

Medicinal cannabis in Australia: the missing links

Cultivation of cannabis for medicinal or scientific purposes needs considered management before it is rolled out as a therapeutic good

Since the publication in the Journal last year of a perspective on cannabis that stated: “Australia is behind the times on the medicinal use of cannabis”,¹ there appears to have been a palpable change in community attitudes around cannabis as medicine.²⁻⁴ This has occurred alongside anecdotal reports from people with intractable illnesses who have had symptomatic benefit with cannabis.⁵ Palliative care specialists have acknowledged a potential role for medicinal cannabis in their specialty.⁶ Internationally, the scene is also changing. For example, the Netherlands Office of Medicinal Cannabis enables dispensation through pharmacies after purchase from a contracted company, which also exports to other European countries.⁷ In the United States, 23 states and Washington, DC, have legalised marijuana in some form, mostly for medicinal purposes, since June 2015.⁸

In Australia, the New South Wales Government Terminal Illness Cannabis Scheme (TICS),⁹ established in 2014, enables compassionate access to adults with a terminal illness. Under TICS, a registered medical practitioner involved in a person’s ongoing care must certify that he or she has a terminal illness as defined by the scheme. In 2015, the New South Wales Government-funded trials of cannabis in palliative care and in children with a specific type of epilepsy,¹⁰ and in Victoria, a cannabidiol study for paediatric epilepsy is also in process.¹¹

Adding to this momentum, in what some consider an “historical” move, Australia’s federal parliament has recently passed amendments to the *Narcotic Drugs Act 1967* (Cwlth) to allow controlled cultivation of cannabis for medicinal or scientific purposes through a single national licensing scheme. This legislation enables commercial manufacture of cannabis, thereby enabling consistency of product, which should facilitate the collection of pharmaceutical and pharmacological data. These amendments should also facilitate human clinical trials on the efficacy and effectiveness of cannabinoids, including comparisons with placebo or alternative therapies. In addition, rescheduling of medicinal cannabis from S9 (prohibited drug) to S8 (controlled drug) is currently being considered by the Therapeutic Goods Administration’s Advisory Committee on Medicines Scheduling.

With these measures in place, and assuming subsequent authorisation under the *Therapeutic Goods Act 1989* (Cwlth) and relevant state and territory legislation, a patient with a prescription will in future be able to use a medicinal cannabinoid manufactured from legally cultivated cannabis plants in Australia. In anticipation, Queensland has already released a draft Bill for discussion — the Public Health (Medicinal Cannabis) Bill

2016 — discussing, among other aspects, the requirement for approval by the Director General of Queensland Health to allow access by a patient to medicinal cannabis.

Missing links in access to medicinal cannabinoids

Although Minister for Health, Sussan Ley referred to this federal legislation as the “missing link” in the supply of cannabis for patients,¹² there are multiple missing links before patients can access medicinal cannabinoids in Australia. Several changes to medicines and poisons legislation, as well as significant scientific, pharmaceutical, pharmacological and clinical input are required. In this article, we discuss (in order of priority from a patient efficacy and safety perspective) what we believe are the missing links, based on the assumption that the legislation sets out to cover all of pharmaceutical grade extracts and use of plant products.

1. Data required on indications, efficacy, safety and dose range of cannabinoids

Some cannabis products (eg, botanical leaf extract) contain more than one cannabinoid, and several cannabinoids metabolise to compounds that may also be active. Other cannabinoids may consist of one molecule only, similar to most current therapeutic goods on the market. How these different molecules and combination of molecules will be handled is unknown at this stage.

Currently, when a pharmaceutical company is requesting to use a molecule, or combination of molecules (as in the combined antihypertensive therapies) clinically, a tight regulatory process is specified. In brief, this requires evidence about the molecule’s pre-clinical toxicity, human safety, basic physiochemical processes (ie, stability over time and in different physical circumstances, and drug dissolution in the body), basic and clinical pharmacokinetics and efficacy.¹³ Medical devices for administering drugs (eg, devices for vaporisation) are assessed in a separate process, and also require specific registration. Efficacy of the therapy is tested through a variety of early- and late-phase human clinical trials. For cannabinoids, the evidence for some of this early phase work is currently being developed through state government-funded trials in NSW, in particular, the clinical pharmacology study in Newcastle.¹⁴ However, that study will only provide safety and dose-finding data for vaporised botanical leaf cannabis, and within a tight dose range for patients with cancer cachexia. Patients with cancer cachexia are likely to exhibit cannabinoid pharmacokinetics and dynamics that are significantly different from those of other groups of

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doi: 10.5694/mja16.00234

Online first 30/05/16

patients who might benefit from therapeutic cannabinoids — younger, physiologically more stable individuals with chronic pain.¹⁵ Although data are available for some already registered cannabinoids,¹⁶ in general, appropriate starting doses and likely toxic doses for other forms of cannabinoids, and in other population groups with different pharmacokinetics are not known. Similarly, central nervous system or other toxicity data, particularly for children or adolescents or in “end-of-life” patients with significant neuropsychiatric changes and who are already taking a range of concomitant medications, are still to be determined. Placebo-controlled efficacy data to date are sparse¹⁷ and registration of cannabinoids may potentially lead to widespread uptake with reduced impetus for research into efficacy.¹⁷

2. Confirmation that drug constituents are consistent and of high, reproducible quality

In addition to the abovementioned lack of standard drug dossier data submitted to the Therapeutic Goods Administration (TGA), the pharmacology of different parts of the plant and its species need to be clarified.¹⁸ For instance, there may be batch variation between cultivation sites or over time. Thus, experience with good manufacturing practice (GMP) frameworks for other plant-derived drugs such as opium will be helpful. The clinical relevance of batch variation is also becoming apparent with other biological agents that are entering clinical use in Australia. The relative benefits of prescribing plant-derived molecules versus those synthesised in laboratories will need to be determined. Lastly, safety and regulatory aspects of cannabinoids obtained from a range of different (mostly domestic) sources that will be compounded by pharmacies is a major area for policy work; this is already underway in NSW.

3. Confirmation of drug stability in different storage conditions

It is likely that drugs for inpatients will be stored in more stringent and reproducible physical conditions than those provided to outpatients. Thus we need to understand factors such as the decay over time, outside of the fridge, and the effects of variable humidity, for different products.

4. Concerns specific to prescribing

Assuming that appropriate, evidence-based clinical indications for prescribing cannabinoids can be ascertained, an understanding of the pharmacology, including the percentage and amount of tetrahydrocannabinol, cannabidiol or other cannabinoid and their pharmacological actions, will inform prescribing for different conditions. Patients may have a preference for a particular route of administration (eg, oral versus vaporised), so effects on bioavailability via these methods may need to be considered for a particular patient and the condition being treated. For example,

cannabis for cachexia may best be taken before meals with a rapid time to maximum concentration and rapid wear-off; but for chronic pain, a relatively constant plasma concentration above that known to be of benefit may be preferred. Depending on the underlying condition, decisions will need to be made about whether a supply for 1 month (eg, palliative care context) or longer (eg, chronic pain context) can be provided because of the potential for stockpiling.

5. Concerns around medical supply of a potentially misusable substance

Here, we can learn from local and international experience.¹⁹ Assuming that medicinal cannabis is rescheduled from S9 to S8, the states and territories have a key role, as they do for other scheduled substances, in enabling access to this drug.

Additional controls include restricting access to poisons to state and territory authorised medical practitioners. Restriction of prescribing to specific practitioners, such as palliative care, pain or addiction medicine specialists will be important, especially in the early stages of prescribing while the clinical experience is accumulating. In other contexts, access can be restricted to clinical trials conducted under the *Therapeutic Goods Act 1989* (Cwlth) — that is, by applying to use an unapproved product under the Clinical Trial Notification or Clinical Trial Exemption schemes, under the TGA Special Access Scheme or under an Authorised Prescriber scheme.

In Canada, doctors are gatekeepers for the system, but many cite lack of research and guidance from authorities as the reason for declining to prescribe cannabis, even though most support a perceived public health aspect.¹⁶ Clearly, medical practitioners, pharmacists and other health professionals will need training so that inappropriate prescribing and drug diversion are minimised. Looking ahead, curricula in medical and other undergraduate health professional courses are currently relatively devoid of formal structured clinical pharmacology and addiction medicine teaching, particularly with regard to cannabis. This should be rectified through collaboration with, for example, the Australian Medical Council and Medical Deans of Australia and New Zealand.

Solutions

While a national regulatory framework is under discussion, there are several ways to promote the process, described below.

- There is likely to be a call for professional input once the TGA processes are finalised (submissions to the TGA closed in February 2016). This will include pharmacy input concerning storage and dispensing, and registration of, or use of an authorised prescriber or other scheme by prescribers.
- Support should be given to the unprecedented approach in Australia to develop the evidence base

through the NSW and Victorian state government studies.

- Guidelines could be developed for medical practitioners regarding management of patient requests for cannabinoids that are outside the legislation/registration.

Interface with non-medical cannabis use

Like many doctors, we consider the discussion surrounding medicinal cannabis to be separate from the increased calls from some sections of the community to legalise cannabis for non-medical or recreational, use. Non-medical cannabis raises ethical concerns about substances that are documented to be harmful to some individuals and society. Medicinal cannabis, however, as proposed in recent amendments to the *Narcotic Drugs Act*, falls within the framework of a therapeutic good for clinical use.

Summary

For users of medicinal cannabis, this legislation is a significant move. It provides access to cannabis for people who gain alleviation of their symptoms and who have, until now, been cultivating cannabis or importing it illegally. However, prescribing of medicinal cannabis by doctors remains outside the standard regulatory framework for medicinal products.

For researchers interested in building an evidence base around cannabis, this legislation will simplify current onerous processes for permitting access to cannabis for the studies required to ensure safety, reliability, and the

range of doses likely to be effective. For the current NSW pharmacology study, for example, there were significant delays owing to problems with licenses for possession and handling, import licenses, concerns about storage in the hospital of a non-scheduled drug and the use of a non-TGA-registered medical device, even with state government facilitation of these processes.

For the medical community, both experience in providing access to potential drugs of misuse and appropriate concerns based on previous examples of medicinal products that can be misused will guide some of the journey and appropriate regulation. These experiences include the exponential rise in the use of oxycodone in the community²⁰ as well as misuse of benzodiazepines and antipsychotic medications. We can learn from these problems, as long as pressure from the community for access to cannabis is managed. Disease symptoms are not new. There are already several safe and effective registered therapeutic goods available for most conditions for which patients are requesting access to medicinal cannabis. If trial data for cannabis reveal evidence that supports its use, and if this use can be regulated in a way that enables suitable provision to those who may benefit, then it appropriately becomes another agent in the armamentarium of pharmacotherapy.

Competing interests: Jennifer Martin is involved in the NSW Health-funded medicinal cannabis trials and Yvonne Bonomo is leading cannabis research and education programs in Victoria.

Provenance: Commissioned; externally peer reviewed. ■

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