# CANNABIDIOL MITIGATES OPIOID REWARD ON CONDITIONED PLACE PREFERENCE IN MICE

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ABSTRACT

This study sought to determine whether the cannabis constituent, cannabidiol (CBD), is able to attenuate morphine reward in the conditioned place preference (CPP) paradigm. Mice received IP injections of either saline or morphine and increasing doses of CBD that were paired with a distinct environment in the CPP apparatus. Morphine-produced place preference was dose-dependently blocked by CBD. Furthermore, none of the tested doses of CBD exhibited reward or aversion. The finding that CBD blocks opioid reward suggests CBD may be useful as an abuse deterrent, particularly in the setting of opioid use for pain management.

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# 1. INTRODUCTION

Opioids are a common and effective treatment for acute and chronic pain. These drugs rapidly and effectively relieve pain and have the potential to greatly improve the patient's quality of life. Alongside the less potent nonsteroidal anti-inflammatory drugs (NSAIDs), opioids are the primary medication prescribed in the treatment of pain (Li & Zhang, 2012). In 2012, United States pharmacies filled 289 million opioid analgesic prescriptions, accounting for almost seven percent of all medications dispensed (Levy et al., 2015). Trends in the utilization of this pharmacotherapy show that it has continued to increase in prevalence with 6.9 percent of the United States population using opioid analgesics in 2006 as opposed to 5.0 percent in 1999 (Frenk et al., 2015).

Depending on the type and duration of pain experienced, there are various options for the type of opioid and length of treatment required. Almost 85 percent of opioid prescriptions in 2009 were for medications containing hydrocodone or oxycodone, and roughly the same percentage were for short-term treatment courses no more than three weeks long (Volkow et al., 2011). The rest of these treatments are long-term regimens. Additionally, from 1999 to 2012, the proportion of pain patients who used an opioid analgesic more powerful than morphine rose from 17 to 37 percent (Frenk et al., 2015).

While opioids provide effective pain relief, their use is complicated by major risks and side effects. Between 76 and 96 percent of patients report aversive side effects, resulting in a diminished quality of life (Guindon & Hohmann, 2009; Toth & Au, 2008). Opioid receptors are distributed widely throughout the body, located in both the central and peripheral nervous system. Based upon the location of these receptors, these side effects can be traced. Activation of mu opioid receptors in the gastrointestinal tract decreases GI motility and leads to constipation. With

40 to 95 percent of patients reporting symptoms of constipation, impeded bowl movements are very common (Kalso, 2004; Swegle & Logemann, 2006). Nausea is also a common complication of opioid treatment, with 25 percent of patients reporting it as a side-effect (Cepeda, 2003). The activation of the mu-opioid receptor by opioid drugs activates a region of the medulla called the area postrema, which can cause the patient to feel sick or vomit. Because these receptors are found in the medulla, the region of the central nervous system which controls respiration, heart rate, and blood pressure, vital functions can be affected. Higher doses of opioids can cause sedation as well the suppression of respiration. It comes as no surprise, then, that opioids result in a diminished quality of life for many of those who use them to manage pain. Furthermore, opioid overdose is attributed the suppression of respiration, causing respiratory collapse and even death.

In addition to these side effects, long-term opioid usage carries the liability of addiction development. Initially, the opioid treatment is mitigating pain and providing negative reinforcement for continuing the medication. However, as the pain subsides, the drugs begin to provide positive reinforcement. At this point the patient is expected to begin weaning off of the treatment, but the aversive side effects of withdrawal make this process difficult. Thus, both positive reinforcement of the drugs' pleasure-inducing properties and the aversion of withdrawal make quitting opioid treatment all the more difficult and exacerbate addiction. It is estimated that addiction to opioids after the cessation of pain treatment occurs in up to 50 percent of chronic pain patients (Højsted & Sjøgren, 2007). These addictive qualities pose a major obstacle for opioid users navigating life with chronic pain.

The addiction that ensues can result in a cycle of drug abuse that carries exacerbated side effects previously mentioned as well as high risk of overdose and death. Over the course of the

past decade, a crisis of abuse been seen in opioid use, often stemming from an initial use for medical purposes (Warner et al., 2014). In the timespan of 1999 to 2012, the rate of opioid analgesics and heroin drug overdose deaths per 1,000 people more than doubled, from 6.1 to 13.1 percent (2014). Additionally, 37 percent of the 44,000 drug-overdose deaths in 2013 were caused by pharmaceutical opioids (Volkow & McLellan, 2016). Clearly, this rise in addiction and overdose rates elucidates the major challenges faced by patients using opioids for chronic pain management.

*1.1 Attempts to Formulate Abuse-deterrent Opioid Therapies:*

Given that opioids produce robust analgesia across a broad range of pain conditions but have such a high abuse liability, research has aimed to create an opioid formulation void of addiction potential. The first generation formulation intended to act as a non-addictive opioid utilized slow, time-release properties to deter abusers. In 1996, Purdue Pharmaceuticals introduced a new oxycodone-based opioid formulation called OxyContin, characterized as having long-acting and sustained-release properties (Cicero & Ellis, 2015). OxyContin, whose makers touted a diminished addiction liability, was marketed aggressively for use, and from 1997 to 2002 its prescriptions grew from 670,000 to 6.2 million (van Zee, 2009). However, the diminished addiction potential marketed proved to be a criminal misrepresentation of OxyContin's true liabilities (2009). Additionally, users of OxyContin had learned that crushing or grinding the tablets unlocked the characteristic rewarding "high" and rendered the time-release quality useless (Jayawant & Balkrishnan, 2005).

The second generation of abuse-deterrent formulations of opioid treatments came in the form of agonist-antagonist combinations. In this approach, the opioid, such as buprenorphine or

morphine, is co-formulated with an opioid receptor antagonist, such as naloxone or naltrexone (Schneider et al., 2010). This means that if a pill is crushed, the antagonist or aversive agent either renders the drug inactive or produces highly aversive side effects. The aversion experience also raised concerns that full analgesia is not being maintained. Unfortunately, even this combination of aversion has not proven to be successful in mitigating addiction rates.

Third generation formulations look to block reward altogether, while not interfering with opioid receptors and full pain relief. One avenue is to continue exploring agonist-antagonist combinations that act upon the mu, kappa, and delta opioid receptors in order to diminish the euphoric high that can cause abuse (Simon et al., 2015). Kappa opioid receptor agonism can provide intense aversion, so this presents challenges in allowing for the attenuation of pain while discouraging the continuation of the opioid pain treatment (Carroll & Carlezon, 2013). Other novel combinations of opioid receptor agonism/antagonism continue to be explored as abuse deterrents.

### *1.2 Exploring the Effects of Cannabidiol on Opioid Reward*

Cannabidiol is a non-psychoactive component of the *Cannabis sativa* plant. There is an emerging literature that suggests cannabidiol mitigates the rewarding properties that accompany opioid treatment. For this reason, a dual formulation of CBD and opioid medication appears to be a possible avenue for the creation of a therapy void of aversive properties.

Furthermore, in a 2013 paper, Katsidoni et al. sought to determine whether cannabidiol affects the reward facilitating effect of morphine in the intracranial self-stimulation (ICSS) paradigm. The ICSS paradigm is one model that is useful to predict abuse liability of compounds. Animals are trained to self-stimulate the brain's reward center via an implanted electrode. While

low doses of CBD had no effect, higher doses significantly elevated the threshold frequency required for medial forebrain bundle ICSS. This indicated CBD alone does not exhibit reinforcing properties in the ICSS paradigm, while it does decrease the reward-facilitating effects of morphine (Katsidoni et al., 2013). These results suggest that it may be possible to create a dual cannabidiol-opioid formulation that is void of reward-facilitating properties, while maintaining efficacious pain relief.

Another paradigm of animal modeling used to determine the abuse liability of compounds is the conditioned place preference (CPP) paradigm. CPP is based on the principles of associative learning, whereby subjects learn to associate distinct environments with drug states. Subjects will approach and maintain contact with environments previously paired with rewarding drugs but avoid environments previously paired with aversive drug states. In this paradigm, the properties of a drug serve as an unconditioned stimulus (UCS) that is repeatedly paired with a previously neutral set of environmental stimuli (Tzschentke, 1998). After repeated conditioning trials, the previously neutral stimuli acquire secondary motivational properties and can act as conditioned stimuli (CS) (1998). In this CPP paradigm, a drug can be administered to a subject in a distinct environment, pairing the sensation or lack thereof, produced by the drug, to that specific environment or drug chamber. When concerning abuse liability, higher preference shown for the environment where a drug was administered is indicative of that drug's higher abuse potential. In hopes of elucidating an opioid formulation with full analgesic properties and no abuse liability, we sought to determine the effect of cannabidiol on the rewarding effect of morphine in the conditioned place preference paradigm.

## 2. MATERIALS AND METHODS

### *2.1 Subjects*

Male C57BL/6 mice (25-30 g; Envigo, Indianapolis, IN) were housed 5 per polycarbonate tub with soft bedding in a temperature and humidity controlled vivarium. Mice were maintained under a 12-hour light/dark cycle with lights on at 06:00. Food and water were available ad libitum. Animals acclimated to the vivarium 1 week prior to experimental manipulations. All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Mississippi (Protocol #15-022).

### *2.2 Drugs*

Morphine sulfate (Research Biochemicals International; Natick, MA) was dissolved in 0.9% saline to yield a dosage of 2.5 mg/kg/mL. Cannabidiol (>98% purity) solutions of 2.5, 5.0, 10.0, and 20.0 mg/kg/mL (ELI Laboratories; Oxford, MS) were dissolved in a vehicle solution of 5% ethanol, 5% cremophor, and injectable water. Mice received dual IP injections of saline or 2.5 mg/kg morphine in combination with vehicle, 2.5, 5.0, 10.0, or 20.0 mg/kg CBD.

### *2.3 Apparatus*

Five place preference chambers (Model MED-CPP-3013; Med Associates, St. Albans, VT) were used for these experiments. Each chamber had two stimulus-distinct (black versus white colored walls and metal rod or wire mesh flooring) drug-conditioning chambers separated by a central, neutral start chamber (colored gray with a smooth solid floor). The conditioning chambers were separated by guillotine doors.

*2.4 Experimental Protocol*

Prior to conditioning trials, animals were allowed to acclimate to the testing room for at least 30 minutes. Day 1 served as a habituation trial whereby animals were placed in the gray center chamber for 5 minutes, after which the guillotine doors were opened for 15 minutes. Day 2 of testing served as a pre-conditioning baseline preference test to determine each subject's initial preference between the two conditioning chambers. Days 3-8 involved six 40-minute conditioning trials. On Day 9, animals were given a 20-minute post-conditioning preference test, identical to the Day 2 test, under a drug-free state. Subjects' baseline preference scores were calculated as the time spent in the black chamber divided by the time spent in the black and white chambers. This formula is written: baseline preference score = (B)/[(B)+(W)]. From this calculation, the drug was assigned to the non-preferred chamber, called the S+ chamber. Preconditioning CPP scores were then calculated as $CPP_{Preconditioning}$ = (S+)/[(S+)+(S-)]. Postconditioning CPP scores were calculated using the same formula. Overall Mean Place Preference scores were then defined as the difference in the Post-conditioning and Pre-conditioning Preference Scores: $(CPP_{Post\text{-}conditioning}) - (CPP_{Pre\text{-}conditioning})$, so that more positive scores were indicative of greater reward potential. Conditioning trials involved alternate day (counterbalanced for drug order) pairings of test compound in one confined compartment (S+) and vehicle in the other (S-). Conditioning trials were counter-balanced (drug/vehicle) within treatment conditions. Assignment of test compound to a given S+ compartment was based on baseline preference scores where compounds were assigned to the non-preferred compartments. The test apparatus was thoroughly cleaned with 70% ethanol after each trial.

*2.5 Statistics*

Data analyses were conducted using SPSS software. CPP was analyzed using one-way and two-way ANOVAs. Separate one-way ANOVAs were performed on Vehicle, Saline, and Morphine subgroups to determine Morphine CPP, CBD preference or aversion, and the effects of CBD on Morphine CPP. Planned comparisons using Fisher's LSD were used to determine the statistical significance ($p < 0.05$) of drug effects on CPP scores.

## 3. RESULTS

The effects of Cannabidiol on Morphine conditioned place preference scores are summarized in **Figure 1**. For the Vehicle group, preference scores were near zero, which reflects little change between pre- and post-conditioning place preference. Under the Vehicle condition, the Morphine group showed higher preference scores compared to the Saline group. In the Saline treatment groups (open bars), mice receiving CBD at any dose did not show place preference. In the Morphine groups (shaded bars), CBD dose-dependently attenuated morphine reward, as indicated by a diminished CPP score with the greatest effect observed at 10.0 mg/kg.

A two-way ANOVA revealed a significant main effect for Morphine $F(1,78) = 30.048$, $p < 0.001$. The main effect for Cannabidiol and the Cannabidiol x Morphine interaction were not significant $F(4,78) = 1.682$, $p = 0.163$; $F(4, 78) = 1.57$, $p = 0.191$ respectively. To determine whether morphine produced significant place preference, a one-way ANOVA of the Vehicle groups was performed, revealing a significant effect for morphine $F(1,15) = 15.692$, $p = 0.001$. To test whether CBD possesses rewarding or aversive properties, a one-way ANOVA among the Saline groups was conducted and no significant treatment effect was found $F(4,39) = 1.211$, $p = 0.322$. In order to determine whether CBD attenuated opioid reward, a one-way ANOVA on Morphine groups was performed, revealing a treatment effect that approached significance $F(4,37) = 2.304$, $p = 0.077$.

Planned comparisons using Fischer's LSD revealed that among the Morphine groups, mice receiving 10.0 mg/kg CBD had significantly lower preference scores than mice receiving CBD Vehicle ($p = 0.033$).

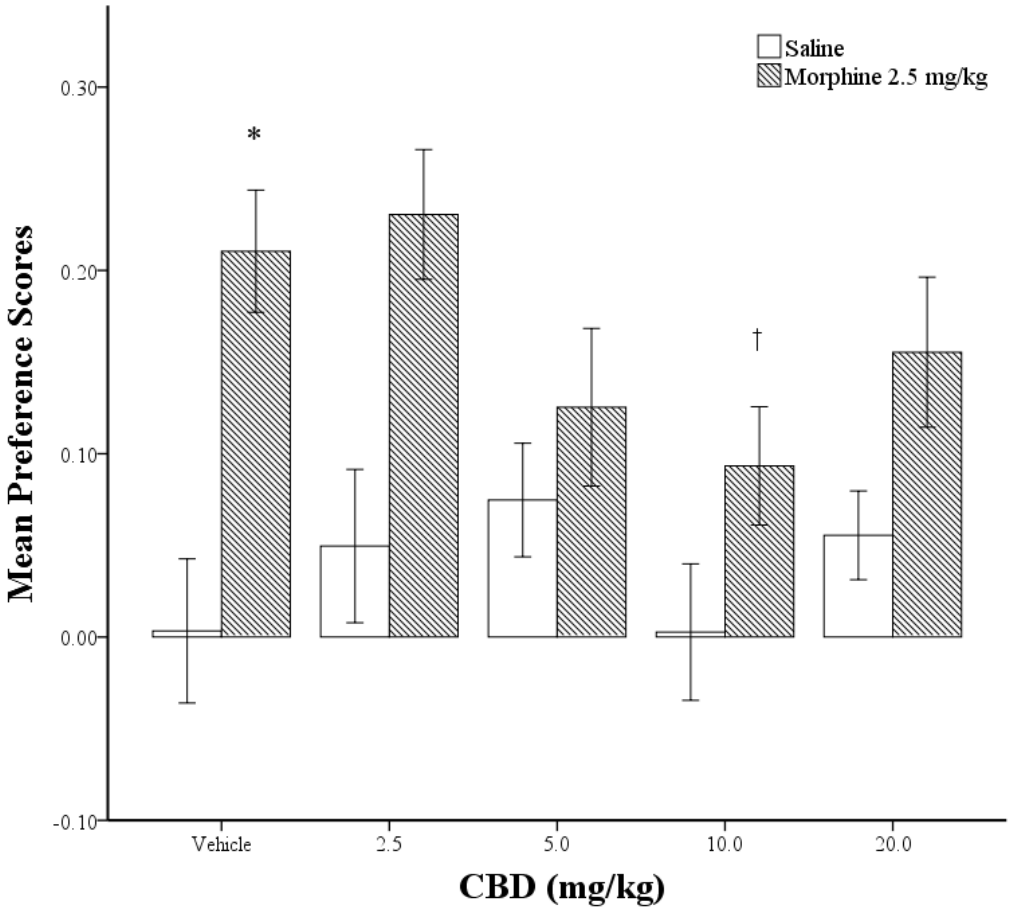


**Figure 1.** The effects of CBD on morphine place preference scores. Values represent the difference in the mean post- and pre-conditioning preference scores. Open bars reflect saline treated animals and striped bars represent morphine treated animals. Vertical lines show standard error of the mean. * denotes significant difference from the vehicle group. † denotes significant attenuation of morphine CPP. Sample sizes were n= 7-10.

## 4. DISCUSSION

This study sought to determine whether cannabidiol is able to mitigate the rewarding properties of morphine. Morphine reward was quantified using the conditioned place preference (CPP) paradigm. A range of CBD doses were pre-administered in an attempt to block morphine CPP. In the CPP paradigm, positive scores are indicative of reward, whereas negative scores indicate aversion. A place preference score closer to baseline, or zero, signifies no reward or aversion was experienced.

In performing this experiment, morphine was found to produce robustly positive CPP scores. This is consistent with an extant literature that a wide variety of opioids, such as morphine (Parker et al., 1994; Gaiardi et al., 1998), heroin (Hand et al., 1989; Tierney et al., 1998), and fentanyl (Finlay et al., 1998; Pchelintsev et al., 1991) produce reward in the CPP paradigm and other animal models of quantifying abuse liability, including self-administration and intracranial self-stimulation (ICSS). We found that morphine's positive place preference scores were returned to baseline in a dose-dependent fashion by cannabidiol, indicative of CBD diminishing the amount of morphine reward experienced. Peak CBD effects on morphine CPP were observed at 10.0 mg/kg. These findings demonstrate that CBD mitigates morphine reward.

It could be postulated that CBD's attenuation of reward may be due to an aversive quality of CBD. However, there is data supporting that CBD produces no aversion. The wide range of CBD doses administered alone produced no change in CPP scores in either the positive or negative direction. These findings suggest that CBD neither has an abuse or aversion liability that may limit its potential as an abuse deterrent. These results confirm an existing literature supporting that CBD does not have any hedonic or aversive actions (Mechoulam, Parker, & Gallily, 2002; Mechoulam et al., 2007; Parker et al., 2004).

The work described herein is consistent with published literature on cannabidiol effects in other animal models of reward and addiction. Intracranial self-stimulation (ICSS) is another method for evaluating reward. In this paradigm, animals are trained to self-stimulate the brain's reward circuitry after an electrical stimulator has been surgically implanted in the brain. An animal will maintain a baseline level of self-stimulation, and when a compound with higher abuse potential and reward is added, a decrease in the amount of self-stimulating behavior needed to maintain that baseline level will be observed. The observation of CBD's opioid reward-mitigating properties is consistent with those of the Katsidoni et al. 2013 model of intracranial self-stimulation, whereby changes in CBD dosage produced altered morphine administration (Katsidoni et al., 2013). In the study, it was first observed that administration of opioids caused a decrease in the frequency of self-stimulation observed because the opioid drugs' rewarding properties were experienced alongside self-stimulation. However, adding doses of 10 and 20 mg/kg CBD with the opioids resulted in a significantly elevated frequency of self-stimulation, returning them to baseline (2013). The results of this study can be interpreted as being consistent with our study as CBD mitigated the reward experienced by opioid drugs in the ICSS paradigm.

Our study was the first to measure cannabidiol's ability to block opioid reward in the CPP paradigm. However, the work described herein is not the first attempt to study cannabidiol using the CPP measure. Parker et al. 2004 used CBD in a CPP model of relapse and the extinction of already established cocaine and amphetamine addictions. Before the administration of CBD, conditioning trials were conducted so that animals paired these addictive drugs to a specific environment. Administration of CBD after conditioning trials but during preference trials diminished preference-seeking behavior in the face of drug-associated cues and

"potentiated the extinction of both cocaine-induced and amphetamine-induced conditioned place preference learning" (Parker et al., 2004). Thus, cannabidiol hastens the extinction of cocaine and amphetamine addiction and prevents cue-induced relapse.

Collectively, the results of these studies and ours argue strongly that cannabidiol is capable of broadly blocking reward mechanisms as well as affecting brain centers involved in abstinence that lead to relapse. Because CBD exhibits these properties, it may be that CBD could be used to prevent relapse and promote abstinence in substance abuse treatment facilities. Patients in substance abuse treatment programs may benefit from clinical trials that explore CBD's ability to lessen the ongoing risk of relapse in addiction treatment.

A second possible application of cannabidiol we suggest is as an abuse deterrent in formulation with opioid medications in order to prevent opioid addiction in pain management settings. Thus, we suggest it is possible to use cannabidiol as an abuse deterrent to create an opioid drug formulation that would be void of an abuse liability. There are concerns, though, that in said formulation analgesic properties would not be retained. Given that cannabidiol was shown to block morphine reward, one might assume that it may block all properties of the drug, including relief of pain. However, there are data that suggest this is not the case. Neelakantan et al. 2015 found that in two assays, the hot plate thermal nociceptive assay and the acetic acid-decreased operant responding for palatable food assay, the drugs in combination produced subadditive analgesia (Neelakantan et al., 2015). Furthermore, this literature supports that CBD can actually potentiate synergistic opioid analgesia in some pain models. Specifically, administering cannabidiol and morphine in combination produced synergistic analgesic effects in reversing acetic acid-stimulated stretching behavior (2015).

Moreover, recent research in our laboratory has also shown morphine-CBD synergism. In the cisplatin-induced neuropathy model of pain, the combination of CBD with subanalgesic doses of morphine produced synergistic analgesia in the electronic von Frey assay of mechanical allodynia (Harris et al. 2017, *In Preparation*). These findings provide substantial support to our claim that while cannabidiol blocks morphine reward, it allows for the retention and even synergism of morphine analgesia.

Future research will aim to determine analgesic properties of a cannabidiol-opioid formulation that is void of abuse liability in pain assays such as acetic acid writing, tail flick response, hot plate latency, and Freund's adjuvant tests. The creation of this theorized non-addictive cannabidiol-opioid formulation that retains full or synergistic analgesic properties would be revolutionary for the medical treatment of chronic pain and the quality of life experienced by the millions of opioid users around the world.

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