



UNIVERSITY  
OF WOLLONGONG  
AUSTRALIA

University of Wollongong  
Research Online

---

Faculty of Social Sciences - Papers

Faculty of Social Sciences

---

2018

# Clinical issues in cannabis use

Yvonne Bonomo

*St Vincent's Hospital Melbourne*

Jose Souza

*Universidade de Sao Paulo*

Aidan Jackson

*St Vincent's Hospital*

Jose Crippa

*University of Sao Paulo*

Nadia Solowij

*University of Wollongong, [nadia@uow.edu.au](mailto:nadia@uow.edu.au)*

---

## Publication Details

Bonomo, Y., Souza, J., Jackson, A., Crippa, J. & Solowij, N. (2018). Clinical issues in cannabis use. *British Journal of Clinical Pharmacology*, Online First 1-4.

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library:  
[research-pubs@uow.edu.au](mailto:research-pubs@uow.edu.au)

---

# Clinical issues in cannabis use

## **Abstract**

2018 The British Pharmacological Society Cannabis is the most commonly used illicit substance worldwide and the prevalence of users continues to increase. Over the last 2 decades, the world has seen significant changes regarding cannabis for recreational use as well as application in its use as a therapeutic medicine. This is likely to have influenced the decreasing perception of risks associated with the use of cannabis. Cannabis, however, is not benign and, depending on the pattern of its use, can incur a range of harmful effects, which have implications when prescribing medicinal cannabinoids for individuals. Based on research evidence from recreational use of cannabis as well as the emerging data from trials of medicinal cannabis, we propose some clinical domains that will need specific considerations when prescribing medicinal cannabis.

## **Disciplines**

Education | Social and Behavioral Sciences

## **Publication Details**

Bonomo, Y., Souza, J., Jackson, A., Crippa, J. & Solowij, N. (2018). Clinical issues in cannabis use. *British Journal of Clinical Pharmacology*, Online First 1-4.

# REVIEW-THEMED ISSUE

## Clinical issues in cannabis use

**Correspondence** Yvonne Bonomo, Department of Addiction Medicine, St Vincent's Hospital, Melbourne, Australia. Tel.: +61 03 9231 2627; Fax: +61 03 9231 2642; E-mail: yvonne.bonomo@svha.org.au

**Received** 8 March 2018; **Revised** 18 June 2018; **Accepted** 19 June 2018

Yvonne Bonomo<sup>1,2,3,4</sup> , José Diogo S. Souza<sup>5</sup>, Aidan Jackson<sup>1</sup>, José Alexandre S. Crippa<sup>5</sup> and Nadia Solowij<sup>4,6</sup>

<sup>1</sup>Department of Addiction Medicine, St Vincent's Hospital, Melbourne, Australia, <sup>2</sup>Women's Alcohol and Drug Service, Royal Women's Hospital, Melbourne, Australia, <sup>3</sup>Department of Medicine, University of Melbourne, Melbourne, Australia, <sup>4</sup>Australian Centre for Cannabinoid Clinical and Research Excellence, New Lambton Heights, Australia, <sup>5</sup>Department of Neuroscience and Behavior, Ribeirão Preto Medical School, Ribeirão Preto (SP) Brazil and National Institute of Science and Technology–Translational Medicine (INCT-TM), Ribeirão Preto, Brazil, and <sup>6</sup>School of Psychology, University of Wollongong and Illawarra Health and Medical Research Institute, Wollongong, Australia

**Keywords** addiction, cannabinoids, evidence-based medicine, prescribing

Cannabis is the most commonly used illicit substance worldwide and the prevalence of users continues to increase. Over the last 2 decades, the world has seen significant changes regarding cannabis for recreational use as well as application in its use as a therapeutic medicine. This is likely to have influenced the decreasing perception of risks associated with the use of cannabis. Cannabis, however, is not benign and, depending on the pattern of its use, can incur a range of harmful effects, which have implications when prescribing medicinal cannabinoids for individuals. Based on research evidence from recreational use of cannabis as well as the emerging data from trials of medicinal cannabis, we propose some clinical domains that will need specific considerations when prescribing medicinal cannabis.

### Introduction

Cannabis is the most commonly used illicit substance worldwide [1] and the prevalence of users continues to increase. Over the last 2 decades, there have been significant changes around the world regarding cannabis, including decriminalization, and in some states or countries, legalization for recreational use as well as access to cannabinoids for use as a therapeutic medicine. Some, albeit not all, countries where changes in relation to cannabis have occurred include Canada, Australia, Israel, Uruguay, the USA, and some European and Scandinavian countries. This is likely to have influenced the decreasing perception of risks associated with the use of cannabis. Cannabis, however, is not benign and depending on the pattern of its use, can incur a range of harmful effects, which have implications when prescribing medicinal cannabinoids for individuals.

Therapeutic indications for cannabis are assumed to target the endocannabinoid system, which has receptors (CB1 and CB2) involved in cognition, memory, analgesia, psychomotricity, appetite and immune function. There are, however, few data specifically on the efficacy of medicinal cannabinoids for the various indications suggested to date.

There are even fewer data for a variety of specific populations such as pregnancy, young people, elderly individuals with complex comorbidities and those with mental health issues. Substantial reliance on research evidence from recreational use of cannabis is therefore required until robust data specifically for medicinal cannabinoids become available.

A broad range of therapeutic effects of cannabinoids has been suggested [2] and is currently the focus of much research. Delta-9-tetrahydrocannabinol (THC) has been proposed to be of benefit for chronic pain, nausea and vomiting induced by chemotherapy, and in the reduction of spasms in multiple sclerosis [2]. Cannabidiol (CBD) has antipsychotic, anxiolytic and anticonvulsant properties and may reduce Parkinsonian symptoms [2]. As the evidence base for clinical indications for medicinal cannabinoids becomes clearer, certain populations will require further special consideration:

### Young people prescribed medicinal cannabinoids

Cannabis is the most common illicit substance used by youth in the western world. Evidence from this nonmedical use

indicates that frequent use of cannabis during adolescence is associated with a range of adverse psychosocial outcomes in young adulthood, including other substance use and poorer educational attainment and mental health [3]. Alterations to the structure and function of the brain associated with exposure to cannabis, particularly of high THC content, is concerning for the developing brain [4–6]. Long-term medicinal cannabinoids may be contraindicated in this population unless the condition is life limiting or severely debilitating. There is some evidence of benefit in children and adolescents for chemotherapy-induced nausea and vomiting and potentially for epilepsy, but adverse effects are under-investigated at present [7].

## Elderly individuals

Elderly individuals may also be sensitive to the cognitive effects of cannabis. There is growing concern that cannabis use may be associated with dementia. Similarly, the cardiometabolic profile of medicinal cannabinoids needs clarification, as this is especially important in the context of complex comorbidities in elderly individuals who often have a combination of cardiovascular disease, diabetes, liver or renal impairment [1, 2].

## Pregnancy

Placental transfer of cannabis to the fetus is known to occur, although the exposure to cannabinoids is in smaller doses compared to that of the mother. There are few data, however, to indicate what effect cannabis specifically has on fetal development, because of substantial confounding by tobacco and other significant comorbid factors such as other substance use, mental health disorders, physical health conditions and psychosocial factors. Notwithstanding, definitive evidence of premature birth, growth restriction or a neonatal withdrawal syndrome in babies or significant deficits in early childhood development has not been reported for those exposed *in utero*. With regard to breastfeeding, transfer of cannabinoids into breast milk does occur [8] and clinicians will need to advise patients of the risks of exposing a child to a lipid soluble drug known to affect brain development.

## Driving

Cannabis has been associated with road traffic accidents and fatal injuries [9]. The effects of cannabis on motor coordination, reaction time, judgement and tracking ability are well documented, but a definition of a threshold serum cannabinoid level that would be expected to impair most people's driving capacity remains elusive, complicated further by findings differing substantially between those recently exposed to cannabis compared to cannabis-habituated individuals [10]. It is therefore important for clinicians to inform patients that driving is not recommended while taking medicinal cannabinoids.

## Mental health

Nonmedical cannabis use, and in particular THC, has been associated with depression, anxiety and psychosis [2]. This has implications when cannabinoids are being considered for therapeutic purposes. CBD, by contrast, has shown promising improvements in positive, negative and cognitive symptoms of schizophrenia with fewer extrapyramidal side effects than antipsychotics currently available. CBD may therefore serve as a useful alternative or adjunct medication for psychosis and possibly a range of other mental health conditions. Such hypotheses need to be tested with rigorous clinical trials and robust evidence.

## Addiction

Estimates suggest that over 180 million people use cannabis for nonmedical, or recreational, purposes globally and that approximately 13 million people are dependent on cannabis [11]. The number of cannabis users seeking treatment for cannabis use disorder has increased over the past 2 decades in many countries such as Australia, Europe and the USA. European figures show that the number of users who started treatment for the first time due to cannabis-related problems has increased by >75% in 10 years [12]. This increase in the demand for treatment may be linked to a number of factors. The increased prevalence of cannabis use, including heavy use, in the general population, increased concentration of THC in street cannabis, and higher prevalence rates of self-medication with cannabis. Given this, and as occurs with all drugs with addiction liability, the potential for misuse (defined as use that is not as prescribed or use in individuals for whom there are contraindications to use), or diversion (defined as use by individuals for whom the prescription was not intended) of medically prescribed cannabinoids (especially THC) needs to be anticipated and managed to reduce public health harm [13]. Future prevalence of dependence or addiction in those prescribed medicinal cannabinoids is difficult to predict. The current prescription opioid crisis in the western world, however, is a salient reminder that when prescribed widely, in high-dose and long-term for chronic pain, rates of dependence in the community could be high. Whether medicinal cannabinoids have a role as substitution treatment in cannabis use disorder, analogous to opioid substitution treatment for opioid dependence, or for other substance use disorders, is unclear at present.

## Administration of medicinal cannabinoids

Data on cannabinoid components (e.g. THC:CBD ratio), dosing and frequency regimen effective for various clinical conditions are beginning to emerge. Cannabinoid effects vary between products. Side-effects such as panic attacks, short-term memory loss, tachycardia or hypertension may occur even in recreational users but may be more severe in those with complex conditions for which medicinal

cannabinoids are prescribed, as the pharmacokinetics and the pharmacodynamics are not well characterized in these populations. Physicians also must decide on optimal mode of administration; for example, smoking cannabis cannot be recommended given the harmful products of combustion [14]. The latter can be avoided through modes of administration such as vaporisation, oromucosal sprays or sublingual preparations (as in the case of nabiximols or Sativex). These preparations also enable more immediate onset of effect thus allowing titration of dose to optimal effect. Oral formulations such as capsules and oils, less amenable to titration, may also not be tolerated in the context of profound nausea and vomiting characteristic of some conditions. The use of transdermal patches may have promise in clinical contexts where slower onset but longer duration of action is required. Physicians must also monitor potential drug interactions as the evidence emerges; for example, in the trial of CBD in children with Dravet Syndrome, hepatic aminotransferase levels increased in patients on concomitant valproate [15].

## Nonpharmaceutical grade medicinal cannabinoids

In addition to the gradual emergence on the market of approved pharmaceutical grade products containing cannabinoids in specified amounts, many people continue to consume illegal cannabinoid products of varying composition. The latter can be harmful because of their unknown concentrations of cannabinoids, as well as inclusion of potentially harmful contaminants and impurities [16]. In general, more adverse effects might be expected from self-medication with high potency cannabis products, particularly if used frequently over the long-term.

## Conclusion

As greater understanding about the therapeutic potential of cannabinoids emerges, their relevance to public health is also increasing. Use of unknown concentrations of cannabinoids for therapeutic purposes can potentially be harmful. Urgent clinical issues that need to be addressed include:

- High-quality scientific evidence regarding the therapeutic effects of cannabinoids for specific conditions through rigorous clinical trials is essential to inform appropriate use of cannabis-derived substances by physicians.
- Reliable and comprehensive monitoring of cannabinoids that are being used for therapeutic purposes in different countries with oversight of the appropriate regulation agency (e.g. Food and Drug Administration, European Medicines Evaluation Agency, Anvisa, Therapeutic Goods Administration or equivalent) to ensure that the cannabinoids available to patients are of high quality and safe to use
- Prompt communication of the findings of pharmacovigilance activities to health professionals and the community as they emerge to facilitate safe and effective translation for therapeutic purposes.

In accordance with the principles of evidence-based medicine, this will promote the effective and safe use of cannabinoids.

## Competing Interests

J.A.S.C. is coinventor (Mechoulam R, JC, Guimaraes FS, AZ, JH, Breuer A) of the patent “Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023” Def. US no. Reg. 62 193 296; 29/07/2015; INPI on 19/08/2015 (BR1120150164927). The University of São Paulo has licensed the patent to *Phytecs Pharm* (USP Resolution No. 15.1.130002.1.1). The University of São Paulo has an agreement with *Prati-Donaduzzi* (Toledo, Brazil) to “develop a pharmaceutical product containing synthetic cannabidiol and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson’s disease, and anxiety disorders”. J.A.S.C. has received travel support from and is medical advisor of BSPG-Pharm. All other authors have no competing interests to disclose.

*Y.B. and N.S. are investigators within the National Health and Medical Research Council Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE). J.A.S.C. holds a Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) productivity fellowship (1A). Research was supported in part by grants from (i) Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); (ii) Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, São Paulo, Brazil (NAPNA); and (iii) National Institute for Translational Medicine (INCT-TM; CNPq, Brazil). The present study was supported by a CNPq grant (CNPq/MS/SCTIE/DECIT N°26/2014 – Pesquisas sobre Distúrbios Neuropsiquiátricos; 466805/2014–4). J.A.S.C. and N. S. hold a University Global Partnership Network (UGPN) grant – Global priorities in cannabinoid research excellence.*

## References

- 1 The Health and Social Effects of Nonmedical Cannabis Use. Geneva: World Health Organisation, 2016. Available at [http://www.who.int/substance\\_abuse/publications/msbcannabis.pdf](http://www.who.int/substance_abuse/publications/msbcannabis.pdf) (last accessed 18 June 2018).
- 2 The Health Effects of Cannabis and Cannabinoids: the current state of evidence and recommendations for research. Washington, DC: National Academies of Science, Engineering, and Medicine, 2017.
- 3 Silins E, Horwood LJ, Patton GC, Fergusson DM, Olsson CA, Hutchinson DM, *et al.* Young adult sequelae of adolescent cannabis use: an integrative analysis. *Lancet Psychiatry* 2014; 1: 286–93.
- 4 Broyd SJ, van Hell HH, Beale C, Yücel M, Solowij N. Acute and chronic effects of cannabinoids on human cognition – a systematic review. *Biol Psychiatry* 2016; 79: 557–67.
- 5 Lorenzetti V, Alonso-Lana S, Youssef GJ, Verdejo-Garcia A, Suo C, Cousijn J, *et al.* Adolescent cannabis use: what is the evidence for functional brain alteration? *Curr Pharm Des* 2016; 22: 6353–65.

- 6** Lorenzetti V, Solowij N, Yücel M. The role of cannabinoids in neuroanatomic alterations in cannabis users. *Biol Psychiatry* 2016; 79: e17–31.
- 7** Wong SS, Wilens TE. Medical cannabinoids in children and adolescents: a systematic review. *Pediatrics* 2017; 140: e20171818.
- 8** Baker T, Datta P, Rewers-Felkins K, Thompson H, Kallem RR, Hale TW. Transfer of inhaled cannabis into human breast milk. *Obstet Gynecol* 2018; 131: 783–8.
- 9** Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *Br Med J* 2012; 344: e536.
- 10** Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem* 2013; 59: 478–92.
- 11** Degenhardt L, Ferrari AJ, Calabria B, Hall WD, Norman RE, McGrath J, *et al.* The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: results from the GBD 2010 Study. *PLoS One* 2013; 8: e76635.
- 12** European Drug Report 2017: Trends and Developments. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction, 2017.
- 13** Results from the 2012 National Survey on Drug Use and Health: summary of national findings. Rockland, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration; 2013. Available at <https://www.samhsa.gov/data/sites/default/files/NSDUHresults2012/NSDUHresults2012.pdf> (last accessed 18 June 2018).
- 14** Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse health effects of marijuana use. *N Engl J Med* 2014; 370: 2219–27.
- 15** Devinsky O, Cross JH, Laux L. Trial of cannabidiol for drug-resistant seizures in the Dravet Syndrome. *N Engl J Med* 2017; 276: 2011–20.
- 16** Kuehn B. Synthetic cannabidiol poisoning. *JAMA* 2018; 319: 2264.