The World Journal of Biological Psychiatry

ISSN: 1562-2975 (Print) 1814-1412 (Online) Journal homepage: https://www.tandfonline.com/loi/iwbp20

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To cite this article: Gabriella Gobbi (2019) A role for cannabidiol in psychiatry? Keep calm and follow the drug development rules, The World Journal of Biological Psychiatry, 20:2, 98-100, DOI: 10.1080/15622975.2019.1584680

To link to this article: https://doi.org/10.1080/15622975.2019.1584680

Published online: 11 Apr 2019.

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
2019, VOL. 20, NO. 2, 98–100
https://doi.org/10.1080/15622975.2019.1584680

COMMENTARY

A role for cannabidiol in psychiatry? Keep calm and follow the drug development rules

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Along with tetrahydrocannabinol (THC), cannabidiol (CBD) is one of the main pharmacological components of *Cannabis sativa* and *indica*. Unlike THC, which binds CB1 receptors, CBD does not cause any dependence, and acts mostly via 5-HT1A and TPRV1 receptors (De Gregorio et al. 2018). Khoury et al. (2019) recently published a systematic review on the role of cannabidiol in psychiatry in the *World Journal of Biological Psychiatry*. After analysing 609 articles, they found six case reports, seven randomised clinical trials and 21 registered clinical trials, with a total of 201 subjects included. They then classified the level of evidence following criteria A (the highest) to C2 (the lowest), following the WFSBP task forces standards (Bandelow et al. 2008). Their results indicated that, while it seems clear that CBD has no efficacy in major depressive and bipolar disorders, the level of evidence for cannabis withdrawal is B, cannabis addiction is C2, and treatment of positive symptoms in schizophrenia and anxiety in social anxiety disorder is C1. The most frequently reported side effects were sedation and dizziness without any severe adverse events.

They also reported many RCT registered trials (from clinicaltrials.gov databases) whose results are still unpublished or incomplete. Altogether, the evidence regarding efficacy and safety of CBD in psychiatry is still scarce. The scarcity of conclusions about the use of CBD in psychiatry is due to the following factors:

(1) CBD studies are not supported by solid preclinical studies demonstrating the 'proof of concept' for specific therapeutic use in animal models of psychiatric diseases.
(2) Several clinical studies did not reach statistical significance due to a low power analysis.
(3) Preclinical and clinical studies used very different doses even for the same indication, spanning from 200 to 800 mg a day.
(4) The formulation of CBD administered in clinical studies was very different, spanning from powder to different galenic oil preparations.
(5) The CBD used in many studies was not pure, but a THC:CBD mixture, in which the CBD concentration often varied. While CBD must be used in high doses (200–800 mg), THC is potent at a dose of 1–20 mg, meaning that using a concentration of 1:25 (THC:CBD, where THC is 0.9 mg/mL and CBD is 23.8 mg/mL), a patient will simultaneously receive 476 mg of CBD and 18 mg of THC. This very potent dose of THC will consequently mask the intrinsic effects of CBD and instead produce the side effects of THC, including euphoria, memory impairment, tolerance, dependence and sleepiness (Huestis et al. 2001). However, recent studies suggest that CBD could protect from side effects of THC, such as paranoia (Englund et al., 2013), even if more research would be required to prove this.
(6) CBD has a very complex and still unknown pharmacodynamic profile, with a long half-life, likely active metabolites, and its T_{max} and C_{max} are highly influenced by the formulation and route of administration (Deiana et al. 2012).

At this point, one might wonder how it is possible that after so many years after the legalisation of medical marijuana, the therapeutic use of CBD or THC remains unknown. For complex historical and sociological reasons, its medical development has been prevented by two polarised positions. The first is the prohibition policies that started with the Uniform State Narcotic Drug Act in 1934 (Bridgeman and Abazia 2017), which prevented cannabis from being used for medicinal purposes. Then, at the end of the 1990s, social pressure from cannabis advocates and patients made medical cannabis accessible after court rulings such as the one in Canada in 1999 (Lucas

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2008), or through laws such as those in California, USA, in 1996 (Bridgeman and Abazia 2017), or in Italy in 2006 (Ministry of Health, Italy 2006), which bypassed clinical studies and approval by governmental regulatory agencies such as the Food and Drug Administration (FDA), Health Canada or the European Medicines Agency. Consequently, medical cannabis never underwent the drug discovery process, which includes proof of concept in preclinical studies for a specific indication, Phase I for safety in healthy volunteers, Phase II for efficacy and side effects in patients, and Phase III for efficacy and effectiveness in a larger and more diversified population. Therefore, consistent with several systematic and meta-analytic reviews, evidence-based use of CBD is still poor (Whiting et al. 2015; National Academies of Sciences, Engineering, and Medicine 2017).

One of the main reasons in public opinion for legalising medical marijuana is that cannabis is a plant. However, more than 40 of the most essential medicines currently used to treat diseases (including cancer, cardiovascular diseases, etc.) are also derived from plants. The difference between these FDA-approved plant-derived drugs (e.g., from vincristine to digitoxin, from ergotamine to theophylline) and cannabis is that the former have gone through clinical trials and been declared safe and efficacious for large populations by governmental agencies. If we want to have a rational approach to medicinal cannabis, we should go through systematic clinical studies and finally determine its efficacy in the treatment of specific diseases (i.e., depression) and its safety compared to standard treatments (e.g., antidepressants, analgesics). We need to know the recommended dosages of these plant-derived medicines, their side effects, possible drug–drug interactions, duration of treatments, and we need to know if more vulnerable populations (e.g., pregnant or breastfeeding women, the elderly) can use these drugs as well.

It is time to take a more rational, scientific approach to medicinal cannabis, that is, to start asking the right clinical questions and answering them with clinical trials, as we do for any other plant-derived medicine.

The good news is that, despite this chaotic and unfortunate CBD drug development in the past years, there is a success story: the development of a particular formulation of CBD has been approved by the FDA (U.S. FDA 2018). This CBD formulation was approved by the FDA in June 2018 for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome, two rare and particularly difficult-to-treat forms of epilepsy. This particular CBD is a purified form of CBD, extracted from *Cannabis sativa*, and has received FDA approval after extensive Phase III studies, which have been published in peer-reviewed medical journals (Devinsky et al. 2017; Devinsky, Patel, Cross, et al. 2018; Devinsky, Patel, Thiele, et al. 2018; Thiele et al. 2018). The drug can now be prescribed by doctors, and the appropriate doses to treat children with LGS or Drevet syndrome, the side/adverse effects and the use in people with liver impairment are properly reported.

On the other hand, other formulations of CBD are internationally available on the internet, but have not undergone clinical studies and quality control. A recent study has found that nearly 70% of all CBD products sold online are either over- or under-labelled, meaning that the concentration of CBD was too low or too high compared to what was reported on the label, or that these products also contain THC, which is more harmful than CBD (Bonn-Miller et al. 2017).

The example of FDA-approved CBD indicates how novel research on CBD and cannabis-derived pharmacological extracts are to be carried out. Indeed, without systematic preclinical research, followed by Phase I, II and III trials, it is simply not possible to have cannabis-based medicine.

In particular, since CBD is used by very vulnerable patients, such as individuals with chronic pain, terminal cancer, mental conditions and/or untreatable epilepsy, it is mandatory for the medical community, and society as a whole, to protect these patients. Doing so requires informing them not only about the appropriate regimen needed, but also about the possible adverse effects that CBD might have, as well as the side effects related to its interaction with other drugs.

This kind of research undoubtedly requires a better harmonisation among scientists, clinicians, regulatory agencies and stakeholders, including pharmaceutical companies, governmental research agencies and non-profit foundations. Finally, in this complex situation on cannabis drug discovery, it is important to increase government-funded research, where both scientists and patients would be involved in order to make cannabis-derived medicine more cost-efficient and economically accessible.

Making these adjustments will put medicine-based cannabis on the high road for success, far removed from the 'alchemistic' detours proposed so far. This is the way to protect public health, as proclaimed in the Helsinki declaration (World Medical Association 2001) and as expressed in the Hippocratic oath '*primum non nocere*' to which all doctors are ethically bound to adhere.

Acknowledgements

None.

Statement of interest

Dr Gobbi has received a grant from the Ministry of Education, Science and Innovation of Quebec with the participation of Aurora Cannabis Inc to study the cannabidiol in neuropathic pain; a grant from Mitacs with the participation of Inolife Sciences.

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