

Medicinal cannabis: moving the debate forward

Giles Newton-Howes, Sam McBride

ABSTRACT

There has been increased interest in cannabis as a medicine both nationally and internationally. Internationally, cannabis is accepted as a medication for a variety of purposes in a variety of legal guises and this, associated with anecdotes of the utility of cannabis as medication has led for calls for it to be 'medicalised' in New Zealand. This viewpoint discusses the issues associated with this approach to accessing cannabis and some of the difficulties that may be associated with it. It is important doctors are at the forefront of the debate surrounding medicalised cannabis. Recommendations as to the ongoing debate are offered.

Recent debate on medicinal cannabis has occurred with doctors, those expected to prescribe, largely silent. The use of medicinal cannabis in some overseas jurisdictions has seen the introduction of a product as a medicine outside of usual criteria and driven by legislation and popular demand rather than strong evidence for efficacy.¹ The lines between recreational use and that of cannabis for medicinal reasons are blurred. These factors have the potential for prescribers to become either the gatekeepers for recreational use or to prescribe in situations in which diagnostic categories become meaningless. The medical profession needs to not only contribute to but also lead any debate on medicinal cannabis. This viewpoint aims to encourage this debate by outlining the context of medicinal cannabis, surrounding issues and providing a framework for consideration of medicinal cannabis in New Zealand.

The context

Cannabis is one of the first recorded medications with prescriptions for its use dating back to 1500BC.² The introduction of cannabis into Western medicine occurred via physicians exposed to its use in India with reported use as an analgesic, appetite stimulant, anti-emetic, muscle relaxant and anticonvulsant.³ Use was not just restricted to the most impoverished as, potentially, an escape from the hardship of life. Dr J Reynolds, Queen Victoria's personal physician, described 30 years of use in a range of conditions.⁴ In the US, cannabis

was included in the US Pharmacopoeia from 1850 through to 1937.⁵ Prohibition in the first half of the twentieth century reflected less the harms of cannabis than the socio-political prejudices of the day. One profound consequence of prohibition was to confound research into the medical potential of cannabis, a situation that is only just being addressed in some jurisdictions today.

Levels of cannabis restriction vary from minimal restraints as found in countries such as the Netherlands to a strict prohibitionist approach such as occurs at a US Federal level,⁶ New Zealand being more closely aligned to the latter. Despite the criminal liability associated with cannabis, its use in New Zealand is widespread. The reported annual prevalence of use of 10.2% is high by international standards and cannabis remains the most widely used illicit drug in New Zealand.⁷ The high levels of cannabis use suggest a degree of acceptance of use within New Zealand and imply a ready population of people who may wish to access cannabis should it be available medically.

Greater acceptance of cannabis has contributed to the increasing advocacy for medicinal use of cannabis. Medical regimes are more likely to be introduced where use in general is higher and medicinal cannabis has largely been a consumer-led initiative.^{8,9} This dynamic is reflected in New Zealand. Public figures have spoken about their use in New Zealand typically in the context of serious illness. The New Zealand Drug Foundation and the New Zealand Law Commission have argued for increased

access to medicinal cannabis.¹⁰ Advocacy groups such as Green Cross, United in Compassion and NORML campaign vigorously. Industry is also calling for development of a legal market extolling the potential economic benefits.

This local support occurs against a backdrop of increasing international use of cannabis in health settings, though models of use vary widely from use of cannabinoid medications, removal of criminal sanctions for patients using cannabis for medical purposes to access to 'medical grade' herbal cannabis. Use of herbal cannabis is authorised or legislated for in some jurisdictions in the US, Netherlands, Canada, Israel, Finland, Denmark, Uruguay and the Czech republic.¹¹ Australia has recently passed amendments into their Narcotics Drugs Act 1967 allowing cultivation of cannabis for medical and scientific purposes, and paving the way for trials into and the potential use of herbal cannabis for medical purposes.¹²

What is cannabis?

The leaves and flowers of cannabis contain over 400 distinct compounds and contain at least 100 different phytocannabinoid compounds (cannabinoids occurring naturally within the cannabis plant). The two major constituents are Δ^9 tetrahydrocannabinol (Δ^9 THC or THC) and cannabidiol (CBD). THC is responsible for most of the psychoactive properties of cannabis, including effects sought by recreational users. Cannabidiol has anxiolytic and anti-psychotic properties and may moderate some of the psychoactive effects of THC.¹³ Emphasis has been placed upon isolating individual components of cannabis to use as therapeutic compounds, such as the use of cannabidiol for childhood epilepsy. However, the approach has had limited success and it is postulated that the efficacy of cannabis-based medications relies upon synergy between the compounds or the "entourage effect".¹⁴

Cannabinoids interact with the endocannabinoid system, which is made up of the cannabinoid receptors (CB1 and CB2) and endogenous cannabinoids of which anandamide and 2-arachidonoyl glycerol have been isolated.¹⁵ CB1 is the most common G-protein-coupled receptor in the brain. It is widely distributed with high levels in the hippocampus, cerebellum, basal ganglia

and neocortex in addition to peripheral nerve terminals. CB2 receptors are found largely within peripheral areas, including cells of the immune system. The endocannabinoid system is believed to be involved in a large range of bodily functions, including analgesia, vomiting, immune system regulation, appetite, cognitive processes and motor control, providing biological plausibility to the use of cannabis as a medicine and potential targets.¹⁵

The argument for the use of cannabis as a medicine

Despite the hiatus in the investigation of cannabis, largely related to prohibition, sufficient data has been accumulated to allow formal review. A systematic review into the use of cannabis for treatment of chronic non-cancer pain concluded that there was evidence for moderate efficacy of cannabinoids in neurological pain with preliminary evidence for fibromyalgia and rheumatoid arthritis.¹⁶ A recent systematic review and meta-analysis concluded that there was moderate-quality evidence to support the use of cannabinoids for treatment of chronic pain and spasticity with low-quality evidence to support cannabinoids being useful in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders and Tourette syndrome.¹⁷

Other evidence for the utility of cannabis as a medicine is limited. Trials of other neurological conditions including: levodopa induced dyskinesia in patients with Parkinson's disease, non-chorea-related symptoms of Huntington's disease, Tourette syndrome, cervical dystonia and epilepsy have occurred.¹⁸ Despite enthusiasm for cannabinoids in epilepsy, a 2012 Cochrane Review concluded "No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy" with similar results published by expert systematic reviews.^{19,20}

Outside of this limited range of conditions there is little current evidence to suggest that cannabis has any medical role. However, there is increased adoption of medicinal cannabis internationally for conditions that include hepatitis C, Parkinson's disease, PTSD, glaucoma, Crohn's disease and Alzheimer's disease. This slippage into other diagnostic categories is, unfortunately, not uncommon in medicine but does raise

concerns as to who cannabis would be prescribed for. The introduction of cannabis by accord, rather than evidence, has led to the invidious situation of doctors being asked “to authorise our patients’ access to a product with little evidence to support its use”.²¹ This creates ethical and practical problems for physician who may be asked for an intervention with little or no evidence over a treatment that is well evidenced.

Cannabis and cannabinoids: medication or flower?

Complicating any debate about medicinal cannabis is that it may refer to herbal cannabis or standardised cannabis extracts and synthetic cannabinoids used in regulated doses.

The Ministry of Health (MOH) allows potential access to pharmaceutical grade products that have consent for distribution in New Zealand, pharmaceutical grade products that do not have consent for distribution in New Zealand and non-pharmaceutical grade products.

Only one pharmaceutical grade product, Naboximols (marketed as Sativex[®]), an extract of cannabis, is licensed for use in New Zealand. It is approved by Medsafe for add-on treatment for symptom improvement in patients with moderate to severe spasticity due to Multiple Sclerosis where response to anti-spasticity medication has not occurred and who respond to initial trials of therapy. Ministerial approval may also be made for non-approved authorisations such as cachexia, neuropathic and chronic pain. Unlike other drugs whose access is restricted, Ministerial approval is required for use due to concern about risks of diversion and dependence. The utility of this is questionable considering the expense associated with Naboximols compared to illicit cannabis, making diversion highly unlikely. The level of scrutiny is also inconsistent with other drugs such as methadone or methylphenidate, where ‘home production’ is virtually impossible and the expense is low (as these drugs are funded), making diversion considerably more likely. This appears to be a conflation of the illegal status of recreational cannabis and the use of cannabinoids as pharmacotherapy.

Synthetic preparations of THC available for medicinal use, though not licensed within New Zealand, include Drobinol

(Marinol[®]), marketed as treatment for nausea/vomiting associated with chemotherapy and acquired immune deficiency syndrome (AIDS) associated anorexia and weight loss. Nabilone (Cesamet[®]) is marketed for nausea and vomiting associated with chemotherapy. Both products contain synthetic THC alone.

The application criteria for access to non-pharmaceutical grade products are more stringent including restriction of use to a severe or life threatening condition, evidence that conventional products have been trialed without adequately controlling symptoms, that the risk benefit analysis of medications has been adequately considered by a qualified clinical specialist, application to be made by appropriate specialist or chief medical officer of a district health board, provision of a certificate of analysis and informed consent from either parent or guardian for minors. This allows the potential to access cannabis-based products for compassionate purposes in conditions such as terminal illness where conventional products have failed to control symptoms or forms of childhood epilepsy such as Dravet syndrome.

However, guidance for use for these products is lacking with no clear pathway as to how patients or practitioners may access appropriate information. Given the public interest in medicinal cannabis it is inevitable that doctors will be asked about products and at present most are operating in a vacuum. There is an urgent need for doctors to take a lead in determining what products may be appropriate and both monitoring and disseminating response to their use. Neurologists, palliative care and pain specialists have a particular role in this regard.

A case for herbal cannabis?

Importantly, patients prefer herbal cannabis.²² Herbal preparations are variously available as standardised cigarettes, loose herb, food and drinks. Unsurprisingly however, the bulk of herbal cannabis use is smoked, the form in which cannabis is typically used recreationally.²² Compared to oral use, smoking cannabis results in rapid uptake and avoids first pass metabolism with resulting faster onset of action, not to mention the significant health hazards associated with smoking. Preference for herbal cannabis may also reflect the unantagonised THC in synthetic compounds.

Dosage is also problematic, in contrast to some prescribing practices in which medicines are provided in regulated doses, instructions to patients are essentially to smoke to effect.²¹ This may be because the amount of psychoactive ingredients in botanical cannabis can vary and be further altered by mode of preparation and method of smoking. Although 'use to effect' regimes may exist for the short term control of pain (eg with nitrous oxide or methoxyflurane), they are rare for chronic conditions and non-existent where the 'medication' is smoked and the dose is not known to the prescriber. This is further complicated by the lipophilic properties of cannabinoids and second order kinetics of metabolism, leading to prolonged release from fat in chronic users.

Prescribing considerations

As with any medication, for cannabis to be considered as a pharmacotherapy requires conformity with other regulated medications. This is the process undertaken for the licensing of Nabimixols and herbal cannabis would need to fulfil the same licensing regulations. This requires at minimum a consistent reproducible medication delivering the same dose of drug, evidence of efficacy and ideally effectiveness, indications as to which disorder(s) the pharmacotherapy is licensed for and symptom targets. All this requires strong evidence, provided for in stage II and III randomised controlled trials (RCTs). A structure by which herbal cannabis could be introduced to Australia and the complexities involved is outlined by Martin and Bonomo and should be given consideration in New Zealand.¹²

Risks relating the use of medicinal cannabis are wide ranging, though often overstated, and need to be held in context with commonly used medications such as anti-convulsants. The effects of regularly smoked cannabis seem to be largely associated with symptoms of bronchitis and inflammation, although an association with respiratory cancer remains unclear.²⁴ These risks may be reduced by the use of vaporizers, though evidence is lacking and complicated by the range of devices available and variable sophistication.²⁵ Prescription of cannabis in adolescence or early adulthood is associated with an increased risk of psychosis and reduced

educational outcomes in a dose-dependent fashion.^{26, 27} Recent use of cannabis is associated with impairment of executive function including memory, and heavy use may be associated with deficits in decision making and concept formation that may not resolve with abstinence.²⁸ While cannabis has been associated with increased rates of motor vehicle accidents, early evidence from Colorado where cannabis is legal has not substantiated concerns.²⁹ Use disorders are also a significant consideration. New Zealand surveys suggest that there is a 1.4% prevalence of abuse and dependence related to illicit use of cannabis; this is of note given that many of the indications for which medicinal cannabis is suggested are chronic conditions for which on-going medication is likely to be required.³⁰

The implications of such findings for widespread use of medicinal cannabis are complex and need to be weighed against the side-effect profile of other medications. In this regard, proponents of medicinal cannabis note that concerns about the risks associated with medicinal cannabis are inconsistent with those associated with opioid analgesia, with a lower risk of dependence and toxicity.³¹ However, the uncertainty in relation to the effectiveness and side-effects prevents clear conceptualisation that would allow prescribers and patients to make fully informed decisions about their pharmacotherapy.

The intersect between medicinal cannabinoids and recreational cannabis

What is the threshold for which cannabis might be used? While public debate often concentrates upon the role of cannabis in terminal illness, studies suggest that cannabis is largely used for a variety of conditions, not all of which might meet criteria for disorder, including: pain, insomnia and anxiety.³² A study reporting data from Te Rau Hinengaro: the New Zealand Mental Health Survey, in contrast to expectations of those with chronic disease, cannabis users were predominantly young, with 45% under the age of 34.³³ These results suggest that the effects of cannabis across a range of disorders may be a non-specific anxiolytic effect reinforcing the confluence between recreational and medicinal use.

The similarity between recreational and medicinal users of cannabis is also shown in other ways. Often smoked preparations are preferred and medicinal users of cannabis typically have a history of recreational use.²² A recent study examining recreation and reported medicinal users of cannabis found a significant crossover with 86% of those reporting medicinal use also using cannabis recreationally.³⁴ The availability of medicinal cannabis does not preclude either continuing to grow supplies or purchase outside pharmaceutical supplies.²² The use of cannabis and use disorders is higher in settings where medical use is approved, and it is speculated that this reflects more positive attitudes to cannabis use.³⁵ It is possible that this relationship is bi-directional where the introduction of medical cannabis leads to normalisation of use. Advocacy for medical cannabis may in part reflect a desire for change of the prohibitive approach to cannabis in general. That cannabis is certain to have a greater safety profile than alcohol despite the latter drugs' highly commercial status and the similar aims of users is likely to add to the level of perceived injustice among advocates and confound informed debate.³⁶ However, the authors argue that medicinal use of cannabis and re-consideration of prohibition must be considered separately, on their own merits and within appropriate frameworks.

A pathway forward for medicinal cannabinoid?

There is the possibility that medicinal cannabinoids will prove of value to New Zealanders as pharmacotherapy. This may be of particular value as the likely conditions treated are vulnerable populations with chronic conditions. It will be important, however, to have a framework moving forward that allows for rational discussion. We propose the following as a general framework for this discussion:

1. The discussion between the legal framework of cannabis and the medicinal framework of cannabinoids be kept separate. As much as possible the licensing of medicinal cannabinoids needs to conform to the framework for all medications. This is to prevent the 'decriminalisation' of cannabis via a medical route.
2. In fact however, current legislation allows for the use of cannabis in some medical circumstances. Doctors need to be engaged in this debate and the use of cannabis for the management of disease. This is akin to medical professional providing advice about non-pharmaceutical products for the treatment of medical disorders such as fish oil for mood disorders.
3. The use of medicinal cannabinoids needs a dialogue that clearly differentiates it from the dialogue about the legal status of cannabis. To this end we would suggest, if discussion about cannabinoids as a medicine occurs, it is referred to as medicinal cannabinoids, not cannabis.
4. The use of cannabinoids as therapies may be beset with possible risks, both individual and societal, however these need to be considered in a similar light to other medications rather than used *carte blanche* to suggest there is no place for cannabinoids in medicine.
5. It is hard to justify a place for a smoked medication, in light of the serious public health harms related to smoking and availability of other methods of delivery. For this reason the authors would not recommend continuing a debate about the use of smoked medicinal cannabinoids.
6. As with any medication, there needs to be sufficient evidence for effectiveness to warrant prescription. This is a central component of the medicinal cannabinoid debate and currently lacking.
7. There is recognition of the use of regulatory systems already in place in New Zealand, such as the special authority forms for funded medication, that could be put to good effect should medicinal cannabinoids be licensed and publically funded. This avoids the conflation of a medicine with a prohibited substance.

It is important that all areas of society engage in the medicinal cannabis debate, and the authors of this paper encourage ongoing robust discussion.

Competing interests:

Dr Newton-Howes reports that he sits on PTAC.

Author information:

Giles Newton-Howes, Department of Psychological Medicine, University of Otago, Wellington; Sam McBride, Community Alcohol and Drug Service, Te-Upoko-me-te-Whatu-o-Te-Ika Mental Health, Addictions & Intellectual Disability Sector 3DHB, New Zealand.

Corresponding author:

Giles Newton-Howes, Department of Psychological Medicine, University of Otago, Mein Street, Wellington 6324.
giles.newton-howes@otago.ac.nz

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