European Journal of Integrative Medicine 28 (2019) 114–120

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Opinion paper

Medicinal Cannabis: Issues of evidence

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ARTICLE INFO

Keywords:
Cannabis
Cannabinoids
CBD
THC
Evidence-based medicine

ABSTRACT

Introduction: Medicinal cannabis has been used for over 6000 years. It may be accessed legally in many western countries, yet in Australia, access is very difficult. It is treated as a pharmaceutical and an *'unapproved therapeutic good'*, and is subsequently subject to a complex regulatory system around prescribing. There have been calls by authoritative bodies in Australia for more evidence in relation to its efficacy and safety, suggesting that this is inadequate. The adoption of the evidence-based medicine (EBM) approach as the basis of decision-making in the healthcare sector positions systematic reviews and randomised controlled trials (RCTs) at the top of the hierarchy of evidence. It is largely this form of evidence that has been used to argue for or against the efficacy and safety of cannabis and to substantiate the current regulatory system in Australia. It is therefore important to understand the EBM approach and factors that need to be considered when examining scientific research into cannabis, in order to decide whether there is sufficient evidence or not. It is argued that regulation of cannabis is inappropriate, based on a limited understanding of evidence, and continues to limit access to medicinal cannabis by patients.

Methods: This paper examines the notion of evidence in medicine, points of consideration in scrutinizing research methodology, what the actual evidence is in relation to safety and efficacy of medicinal cannabis, the implications of evidence and whether it supports the current regulatory framework around medicinal cannabis in Australia. It poses an alternative regulatory approach.

Results: A robust definition of EBM goes beyond the notion of simply scientific evidence in the form of RCTs and systematic reviews. Rigorous scrutiny of the evidence about cannabis is required, since evidence is being used to control access. Scientific evidence including reports from authoritative bodies indicates there is much evidence to support the safety and efficacy of medicinal cannabis. CBD has been found to be relatively safe, non-addictive and efficacious. Access to medicines that alleviate suffering in a timely manner is a human right and a medical responsibility. There is enough evidence to justify regulatory changes to significantly increase access to medicinal cannabis in Australia.

Conclusion: We need to bring back the human element when considering what evidence we use and how we use it in medicine. Cannabis has the potential to alleviate much suffering, and patient (human) rights must be central in public policy. There is already much scientific evidence in relation to safety and efficacy of cannabis and cannabinoids such as CBD and THC. In Australia, the current regulatory system needs to be disbanded, cannabis products treated as 'approved goods' and regulated as complementary medicines (for products containing CBD and low THC) or in the case of high THC-containing products, regulated under the SUSMP as an S4 (rather than S8) medicine.

1. Introduction

Medicinal cannabis is a plant medicine in use for over 6000 years [1]. In the US, cannabis is prohibited under the US (federal) Controlled Substances Act, though medical use is legal in over 31 states and districts in the US with some also allowing recreational or 'adult use' [2]. Israel allows access to medicinal cannabis. Canada previously allowed only medicinal use but now allows 'adult use' and Thailand and Malaysia, countries with historically tough drug laws, are considering legalising medicinal use. In some countries within Europe such as the Netherlands, 'adult use' is legal, whilst in other countries such as the UK and the Czech Republic, medicinal use when prescribed by a doctor, is

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https://doi.org/10.1016/j.eujim.2019.05.009
Received 7 January 2019; Received in revised form 8 April 2019; Accepted 21 May 2019

permitted.

In contrast, access to medicinal cannabis in Australia is very difficult, with over 100,000 Australians estimated to be procuring it through the black market [3] despite access to medicinal cannabis becoming 'legalised' in 2016. In Australia, the main (legal) medicinal cannabis products available on prescription are proprietary forms, typically oils or tinctures for oral use (though some may be vaporised) or capsules containing oil. Buds are also available on prescription, though not commonly prescribed.

There are several reasons access to medicinal cannabis is difficult in Australia, a country in which almost 70% of the population use some form of complementary medicine [4]. Its treatment as a pharmaceutical and an 'unapproved therapeutic good' makes it subject to a complex regulatory system for prescribing, it is treated as a drug of addiction and a gateway drug, and there is a lack of understanding about its medicinal properties (including by doctors, other healthcare providers, politicians and consumers). With the complex regulatory system comes an attendant and onerous amount of paperwork that reportedly is a disincentive for doctors to prescribe medicinal cannabis, as described below. And with the complex regulations, costs borne by cannabis companies are shifted to the consumer, with prices for cannabis products out of reach for most (a one-month supply can be of the order of AUD $300 or more).

In Australia, tetrahydrocannabinol (THC) is contained in Schedule 8 (S8, Controlled Medicine) and cannabidiol (CBD) is contained in Schedule 4[1] (Prescription Only Medicine) of the Australian Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). In addition, medicinal cannabis products are considered 'unapproved therapeutic goods' under the Therapeutic Goods Administration (TGA) which regulates medicines and complementary medicines. As a result, a complex regulatory system has been applied to the prescribing of, and therefore access to, medicinal cannabis. Under this system, only medical practitioners may prescribe it, and only if they gain approval via one of two access schemes managed by the Therapeutic Goods Administration (TGA). One is the 'Special Access Scheme' whereby a doctor applies to the TGA to prescribe a medicinal cannabis product for a particular patient and the other is the 'Authorised Prescriber Scheme' whereby the doctor applies via a Human Research Ethics Committee or specialist college to be approved to prescribe particular product(s) for particular medical conditions, with final approval granted by the TGA. If the doctor wishes to prescribe a medicinal cannabis product in Schedule 8 (i.e. a medicinal cannabis product containing THC or a CBD product where less than 98% of the total cannabinoids are CBD) they must also gain approval from the state/territory health department. The prescription is presented by the patient to a pharmacy which typically then contacts the medicinal cannabis company to arrange delivery of the product to the pharmacy where it is then dispensed. As a consequence of scheduling, medicinal cannabis products, even those just containing CBD (no THC) cannot be obtained (or sold) online in Australia, unlike in parts of Europe and in other countries. To complicate matters, while most states and territories allow general practitioners to prescribe it, in some states the support of a specialist is required, and in Tasmania only specialists may prescribe it. As of 31 March 2019, 57 Authorised Prescribers applications and over 5200 SAS Category B applications for unapproved medicinal cannabis products had been approved by the TGA [5]. Yet, access to medicinal cannabis was legalized in 2016. This indicates a very small percentage of the population are being prescribed medicinal cannabis legally.

In addition, Australia's current driving laws make it an offence to have any amount of THC in the body, even if medicinal cannabis containing THC has been prescribed. This is a further disincentive for patients and doctors alike to have prescribed or prescribe THC-containing products respectively. This is in contrast to Canadian laws where it is only an offence if the driver is impaired by cannabis.

Whilst Australia is not dissimilar to those states in the US and countries in Europe for which medicinal cannabis is legal in treating medicinal cannabis as a pharmaceutical, it differs in that in Australia the TGA does not specify a list of medical conditions for which medicinal cannabis has been approved for prescription. In this sense, there is more professional freedom, *in theory*, to prescribe for particular medical conditions as long as the doctor can justify why an unapproved good is more beneficial than an approved good.

In Australia there have been calls for more evidence in relation to cannabis by authoritative bodies. In a paper setting out the perspectives of the Royal Australasian College of Physicians (RACP), the authors state that: *'It is too early to form conclusions, and there are risks associated with liberalising access in the absence of standard regulatory requirements demonstrating quality, safety and efficacy'* [6]. The Royal Australian College of General Practitioners (RACGP) 2016 Position Statement includes the following: *'Further research is warranted and desirable to clarify the uncertainties of the relative efficacy and safety of medical cannabis products'* [7]. In a newspaper article in May 2017, Head of Deakin University's School of Medicine was reported as stating that more research was needed before integrating medicinal cannabis into undergraduate medicine programs, and the Director of the Australian New Zealand College of Anaesthetist's Faculty of Pain Medicine was reported to have told a meeting of pain specialists that evidence to support medicinal cannabis is 'not good enough' [8]. Are these cautions prudent or simply an argument to maintain the current regulatory system which keeps prescribing in the hands of medical practitioners? And if not the current regulatory approach, what would be an alternative? One possibility is to regulate medicinal cannabis as a complementary medicine and a pharmaceutical, depending on the constituents of the product.

This paper explores the evidence-based medicine (EBM) approach, its application to medicinal cannabis, and some of the important points in scrutinizing published evidence, including study designs and their virtues and limitations. It also contends that the evidential basis upon which authoritative statements must also be carefully examined. It reports on the evidence of efficacy and safety in major reviews and argues that the notion of insufficient evidence is not accurate. The issue of access to a medicine as a fundamental human right is raised, returning to a central point about evidence in medicine and how a broader understanding is needed, not the least in relation to cannabis. Finally, it concludes that, on the basis of available evidence, there is no reason why CBD-containing products should be regulated as a pharmaceutical in Australia (or elsewhere) and that the alternative, to regulate it as a complementary medicine, would not only be sensible but would also open up access to Australians.

2. The evidence-based medicine approach

It is important to consider fundamentally what constitutes evidence in western medicine, since the evidence-based medicine (EBM) approach is used to make decisions in relation to access to medicines (pharmaceutical and complementary), medical technology and therapeutic modalities, and in recent times, medicinal cannabis. Evidence is also used by other bodies, such as professional associations and health insurance companies.

Sackett and colleagues' definition of EBM, regularly quoted is that:

> *'Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research' [9].*

This first part of the definition is regularly truncated here and quoted in medical publications. However it goes further:

'By individual clinical expertise we mean the proficiency and judgment

[1] When preparations for therapeutic use contain 2% or less of other cannabinoids found in cannabis.

that individual clinicians acquire through clinical experience and clinical practice. Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care. By best available external clinical evidence we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient centred clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens' [9].

It is within the second part that contains a vital element that needs to be considered, and this is no less relevant in decisions about access to plant medicines such as medicinal cannabis*: 'the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care'* [9].

Systematic reviews and RCTs are considered the gold standard in terms of hierarchy of evidence in western pharmaceutical-dominated medicine. However, Sackett and colleagues make it very clear that in their paper, EBM is not confined to RCTs and meta-analyses, and that EBM is about respecting the patient's preferences and rights and the proficiency, expertise and experience of individual clinicians [9].

The notion of self-care is relevant, defined by a World Health Organization working group back in 1983 as referring to 'the activities of individuals, families and communities undertake within the intention of enhancing health, preventing disease, limiting illness and restoring health. These activities are derived from the knowledge and skills from the pool of both professional and lay experience. They are undertaken by lay people on their own behalf, either separately or in participative collaboration with professionals' [10]. Championing self-care is a key objective of the Australian Self Medication Industry [11]. It is important that modern-day regulatory frameworks reflect patient discretion, with the recent Samson Review of Medicine and Medical Devices Regulation highlighting the risk entailed in not facilitating patient access to medicinal products which may personally benefit them [12].

A broader definition of EBM, then, considers the rights and preferences of lay people, as well as their right to handle their own health needs. With this broader and more inclusive definition in mind, let us now look at how the EBM approach has been applied in relation to medicinal cannabis, including some important issues to consider in the scrutiny of evidence about safety and efficacy. Then, we will look at what evidence actually exists, and whether it supports a restrictive approach to regulation in Australia.

3. Applying the EBM approach to medicinal cannabis: important points in scrutinising evidence

In examining published studies of safety and efficacy of cannabis, several points should be considered. For example, is the data related to the medicinal or 'adult use'. Is it related to a synthetic cannabinoid, a single extract of the plant, or the whole plant extract as a standardised medicine or the whole plant in its natural (raw) form? Efficacy studies are likely to yield very different results depending on the type of cannabis product, its cannabinoid and terpene profile, and route of administration. The terpenoids and the other plant nutrients are understood to provide the '*entourage effect*' which refers to the variety of beneficial actions of the whole cannabis plant that may be additional and/or synergistic to the actions of the phytocannabinoids, and it is the synergism between the active constituents that is likely to be responsible for its therapeutic efficacy and the mitigation of side effects of the dominant active ingredients [13,14]. Systematic reviews need to clearly delineate the different forms of medicinal cannabis included in the RCTs. Safety data on recreational cannabis use cannot simply be generalised to medicinal use of cannabis.

3.1. Scrutinising study design

When examining scientific evidence in relation to medicinal cannabis, study design requires careful consideration as methodology can greatly influence the conclusions made by the researchers. RCTs have specific inclusion and exclusion criteria and may have limited generalisability to greater populations or different subpopulations. Systematic reviews and meta-analyses also have limitations. N-of-1 study designs may be more useful in the study of medicinal cannabis where individualization is important, and certainly fits the notion of personalised medicine. Quantitative research dominates medical research with qualitative research barely getting a hearing in comparison, despite its value in being able to answer different kinds of questions, particularly those about human experience. Cross-sectional surveys give information at a point in time, but it is difficult to control confounding factors, and recall in relation to subjective symptoms (eg. pain) can be inaccurate.

How the medicine is used in clinical practice is vital to factor into clinical trial designs, and for medicinal cannabis, individualisation of route and dosage are important. Pharmacokinetics and pharmacodynamics of medicinal cannabis and cannabinoids will vary with individuals and with route of administration and formulation [15,16]. Cannabinoid plant chemistry is far more complex than that of pure THC, or pure CBD or synthetic cannabinoids. Therapeutic effects will be dependent on the cannabinoid and terpene (and other phytochemicals) profile of the plant or product [16]. Bioavailability of THC varies with route of administration [16]. Absorption of CBD from the GI tract has been found to be erratic, with a variable pharmacokinetic profile. Bioavailability of CBD is estimated to be 6% due to the first pass mechanism [17]. Individual variability in bioavailability is likely to influence RCT results, as is genetic variation, just starting to be unravelled in relation to the endocannabinoid system. For example, the human CB1 receptor gene *(*CNR1*)* is located at chromosome 6q14–15 and there are multiple single-nucleotide polymorphisms (SNPs) in CNR1 [18].

3.2. Scrutinising the conclusions of publications

A recent four-year prospective, observational cohort study in an Australian population (2012–2014) who were prescribed opioids for non-cancer chronic pain concluded, in the Abstract, that *'We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference or no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation'*. It went on to state in the Conclusion of the Abstract that *'….we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect'* [19]. This survey was conducted in people primarily using illicit cannabis, since it was conducted prior to legalization of medicinal cannabis in 2016. This conclusion is somewhat at odds with their finding, discussed later in the paper, that: *'The percentage of participants reporting that they would use cannabis if they had access to it increased from 33% at baseline to 60% at 4-year follow-up*' which seems to suggest a perceived benefit from participants [19]. They did note that there were inconsistencies in their findings between what participants reported, and their statistical assessment of associations. At best, the outcome results can be generalised to those using illicit cannabis but have very limited applicability to medicinal cannabis (typically prescribed in a standardised form, individualised to the patient, titrated to the dose that is therapeutically efficacious). The authors of the paper did point out that in their study, it was unlikely that the cannabis was consumed under the guidance of a medical practitioner. This simply illustrates the necessity of scrutinizing the study details of a paper (and not just reading the abstract).

3.3. Scrutinising the evidential basis upon which position statements are made

The basis upon which position statements from professional bodies and other authoritative figures about medicinal cannabis requires careful examination, since they have great influence. The 2016 RACGP Position Statement, described earlier, sets out levels of evidence for efficacy of treatment of specific conditions with medicinal cannabis. It states that the level of evidence for treating chemotherapy-induced nausea and vomiting (CINV) is very low and for chronic non-cancer pain, moderate [7]. Conclusions about these two conditions is based on two published studies, both by Whiting and colleagues (2014, 2015 papers), systematic reviews. In contrast, the National Academies of Sciences, Engineering and Medicine 2017 report on medicinal cannabis concluded there is 'conclusive or substantial evidence' that medicinal cannabis is effective for the treatment of chronic pain in adults, and 'conclusive or substantial evidence' for the efficacy of oral cannabinoids in the treatment of chemotherapy-induced nausea and vomiting [20]. Their conclusion about chronic pain is based on five systematic reviews (though relied heavily on the Whiting et al. 2015 study), and two additional studies, and their conclusion about CINV is based on three systematic reviews and an RCT [20].

The RACGP Position Statement recognises the potential importance of synergism, and cautions about potential drug-herb interactions: *'Similarly, how the constituent compounds may interact with other medications is not understood'* [7]. However, there is quite a bit known about drug-cannabis interactions, discussed later.

Authoritative bodies have tremendous power to influence opinion of doctors, policy makers and many others, and the evidence that they base their conclusions and advice on should be carefully examined. This is very difficult for the average clinician who just wants to practice medicine and the best health care. Position statements based on evidence require updating as more information comes to light. In a rapidly moving field of research into medicinal cannabis, this is particularly important as this evidence is used at the level of government to argue for or against access, as well as by clinicians who want to understand the current evidence-base.

4. So, what is the evidence of efficacy and safety of medicinal cannabis?

4.1. Efficacy

The *National Academies of Sciences, Engineering and Medicine Report: The Health Effects of Cannabis and Cannabinoids,* a comprehensive review of systematic reviews and RCTs released in 2017, states that there is 'conclusive' or 'substantial evidence' that medicinal cannabis or cannabinoids are effective for the treatment of adult chronic pain, chemotherapy-induced nausea and vomiting, and patient-reported spasticity associated with multiple sclerosis (MS), and moderate evidence that cannabinoids or cannabis are effective include improving short term outcomes in individuals with sleep disturbance associated with obstructive sleep apnoea, fibromyalgia, chronic pain and MS [20]. The basis of the conclusions were systematic reviews and RCT evidence.

The World Health Organization (WHO) published reviews of cannabis in 2018, including reports focused on cannabis and its resins [21], THC [15], and CBD [17]. The evidence used in the WHO reports includes preclinical and clinical data including toxicology, pharmacokinetic and pharmacodynamic studies, plus RCTs and systematic reviews. The WHO CBD report [17] states that the clinical use of CBD is most advanced in the treatment of epilepsy, citing several studies including one of Dravet Syndrome [22], and that there is also evidence that it may be useful for a number of other medical conditions. However, it states that for most indications, there is only pre-clinical evidence, or in some cases a combination of pre-clinical and limited clinical evidence [17]. The WHO *Pre-Report on THC* [15] reports evidence of a positive therapeutic effect for pure THC for decreasing neuropathic pain and subjective muscle spasticity in MS patients, and some evidence in support of the efficacy of dronabinol (synthetic THC) in anxiety disorder, anorexia nervosa (weight gain), appetite stimulation in HIV/AIDS, cannabis use disorder, chronic pain, non-cardiac chest pain, obstructive sleep apnoea, and the Tourette Syndrome. It found mixed results for neuropathic pain associated with MS, spasticity associated with MS (patient vs physician reported), and opioid use disorder. However, it did not find evidence of efficacy for dronabinol for several other conditions. [15].

On the basis of these reports, it would seem there is robust evidence of efficacy in several conditions, though there is less in others. Many other studies have since been published. There are many studies of the endocannabinoid system (ECS), and evidence is emerging that dysfunctions in the ECS may be implicated in the pathogenesis of many conditions. There is a large bank of preclinical research and human research which has elucidated the many biological pathways and mechanisms of action of endocannabinoids, cannabis, phytocannabinoids and other phytochemicals, not discussed here. Taken as a whole, there is already a sound scientific basis for the efficacy of cannabis in many conditions.

4.2. Safety

Most of the available evidence of adverse effects involves cannabis used recreationally, where the cannabis is self-administered, of unregulated quality and smoked [23]. Cannabis strains bred for the recreational market are generally high in THC. Such data is not readily generalizable to the medicinal use of cannabis.

The WHO Report on CBD concluded that CBD is *'generally well tolerated with a good safety profile'* and that there is no evidence of 'any public health related problems associated with the use of pure CBD' [17]. In June 2018, the WHO's Expert Committee on Drug Dependence (ECDD) recommended that preparations considered to be pure CBD not be placed under international drug control as the substance was not found to have psychoactive properties, and presents no potential for abuse or dependence [24].

The WHO report on THC concluded that THC has similar pharmacological and subjective effects to cannabis in humans, and that these include euphoria, laughter, increased appetite, dry mouth, occasional dizziness and enhanced visual, olfactory and auditory perceptions. In some cases, THC can cause nausea and vomiting, and its side effects are mostly subject to tolerance with repeated exposure. THC can cause subtle cognitive deficits such as impaired attention and short-term memory impairment and higher doses can cause anxiety, panic, confusion, and disorientation in some users. Other effects that can occur in some include transient psychosis-like psychological phenomena, fragmented thinking, paranoia and grandiose delusions. However, these have been found to be modest in magnitude and reversible. The report also states that RCTs in which THC is sometimes given daily for periods of years generally report low to moderate toxicity and a low incidence of serious adverse effects [15].

Much is already known about potential interactions of CBD and THC with particular pharmaceuticals [25,26]. Health Canada states that the most clinically significant interactions may occur between cannabis and CNS depressant drugs such as sedative-hypnotics or alcohol. Further, it states that THC, CBD and CBN (cannabinol) are known to inhibit CYP isoenzymes such as CYP1A1, 1A2 and 1B1, and thus cannabis may increase the bioavailability of drugs which are metabolised by these enzymes [25]. Research indicates the potential for CBD and warfarin to interact adversely, with increased risk of bleeding reported in a case study [27], and another study reporting that CBD can inhibit S-warfarin 7-hydroxylase in human liver microsomes [28].

Whilst there are known potential drug-CBD interactions, what is theoretically possible and what occurs in clinical practice can be quite different. According to Health Canada: *'While few clinical studies have*

specifically sought to evaluate cannabis-drug interactions per se, many, if not most, studies investigating the therapeutic effects of cannabis (e.g. smoked, vapourized, or orally ingested) and cannabinoid-based medicines (e.g. dronabinol, nabilone, nabiximols) have used patients that were concomitantly taking other medications (e.g. non-steroidal anti-inflammatory agents, opioids, anti-depressants, anti-convulsants, protease inhibitors) and, in general, did not report significantly increased incidences of severe adverse effects associated with the combination of cannabis or cannabinoids and these other medications' [25]. Responsible prescribing of any herbal medicine or pharmaceutical requires checking potential interactions (including with food) and careful monitoring.

The argument that government regulators and the Australian Federal Minister for Health (in a letter responding to an industry position paper in 2018) have used to justify keeping CBD on Schedule 4 of the SUSMP in Australia has related, in particular, to potential drug-CBD interactions. However, many herbs (and foods) potentially interact with pharmaceuticals, such as St John's Wort, yet they are not scheduled on the SUSMP. Instead they are regulated as a complementary medicines on the Australian Register of Therapeutic Goods. The rationale for singling out CBD, either as a botanical extract (containing other phytonutrients) or a single isolate, from other herbs or nutritional supplements (remember vitamins are single isolates) which are treated as complementary medicines is weak.

Interestingly, it has been found in the US that legalization of medicinal cannabis is associated with reduced hospitalisations related to opioids. A study published in 2017 that examined the associations between state medical marijuana policies and hospitalisations related to marijuana and opioid pain relievers (OPR) found that: '*Medical marijuana legalization was associated with 23% ($p = 0.008$) and 13% ($p = 0.025$) reductions in hospitalizations related to opioid dependence or abuse and opioid pain reliever overdose, respectively*' [29]. The researcher concluded that: '*Medical marijuana policies were significantly associated with reduced opioid pain reliever-related hospitalizations but had no associations with marijuana-related hospitalizations'* [29]. In Australia where we also have an opioid crisis, such findings should be kept in mind when considering public health policy around medicinal cannabis. Such findings might seem at odds with the results of the previously-mentioned Australian study conducted in cannabis users prior to legalization of medicinal cannabis which reported no change in opioid use and no evidence in support of claims that cannabis and cannabinoids improved outcomes in chronic non-cancer pain. However, there are substantial differences between these studies. The Australian study was a survey of those primarily using cannabis illicitly, prior to legalisation (which occurred in 2016), and most of those surveyed were unlikely to have been using cannabis under medical supervision, something pointed out by the study authors. The Australian study did not examine opioid-related hospitalisations. In addition, the Australian survey relied on participant recall, which can be problematic (in the sense of accuracy and reliability) [19]. The US study was focused on investigating associations between states which had or did not have policies for legalization of medicinal cannabis and specific outcomes (that is, hospitalisations due to opioid abuse, dependence or overdose, as a result of legalization). These are completely different types of studies. It would, however be interesting to find out whether there has been any change in relation to opioid use now that medicinal cannabis has become legalized in Australia. The problem, however is that so few Australians are using legally prescribed medicinal cannabis yet.

5. Implications of the evidence: does it support the current regulatory system for medicinal cannabis in Australia?

The allegations of insufficient evidence of efficacy and warnings of lack of safety about cannabis that serve to justify a complex regulatory scheme is not substantiated by the scientific literature. There are thousands of scientific studies into the efficacy, safety and mechanisms of action of cannabis and cannabinoids. There is also a very substantial bank of clinical experience of thousands of clinicians around the world. The Merck Physicians Manual used extensively by doctors until the late 1930's described over 100 indications for the use of medicinal cannabis.

There is, however, sufficient scientific data, in particular in relation to safety, to argue that CBD should not be included in the Australian SUSMP. This is discussed in the next section.

There is also a strong argument for Australia's driving laws to be changed in a way similar to those in Canada, where it is only an offence to have THC in the body whilst driving if the person is also impaired. An alternative of setting a threshold THC limit for a driving under the influence conviction, as was done in Washington State and Colorado in the US, is problematic since how the same doses of THC affect individuals is highly variable. In Colorado, if a driver has five nanograms of active tetrahydrocannabinol (THC) in their whole blood, they can be prosecuted for driving under the influence, however law enforcement officers base arrests on observed impairment and *'if a substance has impaired your ability to operate a motor vehicle it is illegal for you to be driving, even if that substance is prescribed or legally acquired'* [30]. An independent member for parliament, Fiona Patten, is currently pushing for changes to the state and territory driving laws around THC in Australia.

6. An alternative approach to regulation of medicinal cannabis

An alternative regulatory approach in Australia would be for the TGA to approve proprietary forms of cannabis (products), such that they are no longer considered 'unapproved therapeutic goods'. This would then remove the need for doctors to apply through the Special Access Scheme or Authorised Prescriber Scheme, along with the onerous paperwork. Australia has a stringent system for regulation of complementary medicines, based on assessment of risk. Complementary medicines are either 'listed', 'assessed listed' or 'registered' in the Australian Register of Therapeutic Goods (ARTG). Basically, lower risk medicines are listed or assessed listed, and higher risk medicines are registered in the ARTG [31].

If a product is listed, it may only make low level claims in relation to health maintenance, health enhancement, prevention of a non-serious vitamin/mineral deficiency or a non-serious form of disease, ailment, defect or injury- there is a list of 'permitted indications' for listed medicines, as well as a list of 'permitted ingredients'. Safety and quality have been assured to TGA standards (including requirements for production by a TGA Good Manufacturing Process [GMP]-certified manufacturer). Evidence of efficacy must be held for each 'permitted indication'- the type of evidence required may be evidence of traditional use (eg. for a Chinese herbal medicine) or scientific evidence, depending on the 'permitted indication'. No premarket evaluation is conducted for listed products by the TGA [31].

There is also a subcategory of the 'listed' category termed *'assessed listed'*. It sits between the lower risk (listed) and the higher risk (registered) categories and allows sponsor companies to list products with higher level indications than permitted in standard listed medicines without having to meet the more extensive requirements for registered medicines. For assessed listed products, there is a list of permitted ingredients allowed in products, it must be produced by a manufacturer with Australian GMP certification, and premarket evaluation is conducted for efficacy (for intermediate level indications) [31].

If a product is registered, it may make higher level therapeutic claims. In this case, premarket assessment of safety, quality and efficacy by the TGA is conducted, and the type of evidence required to support the indication must be scientific data i.e. RCTs or systematic reviews [31]. Readers are referred to the TGA website (www.tga.gov.au) for further information on the regulations.

The majority of complementary medicines, including vitamins, are typically listed on the ARTG. Note that vitamin C, as an example, is a single isolate, synthetically produced. The corollary in cannabis would be a synthetically produced CBD isolate.

Medicinal cannabis is not one 'thing'. It is a broad term that encompasses products that fall broadly into three categories: single isolates derived from the plant, botanical extracts (full plant extracts including the terpenes and other plant nutrients), and synthetic cannabinoids (eg. nabilone, dronabinol). It is argued that products containing CBD only, including isolates, which are no different to Vitamin C for example, or botanical extracts containing CBD plus terpenes (no THC) or products containing low amounts of THC should be regulated as complementary medicines. This would also allow other qualified healthcare practitioners, for example registered Chinese herbal medicine practitioners, or naturopaths the ability to prescribe medicinal cannabis products and would likely increase access to medicinal cannabis products to patients since most herbalists are comfortable prescribing herbs (unlike medical doctors). The issue of potential drug-herb interactions for CBD is no different than for any other herb or nutritional supplement and responsible practitioners check for potential interactions. Products containing high amounts of THC could continue to be regulated via the SUSMP, but as approved medicines rather than 'unapproved' medicines (as they currently are), albeit it is suggested in Schedule 4 (Prescription Medicine) rather than Schedule 8 (Controlled Medicine). If there were concerns about the potential for 'doctor shopping' whereby a patient gathers prescriptions for the same medicine from multiple doctors, this could be monitored via a pharmacy register for THC-containing medicines. Given the prohibitive cost of medicinal cannabis products, however, someone wanting the intoxicant effect that could occur in high doses would probably simply buy cannabis on the black market and smoke it.

7. Fundamental issues at stake

The World Health Organization (WHO) states that, 'Access to essential medicines as part of the right to the highest attainable standard of health ('the right to health') is well founded in international law' [32]. It is a human right. Compassion and a willingness to help alleviate suffering is vital. Patient rights to access medicines of their choice must be taken into consideration by policy-makers.

If we look at chronic pain alone, approximately 5 million Australians suffer from chronic pain [33], one of the main indications for which there is evidence for efficacy of medicinal cannabis. Pharmaceuticals used for pain relief have a wide range of side effects, and in the case of opioids, can be deadly. Cannabis has the potential to relieve this suffering.

For patients facing the end of life, palliation of symptoms can help dying with dignity and is an example of a fundamental human right. The first modern description of the use of cannabis in palliation at end of life related to rabies and was published in 1838 [34]. An Israeli study of the use of medicinal cannabis by cancer patients in a palliative care setting concluded that it was well-tolerated, effective and a safe option to help patients cope with malignancy-related symptoms [35]. Aggarwal reminds us of the benefits of application of cannabis to existential and spiritual suffering, for example the potential to reduce the psychological trauma that a terminal cancer diagnosis and the invasive treatments frequently cause [34]. The mild euphoria or increased sense of wellbeing (which is not the 'stoner's high of recreational use) brought about by cannabis could play an important therapeutic role for patients faced with the despair of terminal illness and the (often) accompanying loss of function [34]. If professional associations and others are to talk of compassion, then we cannot ignore this aspect of dying with dignity, nor the rights of patients.

The Australian TGA states: '**…..**medicinal cannabis is not considered a first-line therapy for any indication' and 'At this time, we suggest that the use of medicinal cannabis may be considered only when registered medicines have been tried and proven unsuccessful in managing the patient's symptoms or medical condition' [36]. This advice oversteps the role of government departments and is certainly regulatory overreach. Decisions about a patient's health should be made by the patient, in consultation if they choose, with a healthcare practitioner. There should be no reason for cannabis not to be considered a medicine of first choice, preferably under the guidance of a knowledgeable healthcare practitioner, if there are indications that it may be efficacious and that is the wish of the patient.

8. Conclusion

In Australia, the regulations around access to medicinal cannabis in Australia are unnecessarily restrictive. There is enough scientific evidence of efficacy and safety already in relation to cannabis, and it supports an argument for change to the regulatory system around medicinal cannabis in Australia. The current regulatory system is failing, evidenced by the small number of patients having accessed it legally since 2016. There is no logical reason CBD-containing products should not be regulated as a complementary medicine under the ARTG as listed products.

When scientific evidence is used as the predominant form of evidence upon which determinations that impact populations are made, we need to be very sure that we have scrutinized it well and understood its limitations. Evidence comes in many forms. The emphasis on RCTs and systematic reviews to the relative exclusion of other study designs is challenged. In relation to medicinal cannabis, other study designs and forms of evidence are relevant, including case studies and n-of-1 studies. Plant medicines cannot be treated as pharmaceutical drugs as they are much more complex.

The battle of access to medicinal cannabis occurring is one of human rights. Healthcare must move towards a more patient-centred, personalised, preventative and predictive self-care model, which empowers patients and respects their rights to decide how they will manage their health. We need to bring back the human element when considering what evidence is used and how we use it in medicine. Cannabis has the potential to alleviate much suffering. If we come back to Sackett and colleagues' definition of evidence-based medicine, we should remember the part of the definition that is often not quoted, that EBM includes '*the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care'*. I would add the following to the end of that sentence: '*…..and in developing public policy in healthcare'*. Public policy is, by definition, something that should serve the public, not deny them a fundamental human right.

Note

This paper reflects the opinions of the author and does not in any way represent the views of the education institutions to which the author is affiliated. All research done by the author.

Financial support

None

Conflict of interest

Prof O'Brien conducts consultancy work for medicinal cannabis companies and works as the CEO for Global Health Initiative, a not-for-profit organization focused on medicinal cannabis education.

Acknowledgement

Helpful editorial comments on the manuscript by Professor Ian Brighthope (Founder of the Australasian College of Nutritional and Environmental Medicine) and Mr Justin Sinclair (NICM Health Research Institute, Western Sydney University) are gratefully acknowledged.

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