REVIEW

Psychosocial and pharmacological interventions for the treatment of cannabis use disorder [version 1; peer review: 3 approved]

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Abstract

Cannabis use has been continuously increasing, and cannabis use disorder (CUD) has become a public health issue. Some psychosocial interventions have demonstrated the ability to reduce cannabis use; however, there are no pharmacotherapies approved for the treatment of CUD. Some drugs have shown limited positive effects on use and withdrawal symptoms, but no controlled studies have been able to show strong and persistent effects on clinically meaningful outcomes. The aim of this review is to synthesize the evidence from the available literature regarding the effectiveness of psychosocial and pharmacological treatments for CUD among adults (that is, 18 years old or older). An analysis of the evidence shows that the current best psychosocial intervention to reduce cannabis use is the combination of motivational enhancement therapy and cognitive-behavioral therapy, preferably accompanied by a contingency management approach. In regard to pharmacological interventions, there are mostly unclear findings. Some drugs, such as CB1 agonists, gabapentin, and N-acetylcysteine, have been shown to produce improvements in some symptoms of CUD in single studies, but these have not been replicated. Other classes of medications, including antidepressants and antipsychotics, have been unsuccessful in producing such effects. There is an imminent need for more clinical trials to develop more effective treatments for CUD.

Keywords

Cannabis, treatment, psychosocial, pharmacological, cannabinoids, CB1, CBD, human clinical trial

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Introduction

Cannabis is one of the most commonly used drugs at the global level, and an estimated 183 million people used cannabis in 2014. Similar to other psychotropic drugs, cannabis has the potential to produce rewarding/reinforcing effects by enhancing dopamine signaling in the mesolimbic and mesocortical pathways¹. The rewarding effects of cannabis are directly associated with the actions of Δ^9 -tetrahydrocannabinol (THC) (the main psychoactive ingredient of cannabis) on cannabinoid CB1 receptors in the brain^{2,3}.

Cannabis use has increased in North America over the past few years, most notably in jurisdictions that have legalized access. For example, in Colorado, cannabis use among young adults (18–25 years old) increased from 20% to 31% between 2000 and 2014⁴. It is estimated that about 8% to 9% of people who have used cannabis in their lifetime will develop cannabis dependence, corresponding to the most severe form of cannabis use disorder (CUD)^{5,6}. An analysis of the numbers in treatment for cannabis use in the United States and Europe shows an increase over the long term⁷. The increase in treatment demand is partially due to the availability of new high-potency strains of cannabis and synthetic cannabinoids^{8,9}. THC levels have increased to as much as 20–25% over the past few years, whereas cannabis concentrate or synthetic cannabinoid products can contain up to 80–90% THC or more potent cannabinoid agonists^{10–13}.

Cannabis use has been associated with several adverse effects^{9,14}. Subjects can present for cannabis intoxication. The main symptoms are euphoria, but symptoms or signs can include increased appetite, tachycardia, tachypnea, and altered judgment, and there can be psychiatric complications (for example, anxiety and psychosis). Discontinuation of cannabis after regular, prolonged use is associated with a withdrawal syndrome that is recognized (anxiety, dysphoria, sleep disturbance, irritability, and anorexia).

Exposure to cannabis can induce medical complications, such as cardiovascular and respiratory problems, but also impact the function of the brain, reducing the ability to drive, decreasing cognitive function, and decreasing memory function^{9,15–17}. Additionally, early onset cannabis users have shown a clear increased risk of CUD development, and there may be alterations of white and gray brain matter and cortical thickness^{18–21}. Frequent use of high-potency cannabis has been associated with increased paranoia, greater CUD severity, elevated risk for psychotic disorder, and cannabis-induced psychosis among individuals with no psychiatric history^{9,22–24}.

CUD is characterized in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) by a pattern of cannabis use that causes clinically significant psychiatric distress and social impairment as well as multiple adverse consequences associated with cannabis use and repeated unsuccessful attempts to stop using²⁵. Cannabis use persists despite negative consequences, and most individuals with CUD perceive

themselves as unable to quit²⁶. Epidemiological studies have estimated that around one in six of those who use cannabis during adolescence and one in two daily cannabis users will meet the criteria for CUD^{27,28}.

Research has focused on interventions to decrease use, promote abstinence, and prevent relapse of cannabis use. Evidence from scientific and clinical literature shows that some psychosocial interventions might help decrease cannabis use, while pharmacotherapies have shown limited effectiveness to treat CUD. The aim of this narrative review is to summarize the evidence regarding the effectiveness of psychosocial and pharmacological treatment interventions for CUD, emphasizing recent advances for the past 3 to 4 years of research.

Methods

The present narrative review on recent advances of psychosocial and pharmacological interventions for CUD followed a structured review approach, based on electronic searches for peer-reviewed publications in relevant scientific databases (that is, MEDLINE, Embase, PsycINFO, and the Cochrane Library). A search strategy was developed for MEDLINE and revised appropriately for all other databases. Keyword examples include “cannabis”, “marijuana”, “treatment”, “intervention”, “psychosocial”, “psychological”, “therapy”, “pharmacological”, “pharmacotherapy”, and “drug” as well as their related terms and variations. Studies presenting data specifically on psychosocial and pharmacological interventions for CUD among adults (18 years old or older) were considered for inclusion. Relevant data were extracted, synthesized, and summarized into a narrative approach.

Discussion/analysis of the recent literature

Psychosocial interventions for cannabis use disorder

There is strong support in the literature and clinical practice for psychosocial interventions for the management of CUD^{29,30}. Most of the recent research on treatments for CUD involves either a combination of psychosocial and pharmacological interventions or pharmacological interventions alone. In the past, a number of clinical trials have explored the effectiveness of psychosocial interventions for CUD, and most studies focused on the effects of primary psychosocial interventions for CUD, such as cognitive-behavioral therapy (CBT) and motivation enhancement therapy (MET). Such interventions can be delivered individually or in groups and focus on the individual or the social environment, teaching coping strategies and problem-solving skills. In general, these psychosocial approaches for substance use disorders aim to build motivation, identify patterns of use and triggers that lead to use, and manage and promote substitution of substance-related behaviors with healthier activities^{31,32}.

Studies have also investigated interventions with alternative approaches for the treatment of CUD. For example, mindfulness-based meditation is a technique that aims to enhance moment awareness in order to decrease the impact of triggers that lead to cannabis use³³. Additionally, drug counseling (DC) might be

offered to promote education regarding drug use and health risks and provide suggestions to help decrease the harmful effects of drug use³⁰.

Most studies showed that CBT and MET present similar treatment effectiveness. Studies comparing either CBT or MET with alternative psychosocial interventions consistently found that these two therapies produce the greatest reduction in cannabis use. For example, a recent study showed that a combined CBT and MET approach reduced the frequency of cannabis use more effectively when compared with either intervention alone³⁴. One study reported that CBT produced superior effectiveness when compared with MET³⁵. Finally, MET demonstrated superior outcomes compared with drug-related health education (both at 6 and 12 months)³⁶ and with inactive controls^{37,38}.

Studies show that the effects of the CBT + MET intervention are positively enhanced by contingency management (CM), a financial incentive for successful abstinence or treatment adherence. For example, CBT + MET enhanced by abstinence-based CM promoted superior results when compared with any other psychosocial approach, such as MET + CBT + adherence-based CM, CBT + adherence-based CM, abstinence-based CM alone, MET + CBT, and finally DC alone^{39–41}.

However, one study showed that, when delivered alone, a 12-session CBT intervention showed greater reduction in the frequency of cannabis use compared with the same CBT duration paired with abstinence-based CM or adherence-based CM over 12 months⁴².

In addition, longer or more intensive interventions have been shown to be superior to shorter durations of treatment. It has been demonstrated that a nine-session MET + CBT intervention outperformed a shorter two-session counterpart for up to 15 months³⁶. Additionally, six-session CBT produced superior results when compared with a single CBT session in another clinical trial²⁵.

In summary, the best intervention for reducing the frequency of cannabis use is likely to be a MET + CBT combination enhanced by abstinence-based CM when available. In the absence of CM, MET + CBT is likely to remain effective, although improvements may not be as immediately noticeable. Although the optimum number of sessions is not clear, evidence suggests that more intensive interventions of more than four sessions are likely to be superior to less intensive interventions, at least in the short term.

Pharmacological interventions for cannabis use disorder

To date, there are no medications approved for the treatment of CUD. Human laboratory studies and clinical trials have tested multiple medications normally approved for other conditions, such as antidepressants, anxiolytics, mood stabilizers, and antiepileptic drugs^{43–49}. For example, the anticonvulsant gabapentin, a GABA/calcium channel modulator, reduced cannabis

use and withdrawal symptoms in adults with CUD⁴⁷. In a recent meta-analysis, selective serotonin reuptake inhibitor (SSRI) antidepressants, mixed-action antidepressants, atypical antidepressants (bupropion), anxiolytics (buspirone), and norepinephrine reuptake inhibitors (atomoxetine) did not demonstrate effects that would suggest that these medications would help for CUD treatment⁵⁰.

Recently, more attention has been given to medications that might act as substitution therapy for CUD, following the same principle as methadone for the treatment of opioid use disorder or nicotine replacement therapy for tobacco dependence. The aim of agonist replacement therapy is to reduce the desire to use the drug, withdrawal symptoms, and the positive subjective and reinforcing effects that are directly mediated by receptor activation.

In the past, THC formulations have been assessed for CUD and have shown some mixed outcomes in both randomized clinical trials and laboratory studies. For example, although the CB1 agonist dronabinol has reduced cannabis withdrawal symptoms and increased retention in treatment when compared with placebo in early studies⁵¹, dronabinol produced no greater effects than placebo when combined with lofexidine (an agonist of the $\alpha 2$ -adrenergic receptor) for cannabis abstinence in a recent clinical trial⁵².

Cannabidiol (CBD) is the second major component of marijuana and has gained high visibility for its multiple therapeutic properties. The mechanism of action of CBD at the CB1 receptor is not yet clear, but recent discussion suggests that it decreases CB1 activity probably through a negative allosteric activity without producing the side effects of inverse agonists^{53,54}. To date, CBD has demonstrated anti-inflammatory, anticonvulsant, antipsychotic, anxiolytic, and neuroprotective effects in pre-clinical studies; some of those effects have been confirmed in human studies. Unlike THC, CBD does not produce psychotropic effects and this is probably because of its low affinity for CB1 receptors^{55–57}. Studies have assessed the effects of CBD for the treatment of CUD, both alone and in a formulation combined with THC (nabiximols, Sativex). Recent studies report that the THC/CBD mixture does not elicit as much of a psychoactive effect as cannabis and, despite not eliciting greater reduction in cannabis use when compared with placebo, was able to reduce withdrawal symptoms and improve retention in treatment in both a clinical trial⁵⁸ and a human laboratory study⁵⁹. However, CBD alone was unable to reduce self-administration in a human laboratory study and did not alter the subjective and physiological effects of smoked marijuana⁶⁰.

Because the rewarding effects of cannabis are directly associated with the actions of THC on the CB1 receptors, CB1 receptor antagonists/inverse agonists also have been evaluated in human laboratory studies^{61,62}. However, psychiatric side effects associated with CB1 antagonists/inverse agonists, such as depression- and anxiety-like states, have been reported in several studies, lead-

ing patients to drop out of studies and discontinue treatment^{63–65}. The recent report that a neutral CB1 antagonist (AM4113) may retain the therapeutic potential of inverse agonists^{66,67}, possibly without the neuropsychiatric side effects⁶⁷, provides some development opportunities in this area.

Recently, a number of trials have evaluated N-acetylcysteine, a modulator of glutamatergic receptors, because of positive results for cannabis use cessation and subjective measures (craving) in past open-label and placebo-controlled trials among adolescents^{68,69}. However, its effect was not replicated in a larger clinical trial among adults, in which N-acetylcysteine and placebo groups did not differ in cannabis abstinence⁷⁰. The potential utility of N-acetylcysteine should be further evaluated in adolescents in the future.

There is currently substantial evidence that the cannabinoid system interacts with other neurotransmitters and neuromodulators. Opioid-focused medications have been considered a potential target for the treatment of CUD, since endogenous opioids play an important role in modulating the addictive properties of cannabinoids. Evidence from pre-clinical studies demonstrates that antagonists of opioid receptors were able to reduce discriminative stimulus and reinforcing effects produced by the activation of CB1 receptors^{71,72}. In addition, studies have shown that cannabinoids produce clear opioid-sparing effects⁷³.

Additionally, some studies have been conducted on the effects of naltrexone, an antagonist of the μ -opioid receptor, on cannabis use. It has been reported that the acute administration of naltrexone potentiated the positive subjective effects of cannabis but that repeated administration decreased such effects^{74,75}. This controversial effect dependent on the duration of treatment can be observed in other neurotransmitter systems. It has been noted that acute compared with chronic antagonism of the dopamine receptor elicits opposite effects on cocaine reinforcement in both human and non-human subjects⁷⁶.

Studies have found that a genetic variation of fatty acid amine hydrolase (FAAH), the enzyme responsible for the degradation of endocannabinoids, is associated with CUD^{77,78}. Among subjects who tried cannabis, those carrying a genetic variation in FAAH (C385A) were significantly less likely to develop CUD⁷⁹. The variation C385A in FAAH reduces both the enzyme's expression and its activity⁸⁰, and FAAH expression is reduced in subjects with CUD⁸¹. An ongoing clinical trial is further exploring the effects of PF-04457845 (a FAAH inhibitor) on cannabis withdrawal⁸².

Currently, there are several clinical trials assessing psychosocial and pharmacological interventions to reduce cannabis use and withdrawal symptoms and prevent relapse. These include trials with CBD⁸³, nabilone⁸⁴, CI-581a (a glutamate modulator) in combination with MET and mindfulness-based relapse prevention⁸⁵, and a combination of numerous behavioral therapies (MET, CBT, CM, individualized assessment, and treatment)⁸⁶. The outcomes from these clinical trials will improve our understanding of treatments for CUD.

Conclusions

CUD is an increasingly important public health issue, and clinical research has been investing in potential treatments for CUD. To date, several studies have investigated psychosocial interventions and concluded that a combination of CBT and MET represents the best approach to treat CUD and that abstinence-based CM (incentives) can enhance effectiveness³⁰.

Recently, several pharmacological interventions have been investigated; however, only a few have shown encouraging results. Specifically, cannabinoid medications have most consistently demonstrated the ability to decrease withdrawal symptoms. However, their utility to reduce cannabis use and prevent relapse still needs further investigation.

For other substance use disorders (for example, alcohol, tobacco, and opiates), treatment guidelines usually recommend a combination of psychosocial and pharmacological interventions⁸⁷. Since this approach has not yet been validated for CUD, the improvement of psychosocial treatments with and without pharmacological therapies for CUD should be further explored in future clinical research.

Author contributions

PS prepared the first draft of the manuscript. PS and BLF revised the draft and have agreed to the final content.

Competing interests

BLF has received in-kind supplies from GW Pharmaceuticals to perform Canadian Institutes of Health Research– and National Institutes of Health–funded studies related to CUD treatment. PS declares that she has no competing interests.

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References

1. Le Foll B: **Is Cannabis Addictive?** Ottawa, Ontario: Canadian Centre on Substance Abuse; 2015.
2. Mechoulam R, Parker LA: **The endocannabinoid system and the brain.** *Annu Rev Psychol.* 2013; **64**: 21–47. [PubMed Abstract](#) | [Publisher Full Text](#)
3. Cooper ZD, Haney M: **Cannabis reinforcement and dependence: role of the**

cannabinoid CB1 receptor. *Addict Biol.* 2008; **13**(2): 188–95. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

4. United Nations Office on Drugs and Crime: **World Drug Report.** 2016. (United Nations publication, Sales No. E.16.XI.7). [Reference Source](#)
5. Lev-Ran S, Roerecke M, Le Foll B, et al.: **The association between cannabis**

- use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychol Med*. 2014; 44(4): 797–810.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Wagner FA, Anthony JC: **Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine.** *Am J Epidemiol*. 2002; 155(10): 918–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
 7. United Nations Office on D. Crime: **World Drug Report 2015.** Vienna, Austria: United Nations Office on Drugs and Crime (UNODC); 2015.
[Reference Source](#)
 8. Malyshevskaya O, Aritake K, Kaushik MK, et al.: **Natural (Δ^9 -THC) and synthetic (JWH-018) cannabinoids induce seizures by acting through the cannabinoid CB₁ receptor.** *Sci Rep*. 2017; 7(1): 10516.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 9. Volkow ND, Baler RD, Compton WM, et al.: **Adverse health effects of marijuana use.** *N Engl J Med*. 2014; 370(23): 2219–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 10. World Health O: **The Health and Social Effects of Nonmedical Cannabis Use.** Geneva, Switzerland: World Health Organization (WHO); 2016.
[Reference Source](#)
 11. Stogner JM, Miller BL: **Assessing the Dangers of “Dabbing”: Mere Marijuana or Harmful New Trend?** *Pediatrics*. 2015; 136(1): 1–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 12. Swift W, Wong A, Li KM, et al.: **Analysis of cannabis seizures in NSW, Australia: cannabis potency and cannabinoid profile.** *PLoS One*. 2013; 8(7): e70052.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 13. Mehmedic Z, Chandra S, Slade D, et al.: **Potency trends of Δ^9 -THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008.** *J Forensic Sci*. 2010; 55(5): 1209–17.
[PubMed Abstract](#) | [Publisher Full Text](#)
 14. National Academies of Sciences E, Medicine: **The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research.** National Academies Press; 2017.
[Reference Source](#)
 15. Tetrault JM, Crothers K, Moore BA, et al.: **Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review.** *Arch Intern Med*. 2007; 167(3): 221–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 16. Gates P, Jaffe A, Copeland J: **Cannabis smoking and respiratory health: consideration of the literature.** *Respirology*. 2014; 19(5): 655–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
 17. Martinasek MP, McGrogan JB, Maysonet A: **A Systematic Review of the Respiratory Effects of Inhalational Marijuana.** *Respir Care*. 2016; 61(11): 1543–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 18. Cooley J, Bernier D, Tibbo PG: **White matter changes in early phase schizophrenia and cannabis use: an update and systematic review of diffusion tensor imaging studies.** *Schizophr Res*. 2014; 156(2–3): 137–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
 19. Jacobus J, Squeglia LM, Sorg SF, et al.: **Cortical thickness and neurocognition in adolescent marijuana and alcohol users following 28 days of monitored abstinence.** *J Stud Alcohol Drugs*. 2014; 75(5): 729–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 20. Lopez-Larson MP, Bogorodzki P, Rogowska J, et al.: **Altered prefrontal and insular cortical thickness in adolescent marijuana users.** *Behav Brain Res*. 2011; 220(1): 164–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 21. Le Strat Y, Dubertret C, Le Foll B: **Impact of age at onset of cannabis use on cannabis dependence and driving under the influence in the United States.** *Accid Anal Prev*. 2015; 76: 1–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 22. Hall W: **The adverse health effects of cannabis use: what are they, and what are their implications for policy?** *Int J Drug Policy*. 2009; 20(6): 458–66.
[PubMed Abstract](#) | [Publisher Full Text](#)
 23. Freeman TP, Winstock AR: **Examining the profile of high-potency cannabis and its association with severity of cannabis dependence.** *Psychol Med*. 2015; 45(15): 3181–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 24. Di Forti M, Marconi A, Carra E, et al.: **Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study.** *Lancet Psychiatry*. 2015; 2(3): 233–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 25. Budney AJ, Novy PL, Hughes JR: **Marijuana withdrawal among adults seeking treatment for marijuana dependence.** *Addiction*. 1999; 94(9): 1311–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Copeland J, Swift W, Roffman R, et al.: **A randomized controlled trial of brief cognitive-behavioral interventions for cannabis use disorder.** *J Subst Abuse Treat*. 2001; 21(2): 55–64; discussion 65–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. Anthony J: **The Epidemiology of Cannabis Dependence.** In: Roffman R, Stephens R, eds. *Cannabis Dependence: It's Nature, Consequences and Treatment.* Cambridge, UK: Cambridge University Press; 2006.
[Publisher Full Text](#)
 28. van der Pol P, Liebrechts N, de Graaf R, et al.: **Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study.** *Drug Alcohol Depend*. 2013; 133(2): 352–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Copeland J, Allsop D: **Dedicated ‘cannabis only’ treatment clinics in New South Wales, Australia: client and treatment characteristics and associations with first-time treatment seeking.** *Drug Alcohol Rev*. 2014; 33(5): 565–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Gates PJ, Sabioni P, Copeland J, et al.: **Psychosocial interventions for cannabis use disorder.** *Cochrane Database Syst Rev*. 2016; (5): CD005336.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 31. Wright FD, Beck AT, Newman CF, et al.: **Cognitive therapy of substance abuse: theoretical rationale.** *NIDA Res Monogr*. 1993; 137: 123–46.
[PubMed Abstract](#)
 32. Miller JH, Moyers T: **Motivational interviewing in substance abuse: applications for occupational medicine.** *Occup Med*. 2002; 17(1): 51–65, iv.
[PubMed Abstract](#)
 33. Praissman S: **Mindfulness-based stress reduction: a literature review and clinician's guide.** *J Am Acad Nurse Pract*. 2008; 20(4): 212–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Hoch E, Bühringer G, Pixa A, et al.: **CANDIS treatment program for cannabis use disorders: findings from a randomized multi-site translational trial.** *Drug Alcohol Depend*. 2014; 134: 185–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. Stephens RS, Roffman RA, Curtin L: **Comparison of extended versus brief treatments for marijuana use.** *J Consult Clin Psychol*. 2000; 68(5): 898–908.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Stephens RS, Roffman RA, Fearer SA, et al.: **The Marijuana Check-up: promoting change in ambivalent marijuana users.** *Addiction*. 2007; 102(6): 947–57.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. Lee CM, Kilmer JR, Neighbors C, et al.: **Indicated prevention for college student marijuana use: a randomized controlled trial.** *J Consult Clin Psychol*. 2013; 81(4): 702–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 38. Stein MD, Hagerty CE, Herman DS, et al.: **A brief marijuana intervention for non-treatment-seeking young adult women.** *J Subst Abuse Treat*. 2011; 40(2): 189–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 39. Kadden RM, Litt MD, Kabela-Cormier E, et al.: **Abstinence rates following behavioral treatments for marijuana dependence.** *Addict Behav*. 2007; 32(6): 1220–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 40. Litt MD, Kadden RM, Petry NM: **Behavioral treatment for marijuana dependence: randomized trial of contingency management and self-efficacy enhancement.** *Addict Behav*. 2013; 38(3): 1764–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 41. Budney AJ, Moore BA, Rocha HL, et al.: **Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence.** *J Consult Clin Psychol*. 2006; 74(2): 307–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. Carroll KM, Nich C, Lapaglia DM, et al.: **Combining cognitive behavioral therapy and contingency management to enhance their effects in treating cannabis dependence: less can be more, more or less.** *Addiction*. 2012; 107(9): 1650–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. Levin FR, McDowell D, Evans SM, et al.: **Pharmacotherapy for marijuana dependence: a double-blind, placebo-controlled pilot study of divalproex sodium.** *Am J Addict*. 2004; 13(1): 21–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. Carpenter KM, McDowell D, Brooks DJ, et al.: **A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence.** *Am J Addict*. 2009; 18(1): 53–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 45. McRae AL, Budney AJ, Brady KT: **Treatment of marijuana dependence: a review of the literature.** *J Subst Abuse Treat*. 2003; 24(4): 369–76.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. Cornelius JR, Bukstein OG, Douaihy AB, et al.: **Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults.** *Drug Alcohol Depend*. 2010; 112(1–2): 39–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 47. Mason BJ, Crean R, Goodell V, et al.: **A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults.** *Neuropsychopharmacology*. 2012; 37(7): 1689–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 48. Weinstein AM, Miller H, Bluvstein I, et al.: **Treatment of cannabis dependence using escitalopram in combination with cognitive-behavior therapy: a double-blind placebo-controlled study.** *Am J Drug Alcohol Abuse*. 2014; 40(1): 16–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Levin FR, Mariani J, Brooks DJ, et al.: **A randomized double-blind, placebo-controlled trial of venlafaxine-extended release for co-occurring cannabis dependence and depressive disorders.** *Addiction*. 2013; 108(6): 1084–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 50. Marshall K, Gowing L, Ali R, et al.: **Pharmacotherapies for cannabis dependence.** *Cochrane Database Syst Rev*. 2014; (12): CD008940.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 51. Levin FR, Mariani JJ, Brooks DJ, et al.: **Dronabinol for the treatment of cannabis**

- dependence: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend.* 2011; **116**(1–3): 142–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
52. **F** Levin FR, Mariani JJ, Pavlicova M, *et al.*: Dronabinol and lofexidine for cannabis use disorder: A randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend.* 2016; **159**: 53–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 53. **F** Laprairie RB, Bagher AM, Kelly ME, *et al.*: Cannabidiol is a negative allosteric modulator of the cannabinoid CB₁ receptor. *Br J Pharmacol.* 2015; **172**(20): 4790–805.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 54. **F** Rohleder C, Müller JK, Lange B, *et al.*: Cannabidiol as a Potential New Type of an Antipsychotic. A Critical Review of the Evidence. *Front Pharmacol.* 2016; **7**: 422.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 55. Crippa JA, Derenussou GN, Ferrari TB, *et al.*: Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol.* 2011; **25**(1): 121–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
 56. Devinsky O, Cilio MR, Cross H, *et al.*: Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia.* 2014; **55**(6): 791–802.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 57. Bergamaschi MM, Queiroz RH, Zuardi AW, *et al.*: Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Curr Drug Saf.* 2011; **6**(4): 237–49.
[PubMed Abstract](#) | [Publisher Full Text](#)
 58. **F** Allsop DJ, Copeland J, Lintzeris N, *et al.*: Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry.* 2014; **71**(3): 281–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 59. Trigo JM, Lagzdins D, Rehm J, *et al.*: Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings. *Drug Alcohol Depend.* 2016; **161**: 298–306.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 60. **F** Haney M, Malcolm RJ, Babalonis S, *et al.*: Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis. *Neuropsychopharmacology.* 2016; **41**(8): 1974–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 61. Klumpers LE, Roy C, Ferron G, *et al.*: Surinabant, a selective cannabinoid receptor type 1 antagonist, inhibits Δ⁹-tetrahydrocannabinol-induced central nervous system and heart rate effects in humans. *Br J Clin Pharmacol.* 2013; **76**(1): 65–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 62. Huestis MA, Boyd SJ, Heishman SJ, *et al.*: Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. *Psychopharmacology (Berl).* 2007; **194**(4): 505–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 63. **F** Després JP, Golay A, Sjöström L, *et al.*: Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med.* 2005; **353**(20): 2121–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 64. Scheen AJ: CB₁ receptor blockade and its impact on cardiometabolic risk factors: overview of the RIO programme with rimonabant. *J Neuroendocrinol.* 2008; **20** Suppl 1: 139–46.
[PubMed Abstract](#) | [Publisher Full Text](#)
 65. Van Gaal LF, Scheen AJ, Rissanen AM, *et al.*: Long-term effect of CB₁ blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study. *Eur Heart J.* 2008; **29**(14): 1761–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
 66. Schindler CW, Redhi GH, Vemuri K, *et al.*: Blockade of Nicotine and Cannabinoid Reinforcement and Relapse by a Cannabinoid CB₁-Receptor Neutral Antagonist AM4113 and Inverse Agonist Rimonabant in Squirrel Monkeys. *Neuropsychopharmacology.* 2016; **41**(9): 2283–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 67. Gueye AB, Pryslawsky Y, Trigo JM, *et al.*: The CB₁ Neutral Antagonist AM4113 Retains the Therapeutic Efficacy of the Inverse Agonist Rimonabant for Nicotine Dependence and Weight Loss with Better Psychiatric Tolerability. *Int J Neuropsychopharmacol.* 2016; **19**(2): pii: pyw068.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 68. **F** Gray KM, Carpenter MJ, Baker NL, *et al.*: A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *Am J Psychiatry.* 2012; **169**(8): 805–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 69. Gray KM, Watson NL, Carpenter MJ, *et al.*: N-acetylcysteine (NAC) in young marijuana users: an open-label pilot study. *Am J Addict.* 2010; **19**(2): 187–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 70. **F** Gray KM, Sonne SC, McClure EA, *et al.*: A randomized placebo-controlled trial of N-acetylcysteine for cannabis use disorder in adults. *Drug Alcohol Depend.* 2017; **177**: 249–57.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 71. Navarro M, Carrera MR, Fratta W, *et al.*: Functional interaction between opioid and cannabinoid receptors in drug self-administration. *J Neurosci.* 2001; **21**(14): 5344–50.
[PubMed Abstract](#)
 72. Justinova Z, Tanda G, Munzar P, *et al.*: The opioid antagonist naltrexone reduces the reinforcing effects of Delta⁹-tetrahydrocannabinol (THC) in squirrel monkeys. *Psychopharmacology (Berl).* 2004; **173**(1–2): 186–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
 73. Nielsen S, Sabioni P, Trigo JM, *et al.*: Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis. *Neuropsychopharmacology.* 2017; **42**(9): 1752–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 74. **F** Haney M, Ramesh D, Glass A, *et al.*: Naltrexone Maintenance Decreases Cannabis Self-Administration and Subjective Effects in Daily Cannabis Smokers. *Neuropsychopharmacology.* 2015; **40**(11): 2489–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 75. Cooper ZD, Haney M: Opioid antagonism enhances marijuana's effects in heavy marijuana smokers. *Psychopharmacology (Berl).* 2010; **211**(2): 141–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 76. Haney M, Speelman R: Controversies in translational research: drug self-administration. *Psychopharmacology (Berl).* 2008; **199**(3): 403–19.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 77. Agrawal A, Lynskey MT: Candidate genes for cannabis use disorders: findings, challenges and directions. *Addiction.* 2009; **104**(4): 518–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 78. Melroy-Greif WE, Wilhelmsen KC, Ehlers CL: Genetic variation in FAAH is associated with cannabis use disorders in a young adult sample of Mexican Americans. *Drug Alcohol Depend.* 2016; **166**: 249–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 79. Tyndale RF, Payne JJ, Gerber AL, *et al.*: The fatty acid amide hydrolase C385A (P129T) missense variant in cannabis users: studies of drug use and dependence in Caucasians. *Am J Med Genet B Neuropsychiatr Genet.* 2007; **144B**(5): 660–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 80. Chiang KP, Gerber AL, Sipe JC, *et al.*: Reduced cellular expression and activity of the P129T mutant of human fatty acid amide hydrolase: evidence for a link between defects in the endocannabinoid system and problem drug use. *Hum Mol Genet.* 2004; **13**(18): 2113–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 81. Boileau I, Mansouri E, Williams B, *et al.*: Fatty Acid Amide Hydrolase Binding in Brain of Cannabis Users: Imaging With the Novel Radiotracer [¹¹C]CURB. *Biol Psychiatry.* 2016; **80**(9): 691–701.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 82. ClinicalTrials.gov (Internet), D'Souza DC: Safety and Efficacy of a FAAH-Inhibitor to Treat Cannabis Withdrawal. ClinicalTrials.gov Identifier: NCT01618656. ClinicalTrials.gov.
[Reference Source](#)
 83. (Internet) Cg: Cannabidiol: a Novel Intervention for Cannabis Use Problems? ClinicalTrials.gov Identifier: NCT02044809.
[Reference Source](#)
 84. ClinicalTrials.gov (Internet), Hill KP: Nabilone for Cannabis Dependence: A Pilot Study (NAB CAN). ClinicalTrials.gov Identifier: NCT01347762.
[Reference Source](#)
 85. ClinicalTrials.gov (Internet): Facilitating the Behavioral Treatment of Cannabis Use Disorder. ClinicalTrials.gov Identifier: NCT02946489.
[Reference Source](#)
 86. ClinicalTrials.gov (Internet), Litt M: Marijuana Treatment Project 4 (MTP4). ClinicalTrials.gov Identifier: NCT02030665.
[Reference Source](#)
 87. NICE: Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. NICE guideline (CG115). London (UK): British Psychological Society and The Royal College of Psychiatrists; 2011.
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