

Case Report: Cannabidiol in the Management of Acute Opioid Withdrawal

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ABSTRACT

INTRODUCTION: Widespread access to prescribed opioid medications and illicit narcotics has contributed to the opioid epidemic in the United States. Despite national efforts to combat opioid use disorder (OUD), including the declaration of a national public health emergency and medication-assisted treatment (MAT), there are limitations to the existing paradigm.

Patients with OUD are especially vulnerable to the rapid and intense onset of precipitated opioid withdrawal (POW) during the minimal 7-day pharmacologic washout period recommended after the last dose of long-acting OUD therapy before transitioning to naltrexone for abstinence maintenance. This washout period represents one of the most challenging and crucial points of treatment, as withdrawal symptoms and cravings may resurface. This leaves many patients with OUD to relapse and fail to maintain abstinence from opioids.

Non-opioid-based novel therapies may hold promise for OUD treatment and may be especially beneficial for patients during this washout period. Evidence is mounting for the use of cannabinoids as an alternative treatment strategy for OUD. New research suggests cannabidiol

(CBD) may be effective in reducing opioid cravings and withdrawal symptoms.

CASE REPORT: We describe a case of a 27-year-old man with an 8-year history of severe OUD achieving successful transition to naltrexone-based abstinence maintenance therapy following cessation of methadone using an intervention of highly purified, high-dose CBD. To our knowledge, this is the first published case report of CBD treatment during the transition to abstinence maintenance.

CONCLUSION: As the opioid epidemic continues to rise, it is clear that a multipronged approach is needed. This case report demonstrates that a 10-day regimen of high-dose, highly purified CBD successfully managed opioid withdrawal symptoms during the necessary washout period prior to introduction of naltrexone for ongoing abstinence maintenance therapy. Although future studies, including randomized controlled trials, are needed to validate CBD's efficacy and safety in this patient population, initial findings are encouraging for patients experiencing mild to moderate opioid withdrawal while transitioning to abstinence maintenance during MAT.

Dr. Shaw has no financial conflicts of interest to disclose.

Dr. Marcu provides consulting, advising, and education services to licensed cannabis operators, private companies, regulatory bodies, and universities. He serves on the PAX Health Advisory Board and as an advisor to Navigator Genomics.

Introduction

Widespread access to both prescribed opioid medications and illicit narcotics (including heroin and clandestine fentanyl) have contributed to the opioid epidemic in the United States. From 1999 to 2018, nearly 450,000 Americans have

died of an opioid overdose, and since 2016, the Centers for Disease Control and Prevention report an average of 130 deaths from opioid overdoses each day.^{1,2} Additionally, the societal costs of prescription opioid abuse are tremendous—estimated at \$55.7 billion in 2007.³

Responding to the opioid crisis, the US Department of Health and Human Services declared a national public health emergency in October 2017 and in 2018, the US Surgeon General's 2018 Spotlight on Opioids report deemed medication-assisted treatment (MAT)—in combination with psychosocial support—the gold standard of care for treating opioid addiction or opioid use disorder (OUD).^{4,5} Currently, there are 3 FDA-approved medications indicated for the treatment of OUD.⁵ Two of them, methadone and buprenorphine, are full and partial μ -opioid receptor agonists, respectively. The third approved drug is naltrexone, a μ -opioid receptor antagonist.

Medication-assisted treatment for opioid dependency progresses through 3 pharmacologic phases: induction, maintenance, and detoxification. During induction with methadone or buprenorphine, the initial dose of medication is introduced to relieve the patient of withdrawal symptoms and cravings. When a dose is reached that no longer requires frequent adjustment and effectively eliminates illicit opioid use, the pharmacologic maintenance phase is achieved. After some time in recovery, the patient and physician discuss initiation of the detoxification phase—the goal of which is to wean the patient off methadone or buprenorphine completely. Current treatment strategies for OUD are comprised of 4 steps (Figure 1)⁵:

1. Treatment initiation with methadone- or buprenorphine-based pharmacotherapy.
2. Stabilization and daily maintenance treatment until the OUD is in remission.
3. Slowly down-titrating the opioid agonist therapy for opioid withdrawal management.
4. Transition to naltrexone for abstinence maintenance during the initial months to prevent relapse.

There are limitations to this paradigm, including the increased degree of clinical oversight that is required to administer the medications that have been FDA-approved for the treatment of OUD. Before initiating naltrexone, a minimal pharmacologic washout period of 7 to 10 days is recommended from the last dose of methadone or buprenorphine. Failure to abstain from an opioid during this 7- to 10-day period can lead to the rapid and intense onset of precipitated opioid withdrawal (POW).⁵ This syndrome can be challenging to manage as there are no evidence-based guidelines to assist clinicians in safely and efficiently managing patients with POW from naltrexone.⁶ Symptoms of

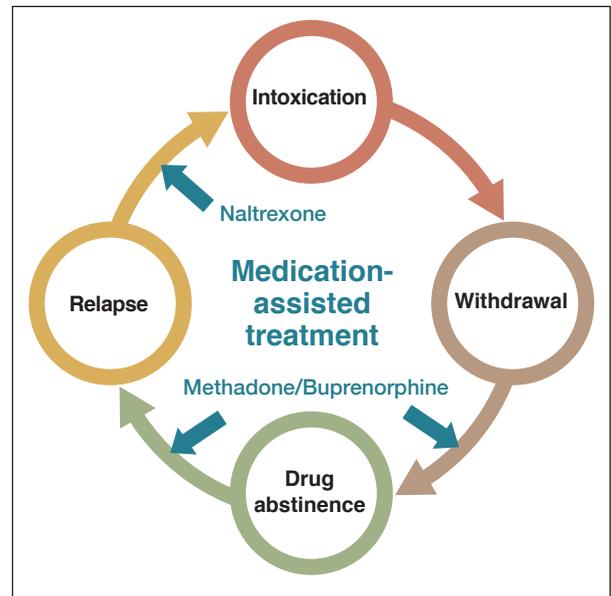


FIGURE 1. Medication-assisted treatment reduces the risk for relapse in patients with opioid use disorder.

POW include but are not limited to autonomic instability, nausea, vomiting, piloerection, diaphoresis, restlessness, rhinorrhea, lacrimation, and mydriasis, according to Kunzler et al.⁶

During this washout period, many opioid-dependent patients may relapse to heroin use and fail to reach the final phase of abstinence maintenance. The currently approved pharmacotherapies for OUD are limited due to their abuse potential, adverse effects, and the heavy regulatory burden for patients and clinicians. More treatment options are needed and strategies that include novel, non-opioid medications may hold promise for the treatment of OUD.⁷

Evidence is mounting for the use of cannabinoids, or medical cannabis, as an unorthodox treatment strategy for OUD.^{8,9} In a double-blind, randomized, placebo-controlled trial of 42 patients with heroin use disorder who were abstaining from the drug at the time, Hurd et al. found that craving and anxiety were significantly reduced among patients who received cannabidiol (CBD) compared with those who were given a placebo.⁹ Additionally, participants who received CBD showed reduced drug cue-induced physiologic measures of heart rate and cortisol levels.⁹ These findings provided the rationale to perform this case study. To our knowledge, this was the first published case report of a patient treated with highly purified, high-dose CBD during the 7-day pharmacologic washout period after weaning off the methadone treatment and before starting naltrexone for abstinence maintenance.

Opioid Withdrawal

continued from page 7

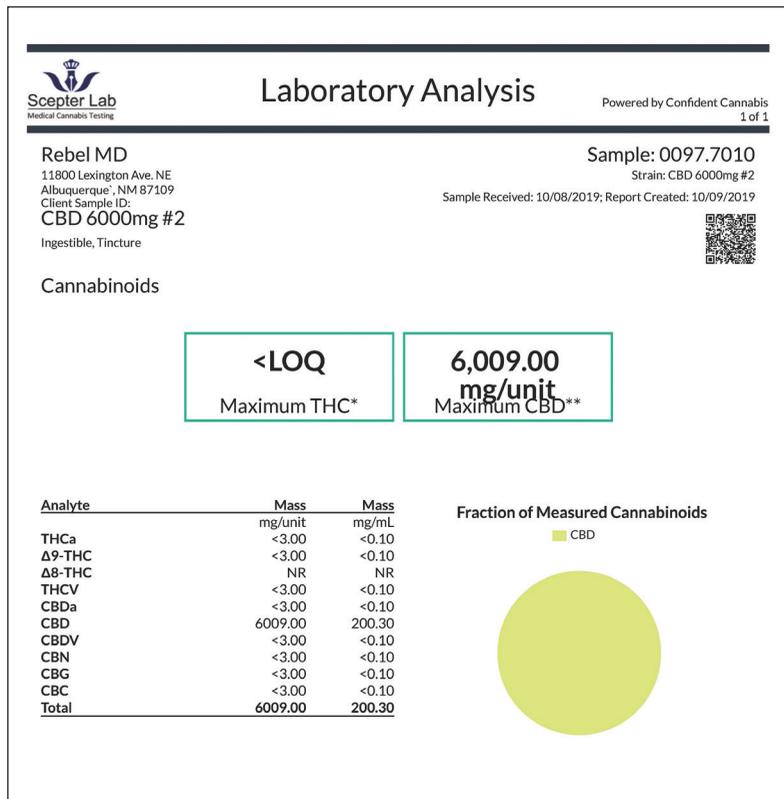


FIGURE 2. Laboratory testing result of the cannabidiol product.

CBD, cannabidiol; **CBG**, cannabigerol; **LOQ**, limit of quantitation; **NR**, not reported because not tested; **THC**, delta-9-tetrahydrocannabinol.

Case Report

BG is a 27-year-old man with OUD who entered treatment at a federally certified opioid treatment program located in Albuquerque, New Mexico in March 2015. The patient reported initial opioid use at 19 years of age—first with illicit pill use, then progressed to non-intravenous (IV) heroin use after 2 years, and later solely IV use. The patient’s past medical history, except for OUD, was unremarkable, and he was not being treated with any medications in addition to MAT.

BG was started on methadone-based medication management in conjunction with behavioral health therapy. For the next 5 years, BG remained in recovery. His methadone dose was initially titrated to 80 mg, but he later required a daily maintenance dose of 120 mg of methadone to abstain from heroin use completely. By the third year of treatment, BG met criteria for sustained remission from OUD, and the decision was made to begin a slow detoxification taper off of methadone. The goal was to wean BG off the medication without jeopardizing abstinence and relapse. During the next 2 years, BG remained adherent to the detoxification schedule.

Assessment

By January 2020, BG had successfully titrated his methadone maintenance dose to 10 mg for 1.25 weeks and had decided it was time to discontinue methadone treatment completely. He was prepared to cease medication use in anticipation of a transition to naltrexone for abstinence maintenance therapy. He also discussed the benefits of an additional intervention, including treatment with high-dose CBD, with his preventive and addiction medicine physician. After undergoing the informed consent process for participation in this case study, BG was instructed to wait 48 hours after his last dose of methadone to ensure he would be in active withdrawal before initiating treatment with CBD.

Medical assessment specific to OUD was performed, including a review of systems, a focused physical examination, and administration of the Columbia-Suicide Severity Rating Scale (C-SSRS) screening, and the Clinical Opioid Withdrawal Scale (COWS). Upon examination, BG reported experiencing symptoms consistent with opioid withdrawal, which was validated by an initial COWS score of 14 at day 0—indicating moderate withdrawal.

Management

BG began a 10-day regimen of third-party tested, highly purified (99.9%) CBD isolate in a medium-chain triacylglyceride oil tincture (Figure 2). Treatment with CBD was administered sublingually at a dose of 200 mg (by 1-mL dropper), 3 times daily. Clinic nursing staff performed a COWS assessment at days 0, 1, 2 and 7 (Table).

Follow-Up

The clinic nursing staff observed a reduction in opioid withdrawal symptoms at day 2, with a reduction in the COWS score from 14 to 5 (Table). The resolution of withdrawal symptoms was observed at day 7 of follow-up, as indicated with a COWS score of 3. BG continued treatment with CBD until day 10, as instructed by his preventive and addiction medicine physician. On day 10, BG initiated oral naltrexone medication without any reported adverse effects or POW symptoms.

Within 30 days, BG discontinued naltrexone for abstinence maintenance. Since the study, BG continues to

TABLE. Symptoms as Observed in COWS of a Patient Treated With High-Dose CBD During Detoxification Phase of Methadone Treatment

COWS Report	Day 0	Day 1	Day 2	Day 7
 Resting pulse rate	1	1	0	0
 Gastrointestinal upset	2	3	2	0
 Sweating	2	2	1	0
 Tremor	2	2	0	0
 Restlessness	3	3	0	0
 Pupil size	1	1	0	0
 Anxiety or irritability	2	2	1	1
 Bone or joint aches	1	1	1	1
 Runny nose or tearing	0	0	0	1
Total COWS score	14	15	5	3

Score: <5 = not clinically significant; 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

CBD, cannabidiol; COWS, clinical opioid withdrawal scale.

maintain abstinence and has had no episodes of relapse. He currently reports taking no medications.

Discussion

This case report demonstrates that high-dose, purified CBD is associated with a marked reduction in withdrawal symptoms during the detoxification phase of MAT. This is noteworthy, as withdrawal symptoms from methadone typically take 2 to 3 weeks to resolve. The detoxification phase represents one of the most challenging and crucial treatment points for

addiction specialists, as withdrawal symptoms and cravings may resurface and leave the patient without a pharmacologic opioid agonist to maintain abstinence from opioids.

As the first published report to conceptually address this clinical hurdle in opioid addiction treatment, findings from this case report are promising but must be validated in future studies, including randomized controlled trials (RCTs).

Recently, the long-acting injectable formulation of naltrexone (Vivitrol, Alkermes, Inc.) came under fire by

Opioid Withdrawal

continued from page 9

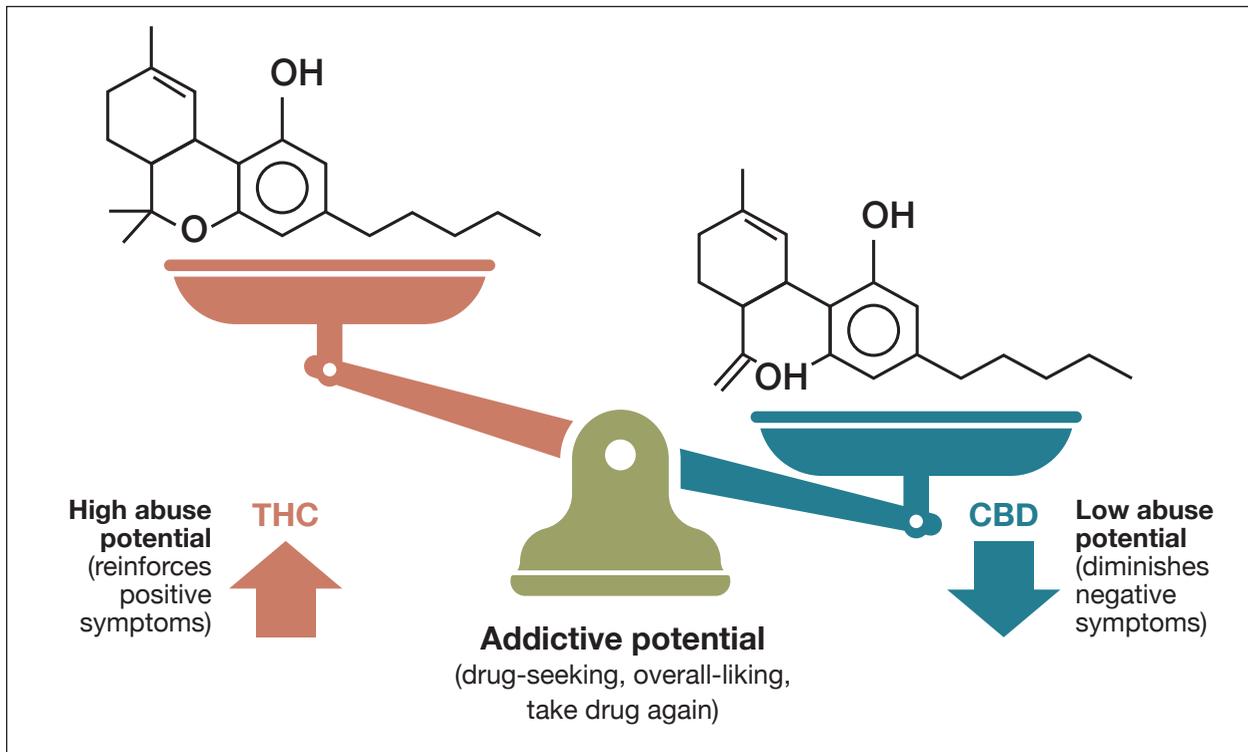


FIGURE 3. The role of THC and CBD in addiction-related behaviors.⁸

CBD, cannabidiol; **THC,** delta-9-tetrahydrocannabinol.

Adapted from Hurd, Y et al. *Neurotherapeutics*. 2015;12(4), 807-815.

the FDA after a California class action wrongful death suit based on its overstated benefits and understated risks for treating OUD.^{10,11} This should not dissuade addiction specialists from the appropriate and intended use of naltrexone as a medication to promote abstinence maintenance for patients whose opioid dependence is in remission and who have successfully titrated off methadone- or buprenorphine-based treatment. Rather, this case study should encourage the use of naltrexone therapy as routine step-down therapy for abstinence maintenance after discontinuation of methadone or buprenorphine treatment.

Emerging research suggests that cannabinoids interact with the endogenous opioid system and may play an essential role in treatment and harm reduction for patients recovering from OUD.⁸

The 2019 seminal report by Hurd et al. is the first RCT to address an alternate treatment option for opioid craving and withdrawal symptoms than opioid receptor-based pharmacologic interventions.⁹

Stress, anxiety, and other factors play a pivotal role in OUD treatment and drug relapse. Consider the persistent challenge of overcoming environmental cue-induced

anxiety (eg, seeing drug paraphernalia) that can trigger cravings. Hurd et al.'s study suggests that CBD may decrease induced cravings, as shown with a reduction in cravings 1-week post-treatment with CBD among patients with heroin use disorder who were abstaining from the drug at the time and who were exposed to videos of drug paraphernalia. Study participants who received CBD also had a protracted effect on prompt-induced anxiety, which has not been seen with other cannabinoids.⁹

Preparations of cannabis that are rich in CBD and low in tetrahydrocannabinol (THC; >0.3%) may reduce opioid use in patients. Specifically, THC may acutely increase the sensitivity to opioids.^{12,13} In contrast, exposure to CBD has been shown to reduce the rewarding properties of morphine (Figure 3).⁸ The link between CBD and decreased stress vulnerability and anxiolytic effects most likely stems from its modulation and activation of 5-hydroxytryptamine 1A serotonergic receptors. CBD also allosterically modulates μ - and γ -opioid receptors. CBD's uptake inhibition of adenosine increases adenosine A2A receptor activity. The anti-anxiety properties of CBD are documented in other patient populations, including patients with social phobia and generalized social anxiety

disorder.¹⁴ The anxiolytic effects of CBD are also linked to the modulation of limbic and paralimbic structures.⁸

Conclusion

As the opioid epidemic continues to rise,² it is clear that a multipronged approach is needed to treat patients with OUD. A medication-free, sober living-based recovery from OUD may be possible for a small number of patients without psychiatric comorbidities who have good support systems, but up to 90% of individuals who detoxify from opioid use, relapse within first 1 to 2 months without MAT.¹⁵⁻¹⁷

The results of this case report not only confirm the previously reported success of CBD in mitigating opioid craving and withdrawal symptoms, but also offer clinical addiction medicine specialists a pathway for managing acute withdrawal symptoms during the vulnerable relapse period—7 to 10 days after discontinuation of methadone or buprenorphine and before introduction of abstinence maintenance pharmacotherapy. This study also aligns with current therapeutic trends and confirms that more research is needed, as indicated by the National Institutes of Health recently awarding a \$3.9 million grant to study cannabis compounds that can reduce the amount of opioid medication a person needs to reduce pain.¹⁸

Consent

Written informed consent was obtained from the patient for publication of the case report and accompanying images.

Acknowledgment

The authors acknowledge the patient discussed in this case report.

References

- Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths - United States, 2013-2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(5152):1419-1427.
- Centers for Disease Control and Prevention. America's drug overdose epidemic: data to action. Accessed March 7, 2021. <https://www.cdc.gov/injury/features/prescription-drug-overdose/index.html>
- Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med*. 2011;12(4):657-667.
- Facing addiction in America. The surgeon general's spotlight on opioids. Accessed March 7, 2021. https://addiction.surgeongeneral.gov/sites/default/files/Spotlight-on-Opioids_09192018.pdf
- The ASAM national practice guideline for the treatment of opioid use disorder: 2020 focused update. *J Addict Med*. 2020;14(2S suppl 1):1-91.
- Kunzler NM, Wightman RS, Nelson LS. Opioid withdrawal precipitated by long-acting antagonists. *J Emerg Med*. 2020;S076-4679(19):31117-5.
- Hurd YL, O'Brien CP. Molecular genetics and new medication strategies for opioid addiction. *Am J Psychiat*. 2018;175(10):935-942.
- Hurd YL, Yoon M, Manini AF, et al. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. *Neurotherapeutics*. 2015;12(4):807-815.
- Hurd YL, Spriggs S, Alishayer J, et al. Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. *Am J Psychiatry*. 2019;176(11):911-922.
- Hurd YL. Cannabidiol: swinging the marijuana pendulum from 'weed' to medication to treat the opioid epidemic. *Trends Neurosci*. 2017;40(3):124-127.
- Facher L. FDA blasts Alkermes for underselling the risks of opioid addiction drug Vivitrol. Accessed March 7, 2021. <https://www.statnews.com/2019/12/11/fda-blasts-alkermes-vivitrol-branding/>
- Miller ML, Chadwick B, Morris CV, Michaelides, M, Hurd YL. Cannabinoid-opioid interaction. In: Campolongo P, Fattore L, eds. *Cannabinoid modulation of emotion, memory, and motivation*. Springer; 2015:393-407.
- Morel LJ, Gitros B, Dauge V. Adolescent exposure to chronic delta-9-tetrahydrocannabinol blocks opiate dependence in maternally deprived rats. *Neuropsychopharmacology*. 2009;34(11):2469-2476.
- Skelley JW, Deas CM, Curren Z, Ennis J. Use of cannabidiol in anxiety and anxiety-related disorders. *J Am Pharm Assoc*. 2019;60(1):253-261.
- Flynn PM, Joe GW, Broome KM, Simpson DD, Brown BS. Recovery from opioid addiction in DATOS. *J Subst Abuse Treat*. 2003;25(3):177-186.
- Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;6(2):CD002207.
- Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;8(3):CD002209.
- Fiore M. Researcher receives \$3.9 million grant to study how cannabis chemicals can help with pain. Accessed April 4, 2002. <https://newsroom.ucla.edu/dept/faculty/scientist-receives-3-9m-grant-to-study-whether-certain-cannabis-chemicals-can-help-with-pain>