Review

Medical cannabis in the UK: From principle to practice

Journal of Psychopharmacology
1–7

DOI: 10.1177/0269881120926677
journals.sagepub.com/home/jop

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Abstract

Background: In the UK, medical cannabis was approved in November 2018, leading many patients to believe that the medicine would now be available on the NHS. Yet, to date, there have been only 12 NHS prescriptions and less than 60 prescriptions in total. In marked contrast, a recent patient survey by the Centre for Medical Cannabis (Couch, 2020) found 1.4 m people are using illicit cannabis for medical problems.

Aims: Such a mismatch between demand and supply is rare in medicine. This article outlines some of the current controversies about medical cannabis that underpin this disparity, beginning by contrasting current medical evidence from research studies with patient-reported outcomes.

Outcomes: Although definite scientific evidence is scarce for most conditions, there is significant patient demand for access to medical cannabis. This disparity poses a challenge for prescribers, and there are many concerns of physicians when deciding if, and how, to prescribe medical cannabis which still need to be addressed. Potential solutions are outlined as to how the medical profession and regulators could respond to the strong demand from patients and families for access to medical cannabis to treat chronic illnesses when there is often a limited scientific evidence base on whether and how to use it in many of these conditions.

Conclusions: There is a need to maximise both clinical research and patient benefit, in a safe, cautious and ethical manner, so that those patients for whom cannabis is shown to be effective can access it. We hope our discussion and outlines for future progress offer a contribution to this process.

Keywords

Cannabis, medical cannabis, d9 Tetrahydrocannabinol (d9THC), cannabidiol, patient access

Introduction

Cannabis is arguably the world's oldest medicine. After a period of being banned for political reasons in the second half of the 20th century, cannabis has now been restored as a medicine in an ever-increasing number of countries. Interest in the therapeutic benefits of medical cannabis has grown rapidly in the past 20 years. This often has been the result of patient interest (House of Commons Health and Social Care Committee (HSCC), 2019) in using cannabis and cannabinoids to treat a variety of conditions, from chronic and cancer pain, through depression, anxiety disorders and sleep disturbances to neurological disorders (amongst others) (Couch, 2020). The scientific evidence in this field is still developing and has been summarised in various meta-analyses (e.g. National Academies of Science, Engineering, and Medicine (NASEM), 2017; Whiting et al., 2015). For some indications this evidence is substantial, for others it is only moderate or limited. Yet many countries (and the majority of US states) now allow or are considering allowing the medical use of cannabis in some form.

In the UK, cannabis was made a medicine on 1 November 2018, largely as a result of patient pressure, including high-profile media campaigns for children whose intractable epilepsy had been remarkably improved (such as Alfie Dingley) (HSCC, 2019). Nevertheless, by March 2020, the medicine is still unavailable to most patients.

The current National Institute for Heath and Care Excellence (NICE) guidelines recommend the prescription of two cannabis-based medicinal products (CBMPs) for the treatment of four main conditions: Sativex for spasticity of adults with multiple sclerosis (MS), Nabilone for chemotherapy-induced nausea and

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vomiting, and Epidyolex for severe treatment-resistant epilepsy, i.e. Lennox-Gastaut syndrome and Dravet syndrome (NICE, 2019).

Whilst welcomed by patients as a move in the right direction, these guidelines have been criticised by patients, campaigners and some doctors as too limiting (Busby, 2019). Many question the narrow choice of recommended products and the lack of recommendation of medical cannabis for the treatment of chronic pain (*The Pharmaceutical Journal*, 2019). Despite the lack of scientific evidence in many cases, there is significant patient demand for access to medical cannabis.

Definitions

There is often confusion about what exactly is cannabis, cannabinoid or tetrahydrocannabinol (THC), as well as the different formulations available. It is important to distinguish between cannabidiol (CBD; not a controlled drug in the UK) and CBD plus THC to ensure a clear understanding of the distinctions in active ingredients and in formulations as these relate to specific applications. Freeman et al. (2019) provide a useful overview, highlighting that cannabis is not one medicine but rather a whole family of medicines. We focus on CBMPs as defined by *The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations* (2018):

> [A] cannabis-based product for medicinal use in humans means a preparation or other product. . . which a) is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers); (b) is produced for medicinal use in humans; and (c) is (i) a medicinal product, or (ii) a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product.

Current evidence of medical value

The previous status of cannabis in Schedule 1 before 2018 severely restricted scientific research in the UK, resulting in a lack of essential information on the health implications of medical cannabis. Despite extensive changes in global policy on medical cannabis, there is still little definite evidence regarding its short- and long-term health effects (both harms and benefits) contributing to the discord between scientific and patient-reported evidence.

Research studies

The 2017 review by NASEM (2017) provides a wide range of research conclusions on the health effects of cannabis and cannabinoids which are presented in Box 1 with recent additions by Drug Science (2019). The scientific evidence (or lack thereof) is controversial, emphasising the need for further research in most areas.

Box 1: Current evidence of the medical value

This panel summarises findings by NASEM (2017) and is kept within the style of their seminal review.

There is substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids, THC specifically)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids, equal amounts of THC and CBD specifically)
- Epilepsy (cannabinoids, CBD specifically) (Drug Science, 2019)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnoea syndrome, fibromyalgia, chronic pain and multiple sclerosis (cannabinoids, primarily THC)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids)
- Improving symptoms of Tourette syndrome (THC capsules)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) and schizophrenia (cannabidiol add-on to current medications) and attention deficit hyperactivity disorder (ADHD) (nabiximols; one small-scale trial)
- Reducing cravings and anxiety for people with opioid use disorder (cannabidiol)
- Better outcomes (i.e. mortality, disability) after a traumatic brain injury or intracranial haemorrhage

Focusing on the effectiveness of cannabinoids in the treatment of psychiatric conditions, including depression, ADHD, Tourette's syndrome, post-traumatic stress disorder (PTSD), psychosis and anxiety, a recent meta-analysis found the evidence to be limited and of a low standard, concluding that a

prescription for mental health treatments cannot be justified (Black et al., 2019). However, in that study the main focus was on pharmaceutical cannabinoids, rather than plant-derived medical cannabis for which the therapeutic potential may differ widely, and is broadly used in the USA, Canada and Germany.

Patient-reported evidence

Notwithstanding the lack of evidence in many cases, people are using medical cannabis for a broad variety of conditions, including many mental health indications. A survey by the United Patients Alliance (UPA; 2018), a UK patient-led medical cannabis support group, found that indications range from (in order of self-reported use) pain, depression, anxiety, insomnia, arthritis, fibromyalgia, muscle spasms, irritable bowel syndrome and migraines to headaches and more.

These findings were largely replicated with a representative sample, drawing attention to patient-reported outcomes (PROs). PROs emphasise the patient's wellbeing and have been shown to be more sensitive to the effects of medical cannabis than traditional symptom-based measures. For example, a large recent naturalistic study on pain syndromes using PROs found adding a CBMP to ongoing medication significantly improved outcomes in patients with neuropathic pain (Ueberall et al., 2019). Further real-world benefits from CBMPs using patient reports have been reported for Parkinson's disease (Balash et al., 2017), autism (Bar-Lev Schleider et al., 2019), pain, depression, and anxiety symptoms (Gulbransen et al., 2020). Many patients experience therapeutic satisfaction when using medical cannabis and report improvements in or relief of a range of symptoms (Gulbransen et al., 2020; Stith et al., 2018; Sexton et al., 2016). Others report using cannabis as an alternative to pharmaceutical prescriptions (Sith et al., 2018) and this can lead to reduced use of opioids for example (Ueberall et al., 2019). Many of these also report that the medical cannabis improves their quality of life (Bar-Leve Schleider et al., 2019; Gulbransen et al., 2020; Sith et al., 2018).

Current barriers to prescribing

In the UK, despite the change in legislation there is ongoing controversy surrounding prescriptions. Medical cannabis is atypical in that its medical use preceded the demonstration of its efficacy in clinical trials, generally required for the marketing of modern pharmaceuticals D'Souza, 2019). Whilst on the one hand, there is strong patient demand for access to medical cannabis to treat chronic illnesses for which there are very few effective treatment alternatives, on the other hand there is only a limited placebo-controlled evidence base on whether and how to use cannabis for many of these conditions. Potential prescribers face a wide range of challenges, particularly as in the UK medical cannabis is regulated as an unlicensed medicine.

Lack of education

Doctors lack the knowledge of cannabis medicines to have the confidence to prescribe, especially off-license: they have not been trained in prescribing them and may not know the dosage etc. This barrier can be overcome by developing an educational programme, e.g. by Health Education England. A priority should be to provide a range of good quality teaching programmes. The Academy of Medical Cannabis (http://taomc.org) provides a free 12-module programme on the basics of cannabis which has now been used by about 1000 doctors. Drug Science launched a similar online resource (https://mymedic.org.uk/), arranged a series of seminars for health-care professionals (HCPs), and developed a teaching module for medical students (https://drugscience.org.uk/medical-cannabis-education-hub/). Further developments should include a diverse range of other teaching possibilities, especially accredited certificate course programmes.

Restrictive guidelines

In addition to the NICE guidelines, doctors are influenced by the guidelines produced by the Royal College of Physicians (2018) (for pain and nausea) and by the British Paediatric Neurology Association (2018) (for childhood epilepsy), which recommend the prescription of medical cannabis only as a last resort when conventional treatment has not been effective. In contrast, the Medical Cannabis Clinicians Society (MCCS) offer more balanced guidelines, proposing that for chronic pain for instance, cannabis medicine could be considered instead of opioids (MCCS, 2019). The British Pain Society (2019) recently released a revised position statement considering the potential role of medical cannabis in pain management, while at the same time continuing to highlight the need for further high quality research, clinical surveillance and patient monitoring. By reference to all these guidelines a physician can now make a more informed decision on prescription in the best interests of their patient.

Fear of adverse effects, especially psychosis and dependence

Concerns about adverse mental health effects, especially psychosis and dependence, have been expressed (Di Forti et al., 2009) but the recent data suggest that these are mainly the result of using street 'skunk' with high levels (>10%) of d9THC and negligible levels of CBD (Di Forti et al., 2019). The large-scale database by Health Canada shows very few, if any, cases of psychosis with medicinal use. Surveys of people using medical cannabis revealed some patients with schizophrenia are using it to treat their symptoms and there are several studies providing experimental support for this application (Leweke et al., 2012; McGuire et al., 2018).

Similarly, whilst the risk of dependence is around 9% for recreational users of street cannabis, it is more common with high potency THC strains with a low CBD content, large 'doses', high frequency use (heavy, daily) and starting use in adolescence (Curran et al., 2016). Risk of dependence can therefore be mitigated with these factors in mind by giving harm-reduction advice. The Canadian database reveals that only about half of patients initiated on medical cannabis continue beyond six months, suggesting dependence liability is low. Moreover, the very easy access to street cannabis further argues that medical cannabis is unlikely to be sought for recreational purposes.

Still, regulations should mitigate against adolescent uptake and against the availability of high potency THC products

lacking CBD. Additionally, in light of the recent outbreak in the USA of respiratory illness, including linked fatalities, associated with the vaping of black market (THC) cannabis oils (Centres for Disease Control and Prevention (CDC), 2019), it is vital to further communicate with the public about related risks and to more effectively regulate products and routes of administration in order to limit illicit products.

It is a serious shortcoming of current research that adverse effects of cannabis have largely been studied in relation to recreational (i.e. non-medical) use, rather than medical use. This is complicated by recent findings indicating that a large proportion of medical cannabis users also report recreational use (Han et al., 2018). Drug Science is currently reviewing existing research to discern if, how, and to what extent, adverse effects apply to prescribed medical use.

Cost

The cost of medical cannabis in the UK is currently high. Some families are forced to pay for private prescriptions, costing up to £40,000 a year, after their National Health Service (NHS) clinicians do not prescribe it (Wickware, 2019). Yet medical cannabis is potentially cheap – saving money on conventional treatments as well as on opioid prescription costs (Boehnke et al., 2016), anxiety prescriptions (Baron et al., 2018) and hospital admissions, for example, epilepsy (Bellnier et al., 2018). Medical cannabis could work out well economically, and a full health economics analysis is vital for conditions for which clinical efficacy has been shown.

Importation and supply chain issues

The high cost of private prescriptions is related to the import challenges of medical cannabis. It is difficult to get access to the right products in a timely manner. Licensing and imports generally are for one patient for one month at a time as bulk import is still limited (Barnes, 2019). However, in March 2020, these restrictions were loosened and the UK government is now allowing bulk, non-patient specific, importation which should improve delivery time to the patient and begin to bring down costs. Current UK standards of regulation as well as of practice need to be fully developed and regularly revised, as is done, for example, by the Royal College of Physicians and Surgeons in Alberta/Canada in their 'advice to the profession' (http://www.cpsa.ca/wp-content/uploads/2018/05/AP_Cannabis-for-Medical-Purposes.pdf).

Ethical issues

The discordance between patient reports and prescribers' confidence and reliance on clinical trial data supports the developing view that randomised controlled trials (RCTs) are not the only way to assess the efficacy of a spectrum of medical products that have subtly different effects and individual responses (Barnes, 2018). Taking into account other evidence, such as observational trials, 'experimental medicine' studies and audits of patients already using the medicine would help to maximise research and patient benefit. Individual cases could be taken into account to build up to a pattern of evidence (indeed, in the case of childhood epilepsy, just two of these effectively changed UK law).

The concern that by using a broader evidence base for medical cannabis would lead to a lowering of scientific standards generally is understandable but misplaced. CBMPs are not the only medicine whereby non-RCT evidence was included – there are over 50 medicines or indications that have been licensed by FDA and/or EMA between 1999–2014 without RCT data (Hatswell et al., 2016).

To include more 'qualitative' evidence is not to diminish the value of RCTs but rather to complement them and to serve as a precursor to later studies. If there is a sole focus on RCTs, it will take many years for results to be available and many disorders may never be studied – yet patients could benefit from the medicine now, making it essential to evaluate harm minimization against patient need.

Balancing patient need and potential for harm

Many patients who request cannabis have not responded to standard treatments and are desperate to find something that helps ease their symptoms. In such cases, the fact that other treatments might be statistically more effective may not be relevant as a contra-indication to use of cannabinoids (Stockings et al., 2018). Now that cannabis substances have been legalised for medical uses, it is the duty of clinicians to assess the balance of legitimate patient need against potential harms as in any other area of medicine, particularly taking into account informed choice on behalf of the patient.

The ethical importance of autonomy interests in medical decision-making means that patients' rights to information that enables them to properly weigh up potential goods and potential harms is paramount. When there is insufficient evidence and/or insufficient clinical understanding to adequately inform patients, patients are at risk of making bad decisions that can lead to harm. In the current context, most patients who use cannabis and their caregivers have decided to access cannabis without the benefit of clinical guidance or support. In so doing, patients are exercising autonomy and it would be excessively paternalistic to argue that such patients are intrinsically wrong in their actions. The desire for access to potentially beneficial treatments is certainly not wrong. Moreover, when a treatment is legally sanctioned by a national healthcare system for the application desired by the patient, then the patient has a right to access, within parameters. A healthcare system that legalises a treatment but then leaves patients to independently access and use those treatments because of a lack of evidence and clinical confidence, is arguably in danger of shirking its duty of care to vulnerable patients. At the same time, the challenges for prescribers have to be addressed as key gaps exist not only in the scientific evidence but also in the detailed information needed (but not yet available) about dosages, types, duration and formulations.

The development of the evidence base for medical cannabis needs to go hand in hand with the pursuit of clinicians' education if the risk to patients of using cannabis from illicit sources is to be minimised. As evidence is being gathered, professional organisations must do what they can to educate clinicians. Given the problematics of clinical responsibility in an area where there is significant medical uncertainty and confusion (Singh et al., 2017), the education process needs to engage explicitly with the ideal qualities of a practitioner. One such important quality is professional integrity, which may invite clinicians to acknowledge the limits of knowledge and confidence in this context, while still seeking to provide the best possible care and support for their patients.

Physicians need to comply with the standards of practice, and develop a healthy physician-patient relationship, rather than simply being 'prescribers employed by a cannabis clinic'. It is essential to develop the UK regulatory regime for medical cannabis so that it can allow for patient access while at the same time avoiding a 'free for all' scenario as in some US states (Schlag, 2020).

Recommendations for best practice

Due to the scarcity of research, few clear and widely accepted standards exist to help guide patients and clinicians to make decisions of if, when and how to use cannabis safely and effectively. It is vital to develop strategies for best practice and ensure that global legislative changes are informed by neuroscience and public health.

Monitoring of prescriptions, patient outcomes and adverse effects

It is essential to monitor patient outcomes and adverse effects, as is already being done by Health Canada. In the UK, Drug Science launched Project Twenty21 in November 2019 to create Europe's largest national medical cannabis database registry (https://drugscience.org.uk/project-twenty21/). Continued monitoring and regulation can play a major role to mitigate risks and to collect and collate experimental and trial data. Efforts to collect valid 'real world data' in responsible and ethical ways need to be further improved. A 'real world data' approach, specifically promoting a digital solution to the multiple complexities of data, evidence, uses and formulations can offer a key resource. In the longer term, anonymous electronic patient records, such as Clinical Records Interactive Search (CRIS) can establish 'real world' data in large quantities.

When new compounds with misuse potential are licensed and deployed, the risks associated with misuse need to be mitigated so that patients are protected, but also so that the compound is not overused so widely that its use attracts stigma. A variety of elements to assure the safe use of such compounds can be instituted. In the UK, the packaging of opiates is to acquire warnings similar to those on cigarettes (Gregory and Wheeler, 2019). In the USA, the use of Spravato, Janssen's intranasal esketamine for depression, is conditional on patients confirming they understand the risks, and on doctors and pharmacies undergoing training (Janssen Care Paths, 2019).

Registries, in which individual prescriptions or treatments are tracked, may offer a partial solution. At one end, the model of clozapine shows how a clear risk is mitigated by a pharmacist-operated algorithm based on a blood test result: no blood result, no dispensing. In some US and Australian jurisdictions, prescribers must check whether a patient is being prescribed an opiate elsewhere before writing the first prescription. In relation to medical cannabis, prescribers and regulators still need to develop and decide on the exact details of registry implementation.

Future progress – the next steps

Medical cannabis as a 'last resort' provision

In the UK, medical cannabis at present is offered as a 'last resort', when other licensed medicines have been shown to be unsuccessful. It would be useful to develop a hierarchy of evidence to see where cannabis medicines sit, which likely would be indication-specific. However, this is a challenging task as cannabis is not one medicine but a whole family of medicines. They would come out poorly in a double-blind trial as, for example, in chronic pain some people might respond to a high CBD product, some to a high THC product and some to a product that combines both. As such, whilst the effect of a single cannabis product might lack statistical significance in a clinical trial, an analysis of different combinations of 'cannabis' could be statistically significant (Namdar et al., 2019).

Comparing benefit-safety balances

Best-practice guidelines for prescribing medical cannabis could be informed by comparing its benefit-safety balance with those of drugs already in use. Multi-criteria decision analysis provides a well-demonstrated basis for making such comparisons based on available evidence and clinical practice (Moore et al., 2017). For example, a multi-criteria decision analysis comparison of drugs for relapsing–remitting multiple sclerosis (RRMS) revealed very different benefit-safety profiles between drugs, which would enable prescribers to accurately select the most suitable drug for their patient (Vermersch et al., 2019). Such an analysis could include options of alternative products, doses and timing in order to aid practitioners' decision-making.

Coordinating a network for clinical studies

There is a need for collaboration between different stakeholders (including patients, prescribers, clinics and scientists), and to develop an overarching mechanism to convene different parties together. A network of clinical studies could report on clinical practice and monitor outcomes (both risks and benefits), to enable innovative use of medical cannabis with care, precaution and foresight. This network group could address particular diseases or more general controversies related to medical cannabis. All these concerns are part of society's move towards increasingly personalised medicine.

Communicating with the public

The 2018 re-scheduling of medical cannabis has been rightly criticised by the public and media alike based on the misperception that these medicines would become freely available on the NHS. Public communication about medical cannabis needs to be much better. Whilst information is available on the NHS website for the public, communication efforts need to be increased. Accusing the public of not understanding is unhelpful and may lead to a lack of trust which is vital for the doctor-patient relationship. If a communication vacuum occurs, this will be filled by other interest groups, such as industry lobbying groups. Hereby, medical cannabis should not be presented as a panacea for all ailments – rather the public needs to understand that not all patients may benefit from the use of cannabis.

Conclusions

Today, medical cannabis policy and research is developing rapidly in line with shifting public attitudes. Yet the current UK procedures to access medical cannabis are not working. High hopes by patients have not been realised in practice.

The re-scheduling of cannabis from Schedule 1 to Schedule 2 should open up urgently needed research opportunities. For other drugs, research funding usually comes from the companies who will benefit financially, yet it remains to be seen if/what funding will be provided by the medical cannabis industry given the problems of patenting. Whilst awaiting RCTs, different methodologies can be applied to move the evidence base forward.

In addition to further scientific studies, the medical cannabis regulatory framework and its application in practice need to be clarified so that this framework can be responsive to patient need whilst adhering to medical practice and high ethical standards. Many questions remain unanswered: What medical cannabis products will be used exactly? How can governments permit the manufacturing and distribution of cannabis for medical purposes? Although these regulatory challenges highlight the complexity of decision-making about medical cannabis they have already been resolved in other jurisdictions, e.g. in the Netherlands.

Concerns by physicians when deciding if and how to prescribe medical cannabis need to be addressed. Because of concern about its recreational use and previous Schedule 1 status, there is still an emotional barrier to prescribing cannabis. It may take time to change doctors' perceptions and to fill the knowledge gap. Hopefully, the various efforts to educate doctors and other HCPs will go some way in this task and the access to a standardised way of data collecting as in Project Twenty21 should help assuage prescribers' anxieties. There is a need to maximise clinical research and patient benefit, in a safe, cautious and ethical manner, so that those patients for whom cannabis is shown to be effective can access it. We hope our discussion and outlines for future progress offer a contribution to this process.

Author contributions:

AKS developed the initial draft, wrote the sections on definitions, scientific evidence, future progress and conclusions and compiled and revised all authors' contributions. DJN wrote the introduction and revised the manuscript. HVC wrote the section on cannabis and mental health. IS contributed the ethical sections. RMS wrote the section on registries, MB on barriers to prescribing, LP on comparing benefit-safety balances, SB on how to aid prescribers and decision makers, RC and DB contributed further references and revised the manuscript. All authors reviewed and accepted the article before submission.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AKS is head of research at the charity Drug Science. DJN is chair of Drug Science. MB is chief medical officer of ECH and Sol Global Investments, chair of the Medical Cannabis Clinicians Society, and director of Maple Tree Consultants. None are employed positions and MB would not benefit from broader prescription of cannabis in any role. All other authors declare no competing interests.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This article was produced with support from Drug Science (DrugScience.org.uk)

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