



# THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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**Palliative Care  
Pharmacy Team:**

**Guest Author:**  
**Emily Leung, 4<sup>th</sup> Year  
Student Pharmacist at  
University of  
Pittsburgh School of  
Pharmacy**

**Clinical Pharmacy  
Specialist:**

**Maria Felton Lowry,  
PharmD, BCPS, BCGP**  
Assistant Professor  
University of Pittsburgh  
School of Pharmacy  
Department of Pharmacy  
and Therapeutics  
Palliative  
Care Clinical Pharmacy  
Specialist  
UPMC Palliative and  
Supportive Institute

**Cell:** 412-627-8473  
**Office:** 412-864-2899  
**Email:** lowrymf@upmc.edu

If you have a topic you  
would like the pharmacy  
team to answer, please  
send your suggestions to:  
lowrymf@upmc.edu

## TODAY'S TOPIC: Cannabis Withdrawal

### Cannabis Withdrawal and How to Address It

#### Background:

Cannabis withdrawal is estimated to affect approximately 47% (up to 50-95%) of people who use cannabis after discontinuation or decrease in dose of cannabis.<sup>1,2</sup> People with a past medical history of substance use disorder, daily cannabis use, and those who use tobacco concurrently with cannabis may be at elevated risk.<sup>1</sup> Withdrawal symptoms are attributed to delta-9-tetrahydrocannabinol (THC). A majority of THC is metabolized in the liver via CYP450 enzymes which could lead to potential drug interactions.<sup>3</sup> According to the DSM-5, cannabis withdrawal symptoms occur after stopping or decreasing the dose of cannabis typically after frequent daily cannabis intake<sup>2</sup> and are commonly observed within the first 1-2 days after discontinuation or decrease in dosage of cannabis, usually peak after 6 days but symptoms can last over 3 weeks.<sup>1</sup> Criteria include presence of three of the following symptoms within one week following cessation or decrease in cannabis intake: irritability/anger/aggression, anxiety, sleep issues, lack of appetite/loss of weight, restlessness, or decreased mood plus one of the physical signs of cannabis withdrawal: tremors, fever, chills, headache, or abdominal pain.<sup>2</sup> There are no FDA approved pharmacotherapies to treat cannabis withdrawal. However, dronabinol is FDA approved for other uses and could potentially be used off-label for cannabis withdrawal.

#### Importance:

Cannabis withdrawal is becoming more prevalent as medical cannabis is becoming more widely used. Given hospital policy, many patients who use cannabis at home are not able to continue to receive cannabis during inpatient admission and could be at risk of withdrawal. It is important for palliative care clinicians to recognize cannabis withdrawal and consider potential symptom management.

#### The Literature:

[Addiction. 2022 Jul;117\(7\):2075-2095.](#)

#### Clinical management of cannabis withdrawal<sup>1</sup>

**Objective:** To present a comprehensive review of the randomized controlled trials (RCTs) regarding cannabis withdrawal and management

**Methods:** Narrative Literature Review

**Results:** DSM-5 and ICD-11 both contain criteria to classify cannabis withdrawal severity

-Lack of studies regarding the non-pharmacological (coping strategies etc.) management of cannabis withdrawal but is offered in addition to pharmacological management in many RCTs

Medication	Evidence/Findings	Potential Application to Clinical Practice
Dronabinol <sup>7</sup>	Could help with cannabis withdrawal symptoms. See RCT below	See RCT below
Gabapentin <sup>4</sup>	A double-blind randomized trial found that gabapentin decreased cannabis withdrawal symptoms/use but question generalizability of the findings (88% male, small N, large dropout)	Participants received gabapentin 300 mg capsules titrated to a dose of 1200 mg/day over four days given as a morning, afternoon, and evening dose (300 mg/300 mg/600 mg)
Quetiapine <sup>5</sup>	A double-blind RCT found it not to be superior to placebo for cannabis cravings or sleep issues (44% dropout rate)	Quetiapine was given to participants using a titration schedule beginning with 25 mg and titrated to 300 mg in the evening over four weeks
Nabiximols/Nabilone <sup>6</sup>	Conflicting RCTs for nabiximols or nabilone regarding evidence for with withdrawal symptoms/cannabis. In the trial with nabilone, "there was no difference in cannabis use between the nabilone group and the placebo group as measured by self-report" <sup>6</sup>	Nabiximols are not currently FDA approved in the US; Nabilone was studied in a small trial (only 12 patients completed the study – 6 placebo, 6 treatment) at an initial dose of 0.5 mg daily titrated to 2 mg daily after 21 days.
Nabilone/Varenicline	Lack of quality RCT/large scale studies in patients with both tobacco use disorder and cannabis use disorder	Nabilone is available in the US for other indications, and Varenicline is available for tobacco use disorder
Oral THC	Study found that oral THC decreased withdrawal symptoms	Dronabinol is the synthetic version of THC
Zolpidem ER	A crossover placebo study and a counterbalanced placebo study found this medication was not helpful for cannabis withdrawal overall compared to placebo	May help with sleep related to cannabis withdrawal. Side effect risk may outweigh benefit
Topiramate, Lithium, Divalproex, Escitalopram, Bupropion SR, Guanfacine	RCTs did not find benefit for cannabis withdrawal	Do not recommend use for cannabis withdrawal

**Conclusion:** The authors concluded that research regarding cannabis withdrawal is still scarce with few placebo controlled studies. Further, many of the studies utilized cannabis withdrawal as a secondary outcome and were small scale studies with high dropout rates. The authors also state "no medications have been shown to be effective in MAW [(medically assisted withdrawal)] in randomized controlled trials. In clinical practice, short-term symptomatic medications have been used for (a) non-specific general cannabis withdrawal syndrome feature and (b) for specific withdrawal symptoms... to improve patient comfort and retention during withdrawal."<sup>1</sup>

**CLINICAL PEARL:** We have little evidence to guide clinical decision-making surrounding pharmacologic management of cannabis withdrawal. Could consider utilizing synthetic THC, dronabinol, after weighing individual patient risk versus benefit.

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[Drug Alcohol Depend. 2011 Jul 1;116\(1-3\):142-50.<sup>7</sup>](#)

## Dronabinol for the Treatment of Cannabis Dependence: A Randomized, Double-Blind, Placebo-Controlled Trial

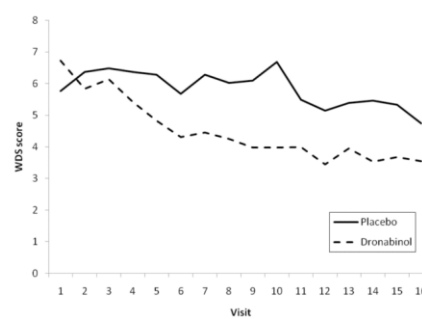
**Objective:** To evaluate dronabinol for the treatment of cannabis dependence defined as self-reporting cannabis use “at least 5 days a week during the prior 28 days to study entry and had a marijuana-positive urine drug screen”.<sup>6</sup>

**Methods:** Participants included were 18-60 years old. The study was “a single-site, randomized, double-blind, parallel group, 12-week clinical trial.”<sup>6</sup> The study continued for twelve weeks with two study visits per week.

- **Week 1:** Placebo lead-in/randomization of participants into dronabinol or placebo group
- **Week 2:** Medication titration (dronabinol group started at 10 mg/day and titrated to 20 mg twice a day or the maximum tolerated dose if less than 40 mg/day)
- **Week 3 to 8:** Medication maintenance
- **Week 9 to 10:** Medication taper of dronabinol group
- **Week 11 to 12:** Placebo lead-out, both placebo and dronabinol group received placebo

Participants were also taught coping skills and had psychosocial support (via therapists) throughout the study.

### Results:



**Figure 3.** Modeled withdrawal discomfort scores (WDS) between the treatment groups over time display a significant two-way interaction between time and treatment ( $P=.02$ ). Results shown are based on an analysis using a mixed effect model.

- Withdrawal discomfort scores were lower in participants who received dronabinol compared to placebo
- However, 17.7% of patients in the dronabinol group compared to the 15.6% of patients in the placebo group were able to remain abstinent in cannabis use over week 7 and 8 of the study, which was not statistically significant compared to placebo.

**Conclusion:** Dronabinol shows promise for cannabis dependence and withdrawal but requires more research.

### Bottom Line:

- More studies are needed in cannabis withdrawal and the clinical management of cannabis withdrawal as little evidence exists
- The studies that are available are typically small-scale studies and may have large drop-out rates
- Dronabinol may be a promising option, however there is question to clinical significance of the difference between the withdrawal discomfort scores between the groups
- Dronabinol can also have side effects: confusion, sedation, GI upset and may weigh risk versus benefit of use considering patient’s current clinical scenario
- Dronabinol, gabapentin, and quetiapine are available in the US and may potentially be helpful in management of cannabis withdrawal (weak evidence)

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