What is medicinal cannabis?
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ABSTRACT
As New Zealand considers cannabis legal reform, we ask: what exactly is medicinal cannabis, and why does this matter? Cannabis is not a single entity but comes in diverse forms with various active ingredients. This contrasts with the legal and pharmaceutical definitions of medicines, with wide-ranging implications for quality control, prescriber practice and the assessment of clinical evidence. We argue that what is considered a medicine in the legal and pharmaceutical sense should not be changed in an ad hoc way to accommodate cannabis, but that cannabis products should be held to the same standards as other medicines.

In line with global trends, New Zealand has recently passed a Bill increasing access to “medicinal cannabis”.1 The Government now has one year (from December 2018) to determine the regulations for a Medicinal Cannabis Scheme. Public survey shows widespread support for increased access to medicinal cannabis,2 yet GPs and clinicians generally remain more reserved.3,4 We believe that part of this difference lies in the lack of clear public understanding of the term “medicinal cannabis”, and a relatively greater awareness by health professions of what generally constitutes a medicine. New Zealand is also about to undergo a binding referendum on recreational cannabis use, the exact wording of which is yet to be determined. Thus, it is timely to consider the question “what is (and isn’t) medicinal cannabis?” Current media use of the term medicinal cannabis encompasses everything from pharmaceutical grade plant derived medicines, such as Sativex, through to home-grown raw plant materials. From the perspective of a potential prescriber these are very different products.

Here we attempt to bring clarity to the issues that the regulations must address. Specifically, we argue that there are already existing cannabis derived medicines approved by Medsafe,5 and others are expected to follow. Hence, what does the current Act seek to achieve? Is it a new definition of “medicine” designed specifically to accommodate cannabis? Or else does it mean (as we prefer) that medicinal cannabis should be held up to the same standards that all other medicines must meet? That is to say, why should cannabis be treated differently from any other medicines?

What is a medicine?
A billboard currently prominently displayed on the Auckland motorway declares “cannabis is medicine”,6 but is this true? The first problem encountered in considering cannabis as medicine is that “cannabis” is not a single entity, but a diverse range of related substances and products all referred to as “cannabis” in popular usage. Which of these may be considered a medicine depends on precisely how the product is constituted, although at an individual level, definitions of “medicine” can vary, when products are assessed at the level of manufacturing and marketing as medicines, the definitions become more precise. Most if not all of products referred to as medicines contain drugs: synthetic chemicals or chemicals from plants (or in some cases from animals or from biotechnology) that can be administered to the body to create a physiological effect. Drugs in their pure form are single molecules, and can be used in biomedical research to elicit particular effects through their actions on specific molecular targets within the body. By contrast, technically a medicine is usually a mixture of chemicals at precisely determined ratios, containing one or more drugs that is administered with the aim of producing a therapeutic effect. Medicines may contain other chemicals than the active drugs such as excipients, stabilisers and solvents.7
This pharmaceutical definition of medicines overlaps considerably with legal terminology in New Zealand, where under the Medicines Act (1981) the term medicine principally refers to a either a substance that is administered to “one or more human beings for a therapeutic purpose; and achieves, or is likely to achieve, its principal intended action in or on the human body by pharmacological, immunological or metabolic means” or to “...a therapeutically active ingredient” in such a substance. The definition is less clear in the Medicines Standing Order (2002), where a medicine “...means a prescription medicine or a specified controlled drug”. Other jurisdictions use similar definitions; notably Australia has a “...two-tiered system for the regulation of medicines, including complementary medicines” such that medicines are classified into higher and lower risk categories, and subject to different regulations.

Whether or not a substance meets the criteria for being treated as a medicine has wide-ranging consequences. A substance that has such regulatory approval will be produced in accordance with exacting and costly standards. Supply chains will be traceable and monitored to ensure the medicine is not diverted into illicit use. It will contain precisely defined amounts of active ingredients, such that dosages are uniform both between administrations and across production runs. With reproducibility, and the possibility for dose titration, safety and efficacy can be tested with high-quality clinical trials. Adverse events can be monitored by post-marketing surveillance, minimising public risk. With reliable dose and effect information, practitioners are able to both prescribe a medicine with clear expectations of potential effects, and ascertain dose adjustments or other interventions following treatment. Patients can receive reliable information about likely effects of the drug, critical for informed consent. The medicine will be in a form that can be practically and reproducibly administered to the patient, with a known shelf life and important patient information such as onset and duration of action.

What is cannabis?
The precise taxonomic classification of Cannabis is still undecided, but prevailing theory recognises one highly diverse species of C. sativa L., with segregates distinguished by morphology and phytochemistry (cannabinoids and terpenoids). The segregates consist of two subspecies: subsp. sativa (European “rope”) and subsp. indica (Asian “dope”). The latter subspecies consists of two domesticated varieties: Central Asian landraces, often hybridised as “Indica”; and South Asian landraces, often hybridised as “Sativa”. Wild-type plants are named C. sativa subsp. sativa var. ruderalis, although a minority of botanists treat the wild-type as a separate species, C. ruderalis. El Sohly has identified 545 distinct compounds in cannabis, among which 120 exhibit the typical C21 terpenopholic skeleton of a cannabinoid. The primary focus therapeutically to date has been on Δ9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, and cannabidiol (CBD). In raw plant material concentrations of these compounds are actually very low, rather they exist as their acid precursors, which are decarboxylated to the active compounds slowly by drying or rapidly by heating, such as when cannabis is smoked or cooked into edibles. Understanding the critical difference between THC and CBD requires an understanding of the system upon which THC acts in the body: the endocannabinoid system.

The endocannabinoid system is comprised of at least two G-protein coupled receptors (CB₁ and CB₂), at least two endocannabinoids (anandamide and 2-arachidonyl glycerol) and the enzymes responsible for the synthesis and degradation of the endocannabinoids. In contrast to classical neurotransmitters that are stored in vesicles, endocannabinoids are N-acyl lipids, synthesised on demand from lipid precursors in the cell membrane. In the brain, endocannabinoids are thought to be retrograde neurotransmitters—released from the post-synaptic neuron following increases in intracellular calcium concentrations and acting on receptors on the pre-synaptic neuron to inhibit further release of neurotransmitter. The effects of endocannabinoids in the brain are primarily mediated by CB₁ receptors, with CB₂ being widespread within the immune system. THC acts on CB₁ receptors in the brain, creating the characteristic “high” of cannabis. THC is a low efficacy (partial) agonist at these receptors with moderate affinity, in contrast...
to extremely high efficacy and high potency synthetic cannabinoids that are driving the current synthetic cannabinoid crisis.18

CBD is traditionally obtained from enriched extracts of industrial hemp, a cultivar of cannabis with naturally low THC content. CBD does not significantly activate cannabinoid receptors, which probably accounts for its lack of “high”. Allosteric antagonism at CB1 and CB2 has been proposed, but CBD's mechanism of action is poorly understood, and a multitude of putative mechanisms have been proposed,19,20 including acting on the equilibrative nucleoside transporter (ENT), the orphan GPCR GPR55, TRPM8 channels, PPAR-gamma, and other targets such as TRPA1, and 5-HT1a, alpha3, and alpha1 glycine receptors. It is a potent antioxidant, and also interacts pharmacokinetically with THC, increasing THC concentrations in serum and brain.21,22

Uniformity is a central feature of medicines, but concentrations of CBD and THC in cannabis plants vary widely. THC concentrations in cannabis sold on the recreational market are high and increasing. In contrast, CBD content is purported to be higher in “medicinal cannabis”.23 However, a recent analysis of 32 cannabis cultivars marketed under the Access to Cannabis for Medicinal Purposes Regulations in Canada quantified 10 of the most common cannabinoids and 14 terpenes.24 THC concentrations varied from 0.24–7.08%, while concentrations of CBD varied from undetectable to 5.52%. The variability in THC and CBD across plants was highlighted in this study which found that plants could be classified into four main types: high THC (6.3%) with low CBD (0.04%); moderate THC (3.84%) with low CBD (0.02%); approximately equal THC and CBD (around 1.3 vs 1.92% of respectively); CBD dominant (only one cultivar fell into this category, with >5% CBD and less than 1% THC).24 In addition, concentrations of other phytochemical constituents varied widely between cultivars—the relevance of these other constituents to therapeutic effect is still being investigated.25,26

Cannabis derived medicines (by the definitions described above) do currently exist. Marinol (dronabinol) is synthetic THC—a single agent medicine containing 2.5, 5 or 10mg THC dissolved in sesame oil. Nabilone is a synthetic THC derivative marketed in 1mg capsules. Sativex is a plant extract, manufactured by GW pharmaceuticals by blending together extracts from two plant varieties (one high THC, one high CBD) to produce a blend and is an oromucosal (mouth) spray administering a metered, actuated dose containing THC (2.7mg/spray), and CBD (2.5mg/spray)—approved by Medsafe in New Zealand for spasticity related to multiple sclerosis and through the medicinal cannabis access scheme for other applications (not funded through PHARMAC). Although not yet approved for distribution in New Zealand, a pharmaceutical grade CBD product, Epidiolex (98% CBD), has recently become the first FDA-approved plant derived cannabinoid medication.

Therapeutic uses of cannabis

A variety of therapeutic effects have been attributed to cannabis. Perhaps the intended effect that underlies much public discussion is as a pain reliever. There is a small amount of evidence for very mild pain relief by CBD,27,28 but most studies have been carried out using THC-enriched preparations. For smoked cannabis the clinical trial evidence for substantial pain relief is mixed.28,29 Indeed, at least one study has shown that habitual cannabis use can increase the need for other pain relief after acute injury.30 In a large prospective study carried out over four years in Australia, researchers concluded that there was no evidence that cannabis use improved patient outcomes.31 Large scale randomised clinical trials using Sativex have also produced disappointing results,32 and meta-analyses have tended to find at best a very mild analgesic effect for any cannabinoids.33,34

Sativex has, however, been found to provide moderate relief for patients with multiple sclerosis, as an add-on treatment for the control of spasticity and painful muscle spasm,35 though only as a third- or fourth-line treatment. CBD in the form of Epidiolex has shown promising results as an add-on treatment for the control of epilepsy in the treatment of seizures in associated with Lennox-Gastaut syndrome36 or Dravet syndrome,37,38 although questions remain as to whether these results might be explained by pharmacokinetic drug interactions.39–41 There are various other effects of THC that are well established, such as an appetite
stimulant for the treatment of cachexia and as an anti-emetic in chemotherapy, but even in these cases THC is at best only indicated as a third line treatment for refractory cases.42 CBD has various anti-inflammatory and anxiolytic properties attributed to it, and although this is currently under clinical investigation, there is as yet no convincing evidence for clinically relevant effects.

Despite the paucity of evidence for strong therapeutic effects from cannabis, it is sometimes claimed that patient anecdotes prove the therapeutic effects of cannabis, and that clinical trial evidence is misleading. One reason that has been suggested to explain this “evidence gap” is the existence of a sub-population of “cannabis responders” that are not accounted for by clinical trials. This claim has been tested recently by trials that use an enriched experimental design, where an initial trial phase is followed up with a second trial phase consisting only of the best responders from the first phase. Using this method, some evidence in favour of this hypothesis has been found for Sativex as a treatment for spasticity caused by multiple sclerosis.43 However, the same trial design in a study of cancer pain did not show a clear therapeutic benefit from Sativex even among those previously classified as responders.52 Another possible explanation is that apparent therapeutic effects of (THC based) cannabis are due to its mood altering and anxiolytics effects.44,45 Also, the absence of adverse effects of opioid treatment such as painful constipation may skew perceptions of the relative efficacy of cannabis. Lastly, Lowe et al46 have argued strongly that experience of self-medication by habitual cannabis users may often be an illusion, where relief from the symptoms of cannabis withdrawal is mistakenly perceived as a therapeutic effect. And in addition to these considerations, it is even possible that cannabis clinical trials may in fact over-estimate therapeutic effects, as the psychoactivity of cannabis may lead to patient unblinding and therefore an expectation of a therapeutic effect.47

The evidence base for any form of medicinal cannabis needs to be as robust as for any other medicines so that risk:benefit profiles can be properly evaluated.48 In this respect, the adverse effects of cannabis also require more serious discussion. These are well known,46,60 and include; effects on mood and sedation, deficits in cognitive ability, dependence and withdrawal effects, and residual effects on cognition that may last for several weeks after cessation. Heavy use also increases the risk of poor life outcomes and decline in socio-economic status as well as the risk of mental health problems, particularly when heavy cannabis use begins at a young age. Moreover, combined with genetic vulnerability cannabis use at a young age can exacerbate a predisposition to schizophrenia. These risks are often downplayed,48 but this is a particularly important consideration as the trend of THC content increasing in cannabis leaf grown for the recreational market50–52 has raised a number of health concerns. Frequent use of high potency cannabis is associated with greater severity of dependence53 and adverse psychological outcomes.54,55 While concentrates (highly purified extracts with 60–80% THC56) are a reasonably new addition to the medicinal market, case reports of psychosis from prescribed products are emerging.57,58

Is “cannabis” a medicine?

Currently the MOH web site lists four categories of “medicinal cannabis”59: 1. Pharmaceutical grade products that have consent for distribution in New Zealand (currently this is just Sativex), 2. Pharmaceutical grade products that don’t have consent for distribution in New Zealand, 3. Non-pharmaceutical grade products and 4. CBD products—which encompasses those products containing CBD with negligible concentrations of THC (there is no requirement that these be pharmaceutical grade).

The Misuse of Drugs (Medicinal Cannabis) Amendment Act1 also provides an exemption for those requiring palliation to the charge of possessing or using illicit cannabis, which would encompass any product not prescribed by a doctor, including dried leaf material, oils and balms, and submissions to the select committee urged for these more “home grown” approaches to be allowed within the new regulatory scheme.60
Until recently Canada provided one example of a medicinal cannabis regulatory framework. In Canada, access was initially allowed to dried plant material either through regulated Health Canada supply or by patients producing their own plants. Due largely to legal challenges the Act changed substantially over time.\(^\text{61}\) In 2013 a commercial industry was developed, responsible for the production of quality-controlled dried cannabis material produced under “secure and sanitary conditions”. More recently other cannabis products were included, allowing licenced producers to produce and sell cannabis oil and fresh cannabis buds and leaves in addition to dried cannabis. However, the requirement to get cannabis only from licenced producers was legally challenged in 2016 and a new Act was developed which laid out a framework for commercial production of fresh and dried plant material and cannabis oils as previously, but extended also to “starting materials” (seeds and plants) and enabled provisions for individuals to produce limited amounts of cannabis for their own medical purposes or to designate someone to produce it for them. All of this was repealed in October of 2018, when recreational use of cannabis became legal in Canada. The new Cannabis Act still regulates aspects around who can produce, the types of products available, packaging and labelling, standardised potency etc and restrictions on promotional activities.\(^\text{62}\)

A market such as this does not fit into any of the traditional definitions of a medicine, regulated by Medsafe in New Zealand, and funded by PHARMAC. Funding is important, one of the major objections from patients about the use of Sativex arises from the high cost per patient. Similar concerns would likely follow if high CBD products such as Epidiolex were not widely funded by PHARMAC. There seems no reason to believe that even local products could be developed that meet pharmaceutical grade, have gone through clinical testing but are significantly cheaper. So, does “medicinal” cannabis fit into any existing frameworks? We would argue no if doctors are asked to prescribe it. This is not to say that non-pharmaceutical grade products couldn’t be treated as something more analogous to recommending a herbal supplement. In such a scenario, quality and safety would still be controlled, but efficacy would not be required to meet medicinal standards.

Regardless of how cannabis is classified, quality standards remain critical. Patients represent a vulnerable and often immune compromised population so in addition to the active ingredients being controlled and clearly labelled, product should be solvent, pesticide—and mould free\(^\text{63}\)—reports suggest this is often not the case in the US medicinal cannabis market.\(^\text{56,64}\)

Implications and conclusions

We argue that even if various cannabis products might have benefit for some patients, it is not helpful to classify anything other than a pharmaceutical grade product as a medicine. “Cannabis” is not a single entity, and the entities under discussion usually do not meet the requirements for other medicines.

The quality control rigors for classification as a medicine, the properties that a substance must have for safe and effective prescribing, the assessment and monitoring of effects—both therapeutic and adverse—are safeguards that should not be compromised or redefined without a careful consideration of the consequences, many of which could be unintended.

Quality controls are also one aspect of a quality evidence base, both for therapeutic and adverse effects; anecdotes are not enough. Nonspecific sedative effects, relief from withdrawal and strong placebo effect all confound patient perceptions, and perceptions cannot replace objective standards when formulating medical policy.

Finally, access to medicines in New Zealand is increasingly limited by funding constraints. With so many pharmaceutical grade medicines that have gone through rigorous testing not available to the New Zealand public, we question the wisdom of spending this limited funding on products that do not meet these standards.
**COMPETING INTERESTS:**
Dr Glass is the chair of the Medicinal Cannabis Research Collaborative, a group that was established to design and carry out research around medicinal use of cannabis, and to provide advice as appropriate to others in this area (government, policy makers or people in the medicinal cannabis industry). She is not paid for this role.

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