

What Is the Role of Medical Cannabis in Substance Use Disorders?

A Q&A With Philippe Lucas, PhD(c)

To better understand the potential role of medical cannabis as a treatment for substance use disorders, Jahan Marcu, PhD, Editor in Chief, *American Journal of Endocannabinoid Medicine*, sat down with prolific researcher Philippe Lucas, PhD(c), Vice President, Global Patient Research and Access, Tilray, Nanaimo, BC, Graduate Researcher, Canadian Institute for Substance Use Research, and Doctoral Candidate, Social Dimensions of Health, University of Victoria, BC. The duo spoke about emerging research and the impact of cannabis substitutions from a public health perspective.

Dr. Marcu: Does current evidence support the efficacy of cannabis in treating substance use disorders?

Dr. Lucas: Cannabis has been shown to be as effective as opioids in the treatment of chronic pain in some patients, and patients on medical cannabis self-report ad hoc reductions in opioid use.¹⁻³ In addition, a growing number of medical cannabis users, and also in some cases recreational users, report that cannabis and cannabinoids seem to reduce not only their use of opioids but also the cravings and other symptoms associated with opioid withdrawal.⁴⁻⁷ Furthermore, data from a randomized controlled trial demonstrated positive effects of cannabidiol (CBD) in the treatment of tobacco dependence, and research suggests that CBD may aid in the treatment of stimulant use disorders.^{8,9}

More recently, findings from the 2017 Tilray Patient Survey suggested that use of medical cannabis leads to reduced use of opioids

and other prescription drugs as well as alcohol, tobacco, and illicit substances.¹⁰ In this study, a high percentage of study participants (N=2032) who were registered in Canada's federal medical cannabis program reported substituting medical cannabis for prescription drugs (69%), alcohol (45%), tobacco (31%), and illicit substances (26%).

The most commonly substituted prescription drugs were opioids (35%) and antidepressants medications (22%; Table).¹⁰ Of the 610 patients who reported substituting cannabis for opioids, 59% completely stopped using opioids and an additional 18% reduced their use by 75%.

Dr. Marcu: If we extrapolate from this recent study of more than 2000 individuals, what seems to be the potential impact cannabis may have on the opioid epidemic from a public health perspective?

Dr. Lucas: From an objective perspective, when we look at the harms to society of opioids, alcohol, tobacco, and a number of illicit substances, cannabis ends up potentially being the least harmful agent as it leads to the fewest health care-related costs and impact on society. The relative risk for addiction to cannabis is mild compared with that of opioids. Additionally, there is no risk for fatal overdose associated with cannabis and cannabinoid use. Thus, in terms of harm reduction, shifting away from the use of potentially more dangerous or highly addictive substances and toward a more benign substance like cannabis offers a net public health benefit.

For 70 years, policymakers, regulators, and governments have suggested that cannabis may be a gateway drug—meaning that people who start using cannabis progress to more dangerous drugs of abuse. Over the past 25 years, the gateway theory has been disproven by academic research.¹¹⁻¹³ Additionally, for at least a percentage of the population, research suggests that cannabis is an effective exit drug for substances of abuse.¹⁴⁻¹⁷

In addition to opioids, the United States and Canada have a rather invisible yet deleterious benzodiazepine crisis. Benzodiazepines are among the most overprescribed medications, are linked to an incredibly high risk for dependency, are dangerous when combined with alcohol, and may lead to long-term side effects such as memory loss.¹⁸ Thus, cannabis and any other agents that can help patients manage anxiety or sleeplessness with a lower risk for dependence and a lower side-effect profile than what is found with benzodiazepines will lead to public health benefits.



Philippe Lucas, PhD(c)

Table. Breakdown of Drugs Substituted With Cannabis¹⁰

Prescription drugs*	n (%)
1. Opiates/Opioids	610 (35.3)
2. Antidepressant	371 (21.5)
3. Non-opioid pain medications	189 (10.9)
4. Antiseizure medications	149 (8.6)
5. Muscle relaxant/Sleep aids	140 (8.1)
6. Benzodiazepines	75 (4.3)
7. Stimulants	59 (3.4)
8. Antiemetics	24 (1.4)
9. Antipsychotics	18 (1)
Illicit drugs†	
1. Cocaine/Crack	89 (17.4)
2. Psychedelics	60 (11.7)
3. Nonprescription opioids	29 (5.7)
4. Stimulants	14 (2.7)
5. Depressants	8 (1.6)

*Of 1730 specific prescription drugs substituted by cannabis.

†Of 511 illicit drugs substituted by cannabis.

Adapted from Lucas P, et al. *Harm Reduct J*. 2019;16(1):9.

► continued on page 26

Dr. Lucas Q&A

continued from page 25

Dr. Marcu: Do you have any updates you can share on clinical research studies that are in the pipeline regarding cannabis as a treatment for alcohol or substance use disorders?

Dr. Lucas: Researchers at the British Columbia Centre on Substance Use are currently planning randomized controlled trials to evaluate cannabis as a substitute for opioids in patients with opioid use disorder.¹⁹

Additionally, Tilray is currently engaged in 2 randomized, double-blind clinical trials of CBD as a treatment for alcohol use disorder (AUD) at New York University. The first is a proof-of-concept study (N=40) designed to assess feasibility and contrast effects of extended (8 weeks) treatment with oral CBD to those of placebo in 40 patients with AUD. The second is a 6-week study of oral CBD use compared with placebo in 48 healthy adults with moderate or severe AUD and comorbid post-traumatic stress disorder.^{20,21}

Tilray has become an international leader in gathering real-world evidence regarding cannabis use via large-scale observational studies, with much of this research suggesting that medical cannabis use can lead to reduction or cessation of prescription drug use, alcohol, tobacco, and illicit substance use.^{10,22}

Dr. Marcu: Some research has linked cannabis use to increased use of alcohol or tobacco, but this seems to be linked to products that are not standardized.²³⁻²⁵

What role does product consistency play in the efficacy and safety of cannabis substitutions found in clinical trials of medical cannabis?

Dr. Lucas: Consistency of product supply is essential when using medical cannabis. If a patient finds a cannabis product that is effective for their symptoms, there is no guarantee of consistency when purchasing products from illicit or unregulated markets. This can lead to widely varying effects of treatment. In fact, a tremendous amount of research suggests that the highly unregulated CBD supply in the United States is leading to inaccurate product labeling regarding CBD and delta-9-tetrahydrocannabinol content.^{26,27} Additionally, products claiming to be purified may contain heavy metals, polycyclic aromatic hydrocarbons, pesticides, or other contaminants. Thus, having a safe and dependable cannabis supply is important, particularly for medicinal cannabis use.

Longitudinal data from the Tilray Observational Patient Study (TOPS; pre-publication results), which tracked the effects of a legally regulated cannabis supply on quality of life and prescription drug use, also found a significant reduction in opioid use over a 6-month period in both cannabis-naïve and non-naïve patients (see TOPS, page 10). Cannabis non-naïve was defined using cannabis 5 or more times in the past year, whereas cannabis-naïve was defined using cannabis less than 5 times in the same time frame.

Thus, non-naïve cannabis users, who might have used cannabis on a regular basis at study entry, experienced the same reduction in opioid use at 6 months as cannabis-naïve patients. This suggests that it is not just access to cannabis that is having this impact, but rather access to a standardized supply that is consistent from one batch or product to the next.

“The findings suggest that patients who are deliberately using cannabis to taper off tobacco, alcohol, or opioids, have greater success in reducing use of these agents. Thus, intentionality seems to be directly related to cannabis substitution.”

—Philippe Lucas, PhD(c)

Dr. Marcu: What role can intentionality play in the efficacy of cannabis substitutions? And how does the support of a patient's health care practitioner factor into the potential substitution effect?

Dr. Lucas: The question of intentionality in regard to cannabis substitutions is an area of interest for me. A January 2019 survey (prepublished data) called the Canadian Cannabis Patient Survey (CCPS2019) conducted by Tilray and developed in cooperation with other international cannabis researchers interested in substitution effect, incorporated the following questions regarding intentionality in a submodule called the Comprehensive Cannabis Substitution Questionnaire (CCSQ):

- If you saw a change in your substance use, were you pleasantly surprised?
- Did you specifically use cannabis to reduce your use of opioids, tobacco, or alcohol?
- Did you work with your physician on using cannabis to reduce your substance use?
- Did your physician design a tapering program for you?

Not surprisingly, we found a very low percentage of patients who were working deliberately with their physicians on substitution programs. However, a high percentage of patients (~50%) initiated medical cannabis with the intention of reducing use of other substances.

Importantly, the greater the patient intentionality, the greater the rates of substitution effect. Maybe it is no surprise, but the findings suggest that patients who are deliberately using cannabis to taper off tobacco, alcohol, or opioids, have greater success in reducing use of these agents. Thus, intentionality seems to be directly related to cannabis substitution.

Although the intentionality rate was relatively high in this group, a gap in support and awareness of substitution from the health care practitioner perspective also was observed. The findings are encouraging in that they suggest that if physicians developed a more deliberate, public health-centered strategy of reducing use of opioids or other addictive substances through deliberate cannabis substitution, a greater level of substitution may occur.

Dr. Marcu: In your study, antidepressants medications were the second most commonly substituted prescription medications. Can you comment on the significance of those findings?

Dr. Lucas: We have different concerns regarding use of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). These agents do not pose

a risk for fatal overdose and are not dependence-forming medications. However, antidepressants are not particularly effective for a large percentage of the population, with mostly modest effect sizes found in a recent meta-analysis of placebo-controlled trials of first- and second-generation antidepressants.²⁸ Additionally, when used in the management of chronic neuropathic pain, the number needed to treat for SSRIs is 6.8 compared with 3.4 for cannabinoids.²⁹

Thus, we need different solutions when it comes to treating patients with depression and other mental health conditions such as trauma, anxiety, and stress. I believe that cannabis and cannabinoids can play a role in treating these conditions.

Dr. Marcu: Is there anything else you would like to tell our readers about the emerging science on cannabis substitutions?

Dr. Lucas: It has become apparent that along with the legalization and regulation of medical and recreational cannabis use has come a very welcomed renaissance of cannabis research. I'm optimistic that as more funding becomes available to examine the therapeutic potential of cannabinoids, entirely new modalities will develop in regards to cancer care, and the treatment of Alzheimer's disease/dementia, arthritis, anxiety and many other serious conditions.

I'm honored to be working with Tilray and international academic partners to spearhead many of these cutting-edge cannabis studies, while also improving access to pharmaceutical-grade cannabis products to critically and chronically ill patients around the globe.

References

- Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. *Cannabis Cannabinoid Res.* 2017;2(1):160-166.
- Russo EB, Hohmann AG. Role of cannabinoids in pain management. In: Deer T, Gordin V, eds. *Comprehensive treatment of chronic pain by medical, interventional and behavioral approaches.* New York: Springer; 2013:181-197.
- Ware MA, Wang T, Shapiro S, Collet JP; COMPASS study team. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *J Pain.* 2015;16(12):1233-1242.
- Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *J Pain.* 2016;17(6):739-744.
- Scavone JL, Sterling RC, Weinstein SP, Van Bockstaele EJ. Impact of cannabis use during stabilization on methadone maintenance treatment. *Am J Addict.* 2013;22(4):344-351.
- Raby WN, Carpenter KM, Rothenberg J, et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. *Am J Addict.* 2009;18(4):301-308.
- Socias ME, Wood E, Lake S, et al. High-intensity cannabis use is associated with retention in opioid agonist treatment: a longitudinal analysis. *Addiction.* 2018;113(12):2250-2258.
- Morgan CJ, Das RK, Joye A, Curran HV, Kamboj SK. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. *Addict Behav.* 2013;38(9):2433-2436.
- Calpe-López C, García-Pardo MP, Aguilar MA. Cannabidiol treatment might promote resilience to cocaine and methamphetamine use disorders: a review of possible mechanisms. *Molecules.* 2019;24(14). pii: E2583.
- Lucas P, Baron EP, Jikomes N. Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduct J.* 2019;16(1):9.
- Degenhardt L, Dierker L, Chiu WT, et al. Evaluating the drug use "gateway" theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. *Drug Alcohol Depend.* 2010; 108(1-2):84-97.
- National Institutes of Health. Is marijuana a gateway drug? Accessed November 27, 2019. <https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-gateway-drug>
- Tarter RE, Vanyukov M, Kirisci L, Reynolds M, Clark DB. Predictors of marijuana use in adolescents before and after licit drug use: examination of the gateway hypothesis. *Am J Psychiatry.* 2006;163(12):2134-2140.
- Lucas P. Rationale for cannabis-based interventions in the opioid overdose crisis. *Harm Reduct J.* 2017;14(1):58.
- Reddon H, DeBeck K, Socias ME, et al. Cannabis use is associated with lower rates of initiation of injection drug use among street-involved youth: A longitudinal analysis. *Drug Alcohol Rev.* 2018;37(3):421-428.
- Socias ME, Wood E, Lake S, et al. High-intensity cannabis use is associated with retention in opioid agonist treatment: a longitudinal analysis. *Addiction.* 2018;113(12):2250-2258.
- Wood S. Evidence for using cannabis and cannabinoids to manage pain. *Nurs Times.* 2004;100(49):38-40.
- Stewart SA. The effects of benzodiazepines on cognition. *J Clin Psychiatry.* 2005;66(suppl 2):9-13.
- British Columbia Centre on Substance Use. News release: Cannabis use may reduce likelihood of illicit opioid use for pain management, new research finds. Accessed November 27, 2019. <https://www.bccsu.ca/blog/news-release/cannabis-use-may-reduce-likelihood-of-illicit-opioid-use-for-painmanagement-new-research-finds/>
- ClinicalTrials.gov. Effects of cannabidiol in alcohol use disorder. Accessed December 17, 2019. <https://clinicaltrials.gov/ct2/show/NCT03252756?term=new+york+university&cond=cbd&entry=US&state=US%3ANY&city=New+York&draw=2&rank=3>
- ClinicalTrials.gov. Cannabidiol as a treatment for AUD comorbid with PTSD. Accessed December 17, 2019. <https://clinicaltrials.gov/ct2/show/NCT03248167?term=Cannabis&cond=alcohol+use+disorder&draw=2>
- Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *J Headache Pain.* 2018;19(1):37.
- Dunn HK, Litt MD. Decreased drinking in adults with co-occurring cannabis and alcohol use disorders in a treatment trial for marijuana dependence: evidence of a secondary benefit? *Addict Behav.* 2019;99:106051.
- Weinberger AH, Delnevo CD, Wyka K, et al. Cannabis use is associated with increased risk of cigarette smoking initiation, persistence, and relapse among adults in the US. *Nicotine Tob Res.* 2019 May 21. pii: ntr085. doi: 10.1093/ntr/ntz085. [Epub ahead of print]
- Vogel EA, Rubinstein ML, Prochaska JJ, Ramo DE. Associations between marijuana use and tobacco cessation outcomes in young adults. *J Subst Abuse Treat.* 2018;94:69-73.
- Food and Drug Administration. Warning Letters and Test Results for Cannabidiol-Related Product. Accessed November 26, 2019. <https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products>
- Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. *JAMA.* 2017;318(17):1708-1709.
- Cipriani A, Furukawa TA2, Salanti G. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet.* 2018;391(10128):1357-1366.
- Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag.* 2014;19(6):328-335

Dr. Lucas is Vice President, Global Patient Research & Access for Tilray, the sponsor of the 2017 Tilray Patient Survey, the Canadian Cannabis Patient Survey 2019, Tilray Observational Patient Study (TOPS), and some of the clinical trials mentioned in the article.