A Budding New Treatment? Cannabinoid Agonists for Cannabis Use Disorder

Pharmacotherapy Grand Rounds

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Learning Objectives

1. Recognize the derivations, pharmacology, and legality surrounding cannabis, cannabidiol, and cannabis use
2. Discuss the epidemiology, pathophysiology, diagnostic criteria, and treatments of cannabis use disorder
3. Evaluate the potential role of cannabinoid agonist therapy as a therapeutic option for cannabis use disorder
4. Construct evidence-based recommendation regarding the use of cannabinoid agonists in the treatment of cannabis use disorder

I. Classification and historical perspective
   a. Species of cannabis[1,2]
      i. Some botanists regard cannabis as a single species while others describe up to three species
      ii. These three species include:
         1. Cannabis sativa
         2. Cannabis indica
         3. Cannabis ruderalis

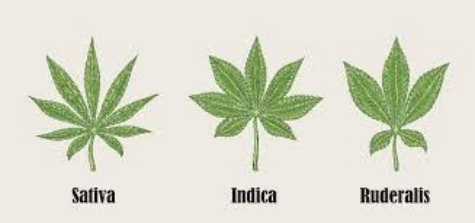

Figure 1. Images of the three species of cannabis – sativa, indica, and ruderalis.

   b. Cannabis sativa may be further divided based on its psychoactive composition and uses[3,4]
      i. Industrial hemp
         1. Defined as any part of the cannabis sativa plant, whether growing or not, that is used exclusively for industrial purposes
         2. Has tall, sturdy stalks and is primarily used in agricultural production
         3. Contains lower amount of delta-9-tetrahydrocannabinol (Δ-9-THC or THC) relative to cannabidiol (CBD) – not more than 0.3% on a dry weight basis
         4. Utilized to create hemp oil or CBD oil
      ii. Marijuana
         1. Many different varieties depending on the strains of cannabis plant used
         2. Contains higher levels of THC relative to CBD
   c. Cannabis through the years[5,6]

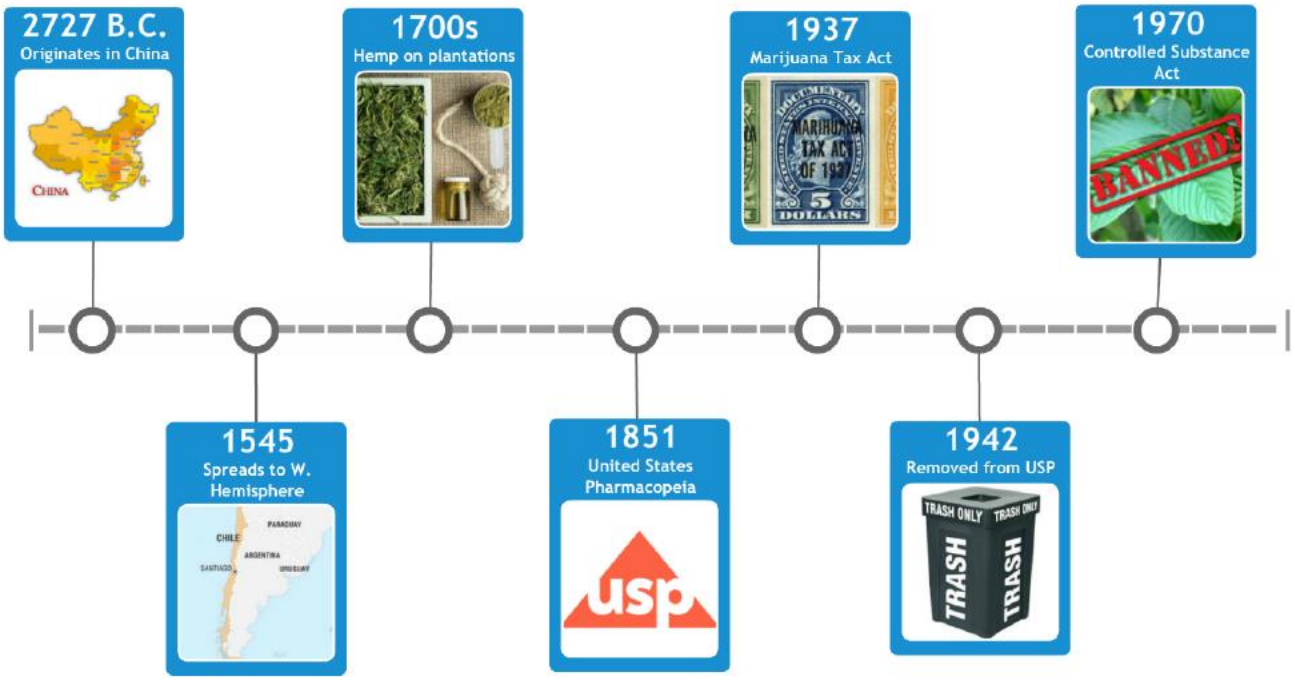

Figure 2. Timeline of cannabis throughout history.

II. Epidemiology
    a. According to the World Health Organization (WHO) cannabis is the most widely cultivated, trafficked, and abused illicit substance[7]
    b. Approximately 147 million people, 2.5% of the world's population, consume cannabis annually[8]
    c. According to the 2015 National Survey on Drug Use and Health conducted by the Substance Abuse and Mental Health Service Administration (SAMHSA), approximately 22.2 million people ≥ 12 years old reported using marijuana during the past month[9]
    d. Cannabis use disorder develops in approximately 10% of people who have tried cannabis at least once[10]

III. Pharmacology
    a. Composition[10-12]
        i. Complex combination of > 400 different chemicals including cannabinoids, flavonoids, and terpinoids
        ii. Cannabinoids of major interest include:
            1. THC
                a. Primary psychoactive component
                b. Can induce feelings of euphoria, as well as have analgesic, antiemetic, anti-inflammatory, and antioxidant effects
            2. CBD
                a. Compound that is structurally similar to THC
                b. Believed to have antipsychotic, analgesic, anti-inflammatory, anxiolytic, and anticonvulsive properties

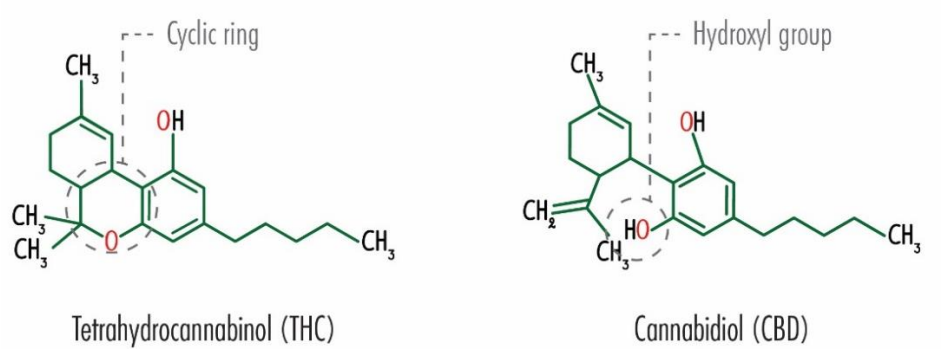

Figure 3. Structural comparison of THC and CBD.

    b. Pharmacologic activity[10,12,13]
        i. Not fully elucidated
        ii. eCB system is a G protein-coupled receptor system
            1. Forms cyclic adenosine monophosphate (cAMP) to release various neurotransmitters, most notably dopamine
            2. Involved in regulating a variety of physiological and cognitive processes, such as appetite, pain/sensation, mood, memory, and exercise-induced euphoria
        iii. eCB responds to endogenous cannabinoids, to include anandamide and 2-arachiodonylglycerol

iv. Primary receptors
    1. Cannabinoid receptor 1 (CB_1) is in the central nervous system (CNS), especially in the brain
    2. Cannabinoid receptor 2 (CB_2) is located in the immune system, peripheral organs and tissue

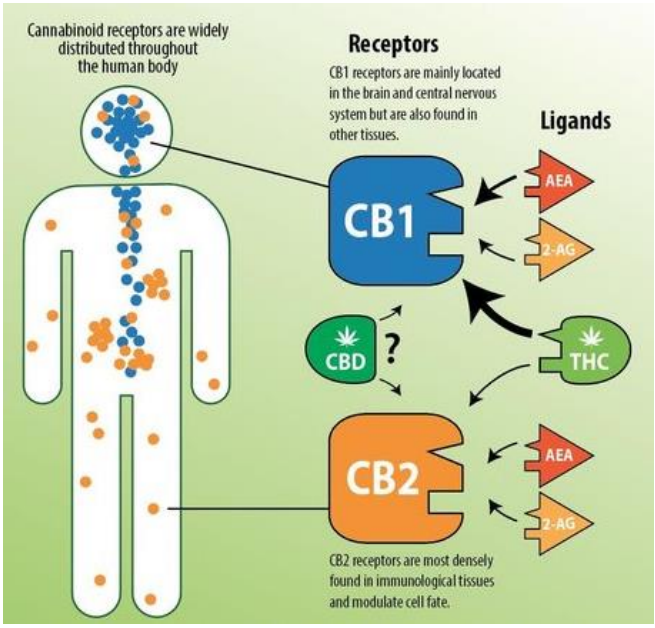

Figure 4. Cannabinoid receptor location and density throughout the human body.

c. Administration[10,14]
    i. Inhalation
        1. Onset of psychoactive effects occurs rapidly with peak effects seen at 15 to 30 minutes
        2. Effects may last for up to 4 hours
    ii. Ingestion
        1. Delayed onset of psychoactive effects when compared to inhalation
        2. Peak effects seen at 30 minutes to 3 hours
        3. Clinical effects may last up to 12 hours

IV. Effects[5,10,11,14]

Table 1. Immediate, acute, and long-term effects of cannabis use

Immediate (within 15 to 30 minutes)	Acute (within 1 to 6 hours)	Long-term (several days to weeks of chronic use)
• Sleepiness • Euphoria • Irritability • Tachycardia • Increased appetite • Slurred speech	• Impairment in attention and concentration, impulse control, planning, decision making, and working memory • Slowed response time in tasks regarding reaction time and motor coordination	• Impairment of cognitive functioning • Development of psychological dependence • Exacerbation of psychotic conditions • Epithelial injury of the trachea and major bronchi • Impairment in fetal development

V. Medical uses[1,9,12]
   a. Chemotherapy-induced nausea and vomiting (CINV)
   b. Nausea and vomiting associated with Acquired Immune Deficiency Syndrome (AIDS)
   c. Asthma
   d. Glaucoma
   e. Depression
   f. Appetite stimulant
   g. Seizure disorder
   h. Chronic pain
   i. Spasticity

VI. Legality concerns
   a. Changing landscape in the United States (US)[7,15,16]
      i. Schedule I medication – high potential for abuse and no currently accepted medical use in the US
      ii. Cannabis is currently legal in 30 states and Washington, D.C. for either recreational or medicinal purposes as of August 2018
      iii. Cannabidiol oil is currently legal in 17 states for medicinal purposes
         1. Specific conditions for which it is legal varies for each state
         2. Percentage composition of THC varies for each state

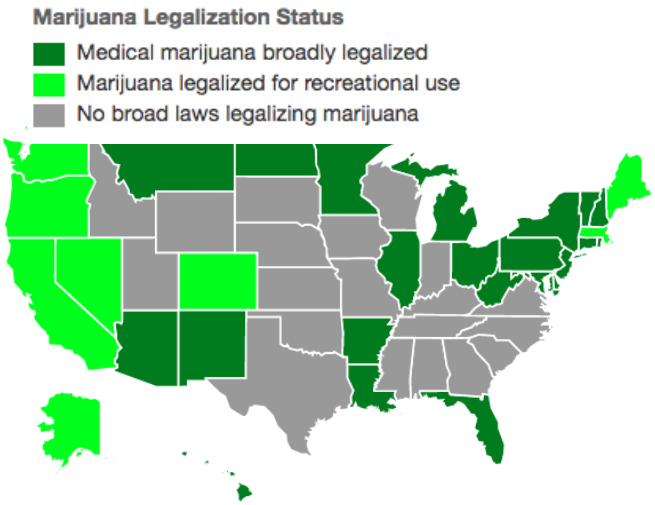

Figure 5. Marijuana legalization status in the United States as of August 2018.

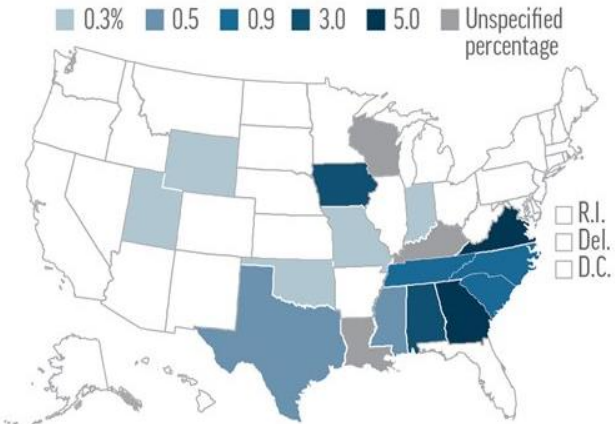

Figure 6. Cannabidiol oil legalization status and THC composition percentages in the United States as of December 2017.

   b. Marijuana laws in Texas[17]
      i. Cannabis is illegal to possess or use under federal law
      ii. Compassionate Use Act of 2015
         1. Low-THC cannabis is permitted for those with qualifying condition of intractable epilepsy
            a. Cannabis sativa that contains no more than 0.5% by weight of THC and not less than 10% by weight of cannabidiol
            b. Ingestion by a means of administration other than by smoking
            c. Other requirements for prescription, including registered physician, qualifying patient and established treatment plan
         2. Three dispensaries now open to produce and sell the low-THC oil

Cannabis Use Disorder

I. Diagnostic criteria of cannabis use disorder is similar to the diagnostic criteria for "substance use disorder" with the substance of interest being cannabis[18]

II. Different nomenclature when transitioning from the DSM-IV to DSM-V[19]
   a. DSM-IV contained substance abuse and dependence
   b. DSM-5 combines the DSM-IV categories of abuse and dependence into "substance use disorders"

Table 2. DSM-IV and DSM-5 Criteria for SUD

	DSM-IV Abuse [a]	DSM-IV Dependence [b]	DSM-5 SUD [c]
Hazardous use	X	-	X
Social/interpersonal problems related to use	X	-	X
Neglected major roles due to use	X	-	X
Legal problems	X	-	-
Withdrawal [d]	-	X	X
Tolerance	-	X	X
Used larger amounts than intended or for longer period of time than intended	-	X	X
Repeated attempts to quit/control use	-	X	X
Much time spent using over other activities	-	X	X
Physical/psychological problems related to use	-	X	X
Activities given up because of use	-	X	X
Craving	-	-	X

[a] One or more abuse criteria within a 12-month period *and* no dependence diagnosis.
[b] Three or more dependence criteria within a 12-month period.
[c] Two or more substance abuse disorder criteria within a 12-month period.
[d] Withdrawal not included for cannabis, inhalant, and hallucinogen disorders in DSM-IV. Cannabis withdrawal added in DSM-5.

Specifiers

Remission
   a. In early remission – 3 to 12 months
   b. In sustained remission – after 12 months
   c. In a controlled environment

Severity
   a. Mild – presence of 2 to 3 symptoms
   b. Moderate – presence of 4 to 5 symptoms
   c. Severe – presence of 6 or more symptoms

III. Pathophysiology
   a. Genetic basis[20,21]
      i. Substantial degree of heritability for both initiation of cannabis use and development of cannabis use disorder
      ii. Twin studies found the proportion of variance in those who initiate cannabis use due to genetic factors was 48% in men and 40% in women

iii. Genetic contribution to cannabis use disorder may be greater in adolescents than older cannabis users and may influence all psychoactive drug use

b. Psychosocial factors[22,23]
   i. Observation studies suggest risk factors for developing cannabis use disorder, however direct causation is unclear
   ii. Risk factors include:
      1. Family dysfunction
      2. Stressful life events
      3. Use of cannabis or other psychoactive substances within the social network

c. Hypothesized mechanisms[10]
   i. Reinforcing effects of substances of abuse are posited to be mediated through the mesolimbic reward pathway
      1. Reward pathway originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens (NA)
      2. Dopamine is the most heavily implicated neurotransmitter involved in addiction
         a. Increases in dopamine in the mesolimbic pathway leads to feelings of euphoria
         b. However, drugs of abuse may often increase dopamine in a way that is more explosive and pleasurable than that which occurs naturally
   ii. Chronic substance use is associated with neuroadaptations that result in the compulsive use and poor decision making

IV. Treatment

a. Psychotherapy[24]
   i. Cognitive-behavioral therapy (CBT)
      1. Psychotherapy approach that emphasizes identification and management of thoughts, behaviors, and external triggers that promote substance use
      2. Involves teaching coping and problem-solving skills that promote replacement of cannabis-related behaviors with healthier alternatives
      3. Reduction of cannabis use frequency at early follow up [mean difference (MD) 10.94, 95% confidence interval (CI) 7.44 to 14.44, one study, 134 participants]
   ii. Motivational interviewing (MI)/motivational enhancement therapy (MET)
      1. Motivational interviewing
         a. Patient-centered psychotherapy that emphasizes the importance of self-efficacy and positive change
         b. Attempts to build motivation for treatment and abstinence in an empathic and non-judgmental environment
      2. Motivational enhancement therapy
         a. Personalized feedback and education regarding the patient's patterns of substance use
         b. Often combined with motivational interviewing
         c. Reduction of cannabis use frequency at early follow up (MD 4.45, 95% CI 1.90 to 7.0, four studies, 612 participants)
   iii. Additional interventions
      1. Contingency management

2. Drug or addiction counseling
3. Screening and brief intervention
4. Mutual help groups
5. Combined interventions

b. Pharmacotherapy
   i. No current FDA-approved medications for cannabis use disorder[10]
   ii. N-acetylcysteine (NAC)[26,27]
      1. Prodrug of the amino acid cysteine
      2. Utilized as an antioxidant or for acetaminophen overdose
      3. Shows mixed results in the treatment of cannabis use disorder (Appendix A)
   iii. Gabapentin[27]
      1. Anticonvulsant agent that is structurally related to gamma-aminobutyric acid (GABA); used for seizure disorders, neuropathic pain, alcohol use disorder, and many other conditions
      2. May lead to short-term reduction in cannabis use compared with placebo (Appendix B)
   iv. Cannabinoid agonists and lofexidine[28-31]

Table 3. Cannabinoid Agonists[28-30]

Agent	Receptor Affinity	FDA-Approved Uses	Dosing
Dronabinol (Marinol®) - synthetic Δ-9-THC	CB_1 and CB_2	Loss of appetite for patients with AIDS, antiemetic for CINV, postoperative N/V	Max 20 mg/day in divided doses (AIDS), 15 mg/m^2/dose (antiemetic)
Nabiximols (Sativex®)	CB_1 and CB_2	Not currently available in the US; approved in Canada as a non-opioid analgesic and skeletal muscle relaxant	Combination of 2.7 mg dronabinol and 2.5 mg cannabidiol in each 100 microliter spray; max of 12 sprays daily
Nabilone (Cesamet®)	CB_1 and CB_2	Refractory CINV	1-2 mg twice daily; max 5 mg/day in 3 divided doses

Table 4. Non-Cannabinoid Agonist[31]

Agent	Receptor Affinity	FDA-Approved Uses	Dosing
Lofexidine (Lucemyra®)	Highly selective for alpha-2A receptor	Opioid withdrawal	0.18 mg four times daily; max of 2.88 mg daily (16 tablets) and no single dose should exceed 0.72 mg (4 tablets)

Clinical Question

Do cannabinoid agonists lead to abstinence for patients with cannabis use disorder?

Table 5. Levin FR, Mariani JJ, Pavlicova M, et al. Dronabinol and lofexidine for cannabis use disorder: A randomized, double-blind, placebo-controlled trial. Drug and Alcohol Dependence. 2016; 159: 53-60.[32]		
Study Design	Randomized, double-blind, placebo-controlled 11-week clinical trial	
Objective	To test if lofexidine and dronabinol (Lofex-Dro) is superior to placebo (PBO) in reducing withdrawal and achieving abstinence	
Participants	<u>Inclusion criteria</u> • Adults between the ages of 18 to 60 • Meeting DSM-IV criteria for current marijuana dependence • Using marijuana ≥ 5 days/week • Providing a THC-positive urine on the day of study entry	<u>Exclusion criteria</u> • Severe mental illness • Unstable physical condition • History of a seizure disorder • Current suicidal risk • Observed cognitive difficulties • Bradycardia (< 50 beats/min), hypotension (sitting or standing BP < 90/50 mmHg) • Currently nursing, pregnant, or a woman refusing to use an effective method of birth control • Physiologically dependent on any other drugs (excluding nicotine) that would require medical intervention • Known sensitivity to dronabinol or lofexidine • Coronary vascular disease • Currently being treated with an alpha-2 agonist antihypertensive medication • Currently being prescribed a psychotropic medication • A job in which even mild marijuana intoxication would be hazardous • Court-mandated to treatment

Methods and Intervention	• One-week placebo lead-in phase
	• 1:1 allocation ratio stratified by joints used per week [< 21 (n=49) vs. ≥ 21 (n=73)]
	• "Fixed-flexible" dose schedule
	  ○ Dose titrated to 1.8 mg (0.6 mg TID) of lofexidine and 60 mg (20 mg TID) of dronabinol, or the maximum tolerated dose
	• Riboflavin added to capsules to assess adherence
	• All participants received manualized MET and CBT/relapse prevention therapy
	• Measures
	  ○ Timeline follow-back (TLFB)
	  ○ Marijuana Craving Questionnaire (MCQ)
	  ○ Modified Systematic Assessment for Treatment and Emergent Events (SAFTEE)	

Outcomes	• Primary: Compare the odds of achieving "consecutive abstinence" (defined as at least 21 consecutive days of abstinence) between the active treatment group vs. placebo group
	• Secondary:
	  ○ Abstinence during the last two weeks of the maintenance medication phase of the trial
	  ○ Peak withdrawal
	  ○ Longitudinal weekly withdrawal
	  ○ Longitudinal weekly proportion of days of use
	  ○ Longitudinal weekly marijuana use
	  ○ Time to dropout of treatment	

Statistical Analysis	• Primary outcome was analyzed using a logistic regression model as a function of treatment and baseline marijuana use • Dichotomous measures analyzed similarly to the primary outcome • Peak withdrawal was analyzed using a linear model as a function of treatment, baseline amount of marijuana use, and baseline withdrawal score • Longitudinal outcomes were analyzed using a generalized mixed effects model • Medication dosing and adherence were tested between treatment groups using non-parametric t-tests (Mann-Whitney U tests) • Side effects and adverse event occurrences were tested using Fisher exact tests • Intent-to-treat sample • Statistical tests were 2-tailed level of significance level of 5%
Results	• Baseline characteristics o 156 total participants evaluated with 122 participants undergoing randomization following the placebo lead-in phase ▪ Lofex-Dro: n=61 (32 completed treatment) ▪ PBO: n=61 (35 completed treatment) o No significant differences in baseline characteristics were seen between placebo and treatment groups o 43 participants dropped out prior to maintenance phase completion • Outcomes o Primary outcome (any 21-days consecutive abstinence) ▪ Proportion of subjects achieving abstinence during any 21 days was 17/61 (27.87%) in Lofex-Dro and 18/61 (29.51%) in PBO ▪ No significant effect of treatment on achieving consecutive abstinence ($X_1^2 = 0.17$, $p = 0.68$) o Secondary outcomes ▪ Marijuana abstinence during last 2 weeks of maintenance medication phase • No significant effect of treatment on achieving two consecutive weeks of abstinence ($X_1^2 = 0.02$, $p = 0.89$) • The odds of achieving abstinence significantly decreased as baseline amount of marijuana use increased ($X_1^2 = 5.79$, $p = 0.02$) ▪ Weekly withdrawal score • No significant effect of treatment on withdrawal scores across time ($F_{1,633} = 0.05$, $p = 0.83$) • No significant effect of baseline amount of marijuana use on withdrawal scores across time ($F_{1,633} = 0.84$, $p = 0.36$) • Withdrawal scores did significantly decrease over time ($F_{7,633} = 2.30$, $p = 0.03$) ▪ Retention in treatment (time to dropout) • No significant difference in retention between treatment groups ($X_1^2 = 1.36$, $p = 0.24$) • Treatment adherence o Medication ▪ Mean tolerated doses of the Lofex-Dro groups was 55.6 ± 13.1 mg/day for dronabinol and 1.28 ± 0.64 mg/day for lofexidine

	▪ Mean tolerated doses in the placebo group was 60 mg/day for placebo dronabinol (Mann-Whitney U test: U = 1934, p=0.01) and 1.74 ± 0.26 mg/day for placebo lofexidine (U = 1641, p < 0.0001) ▪ Median rates of medication adherence was 95.5% (IQR 86.4-98.2%) for dronabinol pills and 94.8 (IQR 85.5-98.1%) for lofexidine pills o Cognitive behavioral therapy ▪ Participants completed a mean of 7.5 (SD = 3.6) of 12 CBT sessions with no significant differences across groups • Side effects and adverse events o Dry mouth, intoxication, and hypotension were more common in the active treatment arm compared to the placebo arm (p<0.001, p=0.004, p=0.008, respectively) o Anxiety was less common in the Lofex-Dro arm (p=0.044)	
Author's Conclusion	The concurrent administration of lofexidine and dronabinol is not more effective than placebo for promoting abstinence, reducing withdrawal symptoms, or retaining individuals in treatment	
Critique	<u>Strengths</u> • Flexible dosing to target patient-specific symptoms/tolerability • Relatively large sample size for a single-site study • Medication adherence addressed through biomarker	<u>Limitations</u> • High dose compared to current FDA-approved indications • High dropout rate during maintenance phase • Urine drug screen to assess abstinence • Lack of power
Take Home Points	Lofex-Dro was not shown to induce abstinence in those with cannabis dependence	

Table 6. Trigo JM, Soliman A, Quilty LC, et al. Nabiximols combined with motivational enhancement/cognitive behavioral therapy for the treatment of cannabis dependence: A pilot randomized clinical trial. PLoS ONE. 2018; 13(1): e0190768.[33]		
Study Design	Double-blind, placebo-controlled, randomized clinical trial over 12 weeks	
Objective	To determine if the self-titrated dosage of nabiximol was well tolerated and sufficient to observe any effects on cannabis use, craving, and withdrawal in comparison with placebo	
Participants	<u>Inclusion criteria</u> • 18-65 years old • Understand and willing to comply with study requirements and restrictions • Willing to use appropriate contraceptive method throughout the study • Physical health based on medical history, physical exam, vitals, ECG, and chemist and hematological laboratory results • Meet DSM-IV criteria for current cannabis dependence • Report cannabis as primary drug of abuse • Report using cannabis at least 5 days a week for at least one month	<u>Exclusion criteria</u> • Meet DSM-IV criteria for a current Axis I disorder including substance use disorder other than cannabis, nicotine, or caffeine dependence • Have a first-degree relative with schizophrenia • History of seizures • History of CV disease • History of pulmonary disease • Clinically significant pathology in oral cavity and poor oral hygiene • Known sensitivity to dronabinol, cannabidiol, propylene glycol, ethanol, or peppermint oil

<table>
<tr><td></td><td>• Have cannabinoid positive urine drug screen
• Treatment-seeking for cannabis dependence
• Smoke less than or equal to the equivalent of 4 joints per day (or four grams per day if participants smoked cannabis in other forms)</td><td>• Unstable medical conditions
• Pregnant or breastfeeding
• Currently taking psychotropic medication for any indication other than treatment of insomnia
• Holding a job that involves driving or operating heavy machinery</td></tr>
<tr><td>Methods and Intervention</td><td colspan="2">• Randomized to placebo or nabiximol plus motivational enhancement therapy and cognitive behavioral therapy (MET/CBT)
• Nabiximol was given as needed spray, up to 113.4 mg THC/105 mg CBD
o Each spray contains 2.7 mg THC and 2.5 mg CBD
o Participants could use up to 42 sprays per day with the following titration
▪ High medication use - ≥ 20 sprays on a treatment day
▪ Low medication use - < 20 sprays on a treatment day
Table 7. Dosing titration schedule of nabiximol<table><tr><td>Day</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td></tr><tr><td>Max # of sprays</td><td>5</td><td>5</td><td>10</td><td>15</td><td>20</td><td>25</td><td>30</td><td>35</td><td>40</td><td>42</td><td>42</td><td>42</td></tr></table>• Nabiximol and placebo were donated by GW Pharmaceuticals
• Compliance to nabiximol and placebo monitored by weighing each vial before use, during each study visit, and upon return (1 spray = 0.1 g)
• Participants could earn up to $855 for their participation in the study
• Measures
o Marijuana Withdrawal Checklist (MWC)
o Others may be found in Appendix C</td></tr>
<tr><td>Outcomes</td><td colspan="2">Assess tolerability and possible trends for efficacy of nabiximols for the treatment of cannabis dependence</td></tr>
<tr><td>Statistical analysis</td><td colspan="2">• Sample of 18 participants per group was calculated for sufficient power to detect a difference in abstinence rates across the two groups if the proportion of subjects who are abstinent in the study group of 50% of higher (Chi square)
• Intention-to-treat analysis
• Generalized Linear Mixed Model (GLMM) with intervention group as between -subjects factor and time (treatment week) as within-subjects factor with no covariates
• One-way ANOVA was used to assess differences between conditions, when appropriate</td></tr>
<tr><td>Results</td><td colspan="2">• Baseline characteristics
o Participants were enrolled from May 2014 to May 2015 with 89 participants being invited for initial screening
o 40 participants were randomized with 27 participants completing the study
▪ Nabiximols + MET/CBT: n=20 (13 completed treatment)
▪ Placebo + MET/CBT: n=20 (14 completed treatment)
• Tolerability objective
o Medication was well-tolerated by all participants and no serious adverse events were observed in any of the experimental conditions
• Abstinence rates
o No significant difference in abstinence rates between the two groups
▪ Seven-day point prevalence cannabis abstinence after the medication phase was 30.8% (n=4) for nabiximols and 42.9% (n=6) for placebo</td></tr>
</table>

- One person in the nabiximols group quit cannabis on the target day (day 21) and remained abstinent for the rest of the study
- Twelve other people in the nabiximols group reduced use and 5 remained abstinent for at least 4 consecutive weeks (range 4-18 weeks)

- Cannabis use decreased by 70.5% (from 6.1 to 1.8 grams) in the nabiximols group at the end of treatment compared to 42.6% (from 5.4 to 3.1 grams) in the placebo group
  - Different levels of cannabis use were observed in the high vs low medication use subgroups
    - High medication use - ≥ 20 sprays on a treatment day
    - Low medication use - < 20 sprays on a treatment day
  - A trend for reduction of cannabis use was observed in high nabiximols users vs. placebo, whereas the cannabis use was similar in the nabiximols and placebo groups in the low medication use subgroups

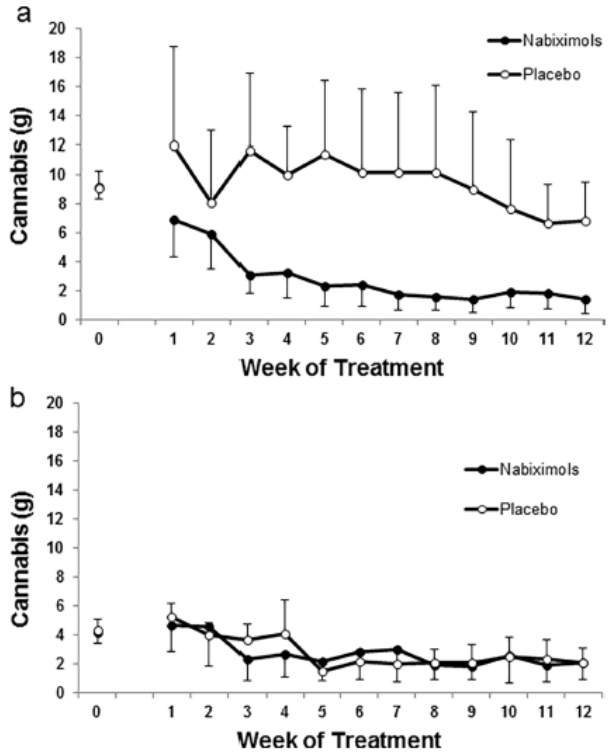

Figure 8. High/low study medication effects on cannabis use. In a) high medication users' subgroup (≥ 20 sprays on any treatment day) and in b) low medication users subgroup (< 20 sprays on any treatment day)

- Cannabis withdrawal
  - Total scores for MWC progressively decreased along the 12-week treatment in both groups, though no statistically significant difference
- Cannabis craving
  - Total craving scores decreased along the 12-week treatment in both groups
  - Noted statistically significant reductions in cravings in the high dose nabiximols group compared to the low dose nabiximols group ($F_{12,90.1}$ = 10.386, p<0.001)

Author's Conclusion	Combination nabiximol + MET/CBT was well tolerated and support the idea that nabiximols may help decrease cannabis use with no increase in craving or withdrawal	
Critique	Strengths • Double-blind, randomized controlled trial • Participants could self-adjust study medication	Limitations • Abstinence was self-reported • Small sample size • Exclusion criteria may limit generalizability • Urine drug screens not an appropriate measure for abstinence • Higher doses than what is currently approved
Take Home Points	• Nabiximols + MET/CBT may prove useful in reducing cravings in those with cannabis dependence • Further studies may require increased dose of medication to reach the goal of abstinence	

Table 8. Hill KP, Palastro MD, Gruber SA, et al. Nabilone pharmacotherapy for cannabis dependence: A randomized, controlled pilot study. Am J Addict 2017; 26:795-801.[34]

Study Design	Randomized prospective pilot study over 10 weeks	
Objective	To assess the safety, tolerability, and preliminary efficacy of nabilone to treat cannabis dependence	
Participants	Inclusion criteria • Between ages 18 and 45 • Meet DSM-IV criteria for current cannabis dependence	Exclusion criteria • Current diagnosis of other drug or alcohol dependence (excluding caffeine and nicotine) • Current serious psychiatric illness • History of psychosis, schizophrenia, or bipolar I disorder • Current suicidal or homicidal risk • Current treatment with opioid analgesics, sedative hypnotics, or other known CNS depressants • Major medical illness • History of seizures, head trauma, or other history of CNS injury • Pregnancy, lactation, or inadequate contraception

Methods and Intervention	• Behavioral intervention included initial 45-minute session, 15-25 minute follow-ups
	• Capsules contained nabilone or placebo + riboflavin 25mg, with nabilone being provided by Meda (now Mylan) Pharmaceuticals
	• Nabilone dosing: 0.5 mg daily x 7 days, then 1 mg daily x 7 days, then 1.5 mg daily x 7 days, then 2 mg daily x 4 weeks before tapering off the medication over the final 3 weeks (reverse titration schedule)
	• Quantitative urine cannabinoid tests (UCTs) were obtained at screening and twice-weekly during the study
	• Measures
	  ○ Timeline Follow Back interview (TLFB)
	  ○ Marijuana Craving Questionnaire (MCQ)
	  ○ Beck Anxiety Inventory (BAI)
	  ○ Quick Inventory for Depressive Symptoms (QIDS)
	• Medication adherence assessed through pill counts, daily diaries, and urinary riboflavin levels
	• Participants could earn up to $955 for participation in the study	

Outcomes	• Primary – Cannabis-dependent participants receiving nabilone would experience no difference in adverse events	

<table>
<tr><td></td><td>• Secondary – cannabis-dependent participants receiving nabilone would use less marijuana as measured by self-report and UCTs</td></tr>
<tr><td>Statistical analysis</td><td>• Intention-to-treat analysis using all randomized participants
• T-tests and Chi square tests to compare baseline demographic and clinical measures between treatment groups
• Repeated measures linear mixed effects regression model was used to estimate the overall effect of nabilone on changes in quantitative test results
• Secondary analyses using linear mixed effects models to assess craving and anxiety
• Significance was set at a two-sided alpha of 0.05 with 95% confidence intervals</td></tr>
<tr><td>Results</td><td>• Baseline characteristics
○ 32 total participants evaluated with 18 participants undergoing randomization
▪ Nabilone: n=10 (6 completed treatment)
▪ Placebo: n=8 (6 completed treatment)
○ No significant differences in baseline characteristics were seen between placebo and treatment groups
• Primary outcome (safety and tolerability)
○ No significant differences between the placebo-treated group compared to the nabilone-treated group
▪ Nausea, vomiting, and sedation were the most common adverse effects reported
▪ No participants in either group discontinued therapy due to adverse events
• Secondary outcomes (efficacy)
○ No significant difference in the number of cannabis sessions
○ No significant difference in percent of days of use
○ No significant difference in the number of inhalations per day
○ No significant difference in the changes in the urine cannabinoid levels
• Other outcomes
○ Craving was assessed using the MCQ total score as well as the subscale scores (purposefulness, emotionality, expectancy, and compulsion)
▪ No significant treatment group differences in MCQ total score at either the end of treatment (z = -0.34, p=0.74) or the end of follow-up (z = -0.40, p=0.69)
▪ Statistically significant within-group differences in MCQ total scores in both the nabilone (z = -2.34, p=0.02) and placebo groups (z = -2.06, p=0.04)
Table 9. MCQ Total and Subscale Results
<table>
<tr><th></th><th>Nabilone (z-score)</th><th>Nabilone (p-value)</th><th>Placebo (z-score)</th><th>Placebo (p-value)</th></tr>
<tr><td>MCQ Total Score</td><td>-2.34</td><td>0.02</td><td>-2.06</td><td>0.04</td></tr>
<tr><td>Factor 1: Compulsivity</td><td>-2.89</td><td>0.004</td><td>-</td><td>-</td></tr>
<tr><td>Factor 2: Emotionality</td><td>-2.63</td><td>0.008</td><td>-</td><td>-</td></tr>
<tr><td>Factor 3: Expectancy</td><td>-</td><td>-</td><td>-3.02</td><td>0.002</td></tr>
<tr><td>Factor 4: Purposefulness</td><td>-2.57</td><td>0.01</td><td>-2.01</td><td>0.05</td></tr>
</table>
○ No significant changes in BAI scores between the two groups
○ No significant differences in QIDS scores between groups</td></tr>
</table>

Author's Conclusion	Nabilone pharmacotherapy was safe and tolerable, though it did not demonstrate an advantage over placebo in cannabis use outcomes	
Critique	Strengths • Randomized, controlled trial • Biomarker used for adherence • Assessed cannabis use as well as addressing cravings, mood, and anxiety symptoms	Limitations • Small sample size • Single site intervention • High dropout rates • Did not evaluate baseline psychiatric conditions • Low-dose of nabilone used during the study • No discussion of power
Take Home Points	Nabilone may be safe and showed a reduction in various craving subscales, but did not lead to abstinence in those with cannabis dependence	

Table 10. Summary of Reviewed Literature

Authors	Medication	Cannabis Abstinence	Cannabis Withdrawal	Cannabis Cravings	Dosing
Levin 2016	Dronabinol + lofexidine	✖	✖	✖	⬆
Trigo 2018	Nabiximols	?	✖	✖	⬆
Hill 2017	Nabilone	✖	✖	○	⇩

Conclusions

I. Summary
   a. Cannabis continues to be one of the most commonly abused substances worldwide, with ~10% of people who use cannabis developing cannabis use disorder
   b. The changing landscape in terms of legalization of marijuana and CBD clouds the picture for treatment strategies for cannabis use disorder
   c. Agonist therapy has proven successful in the treatment of opioid-use and tobacco-use disorders
   d. Limited evidence to support the use of cannabinoid agonists for cannabis use disorder
      i. Only small studies published with high dropout rates
      ii. Agonist therapy may prove beneficial for cravings, but lack of evidence for abstinence

II. Recommendations
   a. Currently available cannabinoid agonists cannot be recommended for patients with cannabis use disorder at this time
   b. Additional studies needed to assess optimal dosing strategies and long-term effects of pharmacotherapies

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Appendices

Appendix A. NAC Literature Review for Cannabis Use Disorder				
Authors	Study Design	Participants	Intervention	Results
Gray et. al. – 2012[25]	Double-blind, RCT	116 treatment-seeking, cannabis-dependent adolescents/young adults	NAC 2,400mg daily or placebo for 8 weeks; weekly individual supportive counseling and biweekly contingency management	NAC group – greater adjusted odds of a negative UDS (OR = 2.4, 95% CI 1.1 to 5.2); two-week point prevalence abstinence rate at end of treatment showed a trend favoring NAC (36.2% vs. 20.7%)
Gray et. al. – 2017[26]	Double-blind, RCT	302 treatment-seeking, cannabis-dependent adults	NAC 2,400mg daily or placebo for 12 weeks; weekly individual supportive counseling and biweekly contingency management	Both groups had the same proportion of UDSs negative for cannabinoids (22.3% vs. 22.5%, OR = 1, 95% CI 0.63 to 1.59)

RCT – randomized controlled trial, UDS – urine drug screen, OR – odds ratio, CI – confidence interval

Appendix B. Gabapentin Literature Review for Cannabis Use Disorder				
Authors	Study Design	Participants	Intervention	Results
Mason et. al. – 2012[27]	Proof-of-concept study	50 treatment-seeking, cannabis-dependent adults	Randomized to receive gabapentin 1,200mg daily or placebo for 12 weeks; weekly individual abstinence-oriented counseling	Gabapentin group had reduced cannabis use based on negative UDS and self-report, decreased withdrawal symptoms, and greater improvement in cognitive tests

Appendix C. Measures Used in Selected Clinical Trials[35]	
Scale	Description
Addiction Severity Index (ASI)	• 200-item scale with 7 subscales • Semi-structured interview designed to address seven potential problem areas in substance abuse patients: Medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status
Beck Anxiety Inventory (BAI)	• 21-item scale that describes common symptoms of anxiety • Recommended for use in assessing anxiety in clinical and research settings
Beck Depression Inventory (BDI)	• 21-item test used to measure the presence and degree of depression • Attempts to assess a specific symptom or attitude associated with depression
Brief Psychiatric Rating Scale (BPRS)	• Clinician-rated tool designed to assess change in severity of psychopathology • 18-item scale measuring positive symptoms, general psychopathology, and affective symptoms • Each symptom construct is rated on a 7-point scale ranging from “not present” to “extremely severe”
Drug Effects Questionnaire (DEQ)	• 5-item measure that assess substance use and revolves around the feelings a person may feel with substance use • Criteria range from “not at all” to “extremely”
Fagerstrom Test for Nicotine Dependence (FTND)	• Ordinal measure of nicotine dependence related to cigarette smoking • 6-items that evaluate the quantity of cigarette consumption, compulsion to use, and dependence
Hamilton Rating Scale for Anxiety (HAM-A)	• 14-item, clinician-administered instrument that measures current anxiety symptoms • Each item is scored on a scale of 0 (not present) to 4
Hamilton Rating Scale for Depression (HAM-D)	• 17-item, observer-rated instrument that measures severity of depressive symptoms • Items are scored on either a 5-point or 3-point rating scale

Marijuana Craving Questionnaire (MCQ)	• 45-items rated on a seven-point Likert-type scale ranging from “strongly disagree” to “strongly agree”
	• Four specific constructs
	  ○ Compulsivity – inability to control marijuana use
	  ○ Emotionality – use of marijuana in anticipation of relief from withdrawal or negative mood
	  ○ Expectancy – anticipation of positive outcomes from using marijuana
	  ○ Purposefulness – intention and planning to use marijuana for positive outcomes

Marijuana Withdrawal Checklist (MWC)	• 10-item measure that assesses mood, behavioral, and physical symptoms associated with marijuana withdrawal • Items rated on a 4-point scale where 0 = none and 3 = severe
Profile of Mood States (POMS)	• 65-item, 5-point adjective rating scale • Measures 6 identifiable mood or affective states: Tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment
Quick Inventory of Depressive Symptomatology (QIDS)	• Assesses the severity of depressive symptoms • 16-item scale that is available as both a clinician- and self-rates scale
St Mary's Hospital Sleep Questionnaire (SMHSQ)	• 14-item scale that assesses the patient's sleep the night prior to administration • Has shown reliability in various patient groups
Systematic Assessment for Treatment and Emergent Events (SAFTEE)	• Used to detect side effects in clinical trials • Divides 76 different side effects by body system into preferred terms for consistency of measure
Timeline Follow-Back (TLFB)	• Assess recent cigarette, marijuana, and other drug use • May be administered by an interviewer, self-administered, or administered by computer • Asks clients to retrospectively estimate their drug use 7 days to 2 years prior to the interview date (ex: number of joints smoked per day)