Compassion and evidence in prescribing cannabinoids: a perspective from the Royal Australasian College of Physicians

The RACP emphasises the need for caution until there is sufficient quality evidence to support the use of medicinal cannabis

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The pace and scale of the introduction of medicinal cannabis are unprecedented and have raised challenges for health professionals, not so much because of its known addictive and psychoactive properties but because its introduction has not followed the usual research-based safety and effectiveness processes. These processes include pharmaceutical, animal, pharmacological and clinical research, recommended under national medicines frameworks upheld by the Therapeutic Goods Administration (TGA) in Australia and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe), as well as by legislation such as the *Narcotic Drugs Act 1967* (Cwlth). The Royal Australasian College of Physicians (RACP) supports timely access to products with safety and effectiveness data. However, it appreciates that there is growing community demand for prescription cannabinoids on compassionate grounds. As such, effective medical leadership and guidance is required to inform public discussion and compassionate access until the necessary data become available and more specific advice can be given.

Calls for compassionate access present challenges to clinicians, given that the usual medical research standards of provision and review of pharmaceutical, animal, pharmacological and clinical research data have not yet been met. The TGA is responsible for regulating the supply, import, export, manufacturing and advertising of therapeutic goods through pre-market assessment, post-market monitoring and enforcement of standards, licensing of Australian manufacturers, and verifying overseas manufacturers' compliance with the same standards as their Australian counterparts. Approval of a registered product is based on satisfactory assessments of its quality, efficacy and safety. The TGA Pharmacovigilance Inspection Program continually monitors and evaluates the safety profiles of registered therapeutics and manages risks associated with individual products. It is important that all therapeutic products undergo this process to ensure that safety risks are known and unknowns are quantified. The RACP encourages that this be undertaken for all therapeutic products, including cannabinoids.

The Special Access Scheme (SAS) provides patient access to cannabis and other unregistered preparations on compassionate grounds without the usual quality and safety data requirements (https://www.tga.gov.au/form/special-access-scheme). The Senate has passed the Medicinal Cannabis Legislation Amendment (Securing Patient Access) Bill 2017, now with House of Representatives, to enable terminally ill patients to access

medical cannabis products from overseas via the SAS Category A (notification only) pathway. However, patient access to locally stored TGO 93-certified cannabis products through SAS Category B (requiring TGA and state review and approval) is currently faster for eligible patients who meet all Category B requirements (www.abc.net.au/news/2017-06-13/faster-path-to-medicinal-cannabis-reopened-senate-vote/8614674) than via Category A, which requires import licences and Customs clearance. Use of the Category A pathway also reduces oversight of the use and storage of these products, and inhibits shared knowledge of their efficacy and toxicity. SAS Category A applications also preclude the use of a local product. The TGA regularly updates its website with information and links on regulatory and other legal issues regarding access to medicinal cannabis across the states and territories (https://www.tga.gov.au/medicinal-cannabis-products-overview-regulation).

The RACP notes the publication in December 2017 of clinical guidance documents by the Therapeutic Goods Administration (https://www.tga.gov.au/access-medicinal-cannabis-products).

While the RACP understands the community interest in cannabinoids as a therapeutic product, it emphasises that the usual regulatory processes designed to protect patients from serious harms are incomplete for medicinal cannabinoids, and that evidence of their effectiveness for many medical conditions is at present limited. The RACP reaffirms the need to maintain appropriate quality, safety and efficacy standards in the knowledge that substantial harms may be experienced by many individuals using these products, including the non-psychoactive cannabinoids.[1-3] While the research into harms and benefits of products containing cannabinoids is in evolution, the RACP position is that a balanced, well

Key messages from the Royal Australasian College of Physicians (RACP) on medicinal cannabis

- The RACP supports the need for further high quality research to define whether or not cannabinoids have a place in contemporary medical practice.
- The RACP recommends caution in clinical prescribing until such time as there is clear evidence (significantly greater than placebo) of benefit outweighing harm for a specific product and a specific condition; current use should be in a research framework.
- The RACP advises that any patients taking medicinal cannabinoids should not drive. ◆

defined, compassionate yet precautionary approach is necessary for legislation and clinical practice. The RACP supports the maintenance of regulatory processes that responsibly protect and improve public health in Australia (Box).

Following is a summary of the current situation concerning prescribing, common perceptions and the state of knowledge, which may help physicians manage increasingly common requests for prescription cannabis.

Social context

Australians' acceptance of cannabis is higher than it has been for generations, for medicinal as well as recreational use.[4,5] However, important potential untoward effects have been described with the use of cannabinoids, and these are often not well understood by the lay community. Early evaluations undertaken in the United States, where cannabis has become more accessible, suggest adverse impacts on public health, such as a near doubling of emergency department presentations involving cannabis since it was legalised for medical use.[6,7]

Media narratives have suggested that for adults and children suffering intractable seizures, pain or other debilitating symptoms:

- using cannabis will improve these symptoms without side effects;
- cannabis is a natural agent and is therefore safe;
- slowing down access until a pharmaceutical grade product and evidence on symptom relief, side effects and long term effects are available lacks empathy; and
- patients are comfortable if therapies of uncertain effectiveness and safety are trialled to improve their symptom control.

Rather than clearly delineating the benefits and adverse effects of use for specific symptoms of specific diseases, a cluster of distress symptoms that benefit from treatment with cannabinoids is commonly described. Experienced clinicians have noted that some patients reporting benefit appear to do so because they welcome temporary relief provided by the affect modulation of cannabinoids, and are cautious given the lessons learned with the opioid class of medicines when used for the same reasons.

There are reasons for concern about the push for doctors to prescribe cannabinoids. For example, in bypassing typical TGA requirements, widespread prescription will likely remove incentives to invest in critical research necessary to understand these potential therapeutic agents and their effectiveness in treating a range of conditions in the long term. Losing the opportunity to gain sufficient high quality data will sacrifice a reliable assessment of clinical benefit and harm associated with cannabinoids prescribed for therapeutic purposes. Treatment of persistent non-cancer pain with opioid medicines similarly began with little supportive evidence and has been associated with an epidemic of overdose deaths and poor pain outcomes, resulting in ongoing suffering.[8]

Recent systematic reviews and meta-analyses of the evidence for the effectiveness of cannabinoids for analgesia show no benefit over placebo in pain reduction[9] and that significantly more patients experience adverse events.[9,10] The Australian and New Zealand College of Anaesthetists Faculty of Pain Medicine echoes statements made by the British Pain Society in not recognising a need for greater availability of cannabinoid medicines in general. Moreover, it does not endorse the use of cannabinoids in chronic non-cancer pain until the scientific literature identifies a clear therapeutic role for them.[11]

To introduce new therapies such as medicinal cannabis into general, undefined medical practice before evidence has been adduced appears to be inconsistent with the RACP's strong endorsement of the use of empirical evidence to guide practice. Initiatives such as EVOLVE (https://evolve.edu.au/about), which the RACP is undertaking in partnership with its affiliated specialty societies, seek to identify common medical practices that do not match the latest evidence regarding effectiveness and safety, and to reduce low value clinical practices.

The RACP acknowledges that significant state and federal funding has been granted to clinicians and researchers to help understand the optimal dose and formulation of specific products.

Physicians and evidence-based practice

Empowering patients to take an active role in their care is an essential component of best medical practice. However, this can compete with the ethical commitment to first do no harm and may be limited by a lack of evidence-based information about the treatment options available.

Australian doctors are required to adhere to the Medical Board of Australia Code of Conduct, which states that "doctors have a duty … to practise medicine safely and effectively" and "to ensure that [they] have adequate knowledge and skills to provide safe clinical care … considering the balance of benefit and harm in all clinical-management decisions".[12]

Other ethical dilemmas in practice include current constraints in treating patients within the health system, small research budgets that favour medicinal cannabis over other research, and opportunity costs in diverting clinical services away from other health priorities to develop guidelines and education for the therapeutic use of cannabinoids. The health budget is not limitless, and countries vary in their approach to spending decisions. In

Australia, it will not be possible to list cannabinoids on the Pharmaceutical Benefits Scheme until clinical effectiveness and cost-effectiveness can be shown. Investment in research now will also enable informed decisions for the benefit of patients in the future.

Conclusion

As is occurring globally, Australia is navigating unchartered waters with pharmaceutical grade cannabinoids. The medical profession, regulatory bodies and policy makers are listening to the community and working together to address the community's desire to access these products for medicinal purposes in as expedient and safe a way as possible.

The RACP emphasises the need for careful assessment. Patience and support for high quality, replicated clinical research is required if we are to continue pursuing cannabinoids as a potential new source of therapeutic agents. 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. Moreover, the medical profession is bound professionally and by law to treat patients based on an impartial assessment of the evidence. The medical profession must engage with patients and the community to articulate the reasons for a cautious approach to prescribing cannabinoids. Supporting patients to take an active part in their care requires us to provide them with evidence-based information about the treatment options available; this is the most compassionate course we can currently take.

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