BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Implementation of Medicinal Cannabis: Innovation or Upheaval? Perspectives from Physicians as Key Informants.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054044
Article Type:	Original research
Date Submitted by the Author:	02-Jun-2021
Complete List of Authors:	Hallinan, Christine; The University of Melbourne, Department of General Practice; Gunn, Jane; The University of Melbourne, Department of General Practice Bonomo, Yvonne; The University of Melbourne, Department of General Practice; St Vincent's Health Australia Ltd Fitzroy, Department Of Addiction Medicine
Keywords:	Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Change management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, QUALITATIVE RESEARCH, Herbal medicine < THERAPEUTICS, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Implementation of Medicinal Cannabis: Innovation or Upheaval? Perspectives from Physicians as Key Informants.

Dr Christine Mary Hallinan, Department of General Practice, Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences of the University of Melbourne, Level 3, 780 Elizabeth Street, Carlton, Victoria, 3053

A/Prof Yvonne Ann Bonomo, St Vincent's Health - Department Of Addiction Medicine 38 Fitzroy Street, Fitzroy, Victoria, 3065

Prof Jane Maree Gunn, Department of General Practice, Melbourne Medical School, Faculty of Medicine, Dentistry and Health Sciences of the University of Melbourne, Level 3, 780 Elizabeth Street, Carlton, Victoria, 3053

Corresponding author at: Dr Christine Hallinan at the Department of General Practice, Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences of the University of Melbourne, Level 3 780 Elizabeth Street, Building 220, Carlton Victoria, 3053. Telephone +61 438 811 595 Email address: hallinan@unimelb.edu.au

MeSH Terms
Cannabinoids
Organization and administration
Therapeutic use
History
Standards

Word Count 4967

This qualitative research is placed within a theoretical framework, the Diffusions of Innovation Model. With this, our methods of data analysis were clearly described and theoretically justified. This contributed to the word count; and adds enhanced rigour to this research.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Implementation of Medicinal Cannabis: Innovation or Upheaval? Perspectives from Physicians

Abstract

Objective

We sought to explore physician perspectives of the prescribing of cannabinoids to patients to gain a deeper understanding of the issues faced by prescriber and policy makers in the rollout of Medicinal Cannabis (MC).

Design

A qualitative analysis of 21 in-depth Key Informants interviews was undertaken to explore the policy and practice of MC prescribing. The analysis used an adaptation of the Diffusion of Innovation (DoI) theoretical framework to model the conceptualisation of MC implementation in the Australian context.

Setting

Informants from the States of Victoria, New South Wales, Tasmania, Canberra, and Queensland in Australia were invited to participate in a interviews to explore the policy and practice of MC prescribing.

Participants

Participants included 21 prescribing and non-prescribing key informants working in specialty areas of neurology, rheumatology, oncology, pain medicine, psychiatry, public health, and general practice.

Results

There was agreement among many informants that MC is, indeed, a pharmaceutical innovation. From the analysis of the informant interviews, the factors which will facilitate the diffusion of MC include, the adoption of appropriate regulation, the use of data to evaluate safety and efficacy, the need for improved prescriber education, and the requirement to monitor quality and cost. Most informants asserted the widespread assimilation of MC into practice is impeded by lack of health system antecedents required to facilitate the safe, effective, and equitable access to MC as a therapeutic.

Conclusions

This research highlights the tensions that arise, and the factors that influence, the rollout of MC into mainstream clinical practice. Addressing these factors is essential for safe and effective MC prescribing in contemporary medical practice. The findings are not only currently relevant to MC, but to other potential novel therapeutics in the future, where there is already consumer and political pressure for their introduction into practice.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Strengths and limitations of this study

- Fills an identified gap in the literature by reporting the perspectives of Australian health professionals about the rollout of MC into clinical practice in Australia.
- The research aligns with conventions for 'quality' in qualitative research with the use of open-ended interview techniques, an established and validated theoretical Diffusion of Innovations Framework and a sampling strategy has been explicitly described.
- Provides a valuable perspective for other countries to consider.
- Provides evidence around the prescribing of other novel therapeutics emerging in similar fashion to medicinal cannabis, for example the serotonergic psychedelics for mental health and addiction.
- Provides evidence around perspectives from Australian key informants only, and as a result the research may not be generalisable to policy and practice in other countries.

Background

Cannabis was first used as a medicine as far back as 5,000 years ago,[1, 2]. Legislation enacted in 1961 in the U.S, U.K and Europe however re-classified cannabis from a therapeutic medicine to a prohibited drug,[1, 3-5]. This legislation not only criminalised the use of cannabis, including for medical purposes but also contributed to a lack of pursuit of evidence for its medicinal effects, as procurement of cannabis for scientific studies became restricted,[1, 5].

Since the nineties, there has been a re-emergence of interest in the use of cannabis as a medicinal product driven by multiple factors including developments in understanding about the endogenous cannabinoid system in the brain; the collateral effect of the harmful opioid epidemic in the Western world; increasing prevalence of use of cannabis in the community; community perceptions that cannabis is relatively inert; and the rapid expansion of the medicinal cannabis (MC) industry,[1, 6-8]. Worldwide, community demand for access to MC products has followed this burgeoning interest resulting, in global changes towards treating cannabis as a medicine,[9].

The Director General of the World Health Organization has recommended re-scheduling of MC in the international drug control framework to facilitate the use of cannabinoid substances for medicinal and scientific purposes,[10]. In the United States, an increasing number of states are legalising both medicinal and non-medicinal cannabis use,[10, 11] despite the opposing Federal Law. In the early 2000s, Israel (2001), the Netherlands (2003), and later other countries, including Switzerland (2011), Italy and Czechia (2013), Australia (2016) and Germany (2017) legislated to allow the use of MC under specified conditions,[10]. The Canada and United Kingdom legalised MC in October - November 2018, and other countries such as Luxembourg are following suit,[10, 12].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Notwithstanding these actions, MC exemplifies one of a suite of therapies, that have been introduced with ambiguous understanding of their therapeutic benefit, and no clear clinical indication supported by accompanying evidence. Other agents in this category have included 'health supplements' such as probiotics,[13, 14], e-cigarettes as nicotine replacement therapy,[15], and other currently illicit substances predicted to be of broader therapeutic value in the future such as psychedelics,[16].

The implementation of MC should be underpinned by the synthesis of evidence. Hence, the collection of information specifically relating to physicians' knowledge, concerns, and experiences with MC is imperative. To date, the majority of studies in the area from a range of countries have highlighted remarkably consistent themes, which include health professionals' lack of confidence in prescribing MC, need for education about cannabinoid therapeutics, and their attitudes to cannabis as a therapeutic agent,[17, 18]. A systematic review undertaken by Gardiner, Singleton, Sheridan, Kyle, & Nissen in 2019, reported on research from 26 studies found that in general, health professionals supported the use of medicinal cannabis in practice,[17]. This review also reported there was a unanimous lack of self-perceived knowledge surrounding all aspects of medicinal cannabis and indicated many health professionals were concerned about direct patient harms and indirect societal harms[17]. The majority of published evidence that provided a focus on physician perceptions has been collected via surveys and questionnaires,[19-25]. Of the evidence collected from interviews, were two studies that examined physician insights around use of MC as a therapeutic agent,[18, 20]. One study published by Braun et al., in 2018, conducted semi-structured interviews on oncology experts from the United States,[20]. This research had a specific focus around perceptions of the use of MC in oncology and cancer care. Zolotov et al., (2018) used narrative analysis of data collected from interviews with twenty-four Israeli physicians with specialities in pain medicine; oncology family and medicine physicians,[18]. While these qualitative data provided vital evidence to the current research landscape, neither examined key informant perspectives on the important broader systemic issues, such as how the 'diffusion' of medicinal cannabis into medical practice is occurring. Specifically, this research aimed to provide evidence around key informant perspectives of the role of the prescriber, the differences between licensed MC products such as *Sativex*® (the sole licenced product in Australia) and unlicensed products such as all other MC products that require TGA approval but can be prescribed, as well as illegally produced MC (sometimes referred to as artisanal MC[1]). Informant perspectives on the relevance of regulatory authorities in the prescribing of MC, and their views on the precedent that MC has set around consumer-lead medicine were also sought.

The theoretical model of the Diffusion of Innovation (DoI),[26] helps conceptualise the implementation of medicinal cannabis globally and the factors needed to facilitate safe and effective rollout. Originating

[1] Artisanal medicinal cannabis are unregistered herbal cannabinoid preparations produced by small-scale artisanal farms. Artisanal (bootleg) MC is complex in nature where the quality and quantity of MC compounds vary from one batch to the next (Sulak, Saneto, & Goldstein, 2017)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

in 1962, the framework explains how a product or idea can gain momentum and 'diffuse' through a social system, with the end result being that the product or idea is adopted and becomes a part of the social system [26]. This framework has previously been used in research relating to innovations in health care, medical sociology and physician practice including prescribing,[26-35]. MC has characteristics relevant to pharmaceutical innovations by virtue of its 'medicinal' name, the requirement for it to be prescribed by a medical professional for a health condition, and oversight occurring via regulatory authorities for pharmaceuticals and other therapeutics, the Food and Drug Administration (FDA) in the United States, European Medicines Agency (EMA) in Europe and equivalent bodies in other countries. Applying MC to the DoI framework, a key to its adoption lies in the perception of both prescribers and community that MC is innovative. Pharmaceutical marketing, drug characteristics, government policies and the behaviour of both medical professionals and patients are additional key factors in uptake of new therapeutic agents,[31]. The principle difference with MC, however, is that unlike other pharmaceutical innovations, it is not a single molecule or single compound, for use in a single, or small cluster of indications, and importantly it has not emerged from traditional pharmaceutical companies, which have standard research and development (R & D) and pharmacovigilance systems.

Legislation authorising the compassionate use of MC was endorsed in Australia by State and Federal governments in October 2016,[36]. Cultivation and production (jointly), research and manufacture of MC in Australia was also de-criminalised at this time,[37]. On the 1st of November 2016, further amendments were made to the scheduling of MC products. These changes resulted in certain MC products (CBD) being down regulated from a Schedule 9 (S9) - Prohibited Substances category, to a Schedule 8 (S8) - Controlled Drug category by the Australian medicines regulatory body, the Therapeutic Goods Authority (TGA),[36]. To date, only one MC product is registered, or licensed, in Australia (*Sativex*®, meaning that all other MC products are therefore unapproved therapeutic goods, not having been assessed by the TGA for safety, quality or effectiveness,[36].

To address increasing demand, in July 2018 an online system was introduced on to enable a more streamlined application process for the lodgement of Special Access Scheme Category B (SAS-B) applications for TGA approval to prescribe unlicenced MC preparations,[36]. Since then, from a baseline of 146 applications recorded in June 2018, applications have increase at an exponential rate with record of 6,682 applications in the month of March 2021,[36]. This represents a 4,477 percentage increase in the number of SAS B approvals, and amounts to a cumulative total of 109,288 approvals across the period (Figure 1),[36]. Notwithstanding this, there is still discord around those who are in favour of MC and those who are not, and this potentially drives a chasm between patients and their physicians, and between physicians and their colleagues.

In terms of the global context, the Australian approach to MC beginning with adoption of legislative changes permitting its prescribing delivers a unique opportunity to gather important evidence for the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

factors which impact on the rollout of MC. It also enables an examination not previously described of what influences the diffusion and dissemination of MC into contemporary clinical practice. Importantly, it provides an opportunity to investigate the health system and regulatory factors that are associated with the provision and monitoring of MC to patients. It is thus timely to examine *de novo,* the 'diffusion' of MC to gain a greater understanding of the facilitators and barriers to the safe and appropriate dissemination of MC to patients by their physicians.

Our aim was to gain a deeper understanding of the factors that are associated with the diffusion of an unlicensed therapeutic into medical practice for which strong consumer demand preceded the research evidence. This is essential to informing both the 'rollout' of MC and the way medicine is practised in the twenty-first century. Furthermore, it provides lessons that will be relevant for the future, with the other potential novel therapeutic agents, subject to the similar influences, being introduced into clinical practice. These findings are also highly relevant to the global context of medicinal cannabis, demonstrating to countries considering the introduction of MC the lessons learned through the Australian experience.

Methods

A qualitative narrative analysis was used to investigate the phenomena around the prescribing of MC in the Australian context. Informants were invited to participate in an in-depth interview which was guided by some key questions (Table 1). The selection of the key informants invited to participate in this research was based on their involvement in the clinical practice where MC might be prescribed or in the development of policy for MC prescribing.

Both prescribing and non-prescribing key informants were interviewed as it was deemed important to understand not only the factors that influenced an individual to prescribe MC, but also the factors that influenced others to decide not to prescribe MC. The focus of the interviews was on MC products that can be prescribed via the TGA-SAS-B scheme. This included the registered MC product, *Sativex*® and non-registered MC formulations such as *Cannabidiol*®, *Capilano*® and *Tilray*®. It was anticipated that informants might raise the issue of non-prescribed artisanal MC products and how illegal access to artisanal MC impacts on patient care. This information was included in the analysis. Informants were advised that use of 'recreational' cannabis for medical or health reasons was considered out of scope for this study.

Key informants were selected using purposive and snowballing techniques. Initially informants were selected following an environmental scan and rapid review of the literature using the search term 'medicinal cannabis'. Environmental scans are increasingly being viewed as a valuable tool in health care scoping,[38] and rapid reviews are a useful methodology for the collection of information in a

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

timely manner, [39, 40]. Other potential key informants were identified following interviews using peer snowballing. This involved invitation of the peers of interviewees following their suggestion to do so. The professional networks of the researchers were also used in the selection process. Classifying MC as an 'innovation', a priori thematic saturation was determined to be interviews from at least 20 key informants,[41]. Informants were sent an email and a postal invitation; this recruitment methodology has been shown to increase response rates,[42]. The informants who did not respond were followed up with either another email and/or a phone call of invitation to participate. All informants were provided a patient information leaflet statement (PLIS), which required their signature, this provided the research informed consent.

Semi-structured interviews, average duration of one hour, were conducted by two authors (CH,YB) face to face, via video conference, or telephone (Table 1). All informants were notified that the interview would be recorded and transcribed verbatim. Notes were taken during the interview. Reflexive notes were developed on completion of interview. This involved a critical analysis of the interview process by the interviewers (CH, YB). All interview data was de-identified and stored in a secure platform. Data was then managed in NVivo12,[43]. Inductive coding of the data was done by two authors (CH, YB). This duplication enabled the validity of the result to be assessed,[44].

Patient and Public Involvement

Patients and members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Results

A broad cross-section of the medical community who had an interest in MC was sought. Twenty-six individuals were approached, twenty-three accepted, of these one withdrew for personal reasons, and another withdrew because of time constraints. There were three potential informants who did not respond to any of the invitations, these individuals were not directly involved in the prescribing of MC. Of the informants who accepted, thirteen were active prescribers, four were non-prescribers, and four were policy makers. The 21 key informants included neurologists, rheumatologists, oncologists, pain specialists, psychiatrists, public health advisors and general practitioners. All informants were based in the Eastern States and Territories of Australia (Victoria, New South Wales, Tasmania, Canberra, and Queensland). There were no informants from other states of Australia (South Australia, Western Australia, and Northern Territory) because at the time of the interviews there was minimal MC prescribing in these jurisdictions. Interviews were conducted between November 2018 and January 2019.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

FACTORS INFLUENCING THE DIFFUSION OF MEDICINAL CANNABIS IN AUSTRALIA

A number of components in the DoI framework were described by the informants in relation to medicinal cannabis (Figure 2).

MEDICINAL CANNABIS AS AN INNOVATION

The information in this domain is depicted in the *Innovation* block (Figure 2).

Relative advantage against other medicines

Several key informants saw innovation in MC in its use for the treatment of several conditions where patients present with significant and debilitating refractory symptoms due to the lack of efficacy of current therapies. Examples of conditions cited by the informants included childhood epilepsy, chemotherapy related nausea and vomiting, pain management for patients in palliative care and chronic non-malignant pain, and young people with anxiety. Some informants perceived MC as relatively inert, and therefore advantageous, especially when comparing adverse events with other therapeutics that have been used to treat the above conditions.

Several individuals reported on the positive benefits from MC that were either observed in their clinical practice, or derived from the scientific literature. On the other hand, some found that not all patients benefited from MC, and in these situations prescribing of MC ceased.

Often, informants articulated vague benefits of MC. One individual described the effects of cannabis as 'different' and 'special'. Several described that patients reported they 'just felt better'. They were also vague about potential harms of MC. Some reported concern about its effects on the developing brain and risks associated with cognitive impairment in young people as well as risks more generally of impairment in relation to driving. Most asserted that MC should only be prescribed for the conditions recommended by the TGA, and highlighted the caveat that risks of harm needed to be considered relative to the severity of the indication for its use. For instance, prescribing MC to a young child posed more of a concern than prescribing to a patient with terminal cancer as part of a palliative care regime (Box 1).

Box 1

it doesn't work for everybody and for some people it has no benefits whatsoever, for some people, it has terrible side effects, but I believe that users are best able to work with their doctors if they think it is a benefit to them. It kind of is one of those things that you kind of have to try.

I am not the fearful cannabis will kill you all and I am not [..convinced..] cannabis will cure all.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Complexities with medicinal cannabis

All informants referred to the prescribing of MC as being fraught with complexities associated with ambiguities around its effectiveness, the political process involved in its 'roll out', the patients and conditions in which it is prescribed and the prescribing process itself.

Some informants also referred to concerns around the purity, concentration, and consistency of MC products. For example, they queried the reliability of MC preparation or concentrations of THC and CBD that may not match the dosages they wished to prescribe. Issues relating to a naivety among some MC companies regarding regulations pertaining to storage of scheduled products, lack of solid data on product efficacy and lack of understanding about the imperative to report adverse events that are standard practice in mainstream pharmaceutical companies. A few informants also described ambiguities regarding where MC 'fits' in contemporary medical models of care, such that, some informants did not view MC as a medicine, rather an 'unregulated herb'. Many reported concerns around the lack of empirical evidence of efficacy and lack of data around adverse events. Several informants reported on concerns about the financial costs incurred by patients wanting cannabis medicines. Some described costs as prohibitive, especially in situations where patients had been enrolled in trials that had come to an end. Informants also recounted lag times, particularly early in the roll out, where a request for cannabis and patient access to the product could take several months (Box 2).

Box 2

There's no reimbursement - no subsidy, I should say, and the companies are just taking advantage of the situation. I find it difficult to believe that it could actually cost $650 a bottle for them to make it and sell it at a profit.

[Costs] to the order of a couple of grand a month. One to two and a half thousand per month. The one thousand is because it's an infant. It's prohibitively expensive. Broadly, if there's a family that are asking and meet that sort of criteria, severe and failed everything, I'm very happy to prescribe the private script. As long as they're properly informed and consented. It's a huge chunk of money for most people.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The vast majority of informants reported on the great divide between the safety and quality of products that have been derived from an unregulated market, such as in MC production, and pharmaceuticals that had been appropriately trialled and accordingly developed to a standard for approval by the TGA. Some mentioned concerns about toxicology of the product and the need to titrate the product slowly to ensure the patient was not receiving 'toxic' levels too quickly that impeded the patient's functioning. Others were concerned about the quality of the product because of uncertainty about the conditions of manufacturing (Box 3).

Box 3

The question is if it's grown outdoors - so, the first thing is, it has to be organic, there can be no chemicals or anything else used, herbicides, because if you're using for medicine. The second thing is it has to be consistent.

Trialability of medicinal cannabis

Many informants indicated they were involved in trialling the product, where they were invited to participate in open-labelled trials by governments and MC companies. In these trials, the prescriber was the conduit between the patient and the cannabis, which was provided to the patient by the MC companies. This provided an opportunity to their patients for cost free access to cannabis and also enabled them to understand more about how to prescribe MC and to monitor their patient's response, whether it be symptomatic relief or reports of adverse events (Box 4).

Box 4

I'm a strong advocate for this being treated the same as any other medicine. In that way ideally cannabinoid trials would continue, just like any other medicine…

Most of us - people are generating trial data but really in very specific…[conditions]

DIFFUSION OF MEDICINAL CANNABIS

The information in this domain is depicted in the *Diffusion* and *Dissemination* block (Figure 2).

Professional information and evidence about innovative pharmaceuticals

All informants discussed the requisite for explicit knowledge to inform prescribers on the effects and outcomes of MC. Many informants reported they gained explicit knowledge through access to peer reviewed publications and through government websites such as the TGA. They also described gaining knowledge from information provided to them by their peers, although a few informants reported they

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

were not confident of the knowledge base of colleagues. The gaining of implicit knowledge by undertaking open-label trials and monitoring their patients who are on the trials, was viewed as informing their own practice as well as contributing to the evidence base. Prescribing to patients provided further tacit knowledge. In this case informants reported unexpected effects, such as symptomatic relief in some patients who were prescribed only a very small amount of product and minimal effects of patients who were prescribed large doses of the same product. The potential for placebo effect was acknowledged, but did not deter from continuing to prescribe MC. Informants also discussed concerns around prescribing MC when the exact quantity of cannabidiol (CBD)[2] compared to (tetrahydrocannabinol) THC[3] is often not confirmed, as the manufacturing of the product is not controlled by any pharmaceutical regulatory body. Many mentioned that the paucity of validated evidence on the effects and adverse outcomes associated with MC use was a limitation in the 'roll out' of cannabis to patients.

Prescribers also reported they had minimal explicit knowledge on the prescribing process, especially regarding how to prescribe an unregulated medicine to a patient. Notwithstanding this, all reported much implicit and tacit knowledge was gained with each prescription that was prescribed (Box 5).

Box 5

The problem - I think that people - general public will have their views about it being useful for x and y because that's already out there. I think the medical profession, hopefully if the data gets better, will have a better idea about what it actually is useful for and what combinations of different compounds are...

DISSEMINATION OF MEDICINAL CANNABIS

Marketing efforts by medicinal cannabis companies

The majority of informants perceived MC companies greatly facilitated the dissemination of medicinal product by actively pursuing doctors and inviting them to either trial their product, or prescribe to patients via newly established Cannabis Access Clinics. Several informants reported MC companies frequently cited overseas 'successes' relating to the roll out of MC. They also mentioned the entrepreneurial nature of the MC industry, and referred to the risks associated with the artisanal MC products as well as patients who can, or will, 'grow their own' particularly if cannabis becomes legalised.

[2] CBD – not psychoactive, exhibits no effects indicative of any abuse or dependence potential. https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf

[3] THC - the major psychoactive constituent in found in cannabis https://www.who.int/substance_abuse/facts/cannabis/en/

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Expert Opinion

Some informants referred to individuals they perceived as MC 'champions' in Australia. These individuals viewed it as a therapeutic product that should be normalised and accessible through unrestricted prescribing pathways.

Policy drivers and the need for technical support

Informants frequently reported the process for prescribing was quite technical, especially regarding the necessary requirements for a prescriber to gain an authorised prescriber status by the Therapeutic Goods Authority. Most reported that support was provided by the TGA around the process. Both the TGA and prescribers reported the technical process around prescribing were both labour intensive and burdensome, particularly initially.

HEALTH SYSTEM READINESS FOR MEDICINAL CANNABIS

The information in this domain is depicted in the *Health System Readiness* block (Figure 2).

Agency for Change

The vast majority of informants reported that the agency for change leading to rapid evolution of cannabis from that of an herb to that of medicine was the political response to patient demand. Many also commented that this had caught much of the medical profession unawares. A striking number of informants referred, without prompting, to metaphors associated with 'the bolting horse' and a few referred to the Trojan horse, where they felt the medicalising of cannabis was a way for recreational users to access legalised cannabis under the guise of a medicine (Box 6).

Box 6

'the horse has bolted'; 'the horse has bolted and left the cart way behind'; 'the horse has bolted so far it's over the horizon'; 'the horse has disappeared over the horizon'; 'given that the horse has bolted', 'given that the horse is a government horse, the jockey has fallen off'; it was a rather opportunistic cart before the horse but good publicity move on behalf of the politicians'

there's a bit of a Trojan horse dynamic here I think, where those who actually, really are dependent and need and want it because they're dependent, have now got an easy way of communicating, give it to me because I've got a medical problem

With the current trend of course we're going to end up with the legalisation of cannabis…That's clearly the hidden - that's the Trojan horse

They [politicians] were, in a way, pushed into this - I mean, it [medicinal cannabis] might act as a Trojan horse to some degree.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Implementation of the 'roll out' of medicinal cannabis – preparedness for regulation

Some informants argued for the need for new governmental arrangements between legislative structures and the 'content experts' to drive the medicinal strategy forward. Most were open to expansion of the program, yet all felt MC was unhinged by the rapid and under-resourced 'roll out' of the innovation, and lack of systemic monitoring (Box 7).

Box 7

That's our challenge now - to re-think our legislative structures and how we manage problems so that we can reduce the induced, indirect harm, which is the legal harms… without increasing access, availability, advertising, promotion, and cost incentives to increase consumption and thereby increase harm.

Power balance: medical professional and patient factors

A number of individuals expressed their view that MC is compatible with the way they work, citing the doctor-patient relationship and a duty of care to their patients as reasons for considering prescribing medicinal cannabis. Some informants commented on the tenacity with which patients believed that cannabinoids would provide benefit, and remarked that this was an influential factor for them to take up prescribing.

Social influences were also cited by a number of informants. They noted that the families of children with chronic conditions, celebrities, advocacy groups and politicians have been strong social influencers to prescribe MC. This had been unprecedented compared to any other area of medical practice. It was felt that this had both benefits, in raising awareness and attracting philanthropic, and to a lesser extent, government funding, but also disadvantages. Informants cited that pressure, even coercion and a lack of acknowledgement by these social influences of the standard process for introduction of a new therapeutics has, to some extent, created a division between the community and health professionals.

IMPLEMENTATION OF MEDICINAL CANNABIS 'ROLLOUT'

The information in this domain is depicted in the *Implementation* block (Figure 2).

Policy and support from government agencies for the 'rollout' of MC

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Many cited a lack of leadership and direction from the medical profession, governments, and government agencies in the initial stages of the rollout, although most of these informants reported this has improved with time. For example, the guidance documents published on the TGA website were described as beneficial and of those who had prescribed, all reported the streamlining of the application processes around the provision of medicinal cannabis to patients most beneficial. One informant felt the TGA had done a remarkably good job in navigating through the issues, especially considering the political pressure they were under and the clinical reality of prescribing an unlicensed product to a patient. Regarding access to formalised education, all informants stated this was greatly needed but that instead they had resorted to being 'self-taught'. They described this as burdensome, but most justified this by saying they were prepared to do this because they felt they had a duty of care towards their patients.

The majority of informants acknowledged the need for a robust and nimble pharmacovigilance system for reporting of adverse events so that they understood what to monitor during patient review as well as review what other health professionals were observing. Most considered that the systematic monitoring of prescribing outcomes was vital for the safely of future patients, and many raised concerns about potential harms associated with the provision of medicinal cannabis to children and young people. All considered the system currently in place for pharmacovigilance was inadequate and described the need for systematic and sustained research around medicinal cannabis and its effect on humans Box 8.

Box 8

There is a dearth of knowledge. We need to have a prospective arrangement in order to supply pharmacovigilance that are also about outcomes - the profiles of people who are benefiting and not benefitting. So I think there's a bit of a direction of duty there.

…the idea of proper pharmacovigilance. And that's safe prescribing, and it's just a whole system that we just don't have in Australia…It would be good if we can make some changes because that'll have a benefit across the board.

The way we make advances in medicine is through research. If it just falls down to anecdotal stories and claims, then we're not going to know the right doses for children with epilepsy.

I think there's a high risk of a poorly regulated market, or limited regulation market, where patients, children, will be able to get maybe partially subsidised products that are probably manufactured well but don't have the trial backing.

Discussion

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

MC has not rolled out into the Australian community smoothly as a potential therapeutic, confirmed by a report from a Senate Inquiry into *Current Barriers to Patient Access to Medicinal Cannabis in Australia* published in March 2020,[45]. This study of 21 key informants provides important details regarding what has been effective and why, as well as which factors are barriers that need to be addressed if safe and effective prescribing of MC is to be made available to the Australian community. The key informants overwhelmingly acknowledged the complexity of MC and highlighted the dynamic and contingent aspects to its implementation, as well as the continually shifting environmental context (including public and political attitudes, economic aspects to its implementation) and other complex service level considerations. Given this, the experience from diffusion of pharmaceuticals,[31] and other innovations,[26], is very helpful to understanding how MC has been implemented to date, as well as, moving forwards, what steps are needed for its rollout to continue to be as safe, appropriate and effective as possible.

MC as an Innovation

The majority of informants viewed MC as an innovation for reasons articulated in the DoI model (Figure 2). It was seen as a therapeutic with potential, albeit not conclusive, advantages over other medicines, especially when used as adjunct treatment. Informants who were prescribers described being able to trial using MC in patients without significant adverse effects. This added to the knowledge required, but as yet difficult to access, in relation to how to prescribe MC.

Diffusion and Dissemination

Factors in the DoI model that facilitated diffusion and dissemination were described by the informants and these included peers and professional networks providing the information needed to take up prescribing (Figure 2). Dissemination via these channels, as well as via MC companies, was also highlighted as positive influences in MC rollout.

MC System Antecedents

The DoI model categorises system antecedents into Structure (e. g. maturity, history, and MC) distributer resources, Knowledge (e.g. pre-existing understanding of the endocannabinoid system and the pharmacology of cannabinoids) and Context (e.g. medical leadership in the prescribing of MC) (Figure 2). It was evident from the informant interviews that this domain in the DoI model had largely been deficient in the rollout of MC. This helps understand how lack of system readiness, reflected in the staggered legislative changes around the various jurisdictions of Australia, has impacted on MC diffusion and dissemination. System antecedents are clearly very important factors and this observation is useful learning for other countries considering the introduction of MC.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Health System Readiness

Some aspects of health system readiness were described, such as agency for change, and system fit, e.g. preparedness for regulation, and the power balance between Supporters (largely patients and their advocates) and Opponents (largely medical professionals and regulatory authorities). Missing components of this domain, and factors that are needed moving forwards not only for Australia, but also other countries, relate predominantly to pharmacovigilance, especially time and resources to perform this monitoring and feedback to regulatory authorities, patients and MC suppliers and the sustainability of this in the longer term (Figure 2).

Prescriber Adoption, Assimilation, and Practice

This remains a stark gap in the diffusion of MC into the Australian community (Figure 2). Understanding the needs, motivation, values, goals, skills and learning style of health professionals in relation to prescribing MC is an area that will need far greater attention for continued rollout of MC. While the most immediate needs such as prescribing guidance and streamlined regulatory approval have been important steps, there are other policy levers that have been shown to be important influences on the uptake of new practices in primary care,[46-50].

Levers used to promote the diffusion of a new therapeutic, often incorporate a blend of financial and non-financial incentives can include direct remuneration, performance feedback and the delivery of information technology systems. For example, financial incentives could incorporate the inclusion of a Medicare item number to report and monitor the prescribing of MC. Similarly, workflow tools, such as GP software for Electronic Medical Records (EMR) that prompt consideration of medicinal cannabinoids as a therapeutic, facilitate the reporting of effectiveness and adverse events are other important instruments that have the potential to leverage change.

Implementation

While helpful, government and policy changes have been mentioned earlier, other notable factors in the DoI framework that will assist safe implementation of MC including training, dedicated resources and, importantly, feedback on progress. This is where pharmacovigilance and patient reported outcome measures (PROM) are vital.

Consequences of MC

Rapid changes in today's world are challenging the traditional ways that authoritative bodies such as regulatory agencies and medical colleges authorise and endorse medical practices, and MC is no exception. Notwithstanding the steps that have been undertaken by these authorities to accommodate

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

MC, their relevance is threatened, and they face substantial pressures to change how they operate, [51]. Most importantly, ongoing dialogue is needed between regulatory authorities, health professionals and the community, both at the outset and throughout the process of rollout, to work through the issues highlighted by the informants in this study. In the first instance, acknowledgement is needed between patients and prescribers that there remains a paucity of knowledge about side effects and adverse events of medicinal cannabinoids and therefore a willingness to contribute to pharmacovigilance systems. Equally, as has been proposed by others, the voice and experience of consumers needs to be incorporated into the way health professionals prescribe, and regulatory authorities facilitate, provision of medicinal cannabis,[52]. This research design enables exploration of many issues and key themes, however ongoing research is needed to continue to explore and understand these, given the constantly changing clinical, economic, and political influences both in Australia and internationally.

Conclusion

Medicinal cannabis marks a new era in the practice of medicine. Informants were, for the most part, comfortable with the increasing trend for consumer-lead advocacy and input into their healthcare, as has clearly been seen with MC. However, many expressed concern that this seemed to be at the expense of 'tried and true' methods in clinical practice. Especially highlighted was, the perception that clinical practice is moving away from the scientific paradigm and evidence-based medicine. Given this, an understanding of the multiple interacting factors known to influence the diffusion of pharmaceutical innovations is imperative to facilitate safe and effective implementation of medicinal cannabinoids into clinical practice. Incorporation of consumer experience into the way physicians prescribe, and regulatory authorities facilitate, provision of medicinal cannabis is needed. Consumers and prescribers also need to be willing to embrace innovative methods of pharmacovigilance to address the gaps in evidence for the wide range of indications for which MC is being prescribed. We have shown that the relationships between the different influencing factors are critical to innovation success. Substantial collaboration is therefore needed moving forwards with MC. Substantial collaboration, both at the outset and during the rollout, is therefore needed moving forwards with MC, including communication, consultation, and dialogue between key stakeholders - consumers, prescribers, regulatory authorities, and politicians. This is fundamental to proceeding safely and effectively with the dissemination of medicinal cannabis into clinical practice.

Contributors

Interviews were carried out by CH and YB. Analysis was led by CH and YB. CH and YB conceived of the study, and participated in its design. CH, YB and JG read and approved the final manuscript.

Funding

This study was supported by the Australian Centre for Cannabinoid Clinical and Research Excellence

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(ACRE), funded by the National Health and Medical Research Council (NHMRC) through the Centre of Research Excellence scheme. ACRE has established several research teams who are involved in gathering evidence to develop a national research and policy framework that ensures quality and safety in the implementation of medicinal cannabis use in the community. The authors also wish to thank all Physicians, Prescribers and Experts who generously contributed their time, expertise, and personal experiences to this research.

Competing interests

Yvonne Bonomo is a principal investigator for industry sponsored clinical trial of the pharmacokinetics of medicinal cannabis for Zelira Therapeutics Ltd.

Ethics Approval

This study had University of Melbourne Human Research Ethics approval (HREC 181524.1).

Data sharing statement

No additional data are available.

Twitter Follow

Follow Christine Hallinan at @Cmhallinan

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Interview Guide

Theme	Question
Medicinal cannabis as an innovative medicine	*Before we start, do you view Medicinal Cannabis as a (pharmaceutical) medicine, or do you feel it should be defined as another type of product?*
Role for medicinal cannabis as a pharmaceutical	*What do you see currently as the role for medicinal cannabis?*
Experience with medicinal cannabis	*Can you tell us a bit about your experiences around medicinal cannabis?*
Rollout of medicinal cannabis in Australia	*Take us through the processes of prescribing medicinal cannabis from when a patient presents, to when they leave and when you review their progress?*
Overall attitude to medicinal cannabis in Australia	*Is there anything that we haven't discussed yet that you think is important for us to know about? Such as a take home or 'chestnut' message.*

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

References

1. Bridgeman, M. B., & Abazia, D. T. (2017). Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. P & T :a peer-reviewed journal for formulary management, 42(3), 180-188. Retrieved October 02, 2019, from https://pubmed.ncbi.nlm.nih.gov/28250701

2. Lancaster, K., Seear, K., & Ritter, A. (2017). Making medicine; producing pleasure: A critical examination of medicinal cannabis policy and law in Victoria, Australia. *International Journal of Drug Policy, 49*, 117-125. doi:10.1016/j.drugpo.2017.07.020

3. Grinspoon, L., & Bakalar, J. B. (1993). *Marihuana: the forbidden medicine*. New Haven, USA: Yale University Press.

4. .Kalant, H. (2001). Medicinal use of cannabis: history and current status. *Pain Reearch and Managment, 6*(2), 80-91. doi:10.1155/2001/469629

5. Taylor, S. (2008). Medicalizing cannabis—Science, medicine and policy, 1950–2004: An overview of a work in progress. *Drugs: Education, Prevention and Policy, 15*(5), 462-474. doi:10.1080/09687630802114038

6. Pertwee, R. G. (1997). Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacology & Theraputics, 74*(2), 129-180. doi:10.1016/s0163-7258(97)82001-3

7. Russo, E. (2004). *History of cannabis as a medicine*. The medicinal use of cannabis and cannabinoids, ed. G. Guy, B. Whittle, and P. Robson. London: Pharmaceutical Press.

8. Iversen, L. (2003). Cannabis and the brain. *Brain, 126*(6), 1252-1270. doi:10.1093/brain/awg143

9. Hazekamp, A., Ware, M. A., Muller-Vahl, K. R., Abrams, D., & Grotenhermen, F. (2013). The medicinal use of cannabis and cannabinoids - an international cross-sectional survey on administration forms. *Journal of psychoactive drugs*, **45**(3): p. 199-210.

10. EMCDDA. (2019). *Cannabis policy: status and recent developments.* EMCDDA Europa. Lisbon, Portugal: European Monitoring Centre for Drugs and Addiction. Retrieved September 10, 2019, from http://www.emcdda.europa.eu/publications/topic-overviews/cannabis-policy/html_en

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

11. Shover, C. L., & Humphreys, K. (2019). Six policy lessons relevant to cannabis legalization. Am J Drug Alcohol Abuse, 45(6), 698-706. doi:10.1080/00952990.2019.1569669

12. CPFG. (2018). *Home Office Circular 1 November 2018: Rescheduling of cannabis-based products for medicinal use in humans.* CPFG Drugs and Alcohol Unit. London, United Kingdom: Crime, Policing and Fire Group (CPFG). Retrieved October 12, 2019, from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/753366/Medicinal_Cannabis_-_Home_Office_Circular_2018_FINAL.pdf

13. Freedman, S. B., Williamson-Urquhart, S., Farion, K. J., Gouin, S., Willan, A. R., Poonai, N., . . . Schuh, S. (2018). Multicenter Trial of a Combination Probiotic for Children with Gastroenteritis. *New England Journal of Medicine, 379*(21), 2015-2026. doi:10.1056/NEJMoa1802597

14. Schnadower, D., Tarr, P. I., Casper, T. C., Gorelick, M. H., Dean, J. M., O'Connell, K. J., . . . Freedman, S. B. (2018). Lactobacillus rhamnosus GG versus Placebo for Acute Gastroenteritis in Children. *New England Journal of Medicine, 379*(21), 2002-2014. doi:10.1056/NEJMoa1802598

15. Byrne, S., Brindal, E., Williams, G., Anastasiou, K. M., Tonkin, A., Battams, S., & Riley, M. D. (2018). E cigarettes, smoking and health. A Literature Review Update. *Commonwealth Scientific and Industrial Research Organisation CSIRO Australia.* Retrieved October 02, 2019, from https://www.csiro.au/en/Research/BF/Areas/Nutrition-and-health/Public-health-and-wellbeing/Case-studies/E-cigarettes-report

16. Rucker, J. J. H., Iliff, J., & Nutt, D. J. (2018). Psychiatry & the psychedelic drugs. Past, present & future. *Neuropharmacology, 142*, 200-218. doi:10.1016/j.neuropharm.2017.12.040

17. Gardiner, K. M., Singleton, J. A., Sheridan, J., Kyle, G. J., & Nissen, L. M. (2019). Health professional beliefs, knowledge, and concerns surrounding medicinal cannabis – A systematic review. *PLoS One, 14*(e0216556). doi.org/10.1371/journal.pone.0216556

18. Zolotov, Y., Vulfsons, S., Zarhin, D., & Sznitman, S. (2018). Medical cannabis: An oxymoron? Physicians' perceptions of medical cannabis. *International Journal of Drug Policy, 57*, 4-10. doi:10.1016/j.drugpo.2018.03.025

For peer review only

19. Ananth, P., Ma, C., Al-Sayegh, H., Kroon, L., Klein, V., Wharton, C., . . . Wolfe, J. (2018). Provider Perspectives on Use of Medical Marijuana in Children With Cancer. *Pediatrics, 141*(1), e20170559. doi:10.1542/peds.2017-0559

20. Braun, I. M., Wright, A., Peteet, J., Meyer, F. L., Yuppa, D. P., Bolcic-Jankovic, D., . . . Campbell, E. G. (2018). Medical Oncologists' Beliefs, Practices, and Knowledge Regarding Marijuana Used Therapeutically: A Nationally Representative Survey Study. *Journal of clinical oncology, 36*(19), 1957-1962. doi:10.1200/JCO.2017.76.1221

21. Carlini, B. H., Garrett, S. B., & Carter, G. T. (2017). *Medicinal Cannabis: A Survey Among Health Care Providers in Washington State*. *American Journal of Hospice and Palliative Care, 34*(1), 85-91. 10.1177/1049909115604669

22. Crowley, D., Collins, C., Delargy, I., Laird, E., & Van Hout, M. C. (2017). Irish general practitioner attitudes toward decriminalisation and medical use of cannabis: results from a national survey. *Harm Reduction Journal 14*(4), 1-8. doi:10.1186/s12954-016-0129-7

23. Doblin, R. E., & Kleiman, M. A. (1991). Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes. *Journal of Clinical Oncology, 9*(7), 1314-1319. doi:10.1200/jco.1991.9.7.1314

24. Karanges, E. A., Suraev, A., Elias, N., Manocha, R., & McGregor, I. S. (2018). Knowledge and attitudes of Australian general practitioners towards medicinal cannabis: a cross-sectional survey. *British Medical Journal Open, 8*(7), e022101. doi:10.1136/bmjopen-2018-022101

25. Schwartz, R. H., Voth, E. A., & Sheridan, M. J. (1997). Marijuana to prevent nausea and vomiting in cancer patients: a survey of clinical oncologists. *Southern Medical Journal, 90*(2), 167-172. doi:10.1097/00007611-199702000-00001

26. Rogers, E. M. (2003). *Diffusion of Innovations (Fifth Edition)* New York USA: Simon & Shuster.

27. Berwick, D. M. (2003). Disseminating Innovations in Health Care. *The Journal of the American Medical Association, 289*(15), 1969-1975. doi:10.1001/jama.289.15.1969

28. Coleman, J., Menzel, H., & Katz, E. (1959). Social processes in physicians' adoption of a new drug. *Journal of Chronic Diseases, 9*(1), 1-19. doi:10.1016/0021-9681(59)90134-1

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

29. Coleman, J. S., Katz, E., & Menzel, H. (1966). *Medical Innovation: A Diffusion Study*. Indianapolis: The Bobs-Merrill Company

30. Greenhalgh, T., Robert, G., Macfarlane, F., Bate, P., & Kyriakidou, O. (2004). Diffusion of Innovations in Service Organizations: Systematic Review and Recommendations. *Milbank Quarterly, 82*(4), 581-629. doi:10.1111/j.0887-378X.2004.00325.x

31. Lublóy, Á. (2014). Factors affecting the uptake of new medicines: a systematic literature review. *BMC Health Services Research, 14*(1), 469. doi:10.1186/1472-6963-14-469

32. Makowsky, M. J., Guirguis, L. M., Hughes, C. A., Sadowski, C. A., & Yuksel, N. (2013). Factors influencing pharmacists' adoption of prescribing: qualitative application of the diffusion of innovations theory. *Implementation Science, 8*(1), 109. doi:10.1186/1748-5908-8-109

33. Sanson-Fisher, R. W. (2004). Diffusion of innovation theory for clinical change. *Medical Journal of Australia, 180*(S6), S55. doi: 10.5694/j.1326-5377.2004.tb05947.x

34. Sanson-Fisher, R. W., D'Este, C. A., Carey, M. L., Noble, N., & Paul, C. L. (2014). Evaluation of systems-oriented public health interventions: alternative research designs. *Annual Review of Public Health, 35*, 9-27.

35. Sugarhood, P., Wherton, J., Procter, R., Hinder, S., & Greenhalgh, T. (2014). Technology as system innovation: a key informant interview study of the application of the diffusion of innovation model to telecare. *Disability and Rehabilitation: Assistive Technology, 9*(1), 79-87. doi:10.3109/17483107.2013.823573

36. TGA (2020). *Access to medicinal cannabis products.* TGA Department of Health Australian Government. Canberra, Australia: Therapeutic Goods Administration . Retrieved October 18, 2020, from https://www.tga.gov.au/access-medicinal-cannabis-products-1

37. McMillion, J. (2019). *Review of the Narcotic Drugs Act 1967 – Final Report The Office of Drug Control Australian Government.* Canberra, Australia: Commonwealth Government of Australia. Retrieved October 18, 2019, from https://www.odc.gov.au/sites/default/files/review-narcotic-drugs-act-1967-final-report.pdf

For peer review only

38. Graham, P., Evitts, T., & Thomas-MacLean, R. (2008). Environmental scans. *Canadian Family Physician, 54*(7), 1022. Retrieved September 8, 2019 from http://www.cfp.ca/content/54/7/1022.abstract

39. Haby, M. M., Chapman, E., Clark, R., Barreto, J., Reveiz, L., & Lavis, J. N. (2016). What are the best methodologies for rapid reviews of the research evidence for evidence-informed decision making in health policy and practice: a rapid review. *Health Research Policy and Systems, 14* (83), 1-12. doi:10.1186/s12961-016-0155-7

40. Watt, A., Cameron, A., Sturm, L., Lathlean, T., Babidge, W., Blamey, S., Facey, K., Hailey, D., Norderhaug, I., & Maddern, G. (2008). Rapid reviews versus full systematic reviews: An inventory of current methods and practice in health technology assessment. International Journal of Technology Assessment in Health Care, 24(2), 133-139. doi:10.1017/S026646230808018

41. Saunders, B., Sim, J., Kingstone, T., Baker, S., Waterfield, J., Bartlam, B., . . . Jinks, C. (2018). Saturation in qualitative research: exploring its conceptualization and operationalization. *Quality & Quantity, 52*(4), 1893-1907. doi:10.1007/s11135-017-0574-8

42. Edwards, P., Roberts, I., Clarke, M., DiGuiseppi, C., Pratap, S., Wentz, R., . . . Cooper, R. (2007). Methods to increase response rates to postal questionnaires. *Cochrane Database of Systematic Reviews,* 2: MR000008. doi:10.1002/14651858.MR000008.pub3.

43. QSR International Pty Ltd (2018). *NVivo (Version 12)*. Retrieved November 2018, 2018, from https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home

44. Lincoln, Y. S., & Guba, E. G. (1985). *Naturalistic inquiry*. London, UK: SAGE Publications Inc.

45. Commonwealth of Australia. (2020). *Current barriers to patient access to medicinal cannabis in Australia*. The Senate Community Affairs Reference Committee. Canberra, Australia: The Senate Retrieved April 09, 2020, from https://parlinfo.aph.gov.au/parlInfo/download/committees/reportsen/024403/toc_pdf/CurrentbarrierstopatientaccesstomedicinalcannabisinAustralia.pdf;fileType=application%2Fpdf

46. Althaus, C., Bridgman, P., & Davis, G. (2012). *The Australian policy handbook*. Crows Nest, N.S.W: Allen & Unwin

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

47. Campbell, S. M., Reeves, D., Kontopantelis, E., Sibbald, B., & Roland, M. O. (2009). Effects of pay for performance on the quality of primary care in England. *New England Journal of Medicine, 361*(4), 368-378. doi:10.1056/NEJMsa0807651

48. Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A. L., Sandercock, P., Spiegelhalter, D., & Tyrer, P. (2000). Framework for design and evaluation of complex interventions to improve health. *The British Medical Journal, 321*(7262), 694-696. doi:10.1136/bmj.321.7262.694

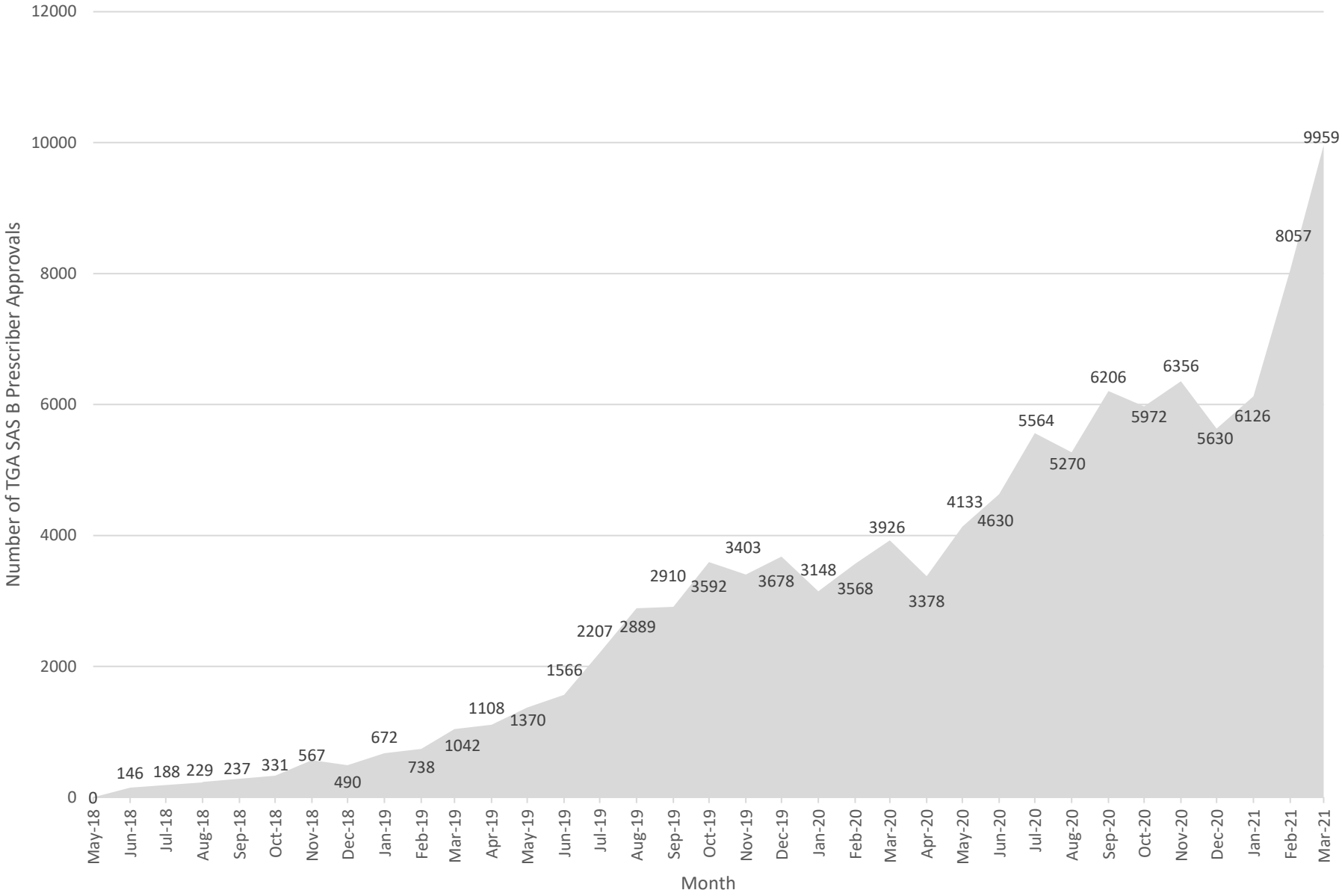
49. Giacomini, M., Hurley, J., Lomas, J., Bhatia, V., & Goldsmith, L. (1996). *The many meanings of money: A health policy analysis framework for understanding financial incentives*. Hamilton, Ontario: Centre for Health Economics and Policy Analysis (CHEPA), McMaster University, 1-42.

50. Hutchison, B. G., Levesque, J.-F., Strumpf, E., & Coyle, N. (2011). Primary health care in Canada: Systems in motion. *Milbank Quarterly, 89*(2), 256-288. doi:10.1111/j.1468-0009.2011.00628.x

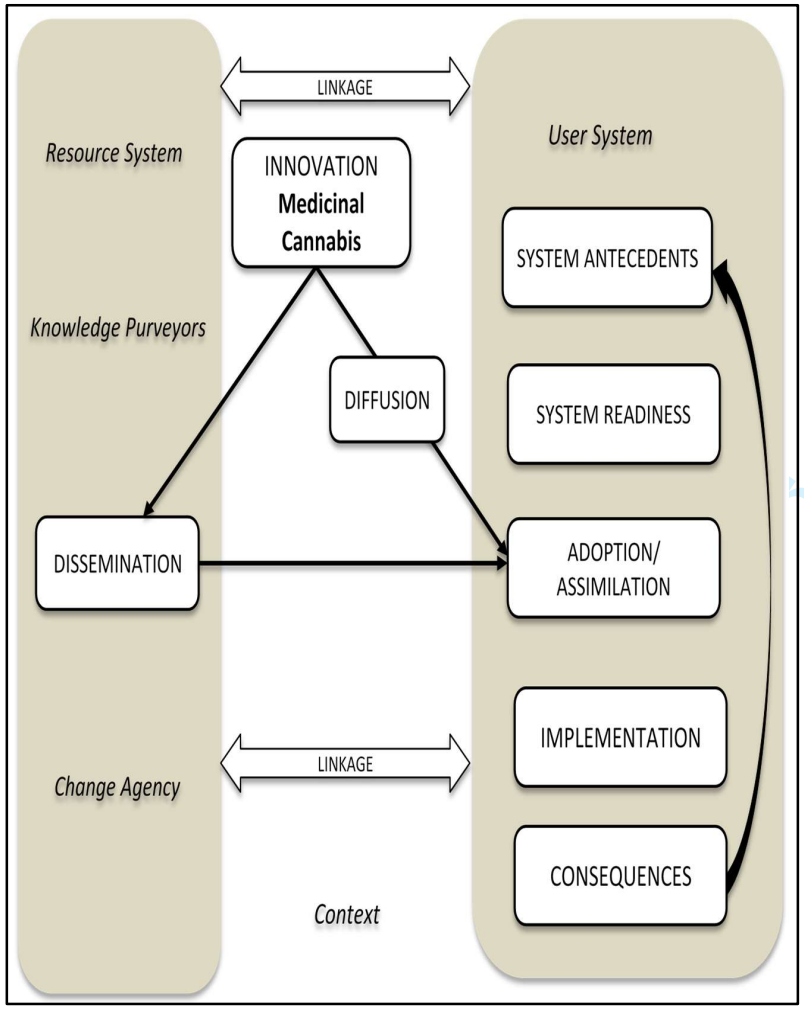
51. Gleeson, P. (2019). The Challenge of Medicinal Cannabis to the Political Legitimacy of Therapeutic Goods Regulation in Australia. *Melbourne University Law Review (advance), 43*. Retrieved November 6, 2019 from https://law.unimelb.edu.au/__data/assets/pdf_file/0010/3214864/Gleeson-432-Advance.pdf

52. Nutt, D., Bazire, S., Phillips, L. D., & Schlag, A. K.(2020). *So near yet so far: why won't the UK prescribe medical cannabis? British Medical Journal Open,. 10*(9): p. e038687.

For peer review only



Source: TGA (2020). Access to medicinal cannabis products. TGA Department of Health Australian Government. Canberra, Australia: Therapeutic Goods Administration . Retrieved October 18, 2020, from https://www.tga.gov.au/access-medicinal-cannabis-products-1



CANNABIS AS A MEDICINE		
INNOVATION Relative advantage against other 'medicines' Compatibility with other treatments Complexity Trialability Risk Knowledge explicit/implicit Technical support	**DIFFUSION & DISSEMINATION** Informal or Formal/Planned or Unplanned DIFFUSION Profession networks Peer opinion	DISEMINATION Marketing Expert opinion Champions Policy drivers
MC SYSTEM ANTECEDENTS	Structure Knowledge Context	Maturity, history, knowledge MC Distributer Resources Developing Integrated Leadership
HEALTH SYSTEM READINESS	Agency for change System fit – Preparedness for regulation Power balance - Supporters vs. Opponents Assessment - Pharmacovigilance Capacity-Time and resources for monitoring Sustainability – Ongoing monitoring and feedback	
PRESCRIBER ADOPTION and **ASSIMILATION** into **PRACTICE**	Needs, Motivation, Values, Goals, Skills, Learning Style	
IMPLEMENTATION **MC Prescribing 'rollout'**	Government and policy Support from Government agencies Training and dedicated resources Feedback on progress	
CONSEQUENCES of MC Prescribing	Outcomes-Positive, Neutral, Negative Un-intended events, Adverse events	

Adapted from Greenhalgh T et. al. (2004) Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Quarterly*, 82 (4), pp 581-629,[30]

BMJ Open

Implementation of Medicinal Cannabis in Australia: Innovation or Upheaval? Perspectives from Physicians as Key Informants, a Qualitative Analysis.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054044.R1
Article Type:	Original research
Date Submitted by the Author:	17-Sep-2021
Complete List of Authors:	Hallinan, Christine; The University of Melbourne, Department of General Practice Gunn, Jane; The University of Melbourne, Department of General Practice Bonomo, Yvonne; The University of Melbourne, Department of General Practice; St Vincent's Health Australia Ltd Fitzroy, Department Of Addiction Medicine
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Pharmacology and therapeutics, Health policy, Health services research, Evidence based practice, Complementary medicine
Keywords:	QUALITATIVE RESEARCH, Herbal medicine < THERAPEUTICS, PUBLIC HEALTH, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MEDICAL EDUCATION & TRAINING

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Implementation of Medicinal Cannabis in Australia: Innovation or Upheaval? Perspectives from Physicians as Key Informants, a Qualitative Analysis.

Dr Christine Mary Hallinan, Department of General Practice, Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences of the University of Melbourne, Level 3, 780 Elizabeth Street, Carlton, Victoria, 3053

Prof Jane Maree Gunn, Department of General Practice, Melbourne Medical School, Faculty of Medicine, Dentistry and Health Sciences of the University of Melbourne, Level 3, 780 Elizabeth Street, Carlton, Victoria, 3053

A/Prof Yvonne Ann Bonomo, St Vincent's Health, Department Of Addiction Medicine 38 Fitzroy Street, Fitzroy, Victoria, 3065

Corresponding author at: Dr Christine Hallinan at the Department of General Practice, Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences of the University of Melbourne, Level 3 780 Elizabeth Street, Building 220, Carlton Victoria, 3053. Telephone +61 438 811 595 Email address: hallinan@unimelb.edu.au

MeSH Terms
Cannabinoids
Organisation and administration
Therapeutic use
History
Standards

Word Count 5327

This qualitative research is placed within a theoretical framework, the Diffusions of Innovation Model. With this, our methods of data analysis were clearly described and theoretically justified. This contributed to the word count; and adds enhanced rigour to this research.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Implementation of Medicinal Cannabis in Australia: Innovation or Upheaval? Perspectives from Physicians as Key Informants, a Qualitative Analysis.

ABSTRACT

Objective

We sought to explore physician perspectives on the prescribing of cannabinoids to patients to gain a deeper understanding of the issues faced by prescriber and public health advisors in the rollout of medicinal cannabis.

Design

A thematic qualitative analysis of 21 in-depth interviews was undertaken to explore the narrative on the policy and practice of medicinal cannabis prescribing. The analysis used the Diffusion of Innovation (DoI) theoretical framework to model the conceptualisation of medicinal cannabis implementation in the Australian context.

Setting

Informants from the States of Victoria, New South Wales, Tasmania, Canberra, and Queensland in Australia were invited to participate in a interviews to explore the policy and practice of medicinal cannabis prescribing.

Participants

Participants included 21 prescribing and non-prescribing key informants working in area of neurology, rheumatology, oncology, pain medicine, psychiatry, public health, and general practice.

Results

There was agreement among many informants that medicinal cannabis is, indeed, a pharmaceutical innovation. From the analysis of the informant interviews, the factors which facilitate the diffusion of medicinal cannabis include, the adoption of appropriate regulation, the use of data to evaluate safety and efficacy, the need for improved prescriber education, and the requirement to monitor quality and cost. Most informants asserted the widespread assimilation of medicinal cannabis into practice is impeded by lack of health system antecedents required to facilitate the safe, effective, and equitable access to medicinal cannabis as a therapeutic.

Conclusions

This research highlights the tensions that arise and the factors that influence the rollout of cannabis as an unregulated medicine. Addressing these factors is essential for the safe and effective prescribing in contemporary medical practice. The findings of this research provides important evidence on medicinal cannabis as a therapeutic, and also informs the rollout of potential novel therapeutics in the future.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Strengths and limitations of this study

- Fills an identified gap in the literature by reporting physician perspectives of the rollout of medicinal cannabis in Australia.
- The research aligns with conventions for 'quality' in qualitative research as reported in the COREQ[1] checklist for the reporting of qualitative research.
- Research was guided by a validated theoretical framework, the Diffusion of Innovations model.
- Provides evidence around perspectives from Australian key informants only, and as a result the research may not be generalisable to policy and practice in other countries.
- The purposive and snowball sampling techniques are non-random, and may not be generalisable across population groups who do have experience of, and or interest in, medicinal cannabis prescribing.

BACKGROUND

Cannabis was first used as a medicine as far back as 5,000 years ago,[1, 2]. Legislation enacted by the Single Convention on Narcotic Drugs in 1961, however re-classified cannabis from a therapeutic medicine to a prohibited drug,[1, 3-6]. This legislation not only criminalised the use of cannabis, including for medical purposes but also contributed to a lack of pursuit of evidence for its medicinal effects, as procurement of cannabis for scientific studies became restricted,[1, 6]. Hence during this time, the focus of cannabis research was around the recreational use of cannabis and associated drug policies rather than that of cannabis for medicinal purposes. It was not until research into the endocannabinoid system was established in the 1990's that interest in cannabis as a medicine gained momentum,[1].

Since the nineties, there has been a re-emergence of interest in the use of cannabis as a medicinal product driven by multiple factors including developments in understanding about the endogenous cannabinoid system; the collateral effect of the harmful opioid epidemic in the Western world; increasing prevalence of use of cannabis in the community; community perceptions that cannabis is relatively inert; and the rapid expansion of the medicinal cannabis industry,[1, 6-8]. Worldwide, community demand for access to medicinal cannabis products has followed this burgeoning interest resulting, in global changes towards treating cannabis as a medicine,[9].

The Director General of the World Health Organization has recommended re-scheduling of medicinal cannabis in the international drug control framework to facilitate the use of cannabinoid substances for medicinal and scientific purposes,[7] This recommendation has followed legislative changes across the globe where in the early 2000s, Israel (2001), Canada (2001), the Netherlands (2003), and later other

[1] Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. https://doi.org/10.1093/intqhc/mzm042

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

countries, including Switzerland (2011), Italy and Czechia (2013), Australia (2016) and Germany (2017) legislated the use of medicinal cannabis under specified conditions,[7]. An increasing number of states in the United States are also legalising both medicinal and non-medicinal cannabis use, despite opposing Federal Laws,[7, 8]. The United Kingdom legalised medicinal cannabis in late 2018, and other countries such as Luxembourg are following suit with the introduction of pilot programs for medicinal cannabis,[7, 9].

Legislation authorising the compassionate use of medicinal cannabis was endorsed in Australia by State and Federal governments in October 2016,[10]. Cultivation and production (jointly), research and manufacture of medicinal cannabis in Australia was also de-criminalised at this time,[11]. On the 1st of November 2016, further amendments were made to the scheduling of medicinal cannabis products. These changes resulted in certain medicinal cannabis products (CBD) being down regulated from a Schedule 9 (S9) - Prohibited Substances category, to a Schedule 8 (S8)-Controlled Drug category by the Australian medicines regulatory body, the Therapeutic Goods Authority (TGA),[10]. To date, only two medicinal cannabis product are registered, or licensed, in Australia (*Sativex*® and *Epidyolex*®), meaning that all other medicinal cannabis products are therefore unapproved therapeutic goods, not having been assessed by the TGA for safety, quality or effectiveness,[10].

To address increasing demand of medicinal cannabis, in July 2018 an online system was introduced on to enable a more streamlined application process for the lodgement of Special Access Scheme Category B (SAS-B) applications for TGA approval to prescribe unlicenced medicinal cannabis preparations,[10]. Since then, from a baseline of 146 applications recorded in June 2018, there has been a 7,291% percentage change[2] in the number of SAS-B approvals, with 10,791 applications approved in the month of September 2021 amounting to a cumulative total of 158,498 approvals across the period (Figure 1),[10]. Notwithstanding this, there is still discord between those who are in favour of medicinal cannabis and those who are not, and this potentially drives a chasm between patients and their physicians, and between physicians and their colleagues.

Medicinal cannabis exemplifies one of a suite of therapeutics, that have been introduced with an ambiguous understanding of their benefit, and no clear clinical indication supported by accompanying evidence. Other agents in this category include 'health supplements' such as probiotics,[12, 13], e-cigarettes as nicotine replacement therapy,[14], and other illicit substances predicted to be of broader therapeutic value in the future, such as psychedelics as a treatment for anxiety and addiction,[15].

Rigorous research is required to contribute to the evidence underpinning the implementation of medicinal cannabis prescribing in any setting. Hence, the collection of information specifically relating

[2] The percentage change between two values in a time series is calculated by finding the difference between those two values then dividing that difference by the starting value and multiplying by 100.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

to physicians' knowledge, concerns, and experiences with medicinal cannabis is imperative. To date, the majority of studies in the area from a range of countries have highlighted remarkably consistent themes, which include health professionals lack of confidence in prescribing medicinal cannabis, need for education about cannabinoid therapeutics, and their attitudes to cannabis as a therapeutic agent,[16-18]. A systematic review undertaken by Gardiner, Singleton, Sheridan, Kyle, & Nissen in 2019, reported on research from 26 studies found that in general, health professionals supported the use of medicinal cannabis in practice,[16]. This review also reported there was a unanimous lack of self-perceived knowledge surrounding all aspects of medicinal cannabis and indicated many health professionals were concerned about direct patient harms and indirect societal harms,[16]. The majority of published evidence that provided a focus on physician perceptions has been collected via surveys and questionnaires,[19-25]. Of the evidence collected from interviews, were two studies that examined physician insights around use of medicinal cannabis as a therapeutic agent,[17, 20]. One study published by Braun et al., in 2018, conducted semi-structured interviews on oncology experts from the United States,[20]. This research had a specific focus around perceptions of the use of medicinal cannabis in oncology and cancer care. Zolotov et al., (2018) used narrative analysis of data collected from interviews with twenty-four Israeli physicians with specialities in pain medicine; oncology family and medicine physicians,[17]. While these qualitative data provided vital evidence to the current research landscape, neither examined key informant perspectives on the important broader systemic issues, such as how the 'diffusion' of medicinal cannabis into medical practice is occurring.

In terms of the global context, the Australian approach to medicinal cannabis beginning with adoption of legislative changes permitting its prescribing delivers a unique opportunity to gather important evidence for the factors which impact on the rollout of medicinal cannabis. It also enables an examination not previously described of what influences the diffusion and dissemination of medicinal cannabis into contemporary clinical practice. Importantly, it provides an opportunity to investigate the health system and regulatory factors that are associated with the provision and monitoring of medicinal cannabis to patients. It is thus timely to examine *de novo,* the 'diffusion' of medicinal cannabis to gain a greater understanding of the facilitators and barriers to the safe and appropriate dissemination of medicinal cannabis to patients by their physicians.

The theoretical model of the Diffusion of Innovation (DoI),[26] helps conceptualise the implementation of medicinal cannabis globally and the factors needed to facilitate safe and effective rollout. Originating in 1962, the framework explains how a product or idea can gain momentum and 'diffuse' through a social system, with the end result being that the product or idea is adopted and becomes a part of the social system,[26]. This framework has previously been used in research relating to innovations in health care, medical sociology and physician practice including prescribing,[26-35]. medicinal cannabis has characteristics relevant to pharmaceutical innovations by virtue of its 'medicinal' name, the requirement for it to be prescribed by a medical professional for a health condition, and oversight occurring via

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

regulatory authorities for pharmaceuticals and other therapeutics, the Food and Drug Administration (FDA) in the United States, European Medicines Agency (EMA) in Europe and equivalent bodies in other countries. Applying medicinal cannabis to the DoI framework, a key to its adoption lies in the perception of both prescribers and community that medicinal cannabis is innovative. Pharmaceutical marketing, drug characteristics, government policies and the behaviour of both medical professionals and patients are additional key factors in uptake of new therapeutic agents,[31]. The principal difference with medicinal cannabis, however, is that unlike other pharmaceutical innovations, it is not a single molecule or single compound, for use in a single, or small cluster of indications, and importantly it has not emerged from traditional pharmaceutical companies, which have standard research and development (R & D) and pharmacovigilance systems.

In this research, we aim to gain a deeper understanding of the factors that are associated with the diffusion of an unlicensed therapeutic into medical practice for which strong consumer demand preceded the research evidence. Specifically, this research aims to provide evidence from key informant perspectives on the role of the prescriber, the differences between licensed medicinal cannabis products such as *Sativex*® and *Epidyolex*® (the only licensed products in Australia) and unlicensed medicinal cannabis including as all other products that require TGA approval. Informant perspectives on the relevance of regulatory authorities in the prescribing of medicinal cannabis, and their views on the precedent that medicinal cannabis has set around consumer-lead medicine were also sought. Furthermore, we aim to provide lessons to inform future policy and practice, especially with the introduction of other potential novel therapeutic agents into clinical practice that are subject to the similar influences. This is essential to informing both the 'rollout' of medicinal cannabis and the way medicine is practised in the twenty-first century.

METHOD

Study Design

A qualitative thematic analysis was used to investigate the narrative around medicinal cannabis prescribing in the Australian context. Informants were invited to participate in an in-depth interview which was guided by a small number of open-ended questions (Table 1). These questions were developed a 'priori, guided by DOI theory, and informed by conference presentations, webinars, grey literature and publications on medicinal cannabis that were authored by clinicians, representivies from peak professional bodies, policy advisors, and researchers,[17, 24, 36-40].

Exclusion and Inclusion Criteria

Key informants were invited to participate in this research based on their: (i) involvement in the development of health policy, (ii) prescribing experiences in clinical practice, and (iii) advocacy roles

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

for and against medicinal cannabis. This provided evidence from both prescribing and non-prescribing key informants as it was deemed important to understand not only the factors that influenced an individual to prescribe medicinal cannabis, but also the factors that influenced others to decide or not to prescribe. The interview focus was on medicinal cannabis products that can be prescribed via the TGA-SAS-B scheme. Non-prescribed artisanal[3] products were included in the analysis as they are known to be accessed by individuals who cannot afford medicinal cannabis prescribed by clinicians,[41]. Recreational cannabis use was excluded from the analysis because this refers to a very large and heterogenous cohort, many of whom have a prior history of cannabis use for non-medical purposes. Given it is difficult to differentiate between cannabis use for recreational purposes versus use for health reasons, the scope of the informant study focused on use of cannabis for medical purposes only.

Recruitment

Key informants were selected using purposive and snowballing techniques. Initially informants were selected following an environmental scan,[42]. The approach involved the opportunistic identification of informants from already established contacts such as physicians and researchers, as well as more focused scoping, that involved the identification of individuals exposed to policy, prescribing, and advocacy for and against medicinal cannabis use. This included those from peak professional bodies, government departments and individuals who have contributed to the research evidence. Other potential key informants were identified following interviews using snowballing. This involved invitation of the peers of interviewees following their suggestion to do so. We excluded informants who were involved in the cannabis production industry and those who worked in or operated cannabis clinics. Informants were sent an email and a postal invitation; this recruitment methodology has been shown to increase response rates,[43]. The informants who did not respond were followed up with either another email and/or a phone call of invitation to participate. All informants were provided a patient leaflet information statement (PLIS) and a consent form prior to the interview. Consent was provided both verbally in the interview and as a signature on the consent form.

Interviews and Analysis

Semi-structured interviews, of an average duration of one hour, were conducted by two authors (CH, YB) either face to face, via video conference, or by telephone (Table 1). All informants were notified that the interview would be recorded and transcribed verbatim. Notes were taken during the interview. Although the interviews were guided by open-ended questions, inductive probing was employed to facilitate response heterogenicity,[44]. Reflexive notes were developed on completion of interview, this

[3] Artisanal MC are unregistered herbal cannabinoid preparations produced by small-scale artisanal farms. Artisanal (bootleg) MC is complex in nature where the quality and quantity of MC compounds vary from one batch to the next (Sulak, Saneto, & Goldstein, 2017).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

involved the critical analysis of the interview process by the interviewers (CH, YB). All interview data were de-identified and stored in a secure platform. Data was then managed in NVivo12,[45].

Given the use of DoI conceptual model, analysis included both inductive and deductive coding. Coding was undertaken by two authors (CH, YB). This duplication provided the analysis, perspectives from different researcher backgrounds, and opportunities to refine the coding system and discuss coding disagreements,[46]. Thematic saturation was ascertained after data collection, and based on saturation of new information threshold, where there was no evidence of the emergence of new themes beyond those already established.

Patient and Public Involvement

The study involved researchers with clinical and research experience from the Department of General Practice and Melbourne Medical School at the University of Melbourne. These researchers designed and conducted the qualitative research that involved interviewing clinicians, public health advisors, and representatives from peak body organisations.

RESULTS

A broad cross-section of the medical community who had an interest in medicinal cannabis was sought. Twenty-six individuals were approached, twenty-three accepted, of these one withdrew for personal reasons, and another withdrew because of time constraints. There were three potential informants who did not respond to any of the invitations, these individuals were not directly involved in the prescribing of medicinal cannabis. Of the informants who accepted, thirteen were active prescribers, four were non-prescribers, and four were public health advisors. The 21 key informants included neurologists, rheumatologists, oncologists, pain specialists, psychiatrists, public health advisors, and general practitioners. All informants were based in the Eastern States and Territories of Australia (Victoria, New South Wales, Tasmania, Canberra, and Queensland). There were no informants from other states of Australia (South Australia, Western Australia, and Northern Territory) because at the time of the interviews there was minimal medicinal cannabis prescribing in these jurisdictions. Interviews were conducted between November 2018 and January 2019.

Factors Influencing the Diffusion of Medicinal Cannabis in Australia

A number of components in the DoI framework were described by the Key Informants in relation to Medicinal Cannabis (Figure 2).

Medicinal Cannabis as an Innovation

The information in this domain is depicted in the **INNOVATION** block (Figure 2).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Several key informants saw innovation in medicinal cannabis in its use for the treatment of several conditions where patients present with significant and debilitating refractory symptoms due to the lack of efficacy of current therapies. Examples of conditions cited by the informants included childhood epilepsy, chemotherapy related nausea and vomiting, pain management for patients in palliative care and chronic non-malignant pain, and young people with anxiety. Some informants perceived medicinal cannabis as relatively inert, and therefore advantageous, especially when comparing adverse events with other therapeutics that have been used to treat the above conditions.

Several individuals reported on the positive benefits from medicinal cannabis that were either observed in their clinical practice, or derived from the scientific literature. Often articulation about the benefits was vague. One individual described the effects of cannabis as 'different' and 'special'. Several described that patients reported they 'just felt better'. On the other hand, some found that not all patients benefited from medicinal cannabis, and in these situations prescribing of medicinal cannabis ceased (Box 1).

Box 1

…it doesn't work for everybody and for some people it has no benefits whatsoever, for some people, it has terrible side effects, but I believe that users are best able to work with their doctors if they think it is a benefit to them. It kind of is one of those things that you kind of have to try. (I-013)

I am not the fearful cannabis will kill you all and I am not [...convinced…] cannabis will cure all. (I-015)

All informants referred to the prescribing of medicinal cannabis as being fraught with complexities associated with ambiguities around its effectiveness, the political process involved in its 'rollout', the patients, and conditions in which it is prescribed and the prescribing process itself.

Some informants were vague about potential harms of medicinal cannabis. They reported concerns about its effects on the developing brain and risks associated with cognitive impairment in young people as well as risks more generally of impairment in relation to driving. Most asserted that medicinal cannabis should only be prescribed for the conditions recommended by the TGA, and highlighted the caveat that risks of harm needed to be considered relative to the severity of the indication for its use. For instance, prescribing medicinal cannabis to a young child posed more of a concern than prescribing to a patient with terminal cancer as part of a palliative care regime.

Most informants referred to concerns around the purity, concentration, and consistency of medicinal cannabis products. For example, they queried the reliability of medicinal cannabis preparation or

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

concentrations of THC and CBD that may not match the dosages they wished to prescribe. Issues relating to a naivety among some medicinal cannabis companies regarding regulations pertaining to storage of scheduled products, lack of solid data on product efficacy, and lack of understanding about the imperative to report adverse events that are standard practice in mainstream pharmaceutical companies.

A few informants also described ambiguities regarding where medicinal cannabis 'fits' in contemporary medical models of care, such that, some informants viewed medicinal cannabis as an 'unregulated herb' rather than that of a medicine. Many reported concerns around the lack of empirical evidence of efficacy and lack of data around adverse events. Several informants reported on concerns about the financial costs incurred by patients wanting cannabis medicines. Some described costs as prohibitive, especially in situations where patients had been enrolled in trials that had come to an end. Informants also recounted lag times, particularly early in the rollout, where a request for cannabis and patient access to the product could take several months (Box 2).

Box 2

There's no reimbursement - no subsidy, I should say, and the companies are just taking advantage of the situation. I find it difficult to believe that it could actually cost $650 a bottle for them to make it and sell it at a profit. *(I-009)*

(Costs)… to the order of a couple of grand a month. One to two and a half thousand per month. The one thousand is because it's an infant. It's prohibitively expensive. Broadly, if there's a family that are asking and meet that sort of criteria, severe and failed everything, I'm very happy to prescribe the private script. As long as they're properly informed and consented. It's a huge chunk of money for most people. *(I-001)*

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The vast majority of informants reported on the great divide between the safety and quality of products that have been derived from an unregulated market, such as in medicinal cannabis production, and pharmaceuticals that had not been appropriately trialled and developed accordingly to a standard for approval by the TGA. Some mentioned concerns about toxicology of the product and the need to titrate the product slowly to ensure the patient was not receiving 'toxic' levels too quickly that impeded the patient's functioning. Others were concerned about the quality of the product because of uncertainty about the conditions of manufacturing (Box 3).

Box 3

The question is if it's grown outdoors - so, the first thing is, it has to be organic, there can be no chemicals or anything else used, herbicides, because if you're using for medicine. The second thing is it has to be consistent. *(I-012)*

Many informants indicated they were involved in trialling the product, where they were invited to participate in open-labelled trials by governments and medicinal cannabis companies. In these trials, the prescriber was the conduit between the patient and the cannabis, which was provided to the patient by the medicinal cannabis companies. This provided an opportunity to their patients for cost free access to cannabis and also enabled them to understand more about how to prescribe medicinal cannabis and to monitor their patient's response, whether it be symptomatic relief or reports of adverse events (Box 4).

Box 4

I'm a strong advocate for this being treated the same as any other medicine. In that way ideally cannabinoid trials would continue, just like any other medicine… *(I-001)*

Most of us - people are generating trial data but really in very specific…(conditions). *(I-009)*

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Diffusion and Dissemination of Medicinal Cannabis

The information in this domain is depicted in the **DIFFUSION & DISSEMINATION** block (Figure 2).

All informants discussed the requisite for explicit knowledge from professional and peer networks to inform prescribers on the effects and outcomes of medical cannabis . Many informants reported they gained explicit knowledge through access to peer reviewed publications and through government websites such as the TGA. They also described gaining knowledge from information provided to them by their peers, although a few informants reported they were not confident of the knowledge base of colleagues. The gaining of implicit knowledge by undertaking open-label trials and monitoring their patients who are on the trials, was viewed as informing their own practice as well as contributing to the evidence base. Prescribing to patients provided further tacit knowledge. In this case informants reported unexpected effects, such as symptomatic relief in some patients who were prescribed only a very small amount of product, and minimal effects of patients who were prescribed large doses of the same product. The potential for placebo effect was acknowledged, but did not deter from continuing to prescribe medicinal cannabis (Box 5). Informants also discussed concerns around prescribing medicinal cannabis when the *exact* quantity of cannabidiol (CBD)[4] compared to (tetrahydrocannabinol) THC[5] was often not guaranteed. Regarding, this informants considered reported ratios between THC and CBD products not reliable, as the manufacturing of the product was not controlled by a pharmaceutical regulatory body Many mentioned the paucity of validated evidence on the effects and adverse outcomes associated with medicinal cannabis use was a limitation in the 'rollout' of cannabis to patients.

Prescribers also reported they had minimal explicit knowledge on the special access scheme prescribing process, especially regarding how to prescribe an unregulated medicine to a patient. Notwithstanding this, all reported much implicit and tacit knowledge was gained with each subsequent prescription application that that was submitted and approved (Box 5).

Box 5

The problem - I think that people - general public will have their views about it being useful for x and y because that's already out there. I think the medical profession, hopefully if the data gets better, will have a better idea about what it actually is useful for and what combinations of different compounds are... (I-018)

[4] CBD – CBD is psychoactive, but exhibits no effects indicative of euphoria or dependence potential. https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf

[5] THC - the major psychoactive constituent in found in cannabis https://www.who.int/substance_abuse/facts/cannabis/en/

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The majority of informants perceived medicinal cannabis companies greatly facilitated the dissemination of medicinal product by actively pursuing doctors and inviting them to either trial their product, or prescribe to patients via newly established Cannabis Access Clinics. Several informants reported medicinal cannabis companies frequently cited overseas 'successes' relating to the rollout of medicinal cannabis. They also mentioned the entrepreneurial nature of the medicinal cannabis industry, and referred to the risks associated with the artisanal medicinal cannabis products as well as patients who can, or will, 'grow their own' particularly if cannabis becomes legalised.

Some informants referred to individuals they perceived as medicinal cannabis 'champions' in Australia. These individuals viewed it as a therapeutic product that should be normalised and accessible through unrestricted prescribing pathways.

Informants frequently reported the process for prescribing was quite technical, especially regarding the necessary requirements for a prescriber to gain an authorised prescriber status by the Therapeutic Goods Authority. Most reported that support was provided by the TGA around the process. Both the TGA and prescribers reported the technical process around prescribing were both labour intensive and burdensome, particularly initially (Box 6).

Box 6

I think initially there were long processing times involved…It was very confusing to know what to do… I think it's much, much quicker than it used to be. *(I-004)*

There used to be quite a complex application…that would typically be rejected multiple times. *(I-010)*

…initially there were long processing times involved. It was very confusing to know what to do. *(I-005)*

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Health System Readiness

The information in this domain is depicted in the **HEALTH SYSTEM READINESS** block (Figure 2).

The vast majority of informants reported that the agency for change leading to rapid evolution of cannabis from that of an herb to that of medicine was the political response to patient demand. Many also commented that this had caught much of the medical profession unawares. A striking number of informants referred, without prompting, to metaphors associated with 'the bolting horse' and a few referred to the Trojan horse, where they felt the medicalising of cannabis was a way for recreational users to access legalised cannabis under the guise of a medicine (Box 7).

Box 7

…the horse has bolted, in fact the horse has bolted so far it's over the horizon…given that the horse is a government horse, the jockey has fallen off'; 'the horse has bolted and left the cart way behind…the cart's sitting behind the barn at the moment'; 'after the horses have bolted, everyone's growing it and setting up'; 'I see a horse that's bolting…and a cart before the horse' 'a rather opportunistic cart before the horse, but good publicity move on behalf of the politicians.

(1-002; 1-006; 1-008; 1-012; 1-015)

They (politicians)] were, in a way, pushed into this - I mean, it (medicinal cannabis) might act as a Trojan horse to some degree.

(0-018)

…there's a bit of a Trojan horse dynamic here I think, where those who actually, really are dependent and need and want it because they're dependent, have now got an easy way of communicating, give it to me because I've got a medical problem. *(0-018)*

With the current trend of course we're going to end up with the legalisation of cannabis…That's clearly the hidden - that's the Trojan horse'. *(0-013)*

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Some informants argued for the need for new governmental arrangements between legislative structures and the 'content experts' to drive the medicinal strategy forward. Most were open to expansion of the program, yet all felt it was unhinged by the rapid and under-resourced 'rollout' of the innovation, and lack of systemic monitoring (Box 8).

Box 8

That's our challenge now - to re-think our legislative structures and how we manage problems so that we can reduce the induced, indirect harm, which is the legal harms… without increasing access, availability, advertising, promotion, and cost incentives to increase consumption and thereby increase harm. *(1-013)*

A number of individuals expressed their view that medicinal cannabis is compatible with the way they work, citing the doctor-patient relationship and a duty of care to their patients as reasons for considering prescribing medicinal cannabis. Some informants commented on the tenacity with which patients believed that cannabinoids would provide benefit, and remarked that this was an influential factor for them to take up prescribing.

Social influences were also cited by a number of informants. They noted that the families of children with chronic conditions, celebrities, advocacy groups and politicians have been strong social influencers to prescribe medicinal cannabis. This had been unprecedented compared to any other area of medical practice. It was felt that this had both benefits, in raising awareness and attracting philanthropic, and to a lesser extent, government funding, but also disadvantages. Informants cited that pressure, even coercion and a lack of acknowledgement by these social influences of the standard process for introduction of a new therapeutics has, to some extent, created a division between the community and health professionals.

Implementation of Medicinal Cannabis 'Rollout'

The information in this domain is depicted in the **IMPLEMENTATION OF MEDICINAL CANNABIS 'ROLLOUT'** block (Figure 2).

Many cited a lack of leadership and direction from the medical profession, governments, and government agencies in the initial stages of the rollout, although most of these informants reported this has improved with time. For example, the guidance documents published on the TGA website were described as beneficial and of those who had prescribed, all reported the streamlining of the application processes around the provision of medicinal cannabis to patients most beneficial. One informant felt the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

TGA had done a remarkably good job in navigating through the issues, especially considering the political pressure they were under and the clinical reality of prescribing an unlicensed product to a patient. Regarding access to formalised education, all informants stated this was greatly needed but that instead they had resorted to being 'self-taught'. They described this as burdensome, but most justified this by saying they were prepared to do this because they felt they had a duty of care towards their patients.

Many informants acknowledged the need for a robust and nimble pharmacovigilance system for reporting of adverse events so that they understood what to monitor during patient review as well as review what other health professionals were observing. Most considered that the systematic monitoring of prescribing outcomes was vital for the safely of future patients, and many raised concerns about potential harms associated with the provision of medicinal cannabis to children and young people. All considered the system currently in place for pharmacovigilance was inadequate and described the need for systematic and sustained research around medicinal cannabis and its effect on humans Box 9.

Box 9

…the idea of proper pharmacovigilance. And that's safe prescribing, and it's just a whole system that we just don't have in Australia…It would be good if we can make some changes because that'll have a benefit across the board. *(I-001)*

There is a dearth of knowledge. We need to have a prospective arrangement in order to supply pharmacovigilance that are also about outcomes - the profiles of people who are benefiting and not benefitting. So I think there's a bit of a direction of duty there. *(I-018)*

I think there's a high risk of a poorly regulated market, or limited regulation market, where patients, will be able to get maybe partially subsidised products that are probably manufactured well but don't have the trial backing. The way we make advances in medicine is through research. If it just falls down to anecdotal stories and claims, then we're not going to know the right doses… *(I-001)*

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

The 'rollout' of medicinal cannabis as a therapeutic into the Australian community has not been streamlined, as has been confirmed by the Senate Inquiry into *Current Barriers to Patient Access to medicinal cannabis in Australia* published in March 2020,[47]. This study of 21 key informants, provides important evidence on the factors that have facilitated patient access to medicinal cannabis and the barriers that need to be addressed to support safe and effective access in the future. The key informants overwhelmingly acknowledged the complexity and shifting context of medicinal cannabis prescribing and also highlighted the need to incorporate a breath of considerations into future policy that include public, political, economic, and health service level perspectives.

The majority of informants viewed medicinal cannabis as an *Innovation*. Several saw medicinal cannabis as a therapeutic that had advantages over other medicines, especially when used as adjunctive therapeutic. Informants who were prescribers, described being able to trial it in patients without evidence of significant adverse effects. *System Antecedents* in the context of medicinal cannabis were categorised in the DoI model as *Structure*, *Knowledge,* and *Context*. *Structure* includes medicinal cannabis maturity, history, and distributer resources, and relates to the preparedness of medicinal cannabis companies to supply the market a quality product without prohibitive cost to the consumer. *Knowledge* relates to stakeholders pre-existing understanding of the endocannabinoid system and the pharmacology of cannabinoids and *Context* relates to medical leadership in the prescribing of medicinal cannabis. It was evident from the informant interviews that these *System Antecedents* had largely been deficient in the rollout of medicinal cannabis. The aspects of *Health System Readiness* reported by informants included evidence of agency for change which arose from multiple voices, with divergent interests. Voices included that of consumers who advocated for access; politicians who responded to the public voice; regulators who advised, cannabis companies who supplied the product and medical professionals who cared for their patients irrespective of their own stance on medical cannabis prescribing. Missing components of the *Health System Readiness* related to lack of resources required to perform monitoring and feedback, and the staggered legislative changes around the various jurisdictions of Australia, that impacted on the diffusion and dissemination of medicinal cannabis prescribing in clinical practice.

Prescriber Adoption and *Assimilation* into practice remains a stark gap in the diffusion of medicinal cannabis into the Australian community. Understanding the needs, motivation, values, goals, skills and learning style of health professionals in relation to prescribing medicinal cannabis is an area that will need far greater attention for continued rollout of medicinal cannabis. While the most immediate needs such as prescribing guidance and streamlined regulatory approval have been important steps, there are other policy levers that are understood to impact on the uptake of an innovative therapeutic,[48-52]. Levers used to promote the safe diffusion of a therapeutic into clinical practice, often incorporate a blend of financial and non-financial incentives that include direct remuneration, performance feedback and the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

delivery of information technology systems. For example, financial incentives could incorporate the inclusion of a general practice (GP) remuneration for the reporting and monitoring of medicinal cannabis prescribing. Similarly, workflow tools, such as GP software for Electronic Medical Records (EMR) that facilitate the reporting of effectiveness and adverse events of medicinal cannabis (such as automatic prompts) are other important instruments that have the potential to promote safe monitoring of medicinal cannabis access. Other notable factors in the DoI framework that will assist safe implementation of medicinal cannabis include training, dedicated resources and, importantly, feedback on progress. This is where pharmacovigilance and the use of patient reported outcome measures (PROMs) is vital.

Rapid changes in today's world are challenging the traditional ways that bodies such as regulatory agencies and medical colleges authorise and endorse medical practice, and medicinal cannabis is no exception. Notwithstanding the steps that have already been undertaken by these authorities to accommodate medicinal cannabis to date, the increasing demand for medical cannabis has exerted substantial pressures on these organisations to continually adapt and change how they operate,[53]. Importantly, ongoing dialogue is needed between regulatory authorities, health professionals and the community, both at the outset and throughout the process of rollout, to work through the issues highlighted by the informants in this study. In the first instance, acknowledgement is needed between patients and prescribers that there remains a paucity of knowledge about side effects and adverse events of medicinal cannabinoids and therefore a willingness to contribute to pharmacovigilance systems. Equally, as has been proposed by others, the voice and experience of consumers needs to be incorporated into the way health professionals prescribe, and regulatory authorities facilitate, provision of medicinal cannabis,[54]. Addressing these factors is essential for safe and effective prescribing in contemporary medical practice.

STRENGTHS and LIMITATIONS

The strength of this research, is that it fills an identified gap in the literature by reporting physician perspectives of the rollout of medicinal cannabis in Australia. The research aligns with conventions for 'quality' in qualitative research as reported in the COREQ[6] checklist for the reporting of qualitative research and was also guided by a validated theoretical framework, the Diffusion of Innovations model. Limitations include the analysis of perspectives from Australian key informants only, and as a result the research may not be generalisable to policy and practice in other countries. Although the purposive and snowball sampling techniques provides qualitative data around informant experience in policy, prescribing, advocacy for and against medicinal cannabis, this strategy is a non-random technique, and may not be generalisable across population groups which do not have experience of, and or interest in, medicinal cannabis prescribing. Notwithstanding this, the themes from this research *are* valuable across

[6] Consolidated criteria for reporting qualitative research (COREQ) : a 32-item checklist for interviews and focus groups https://doi.org/10.1093/intqhc/mzm042

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

all contexts, as they provide an understanding of the dynamics at play, when access to an unapproved therapeutic *precedes* the establishment of scientific evidence from rigorous studies such as randomised controlled efficacy trials.

CONCLUSION

Medicinal cannabis marks a new era in the practice of medicine. Several, but not all, informants were comfortable with the increasing trend for consumer-lead health advocacy in the medicinal cannabis space. Yet, many expressed concern that this practice seemed to be at the expense of 'tried and true' methods in clinical care. They emphasised the prescribing of medicinal cannabis had the potential to move clinical practice away from a scientific paradigm, to that of demand driven care. Given this, an understanding of the multiple interacting factors known to influence the diffusion of pharmaceutical innovations is imperative to facilitate the safe and effective implementation of medicinal cannabinoids into practice. Incorporation of consumer experience into the way physicians prescribe, and the way regulatory authorities facilitate the provision of medicinal cannabis, is needed. Consumers and prescribers also need to be willing to embrace innovative methods of pharmacovigilance to address the gaps in evidence for the indications for which medicinal cannabis is prescribed. We have shown that the relationships between the different influencing factors are critical to innovation success. Collaboration includes active communication, consultation, and dialogue between key stakeholders including consumers, prescribers, regulatory authorities, and politicians. This research highlights the tensions that arise and the factors that influence the rollout of cannabis as an unregulated medicine. Addressing these factors, is essential for the safe and effective prescribing in contemporary medical practice. The findings of this research provides important evidence on medicinal cannabis as a therapeutic, and also informs the rollout of potential novel therapeutics in the future.

Contribution statement

CH made substantial contribution to the conception and design of the work; CH and YB substantially contributed to the acquisition of the data. CH and YB made substantial contribution to the analysis interpretation of data. CH and YB drafted the work. JG provided oversight of the manuscript. YB and CH revised the manuscript critically for important intellectual content. CH contributed substantially to the final version to be published. Final approval was gained from CH, JG and YB, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Funding

This study was supported by the Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE), funded by the National Health and Medical Research Council (NHMRC) through the Centre of Research Excellence scheme. ACRE has established several research teams who are involved in gathering evidence to develop a national research and policy framework that ensures quality and safety

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

in the implementation of medicinal cannabis use in the community. The authors also wish to thank all Physicians, Prescribers and Experts who generously contributed their time, expertise, and personal experiences to this research.

Competing interests

Yvonne Bonomo is a Principal Investigator on an open label study to evaluate the safety, tolerability, and pharmacokinetics of a medicinal cannabinoid oil formulation in chronic non-cancer pain patients for Zelira Therapeutics ACTRN12619001013156.

Ethics statement

Ethics project approval was granted by the University of Melbourne and registered with the University of Melbourne Human Research Ethics Committee (Ethics ID: 181524.1).

Data sharing statement

No additional data are available.

Acknowledgements

The Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE) is established through the National Health and Medical Research Council (NHMRC) Centre of Research Excellence scheme. It draws together over twenty Australian research leaders and clinicians from major national universities and research institutions to establish a research evidence base to inform safe clinical use of medicinal cannabinoids and to guide policy as cannabinoids are introduced into therapeutic practice in Australia.

Twitter Follow

Follow Christine Hallinan at @Cmhallinan

Figure 1 Number of TGA Special Access Scheme Category B approvals of Medicinal Cannabis in Australia May 2018-August 2021

Figure 2 The Application of Diffusion of Innovation theory to the rollout of Medicinal Cannabis in Australia

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Interview Guide

Theme	Question
Medicinal cannabis as an innovative medicine	*Before we start, do you view medicinal cannabis as a (pharmaceutical) medicine, or do you feel it should be defined as another type of product?*
Role for medicinal cannabis as a pharmaceutical	*What do you see currently as the role for medicinal cannabis?*
Experience with medicinal cannabis	*Can you tell us a bit about your experiences around medicinal cannabis?*
Rollout of medicinal cannabis in Australia	*Take us through the processes of prescribing medicinal cannabis from when a patient presents, to when they leave and when you review their progress?*
Overall attitude to medicinal cannabis in Australia	*Is there anything that we haven't discussed yet that you think is important for us to know about? Such as a take home or 'chestnut' message.*

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Bridgeman MB & Abazia DT. MC: History, Pharmacology, And Implications for the Acute Care Setting. *P& T*. 2017;42(3), 180-188. October 2 2019 https://pubmed.ncbi.nlm.nih.gov/28250701

2. Lancaster K, Seear K & Ritter A. Making medicine; producing pleasure: A critical examination of MC policy and law in Victoria, Australia. *Int. J. Drug Policy*. 2017;49, 117-125. doi:10.1016/j.drugpo.2017.07.020

3. Social Council of the United Nations. Single Convention on Narcotic Drug, 1961. 1961;1-44. October 9 2021 https://www.unodc.org/pdf/convention_1961_en.pdf

4. Grinspoon L & Bakalar JB. Marihuana: the forbidden medicine. 1993;New Haven, USA: Yale University Press.

5. .Kalant H. Medicinal use of cannabis: history and current status. *Pain Res. Manag.* 2001;6(2), 80-91. doi:10.1155/2001/469629

6. Taylor S. Medicalizing cannabis—Science, medicine and policy, 1950–2004: An overview of a work in progress. *Drug Edu Prev Policy*. 2008;15(5), 462-474. doi:10.1080/09687630802114038

7. EMCDDA. Cannabis policy: status and recent developments. EMCDDA Europa. Lisbon, Portugal: European Monitoring Centre for Drugs and Addiction. 2019. September 10 2019 http://www.emcdda.europa.eu/publications/topic-overviews/cannabis-policy/html_en

8. Shover CL & Humphreys K. Six policy lessons relevant to cannabis legalization. *Am J. Drug Alcohol Abuse* 2019;45(6), 698-706. doi:10.1080/00952990.2019.1569669

9. CPFG. (2018). Home Office Circular 1 November 2018: Rescheduling of cannabis-based products for medicinal use in humans. CPFG Drugs and Alcohol Unit. London, United Kingdom: Crime, Policing and Fire Group (CPFG). 2018. October 12 2019 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/753366/Medicinal_Cannabis_-_Home_Office_Circular_2018_FINAL.pdf

10. TGA. Access to MC products. Department of Health Australian Government. Canberra, Australia: Therapeutic Goods Administration. 2021. October 8 2021 https://www.tga.gov.au/access-medicinal-cannabis-products-1

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

11. McMillion J. Review of the Narcotic Drugs Act 1967 – Final Report The Office of Drug Control Australian Government. Canberra, Australia: Commonwealth Government of Australia. 2019. October 18 2019 https://www.odc.gov.au/sites/default/files/review-narcotic-drugs-act-1967-final-report.pdf

12. Freedman SB, Williamson-Urquhart S, Farion KJ, Gouin S, Willan AR, Poonai N, … Schuh S. (2018). Multicenter Trial of a Combination Probiotic for Children with Gastroenteritis. *NEJM.* 2018;379(21) 2015-2026. doi:10.1056/NEJMoa1802597

13. Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean JM, O'Connell KJ, … Freedman S. BLactobacillus rhamnosus GG versus Placebo for Acute Gastroenteritis in Children. *NEJM.* 2018;379(21) 2002-2014. doi:10.1056/NEJMoa1802598

14. Byrne S, Brindal E, Williams G, Anastasiou K. M, Tonkin A, Battams S & Riley, MD. (2018). E cigarettes, smoking and health. A Literature Review Update. Commonwealth Scientific and Industrial Research Organisation CSIRO Australia. October 02 2019 https://www.csiro.au/en/Research/BF/Areas/Nutrition-and-health/Public-health-and-wellbeing/Case-studies/E-cigarettes-report

15. Rucker J. JH, Iliff J & Nutt, DJ. Psychiatry & the psychedelic drugs. Past, present & future. *Neuropharm*. 2018;142 200-218. doi:10.1016/j.neuropharm.2017.12.040

16. Gardiner KM, Singleton JA, Sheridan J, Kyle GJ & Nissen, LM. Health professional beliefs, knowledge, and concerns surrounding MC – A systematic review. *PLoS One.* 2019 14(e0216556). doi.org/10.1371/journal.pone.0216556

17. Zolotov Y, Vulfsons S, Zarhin D & Sznitman, S. Medical cannabis: An oxymoron? Physicians' perceptions of medical cannabis. *Int. J. Drug Policy*. 2018;57, 4-10. doi:10.1016/j.drugpo.2018.03.025

18. Arnfinsen J. & Kisa A. Assessment of Norwegian physicians' knowledge, experience and attitudes towards medical cannabis. *Drug Edu Prev Policy*. 2021;28(2):165-71.

19 Ananth P, Ma C, Al-Sayegh H, Kroon L, Klein V, Wharton C, … Wolfe J. (2018). Provider Perspectives on Use of Medical Marijuana in Children With Cancer. *Pediatrics.* 2018;141(1), e20170559. doi:10.1542/peds.2017-0559

20. Braun IM, Wright A, Peteet J, Meyer FL, Yuppa DP, Bolcic-Jankovic D, … Campbell EG. Medical Oncologists' Beliefs, Practices, and Knowledge Regarding Marijuana Used

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Therapeutically: A Nationally Representative Survey Study. *J. Clin. Oncol.* 2018;36(19), 1957-1962. doi:10.1200/JCO.2017.76.1221

21. Carlini BH, Garrett SB & Carter, GT. MC: A Survey Among Health Care Providers in Washington State. *Am. J. Hosp. Palliat. Med.* 2017;34(1), 85-91. 10.1177/1049909115604669

22. Crowley D, Collins C, Delargy I, Laird E & Van Hout, MC. Irish general practitioner attitudes toward decriminalisation and medical use of cannabis: results from a national survey. *Harm Reduct. J.* 2017;14(4), 1-8. doi:10.1186/s12954-016-0129-7

23. Doblin RE & Kleiman MA. Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes. *J. Clin. Oncol.* 1991;9(7), 1314-1319. doi:10.1200/jco.1991.9.7.1314

24. Karanges EA, Suraev A, Elias N, Manocha R & McGregor IS. Knowledge and attitudes of Australian general practitioners towards MC: a cross-sectional survey. *BMJ Open*. 2018;8(7), e022101. doi:10.1136/bmjopen-2018-022101

25. Schwartz RH, Voth EA & Sheridan MJ. Marijuana to prevent nausea and vomiting in cancer patients: a survey of clinical oncologists. *South Med J.* 1997;90(2), 167-172. doi:10.1097/00007611-199702000-00001

26. Rogers EM. Diffusion of Innovations (Fifth Edition). 2003. New York USA: Simon & Shuster.

27. Berwick DM. Disseminating Innovations in Health Care. *JAMA*. 2003;289(15), 1969-1975. doi:10.1001/jama.289.15.1969

28. Coleman J, Menzel H & Katz E. Social processes in physicians' adoption of a new drug. *J. Clin. Epidemiol*. 1959;9(1), 1-19. doi:10.1016/0021-9681(59)90134-1

29. Coleman JS, Katz E & Menzel H. Medical Innovation: A Diffusion Study. 1966. Indianapolis: The Bobs-Merrill Company

30. Greenhalgh T, Robert G, Macfarlane F, Bate P & Kyriakidou O. Diffusion of Innovations in Service Organizations: Systematic Review and Recommendations. *Milbank Q.* 2004;82(4), 581-629. doi:10.1111/j.0887-378X.2004.00325.x

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

31. Lublóy Á. Factors affecting the uptake of new medicines: a systematic literature review. *BMC Health Serv. Res.* 2014;14(1), 469. doi:10.1186/1472-6963-14-469

32. Makowsky MJ, Guirguis LM, Hughes CA, Sadowski CA & Yuksel N. Factors influencing pharmacists' adoption of prescribing: qualitative application of the diffusion of innovations theory. *Implement Sc.* 2013;8(1), 109. doi:10.1186/1748-5908-8-109

33. Sanson-Fisher RW. Diffusion of innovation theory for clinical change. *MJA.* 2004;180(S6), S55. doi: 10.5694/j.1326-5377.2004.tb05947.x

34. Sanson-Fisher RW, D'Este CA, Carey ML, Noble N & Paul CL. Evaluation of systems-oriented public health interventions: alternative research designs. *Annu Rev Public Health.* 2014;35, 9-27.

35. Sugarhood P, Wherton J, Procter R, Hinder S & Greenhalgh T. (2014). Technology as system innovation: a key informant interview study of the application of the diffusion of innovation model to telecare. *Disabil. Rehabil: Assist Technol*. 2014;9(1), 79-87. doi:10.3109/17483107.2013.823573

36. RACGP. The sun sets on GP17. Melbourne, Australia: The Royal Australian College of General of General Practitioners. 2017. October 8 2021 https://www.racgp.org.au/download/Documents/Good%20Practice/2017/December/GP2017Dec-GP17.pdf

37. RACGP. Medicinal cannabis webinars. Melbourne, Australia: The Royal Australian College of General of General Practitioners. 2018. October 8 2021 https://www.racgp.org.au/education/professional-development/online-learning/webinars/medicinal-cannabis

38. MJA. MJA Podcasts 2018 Episode 12: Medicinal cannabis, part 1, with A/Prof Adrian Reynolds. Sydney, Australia: The Medical Journal of Australia. 2018. Accessed November 6 2018 https://www.mja.com.au/podcast/208/3/mja-podcasts-2018-episode-12-medicinal-cannabis-part-1-aprof-adrian-reynolds.

39. MJA. MJA Podcasts 2018 Episode 11: Medicinal cannabis, part 2, with Dr John Lawson. Sydney, Australia: The Medical Journal of Australia. 2018. Accessed November 6 2018 https://www.mja.com.au/podcast/208/3/mja-podcasts-2018-episode-11-medicinal-cannabis-part-2-dr-john-lawson-0

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

40. TGA. Access to MC products. Department of Health Australian Government. Canberra, Australia: Therapeutic Goods Administration. 2018. Accessed March 08 2018 https://www.tga.gov.au/access-medicinal-cannabis-products-1

41 Arnold JC, Nation T, McGregor IS. Prescribing medicinal cannabis. *Aust Prescr* 2020;43 (5):152-9.

42. Graham P, Evitts T, Thomas-MacLean R. Environmental scans. *Can. Fam. Physician.* 2008;54(7):1022.

43. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, et al. Methods to increase response rates to postal questionnaires. *Cochrane Database Syst Rev*. 2007;(2):MR000008.

44. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field Methods.* 2006;18(1):59-82.

45. QSR International Pty Ltd. NVivo (Version 12). 2018. Accessed November 06 2018 https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home

46. Berends L, Johnston J. Using multiple coders to enhance qualitative analysis: The case of interviews with consumers of drug treatment. *Addict Res Theory*. 2005;13(4):373-81.

47. Commonwealth of Australia. Current barriers to patient access to medicinal cannabis in Australia. The Senate Community Affairs Reference Committee. Canberra, Australia: The Senate Accessed April 09 2020 https://parlinfo.aph.gov.au/parlInfo/download/committees/reportsen/024403/toc_pdf/Currentbarrierstopatientaccesstomedicinalcannabisin Australia.pdf;fileType=application%2Fpdf

48. Althaus C, Bridgman P, Davis G. The Australian policy handbook: Allen & Unwin; 2012.

49. Campbell SM, Reeves D, Kontopantelis E, Sibbald B, Roland MO. Effects of pay for performance on the quality of primary care in England. *NEJM.* 2009;361(4):368-78.

50. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. *BMJ.* 2000;321(7262):694-6.

51. Giacomini M, Hurley J, Lomas J, Bhatia V, Goldsmith L. The many meanings of money: a health policy analysis framework for understanding financial incentives. 1996-06 Hamilton,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Ontario: Centre for Health Economics and Policy Analysis (CHEPA) McMaster University, Hamilton, Canada; 1996.

52. Hutchison BG, Levesque J-F, Strumpf E, Coyle N. Primary Health Care in Canada: Systems in Motion. *Milbank Q*. 2011;89(2):256-88.

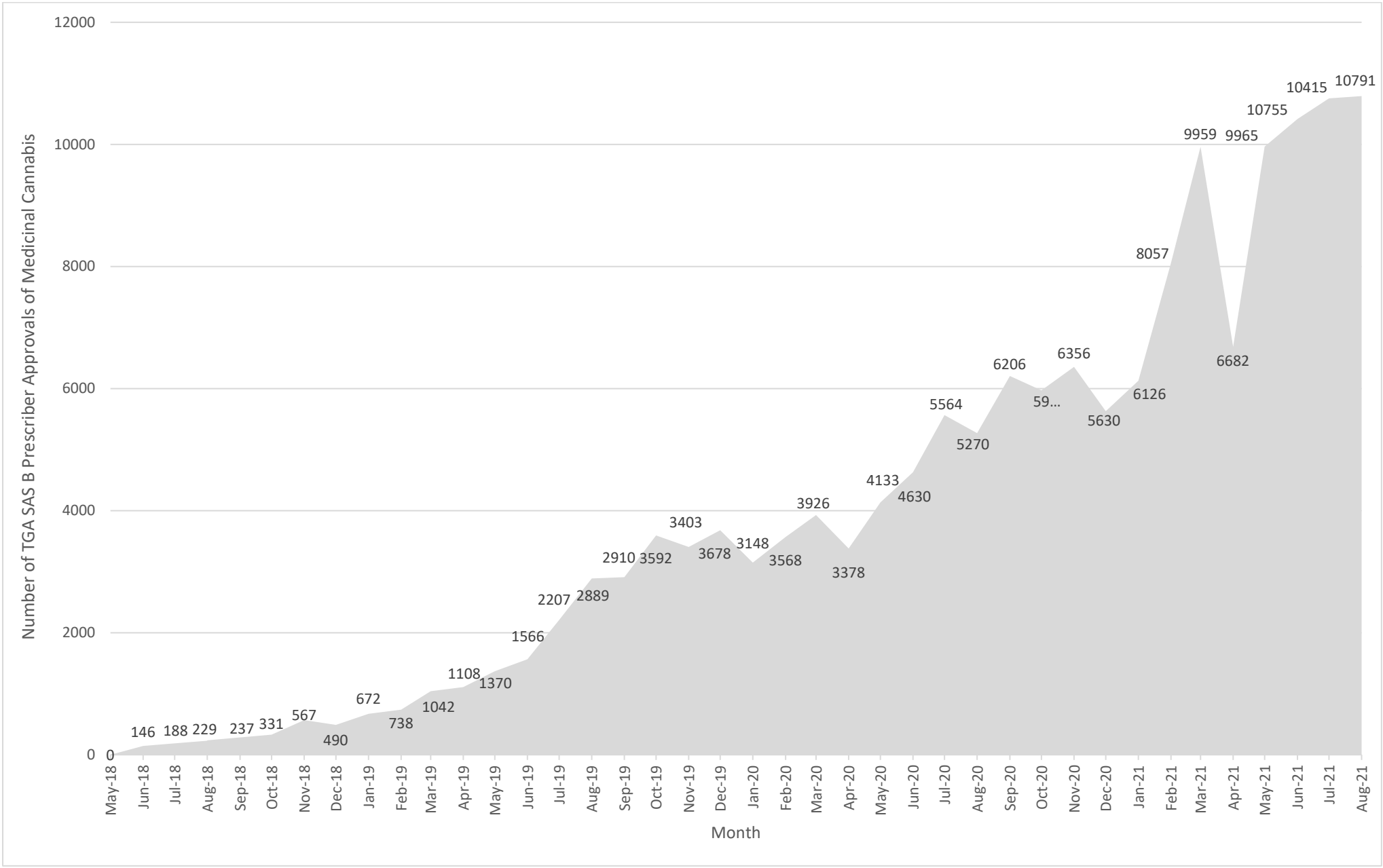
53. Gleeson P. The Challenge of Medicinal Cannabis to the Political Legitimacy of Therapeutic Goods Regulation in Australia. Melbourne University Law Review (advance) 2019;43.43. November 6 2019 https://law.unimelb.edu.au/__data/assets/pdf_file/0010/3214864/Gleeson-432-Advance.pdf

54. Nutt D, Bazire S, Phillips LD, Schlag AK. So near yet so far: why won't the UK prescribe medical cannabis? *BMJ Open*. 2020;10(9):e038687.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

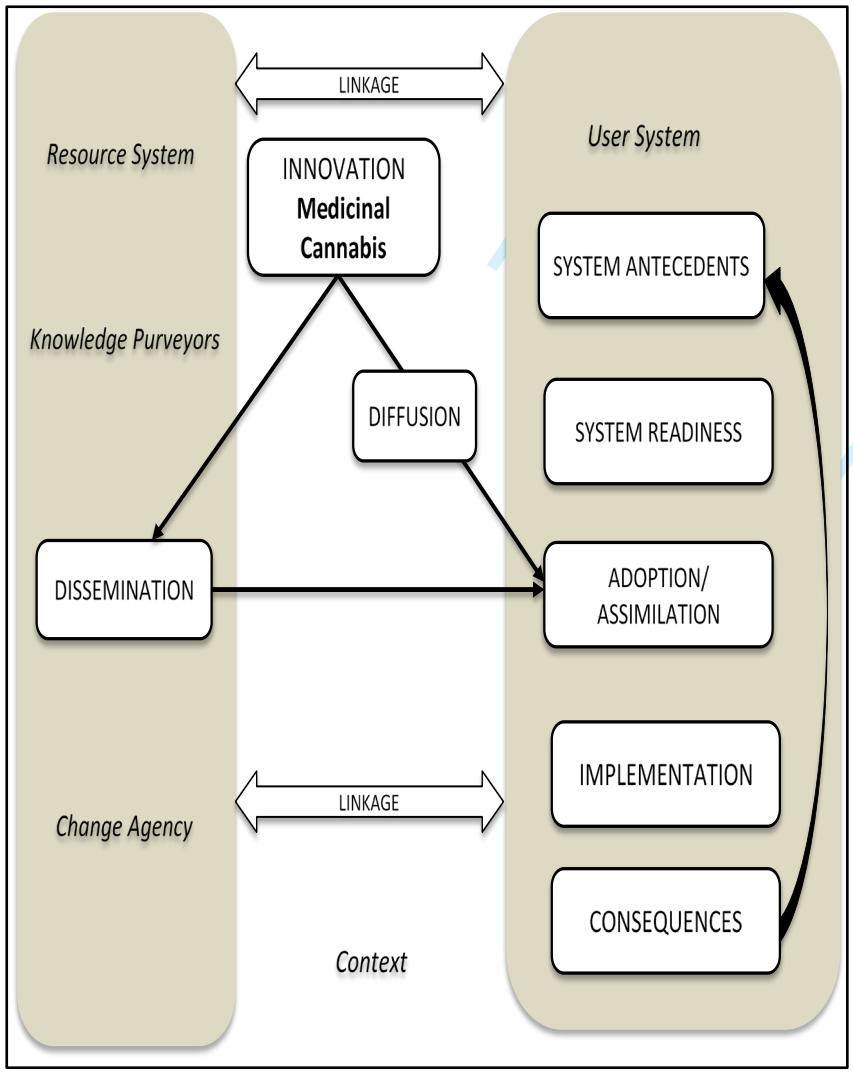
Figure 1 Number of TGA Special Access Scheme Category B approvals of Medicinal Cannabis in Australia May 2018 - August 2021



Source: TGA (2021). Access to medicinal cannabis products. TGA Department of Health Australian Government. Canberra, Australia: Therapeutic Goods Administration . Retrieved September 10, 2021, from https://www.tga.gov.au/access-medicinal-cannabis-products-1

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 2 The Application of Diffusion of Innovation theory to the rollout of Medicinal Cannabis in Australia



CANNABIS AS A MEDICINE		
INNOVATION Relative Advantage against other Medicines Compatibility with other Treatments Complexity Trialability Risk Knowledge Explicit/Implicit	**DIFFUSION & DISSEMINATION** Formal & Informal	
	DIFFUSION Profession networks Peer opinion	DISSEMINATION Marketing Expert opinion Champions Policy drivers
	Medicinal Cannabis System Antecedents	
	Structure	Maturity, History, Knowledge Medicinal Cannabis Company Resources Technical Support
	Knowledge	Explicit & Implicit Developing & Integrated
	Context	Leadership
HEALTH SYSTEM READINESS Prescriber Adoption and Assimilation into Practice	Agency for Change System Fit – Preparedness for regulation Power Balance - Supporters vs. Opponents	
	Assessment - Pharmacovigilance Capacity - Time and Resources for Monitoring Sustainability – Ongoing Monitoring and Feedback	
	Needs, Motivation, Values, Goals, Skills, Learning Style	
IMPLEMENTATION OF MEDICINAL CANNABIS 'ROLLOUT" Consequences of MC Prescribing	Government and policy Support from Government agencies	
	Training and dedicated resources Feedback on progress	
	Outcomes - Positive, Neutral, Negative Unintended events, Adverse events	

Adapted from Greenhalgh T et. al. (2004) Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Quarterly*, 82 (4), pp 581-629.

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist					
	No Item	**Guide Question/Description**			
	Domain 1: Research team and reflexivity Personal Characteristics		Dr Christine Hallinan-CH A/Prof Yvonne Bonomo-YB	Page #	Paragraph
1	Interviewer/facilitator	Which author/s conducted the interview or focus group?	CH & YB	8	1
2	Credentials	What were the researcher's credentials?	CH-AppSc(Registerd nurse), MPH, PhD, Master Biostats(currently undertaking)		
			YB-Addiction Medicine Physician, FRACP,FAChAM PhD		
3	Occupation	What was their occupation at the time of the study?	CH-Research Fellow		
			YB-Physician		
4	Gender	Was the researcher male or female?	CH-Female		
5	Experience and training Relationship with participants	What experience or training did the researcher have?	CH-Department of General Practice Melbourne University		
6	Relationship established	Was a relationship established prior to study commencement?	No prior relationship between CH and YB		
7	Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Partipicants did not have prior knowledge of CH.		
			YB-professional relationships with three of the interviees.		
8	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	We reported work was funded and supported by the Australian Centre for Cannabinoid Clinical and Research Excellence and we are involved in gathering evidence to develop a national research and policy framework that ensures quality and safety in the implementation of medicinal cannabis use in the community.		
	Domain 2: study design Theoretical framework			Page #	Paragraph
	Methodological orientation and Theory Participant selection	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Inductive and Deductive analysis using Diffusion of Innovation Theory	8	1,2
10	Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Purposive and snowball selection	7	2
11	Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	An email and a postal invitation. The informants who did not respond were followed up with either another email and/or a phone call of invitation to participate	8	1
12	Sample size	How many participants were in the study?	21	8	4
13	Non-participation setting	How many people refused to participate or dropped out? Reasons?	26 individuals were approached, 23 accepted, of these 1 withdrew for personal reasons, and 1 withdrew because of time constraints.	8	4
14	Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Two interviews were undertaken in meeting room at YB's place of work, the interviewees office, via zoom and on the phone	8	1
15	Presence of non-participants	Was anyone else present besides the participants and researchers?	No	8	1
16	Description of sample Data collection	What are the important characteristics of the sample? e.g. demographic data, date	Of the informants who accepted, thirteen were active prescribers, four were non-prescribers, and four were public health advisors. The 21 key informants included neurologists, rheumatologists, oncologists, pain specialists, psychiatrists, public health advisors, and general practitioners. All informants were based in the Eastern States and Territories of Australia (Victoria, New South Wales, Tasmania, Canberra, and Queensland). Interviews were conducted between November 2018 and January 2019.	8	4
17	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Interview guide attached. It was not pilot tested.	21	
18	Repeat interviews	Were repeat interviews carried out? If yes, how many?	No		
19	Audio/visual recording	Did the research use audio or visual recording to collect the data?	Interviews were audio recorded	8	1
20	Field notes	Were field notes made during and/or after the interview or focus group?	Yes		
21	Duration	What was the duration of the interviews or focus group?	Between 21-99 minutes (average 57 minutes). Median 60 minutes.	8	1
22	Data saturation	e	Thematic saturation was ascertained after data collection, and based on saturation of new information threshold, where there was no evidence of the emergence of new themes beyond those already established.	8	2
23	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No		
	Domain 3: analysis and findings Data analysis				
24	Number of data coders	How many data coders coded the data?	Two YB and CH	8	2
25	Description of the coding tree	Did authors provide a description of the coding tree?	Not in manuscript-but coding tree was developed		
26	Derivation of themes	Were themes identified in advance or derived from the data?	Derived from the data		
27	Software	What software, if applicable, was used to manage the data?	Nvivo		
28	Participant checking Reporting	Did participants provide feedback on the findings?	No		
29	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number	Yes-participant quotations presented to illustrate the themes / findings Yes placed in deidentifed participant ID	9 -15	All
30	Data and findings consistent	Was there consistency between the data presented and the findings?	Yes	9 -15	All
31	Clarity of major themes	Were major themes clearly presented in the findings?	Yes	9 -15	All
32	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes	16-18	All

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml