication, neuropsychological testing, general AE monitoring, and clinical safety laboratory measures.	***Positive*** Significant reduction in pain in the C group C treated: 26% responded P treated: 15% responded	Intoxication in small number of patients, gastrointestinal events (nausea, vomiting, diarrhea, constipation), psychiatric events (paranoia, mood-related symptoms). No difference in neuropsychological testing. No SAEs.
Neuropathic (peripheral) **[**25]	**1)** Cannabis (0% THC) **2)** Cannabis (1.3% THC) **3)** Cannabis (3.5% THC) *Vaporized*	8–12 puffs *Acute administration*	N = 39 *Crossover design* Abstinence from cannabis / cannabinoids 30 days prior to study	Self-report psychoactive drug effects, including intoxication and positive drug effects (abuse liability), and neurocognitive function testing. Safety measures (vitals) and general AE monitoring.	***Positive*** 3.5% THC: 61% response 1.3% THC: 57% response 0.0% THC: 26% response	Dose dependent increases in intoxication and good drug effect. Subjective reports of impairments, feeling drunk, sedated. Decrements in learning and memory, attention, and psychomotor performance. No SAEs.
Neuropathic (Peripheral diabetic neuropathy) **[**30]	**1)** Cannabis (0% THC) **2)** Cannabis (1% THC) **3)** Cannabis (4% THC) **4)** Cannabis (7% THC)	400 mg (4, 16, 28 mg THC) *Acute administration.*	N = 16 *Crossover design*	Self-report psychoactive drug effects, intoxication, and mood, and cognitive function testing. Safety	***Positive*** Dose dependent reductions in pain intensity 7% THC: 13/16 responded	Dose-dependent increases in intoxication, euphoria and somnolence. Dose-dependent effects in attention and working

Pain	Drug/ Route	Dose / Duration	Design / Sample Size / Cannabis Use	Adverse Effect Assessment	Outcome (30% reduction in pain [responder analysis] or change in pain scores)	Adverse Effects (Related to Cannabis / Cannabinoid)
	Vaporized		History of cannabis dependence, current cannabis use excluded	measures (vitals), and general AE monitoring.	4% THC: 12/16 responded 1% THC: 10/16 responded 0%THC: 10/16 responded	memory (modest deficits,not in the impaired range, but may limit the clinical usefulness of cannabis in some patients). No SAEs.
Neuropathic (Peripheral diabetic neuropathy) **[**40]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	4 × per day *12 weeks*	N = 29 *Parallel group design* Current or past cannabis / cannabinoid use unknown.	General AE monitoring.	***Negative*** C treated:8/15 responded P treated: 9/14 responded	Details of AEs not reported.
Neuropathic (Peripheral with allodynia) **[**23]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	≤ 24 sprays (64.8 mg THC) / day *14 weeks*	N = 246 *Parallel group design* Current cannabis and cannabinoid use excluded	Self-report intoxication and general AE monitoring. Vitals and clinical safety laboratory measures.	***Positive*** C treated: 34/123 responded P treated: 19/117 responded	Attention deficits, dissociation, disorientation, dizziness, feeling drunk, tremor, sedation, nausea, diarrhea, dry mouth, abdominal pain, fatigue, increased appetite. No SAEs.
Neuropathic (mixed) **[**24]	**1)** Cannabis (0% THC) **2)** Cannabis (3.5% THC) **3)** Cannabis (7.0% THC) *Smoked*	9 puffs *Acute administration*	N = 38 *Crossover design* Abstinence from cannabis / cannabinoids 30 days prior to study	Self-report psychoactive drug effects, including intoxication and positive drug effects (abuse liability), and neurocognitive function testing. Safety measures (vitals). General AE monitoring.	***Positive*** 3.5 and 7% THC reduced pain relative to 0% THC	Subjective ratings of good and bad drug effects, intoxication feeling impaired, sedation and confusion. Neurocognitive decrements - learning and memory, attention, and psychomotor speed with higher dose. No SAEs.
Neuropathic (spinal cord injury) **[**26]	**1)** Cannabis (0% THC) **2)** Cannabis (2.9% THC) **3)** Cannabis (6.7% THC) *Vaporized*	8–12 puffs *Acute administration*	N = 42 *Crossover design* Abstinence from cannabis / cannabinoids 7 days prior to study	Self-report psychoactive drug effects, including intoxication and positive drug effects (abuse liability), and neurocognitive function testing. Safety measures (vitals).	***Positive*** Dose-dependent decreases in pain rating. **6.7% THC**: 89% response **2.9% THC**: 69% response **0.0% THC**: 26% response	Increases in good drug effect, drug liking, desire more drug, bad drug effect, intoxication, sedation, nausea, difficulty remembering things, confused, difficulty paying attention, change in time perception. No neurocognitive effects. Syncope (N=1). Non-clinically significant increases in heart rate. No SAEs.
MS [21]	**1)** Cannabis (0% THC) **2)** Cannabis (4.0% THC) *Smoked*	4 puffs *Acute administration*	N = 30 *Crossover design* Abstinence from cannabis / cannabinoids 30 days prior to study	Self-report psychoactive drug effects, including intoxication, and neurocognitive function testing. Safety measures (vitals). General AE monitoring	***Positive*** C reduced pain relative to P	Intoxication, dizziness, fatigue, nausea, and decrements in cognitive function. Increased effects in cannabis naive participants. Non-clinically significant increases in heart rate. No treatment related SAEs.
MS [38]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo Oromucosal spray	≤ 48 sprays (120 mg T HC) / day *3 weeks*	N = 17 *Crossover design* Cannabis naïve	Not described	***Negative / Mixed*** Negative results for primary endpoints. C decreased electrophysiological response to noxious stimuli but did not decrease VAS scores for pain.	Not described

Pain	Drug/ Route	Dose / Duration	Design / Sample Size / Cannabis Use	Adverse Effect Assessment	Outcome (30% reduction in pain [responder analysis] or change in pain scores)	Adverse Effects (Related to Cannabis / Cannabinoid)
MS [41]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	≤ 48 sprays (130 mg THC) / day *4 weeks*	N = 64 *Parallel group design.* Abstinence from cannabis / cannabinoids 7 days prior to study	Mood, neurocognitive testing, general AEs, safety and tolerability monitoring.	***Positive*** C reduced pain rating relative to P	Dizziness, somnolence, dissociation, euphoria, dry mouth, diarrhea, weakness, deficits in learning. Two treatment-related severe AEs included agitation, tachycardia, and hypertension (N = 1) and paranoid ideation (N = 1). No SAEs.
MS [46]	**1)** THC (cannabis derived) (5–8 mg TID) **2)** Placebo *Oral capsule*	15–24 mg /day *4 weeks*	N = 24 *Parallel group design* Current cannabis / cannabinoid use exclusionary	Neurocognitive testing, general AE monitoring and vitals.	***Positive*** C reduced pain ratings on some measures relative to the P	Dizziness, euphoric mood (rated severe in one instance), fatigue, intoxication, headache, muscular weakness, and somnolence. No decline in cognitive functioning.
MS [32]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	≤ 48 sprays (130 mg THC) / day *6 weeks*	N = 154 *Parallel group design.* Abstinence from cannabis / cannabinoids 7 days prior to study	Self-report psychoactive drug effects, including intoxication, mood, and memory. general AE monitoring.	***Negative / Mixed*** Negative results for primary endpoint. Some positive response with secondary analysis	Intoxication, dizziness, disturbances in attention, fatigue, somnolence, disorientation, feeling drunk, vertigo, diarrhea, and mouth ulceration. No SAEs noted.
MS [27]	**1)** THC:CBD (2.5 mg THC + 1.25 mg CBD, cannabis derived) **2)** THC (2.5 mg synthetic) **3)** Placebo *Oral capsule*	≤ 25 mg THC / day *8 weeks*	N = 611 *Parallel group design* Abstinence from cannabis / cannabinoids 30 days prior to study	General AE monitoring.	***Positive*** C treated: 46–50% responded P treated: 30% responded	Dizziness, lightheadedness, dry mouth, constipation, diarrhea, increased appetite. Unknown if SAEs were treatment related.
MS [43]	**1)** THC:CBD (2.5 mg THC + ~1.3 mg CBD) **2)** Placebo *Oral capsules*	10–25 mg THC / day *10 weeks*	N = 224 *Parallel group design* Abstinence from cannabis / cannabinoids 30 days prior to study	Ge neral AE monitoring. Vitals and clinical safety laboratory measures.	***Positive*** Lower pain ratings in the C group compared to P	Dizziness, urinary tract infection (UTI), dry mouth, fatigue. SAEs in 3 participants due to UTI (unclear if treatment related).
MS [42]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	≤ 24 sprays (64.8 mg THC) / day *14 weeks*	N = 337 *Parallel group design* Current or past cannabis / cannabinoid use unknown	General AE monitoring. Vitals and clinical safety laboratory measures.	***Negative / Mixed*** Negative results for primary endpoints. Positive response on secondary analysis demonstrating that responders to C for spasticity also showed improvements in pain.	Dizziness, fatigue, somnolence, nausea, asthenia, and vertigo. Treatment related SAEs included acute confusional state (N=1) and UTI (N=1). SAEs occurred after cessation of study medication (N = 2) and included aggression, agitation, delusions, irritability, severe insomnia and muscle spasms, worsening depression, suicidal ideation, and drug dependence.
MS [34]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo	≤ 12 sprays (32.4 mg THC) / day *14 weeks*	N = 339 *Parallel group design* Current or past cannabis /	General AE monitoring.	***Negative / Mixed*** C: 50% response P: 45% response	Fatigue, dizziness, nausea, somnolence, memory impairment, attention disturbances, dysgeusia, balance disorder, psychomotor

Pain	Drug/ Route	Dose / Duration	Design / Sample Size / Cannabis Use	Adverse Effect Assessment	Outcome (30% reduction in pain [responder analysis] or change in pain scores)	Adverse Effects (Related to Cannabis / Cannabinoid)
	Oromucosal spray		cannabinoid use unknown		Some positive response with secondary analysis	skills impaired, psychiatric disorders (not detailed). No SAEs.
Cancer [28]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD), **2)** THC (2.7 mg) 3) Placebo *Oromucosal spray*	≤ 8–12 sprays (21.6–32.4 mg THC) / day *2 weeks*	N = 177 *Parallel group design* Current or past cannabis / cannabinoid use unknown	Self- report psychoactive drug effects, including intoxication, concentration, and memory. General AE monitoring.	***Positive*** THC+CBD: 43% response THC only: 23% response P: 21% response	Dizziness, somnolence, nausea, and vomiting. Reductions in cognitive function score. SAE related to syncope (N=1).
Cancer [44]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	≤ 10 sprays (27 mg THC) / day 3 weeks	N = 399 Parallel group design. Current or past cannabis / cannabinoid use unknown	Risk of suicide and general AE monitoring. Vitals and clinical safety laboratory measures.	***Negative / Mixed*** Negative results for primary endpoints. Secondary analysis revealed that C was effective at reducing pain in a subset of patients < 65 years of age	Somnolence. SAEs included constipation (N=1) and moderate disorientation and somnolence (N=1). No increased risk of suicidal ideation.
Cancer [36]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	≤ 10 sprays (27 mg THC) / day *3 weeks*	N = 387 *Parallel group design.* Current or past cannabis / cannabinoid use unknown	Risk of suicide and general AE monitoring. Vitals and clinical safety laboratory measures.	***Negative***	Dizziness and nausea. SAEs related to disorientation and visual hallucination. No increased risk of suicidal ideation.
Cancer [29]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	**1) Low Dose**: 1–4 sprays (2.7–10.8 mg THC) /day **2) Mid Dose**: 6–10 sprays (16.2–27 mg THC) / day **3) High Dose**: 11–16 sprays (29.7–43.2 mg THC) / day *4 weeks*	N = 263 *Parallel group design* Abstinence from cannabis / cannabinoids 30 days prior to study	Self-reported mood, cognitive effects, constipation and general AE monitoring.	***Positive*** C was superior to placebo when all C groups were combined, an effect driven by low dose group. **High Dose:** 24% response **Mid Dose**: 30% response **Low Dose**: 33% response **P:** 26% response	Dose-related AEs with increased events in the higher dose group included nausea, vomiting, impaired cognitive functioning, somnolence and headache. No SAEs.
Mixed (neuropathic, postsurgical, posttraumatic) [20]	**1)** Cannabis (0% THC) **2)** Cannabis (2.5% THC) **3)** Cannabis (6.0% THC) **4)** Cannabis (9.4% THC) *Smoked*	25 mg 3 × per day *5 days*	N = 21 *Crossover design* Current cannabis or cannabinoid use excluded	Self-reported changes in mood, intoxication, general AE monitoring. Vitals and clinical safety laboratory measures..	***Positive*** 9.4% THC reduced pain relative to placebo	Most AEs observed with 9.4% THC: Headache, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness, cough. Intoxication was infrequent. No SAEs.
Mixed 53% neuropathic, 47% MS [22]	**1)** THC+CBD (2.5 mg THC + 2.5 mg CBD), **2)** THC (2.5 mg) **3)** CBD (2.5 mg) **4)**Placebo *Oromucosal spray*	1–8 sprays/ day (2.7–21.6 mg/day) *1 week*	N = 34 *Crossover design.* current cannabis use excluded	Self-report psychoactive drug effects, neurocognitive testing, general AE monitoring. Vitals and clinical safety laboratory measures.	***Unknown*** Some evidence of THC and THC:CBD reducing pain relative to placebo	Drowsiness, dizziness, euphoria / dysphoria ('high'), light-headedness, panic and anxiety, time-distortion. Improvements in psychomotor and cognitive testing after cannabinoid treatment. Vasovagal episode (N=1), gastroenteritis (N=1), hallucination (N=1). No SAEs.

Pain	Drug/ Route	Dose / Duration	Design / Sample Size / Cannabis Use	Adverse Effect Assessment	Outcome (30% reduction in pain [responder analysis] or change in pain scores)	Adverse Effects (Related to Cannabis / Cannabinoid)
Mixed (MS, spinal cord injury, brachial plexus damage) [31]	**1)** THC+CBD (2.5 mg THC + 2.5 mg CBD), **2)** THC (2.5 mg) **3)** CBD (2.5 mg) **4)**Placebo *Oromucosal spray*	≤ 48 sprays (120 mg THC) / day *2 weeks*	N = 20 *Crossover group design* Subjects required to abstain from cannabis / cannabinoids 30 days prior to study.	Self-report psychoactive drug effects, including intoxication, mood, and memory. General AE monitoring.	***Positive*** Self-reported pain improved with CBD alone and ThC alone, but not the combination	Headache, sleepiness, anxiety, diarrhea. Modest intoxication and neurocognitive deficit with THC. Possibly treatment related: Sedation, vasovagal episode, gastroenteritis. No SAEs.
Abdominal pain (chronic pancreatitis, postsurgical pain) [35]	**1)** THC (1.5–5 mg, TID) **2)** Placebo *Oral capsules*	15–25 mg/day *6 weeks*	N = 62 *Parallel group design* Current or past cannabis / cannabinoid use unknown	Self-report psychoactive effects. Vitals and clinical safety laboratory measures. general AE monitoring.	***Negative***	Amnesia, decreased appetite, dizziness, nausea, and somnolence. No clinically relevant changes in vital signs or safety parameters. No SAEs
Rheumatoid arthritis [33]	**1)** THC+CBD (2.7 mg THC + 2.5 mg CBD) **2)** Placebo *Oromucosal spray*	≤ 6 sprays (16.2 mg THC) / day *3 weeks*	N = 58 *Parallel group design* Current or past cannabis / cannabinoid use unknown	Not detailed.	***Positive*** C improved pain on some measures	Dizziness, light-headedness and dry mouth. No SAEs:

Serious adverse events reported are treatment related.

KEY: AE = Adverse events; **SAE** = Serious adverse event; **C** = cannabis / cannabinoid treated; **P** = Placebo treated; **THC** = tetrahydrocannabinol; **CBD** = cannabidiol; **MS** = multiple sclerosis; **VAS** = Visual Analog Scale; Cannabis strength defined by % THC (0% THC = placebo)

Table 3.

Cannabis or cannabis-derived products for acute pain (N = 1)

Pain	Drug/ Route	Dose / Duration	Design / Sample Size / Cannabis Use	Adverse Effect Assessment	Outcome (30% reduction in pain [responder analysis] or change in pain scores)	Adverse Effects (Related to Cannabis / Cannabinoid)
Postoperative (abdominal hysterectomy) [47]	**1)**THC, 5 mg **2)** Placebo *Oral capsule*	Single dose *Acute administration*	N = 40 *Parallel group design* Previous cannabis use excluded	Self-report psychoactive drug effects, mood, memory, and physiological symptoms. General AE monitoring.	***Negative***	Increased awareness of surroundings. No SAEs.

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KEY: AE = Adverse events; **SAE** = Serious adverse event; **THC** = tetrahydrocannabinol

Table 4.

Cannabis or cannabis-derived products in experimental pain models (N =8)

Pain	Drug/ Route	Dose / Duration	Design / Sample Size / Cannabis Use	Adverse Effect Assessment	Outcome	Adverse Effects (Related to Cannabis / Cannabinoid)
Cold pressor test [52]	**1)** 0% THC + 0 mg Oxy **2)** 6% THC + 0 mg Oxy **3)** 6% THC + 2.5 mg Oxy **4)** 6% THC + 5.0 Oxy **5)** 0% THC + 2.5 mg Oxy **6)** 0% THC + 5.0 mg Oxy *Cannabis, smoked Oxy, Oral capsule*	560 mg (0 or ~34 mg THC) *Acute administration*	N = 18 *Crossover design* Current cannabis smokers	Subjective ratings of psychoactive drug effects including positive drug effects (abuse liability), intoxication, self-administration, vital signs	***Positive*** C increased low-dose oxycodone analgesia	C increased intoxication, ratings associated with abuse liability, and increased self-administration. Non-clinically significant increases in heart-rate were observed. No SAEs.
Cold pressor test [54]	**1)** 0% THC **2)** 4–6% THC *Cannabis, smoked*	560 mg (0 or ~22–34 mg THC) *Acute administration*	N = 42 *Crossover and between groups design* Current cannabis smokers	Subjective ratings of psychoactive drug effect including positive drug effect (abuse liability), intoxication, vital signs	***Mixed*** Active cannabis increased pain threshold and tolerance only in men, not women	C increased intoxication and ratings associated with abuse liability in both men and women. Non-clinically significant increases in heart-rate were observed. No SAEs.
Cold pressor test [59]	**1)** 0.0% THC **2)** 1.98% THC **3)** 3.6% THC *Cannabis, smoked*	560 mg (0, ~11, or 20 mg THC) *Acute administration*	N = 30 *Crossover design* Current cannabis smokers	Subjective ratings of psychoactive drug effects including positive drug effects (abuse liability), intoxication, vital signs	***Positive*** C dose-dependently increased pain threshold and tolerance compared to P	C cannabis increased intoxication and ratings associated with abuse liability. Non-clinically significant increases in heart-rate were observed. No SAEs.
Capsaicin-induced pain, hyperalgesia [55]	**1)** 0 mg THC **2)** 15 mg THC *Oral capsule*	*Acute administration*	N = 12 *Crossover Design* No history or current cannabis use.	Psychomotor performance, vitals, general adverse effects.	***Mixed*** C decreased unpleasantness of pain, but not perceived intensity.	Deficits in psychomotor performance. Paranoia (N = 1). No SAEs.
Capsaicin-induced pain, hyperalgesia, neurosensory testing [53]	**1)** 0% THC **2)** 2% THC **3)**4% THC **4)** 8% THC *Cannabis, smoked*	3 puffs *Acute administration*	N = 19 *Crossover Design* No history or current cannabis abuse or dependence. Cannabis use within the last 6 months but not within the last 30 days.	Intoxication, depressed mood, neurocognitive testing, vital signs	***Mixed*** 4% C decreased and 8% C increased subjective pain response	Dose-dependent increases in intoxication, no effect on depressed mood, No effect on neurocognitive performance. Non-clinically significant increases in heart rate. No SAEs.
Sunburn- and capsaicin-induced inflammatory pain and hyperalgesia [56]	**1)** 20 mg THC+10 mg CBD **2)** 5 mg diazepam *Oral capsule*	*Acute administration*	N = 18 *Crossover Design* History and current cannabis use unknown	Subject- and observer-rated adverse effects and psychoactive drug effects, vitals	***Negative*** C did not elicit analgesic effects; indication of hyperalgesic effects relative to diazepam.	Drowsiness, sedation, dry mouth, vertigo. Acute psychotic symptom occurred in one participant. Non-clinically significant increases in heart rate. No SAEs.
Stimulation of trigeminal nocisensors [57]	**1)** 0 mg THC **2)** 20 mg THC *Oral capsule*	*Acute administration*	N = 15 *Crossover Design* No current cannabis use.	Subjective ratings of psychoactive drug effects	***Negative*** C did not decrease perception of pain intensity	Increase in drowsiness, euphoria, and nausea. Vomiting, tremor, and dizziness (N = 2). No SAEs.
Radiant heat stimulation [58]	**1)** 0% THC **2)** 3.6% THC *Cannabis, smoked*	0, 3, 9, or 18 puffs *Acute administration*	N = 5 *Crossover Design*	Subject- and observer-rated psychoactive drug effect including positive	***Positive***	Active cannabis increased ratings of intoxication, positive subjective effects (drug liking and drug value),

Pain	Drug/ Route	Dose / Duration	Design / Sample Size / Cannabis Use	Adverse Effect Assessment	Outcome	Adverse Effects (Related to Cannabis / Cannabinoid)
			Current cannabis smokers	drug effects (abuse liability), intoxication, psychomotor testing, vital signs	Active cannabis decreased pain sensitivity	bad effect, sedated, subjective impairment, good effect, bad effect, drug liking, disrupted psychomotor performance. No SAEs.

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