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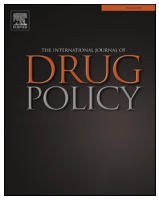

Commentary

A provisional evaluation of Australia's medical cannabis program

Myfanwy Graham [a,b,*], Vivian Chiu [c], Daniel Stjepanović [c], Wayne Hall [c]

[a] Centre for Drug Repurposing & Medicines Research, School of Medicine and Public Health, The University of Newcastle, Australia
[b] Schaeffer Center for Health Policy & Economics, The University of Southern California, United States
[c] National Centre for Youth Substance Use Research, The University of Queensland, Australia

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ABSTRACT

In 2016, the Australian Government legislated to allow cannabis to be prescribed to patients as an unapproved medicine under the special access provisions of the Therapeutic Goods Act. This paper compares the Australian regulatory approach with other national approaches, outlines the main provisions of the Special Access Scheme for medical cannabis, describes how the program has evolved since 2017, includes an analysis of adverse events reported to the Therapeutic Goods Administration, and discusses the barriers that remain for patients who wish to access medical cannabis. It assesses how well the Australian program has addressed the challenges of providing patients with easier access to medical cannabis while ensuring that high-quality products are used safely and effectively under medical guidance.

Introduction

Since 1996, more than 37 US states and Canadian provinces and territories have allowed patients to access medical cannabis products to treat the symptoms of a variety of illnesses (Hall & Degenhardt, 2003; Hall et al., 2019). In the 20 years since then, a growing number of countries have used a variety of regulatory approaches to enable patients to access cannabis products for medical use (De Souza et al., 2022; European Monitoring Centre for Drugs & Drug Addiction, 2018). The Netherlands and Israel were early adopters of prescription and licensing systems. More recent adopters have included Australia and Germany (European Monitoring Centre for Drugs & Drug Addiction, 2018). In this paper, we describe Australia's approach to medical cannabis, compare it with other national models, and assess the degree to which it has increased patient access to safe and effective medical cannabis products. We begin by summarizing the different national approaches to allowing patients to access cannabis products for medical use.

National approaches to medical cannabis regulation

National approaches to medical cannabis regulation can be usefully classified in terms of the type of cannabis products that patients can use, the type of authorization that patients require to access medical cannabis, and how cannabis is cultivated and supplied to patients (Belackova et al., 2018). Due to jurisdictional differences in terminology, medical cannabis will be used throughout this article when referring to "medicinal cannabis" and "cannabis medicines".

Medical cannabis products may be restricted to pharmaceutical cannabinoids (e.g. dronabinol, nabiximols, and Epidyolex®, branded as Epidiolex® in other jurisdictions) that have been approved for medical use on the basis of evidence of their safety and efficacy in controlled clinical trials. Less restrictively, medical cannabis products may include pharmaceutical grade herbal cannabis products. Patients may be allowed to grow their own herbal cannabis, or have a carer grow it on their behalf (Belackova et al., 2018).

In the most restrictive form of *authorization*, patients may only be given an exemption from criminal prosecution if they have one of a specified set of medical diagnoses. *Medical authorization* may require either a prescription or a recommendation from a medical practitioner certifying that a patient has symptoms that may be improved by using cannabis. A medical practitioner may be able to prescribe either a pharmaceutical cannabinoid containing product approved by a national medicines regulator or an unapproved product.

Medical cannabis prescriptions may be restricted to patients with life-threatening illnesses (e.g. cancer or a degenerative neurological disorder) or to patients with a medical condition for which there is evidence of effectiveness, such as chemotherapy-induced nausea and vomiting (CINV), muscle spasticity in multiple sclerosis (MS), or intractable epilepsy. The most liberal prescription systems allow medical cannabis to be prescribed to any patient with any medical condition

* Corresponding author at: Centre for Drug Repurposing & Medicines Research, School of Medicine and Public Health, The University of Newcastle, Australia.
E-mail address: myfanwy.graham@newcastle.edu.au (M. Graham).

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that the prescriber and patient believe will be improved by using a medical cannabis product (European Monitoring Centre for Drugs & Drug Addiction, 2018).

Combinations of regulatory approaches

In the U.S., a number of states have implemented medical cannabis programs that differ in degree of healthcare professional involvement, qualifying medical conditions, composition and quality standards of cannabis products, and cannabis dispensary supply models. Federally in the U.S., cannabis remains in Schedule I and is illegal for medical use (Pacula & Smart, 2017; Pruyn et al., 2022). Canada has, by contrast, adopted a federal medical cannabis program. It involves authorization by a healthcare professional, with cannabis grown for medical purposes by a registered patient or a designated person or access via licensed producers (Health Canada, 2017).

There is substantial variance in the medical oversight of cannabis products and the type of health professional in different countries. North American models can involve medical recommendation or authorization by a medical doctor or other health professionals such as nurse practitioners or podiatrists in some U.S. states.

A prescription system that allows patients with a limited range of medical conditions to obtain approved pharmaceutical cannabinoids from pharmacies had existed in principle in the U.S. before medical cannabis was made legal at the state level. Very few patients accessed these cannabinoids, however, because they were not readily available or were rarely prescribed. Early adopters of medical cannabis licensing and prescription systems, such as those in Israel and the Netherlands allow patients to use herbal cannabis products that meet pharmaceutical standards of quality and do not contain contaminants such as heavy metals, fungi, and other microorganisms. According to De Souza et al. (2022), unapproved cannabis products, including herbal cannabis products, were more often accessed or prescribed than approved pharmaceutical cannabinoids in the 36 countries they examined.

Regulatory priorities of medical cannabis programs

These different regulatory approaches to medical cannabis differ in the priorities that are given to the policy goals shown in box 1 (adapted from Belackova et al., 2018). An approach that only allows an exemption from criminal prosecution places the burden on patients to demonstrate that they are eligible to use medical cannabis. It allows patients to grow their own cannabis, but it provides poor control over the quality and safety of the cannabis products and often involves a minimum of medical oversight.

A prescription system preserves some features of the pharmaceutical regulatory system in requiring a medical prescription (or recommendation) and pharmacies to supply either pharmaceutical quality cannabinoids or herbal cannabis products. These products can be expensive for patients in the absence of a public or health insurance subsidy. The costs to the government of this regulatory system may also be substantial because these require the licensing of cannabis producers; quality testing of medical cannabis products; a system of approving applications to prescribe; and monitoring the operation of the system to ensure the maintenance of medical cannabis quality and prescribing.

The most liberal regulatory approaches are in those U.S. states where medical cannabis was legalized by citizen-initiated referenda (Hall & Degenhardt, 2003). These programs maximize patient access and minimize costs to patients by encouraging retailers to compete on price. Some states also reduce the costs of government regulation by giving a lower priority to ensuring the quality of medical cannabis products. The degree of medical oversight of cannabis use in these programs is variable, and the boundaries between medical and nonmedical cannabis use are often blurred (Hall & Degenhardt, 2003). North American regulation started with the legalization of medical use in several states, and over time, this has shifted to commercialized models.

Australia's medical cannabis program

In February 2016, the Australian Federal Government amended the Narcotic Drugs Act (Australian Government, 2016). The Act permitted the cultivation of cannabis for medical purposes in Australia and subsequently enabled the Office of Drug Control to license companies to cultivate and manufacture medical cannabis products and to oversight their compliance with license conditions (Freckelton, 2016).

Earlier attempts to allow the medical use of cannabis products in Australia in the 1990s and 2000s failed (Freckelton, 2016), despite reports by the British Medical Association and the UK House of Lords that supported the medical use of cannabis (British Medical Association, 1997; the UK House of Lords, 1998). A major reason for the success in the 2010s was a well-organized advocacy campaign led by parents who had treated their children with cancers and epilepsy with illicit cannabis (Freckelton, 2016, 2021). The media sympathetically reported these cases (Freckelton, 2021; Gleeson, 2020) and provided favorable accounts of medical cannabis programs in California, Canada, Israel, and the Netherlands. These parents met with state and federal politicians and persuaded them to allow access to medical cannabis (Freckelton, 2021). In 2015, the NSW Government established a center for Medicinal Cannabis Research and Innovation and allowed compassionate access to cannabis for terminally ill patients (Davey, 2015; Freckelton, 2016). Philanthropists whose grandchild's epilepsy was treated with cannabis oil donated $34 million to the University of Sydney to fund the Lambert Initiative for Cannabinoid Therapeutics (Aubusson, 2016; Barnes, 2014; The University of Sydney, 2015).

In late 2014, a newly elected Victorian Labor Government commissioned the Victorian Law Reform Commission to advise on how to make cannabis available for medical use (Gleeson, 2020; Victorian Law Reform Commission, 2015). The Commission's 2015 report set out the legislative changes that needed to be made by the Victorian and Australian Governments (Andrews, 2015). It attracted broad bipartisan support from State Labor and Liberal Governments and prompted legislative action by the Liberal-National Federal Government (Access to Medicinal Cannabis Bill, 2015, 2016) and the Queensland Labor Government in 2016 (Atfield, 2016).

Medical cannabis access via the Special Access Scheme and Authorized Prescriber Scheme

In late 2016, the Federal Government reclassified the scheduling of cannabis and tetrahydrocannabinols under the Poisons Standard so that physicians could prescribe medical cannabis products as unapproved therapeutic goods using the provisions of the Special Access Scheme (SAS) of the Therapeutic Goods Act. Although the first SAS application for medical cannabis was received by the Therapeutic Goods Administration (TGA) in 1992, the majority of approvals are from 2016 onwards. Several state governments passed similar legislation to allow patients to access medical cannabis (Commonwealth Department of Health, 2020a; Freckelton, 2016).

One of the TGA prescribing pathways for unapproved medicines is the Authorized Prescriber Scheme (Hewett et al., 2022). An "Authorised Prescriber" is a medical practitioner authorized to prescribe a medical cannabis product category and dose form to a class of patients for specified indications. Authorized Prescribers do not need to notify the TGA of each prescription, but they are required to report the number of patients they have treated on a six-monthly basis. They also need the approval of an Ethics Committee or a Specialist College to prescribe medical cannabis. Since November 2021, a second Authorized Prescriber pathway became available whereby Ethics Committee approval or Specialist College endorsement is not required. This pathway involves the selection of an unapproved product (cannabinoid composition category, dose form) from a list with an established history of use

Box 1
Examples of variable elements in the spectrum of regulatory frameworks for medical cannabis programs.

- Patient access
- Quality-controlled cannabis products
- Medical oversight of diagnosis and treatment
- Costs of medical cannabis products
- Costs of regulation to government and
- Diversion of cannabis to the recreational market

(specific conditions e.g. refractory chronic pain or anxiety).

The TGA's SAS also allows any medical practitioner to prescribe an unapproved medical cannabis product for a named patient. Category A in the SAS applies to seriously ill persons whose death is likely within months or who are likely to die in the absence of treatment. Prescribers do not need prior approval to prescribe to these patients under SAS-A provisions, but they must notify the TGA within 28 days of doing so (Therapeutic Goods Administration, 2023a). If the SAS-A pathway is used, the medical cannabis product needs to be imported, and this can take time. These delays often make the SAS-B pathway preferable for patients with a limited life expectancy (NPS MedicineWise, 2022a).

The SAS-B pathway provides access to cannabis products that are available in Australia. This includes products manufactured in Australia and imported products. As part of the SAS-B pathway, prescribers are required to apply for approval from the TGA before they can prescribe medical cannabis. Their application must supply information on the patient's diagnosis, the indication for treatment, the seriousness of their condition, and a history of past treatment. They must provide reasons for using medical cannabis instead of an approved medicine and specify the type of product that will be used (e.g. cannabinoid composition category, dose form), the proposed dosage, duration of treatment, and monitoring. The prescriber is also required to report on adverse events (Therapeutic Goods Administration, 2023a).

In addition to TGA approval, state regulatory authorities differed in the additional approvals that were required for Controlled Drug (Schedule 8) medical cannabis products (ACT Government, 2021; Government of South Australia, 2022; Government of Western Australia, 2023; Northern Territory Government, 2022; NSW Health, 2022; Queensland Health, 2022; Tasmanian Government Department of Health, 2021; Victoria Department of Health, 2022). While jurisdictional differences still exist, over time state approval requirements have been reduced or removed. For example, approval requirements in NSW for Schedule 8 products include but are not limited to drug-dependent patients and pediatric patients (NSW Health, 2022).

Initially, only medical specialists could prescribe medical cannabis in Queensland (Queensland Government, 2017, 2019), and this was required in Tasmania until mid-2021 (Tasmanian Government Department of Health, 2021). The Faculty of Pain Medicine (Choosing Wisely Australia, 2022), the Australian Medical Association (2014), and The Royal Australian and New Zealand College of Psychiatrists (2021) advised their members that safety and efficacy should be assessed in clinical trial contexts. These bodies argued that there was little evidence to support many claimed medical uses of cannabis, and there were more efficacious treatments for those conditions where there was some evidence of efficacy for cannabis. Doctors were also concerned about their legal liability for any harm that patients may experience from prescribed medical cannabis.

Many patients accordingly found it difficult to find doctors who would prescribe medical cannabis (Medical Cannabis Users Association of Australia, 2020). The few doctors who were prepared to prescribe were not permitted to advertise this fact. Patients also complained about the complex approval process and the federal and state approvals required. These complexities often delayed patient access to medical cannabis for several weeks.

After July 2018, federal and state governments made a series of regulatory changes to increase patient access to medical cannabis. The application process to prescribe was streamlined via an online portal that enabled requests to be concurrently assessed by Commonwealth and state authorities. The result was that, in most cases, approval was received within 48 h of applying. In parallel, for-profit medical cannabis clinics were established that facilitated cannabis prescriptions and provided patients with access to medical cannabis products.

An evaluation of Australia's medical cannabis program

Patient access

Australia's medical cannabis program began as a prescription system in which only patients with a restricted range of medical conditions were eligible and extensive evidence was required to support applications for other conditions. Specialist physician support was initially required to prescribe medical cannabis, and the use of pharmaceutical cannabinoids was encouraged. These provisions have been progressively liberalized in response to advocacy to increase patient access. The process of obtaining approval to use a medical cannabis product was initially complex and time-consuming, requiring separate approvals by state and federal health departments. The approval system has been streamlined, ensuring quick and almost universal approval. Eligibility to prescribe was broadened to include family physicians, and prescribers were allowed to prescribe an increasing variety of cannabis products for an increasingly broad range of medical indications. The costs to patients of obtaining a prescription and medical cannabis products and drug driving laws remain the major obstacles to patient access.

These regulatory changes were followed by large increases in the number of approved medical cannabis applications during 2021 and 2022 (Hallinan & Bonomo, 2022; Therapeutic Goods Administration, 2023b). As of July 2023, a total of 385,163 SAS-B approvals and 5084 prescribers; 2020 SAS-A notifications and 1117 prescribers; and 31,190 AP applications and 2100 prescribers were documented on the TGA medical cannabis public dashboard. The public dashboard also provides data on patient age and indications, dose form, and consulting location. These data only include unapproved medical cannabis products; they do not include registered products such as Sativex® and Epidyolex® (Therapeutic Goods Administration, 2023b). Additional limitations to these data are described in detail by Hallinan and Bonomo (2022) and MacPhail et al. (2022). Publication of application approval data is an important source of information to inform research and policy decisions moving forward.

Medical cannabis products

There were also early difficulties in obtaining Australian medical

cannabis products and ensuring a continuous supply of imported products. Australian medical cannabis producers and retailers were licensed in early 2017, but it took considerable time to scale up the production of medical cannabis products that met the TGA's Good Manufacturing Practice (GMP) standards. Medical cannabis products were largely imported from Canada, making it expensive and time consuming to obtain them (Erku et al., 2022). From July 1st, 2023, the TGA required imported products to meet one of the identified GMP standards, bringing the requirements for imported products in line with requirements for locally manufactured products. Medical cannabis product GMP requirements are a strength of the Australian system and a point of difference compared to some models in U.S. states that have legalized medical use (Therapeutic Goods Administration, 2023c).

The TGA initially encouraged the use of approved pharmaceutical cannabinoids but has since allowed patients to use a wide range of different medical cannabis products. These have included oral liquids, oils, tinctures, oro-buccal sprays, capsules, chewable tablets, a pastille product, topical products, and herb dried for vaporization. These products include high and low delta-9-tetrahydrocannabinol (THC) products, cannabidiol (CBD) only and dominant products, and balanced THC/CBD products, and they may contain a variety of other cannabinoids, including cannabinol and cannabigerol. The TGA webpage lists >250 medical cannabis products by cannabinoid composition, strength, and dose form. The TGA and state health departments have provided health professionals and the public with accessible information about medical cannabis products that conform to the TGA's minimum quality requirements (TGO93) and microbiological quality requirements (TGO100) (Therapeutic Goods Administration, 2023d).

Since February 2021, the TGA has allowed over-the-counter sales of registered low-dose CBD products that meet standards of quality, efficacy, and safety assessment, but as yet no CBD product has met these requirements (Therapeutic Goods Administration, 2020a). In late 2021, prescribers were no longer required to specify medical cannabis products by name in applications for approval to prescribe. Instead, the TGA introduced a categorization system based on cannabinoid composition (NPS MedicineWise, 2022b). Based on the advice provided by the Australian Advisory Council on the Medicinal Use of Cannabis in early 2023, a requirement for the provision of supporting evidence from a pediatric or relevant medical specialist is required for the use of THC-containing products by patients under 18 years (Therapeutic Goods Administration, 2023a).

Remaining barriers to accessing medical cannabis

Patients' difficulty in finding doctors willing to prescribe has been largely addressed by the growth of for-profit medical cannabis clinics whose doctors prescribe cannabis and facilitate the supply of medical cannabis products for a fee. The medical fees to obtain a cannabis prescription and the cost of medical cannabis products remain barriers to access, as highlighted in a 2020 Senate Community Affairs References Committee inquiry report on patient access. Patients typically need to pay out-of-pocket costs or, in some cases, the full costs of a consultation and prescription (Commonwealth Parliament, 2020; Erku et al., 2022; Lintzeris et al., 2022). According to the CAMS-20 survey that collected data between September 2020 and January 2021, respondents who used prescribed medical cannabis spent a mean of AUD $79.2 weekly. This was more than those who obtained their cannabis via non-legal pathways, AUD $58.6 weekly. Those who reported accessing cannabis from both prescribed and non-legal pathways reported spending a mean of AUD $114 a week (Lintzeris et al., 2022).

Qualitative interviews of Australian key informants during the early stages of Australian medical cannabis regulatory reform reported a shift towards demand-driven use of medical cannabis products (Hallinan et al., 2021). The willingness of doctors to prescribe medical cannabis remains an identified barrier to patient access (Lintzeris et al., 2022) despite attitudinal shifts reported in surveys of general practitioners (Bawa et al., 2022; Karanges et al., 2018). Two-thirds (66.9 %) of general practitioners surveyed reported inadequate knowledge about medical cannabis, and almost half said that they were not comfortable discussing medical cannabis use with their patients (Bawa et al., 2022).

The high cost of medical cannabis has prompted advocacy groups to call for public funding of products (Commonwealth Parliament, 2020). In Australia, the costs of some pharmaceutical drugs are subsidized under a Pharmaceutical Benefits Scheme (PBS) on the advice of the Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC only recommends a subsidy if there is good safety and efficacy evidence from clinical trials, and economic analyses show that the drug is more cost-effective than an approved drug, or it is as effective as and less expensive than an approved drug. The PBAC has recommended that CBD (Epidyolex®) be subsidized to treat intractable forms of childhood epilepsy. Applications to subsidize a THC and CBD combination product, Sativex®, in treating muscle spasticity in MS were rejected on the grounds that its modest medical benefits did not justify the price requested by the company (Commonwealth Department of Health, 2020b; MS Australia, 2020). None of the medical cannabis products prescribed as unapproved medicines receive a PBS subsidy. Although the Department of Veterans' Affairs will consider funding the cost of medical cannabis for some health conditions, mental health conditions are excluded (Department of Veterans' Affairs, 2023). While some suppliers/sponsors provide compassionate and concession pricing schemes for medical cannabis products and clinical trial enrolment provides another mechanism to counter the costs, these options are only available to patients who meet eligibility criteria.

Patients have also reported that state drug driving laws are a major barrier to using medical cannabis because they fear the loss of their driver's licenses if they test positive for THC on roadside saliva tests (Lambert Initiative for Cannabinoid Therapeutics, 2020; Medical Cannabis Users Association of Australia, 2020). The medical cannabis industry and patient advocates have argued that state road safety laws should exempt authorized medical cannabis patients from prosecution. They argue that saliva tests simply indicate the presence of THC and not driver impairment and that patients who use cannabis regularly for medical purposes develop tolerance to its impairing effects. They also argue that there is an inconsistency between drug driving laws that ban medical cannabis users from driving while exempting persons who use other prescribed medications that may cause driving impairment (Lambert Initiative for Cannabinoid Therapeutics, 2020; Perkins et al., 2021). An added layer of complexity is that the driving of patients may be impaired by serious illnesses (e.g. neurological disorders) and the use of multiple medications that raise the possibility of drug-drug interactions, although this consideration is not limited to medical cannabis patients.

In Tasmania, medical cannabis patients can legally drive if they are not impaired and taking a prescribed medical cannabis product that has been obtained and used in line with the Poisons Act 1971 (Tasmanian Government Department of Health, 2022). While there are medical exemptions for other prescribed substances in other states and territories, these do not include prescribed medical cannabis (Perkins et al., 2021).

Quality of medical cannabis use

A review of the SAS program that preceded the legalization of medical cannabis use questioned the adequacy with which medical necessity applications were assessed under SAS-B (Sansom et al., 2015). SAS-B applications for medical cannabis are assessed by a delegate of the Secretary of the Department of Health and Aged Care, and 98 % of applications have been approved (see Fig. 1) (Therapeutic Goods Administration, 2023b). Given the high rate of approval of SAS applications for medical cannabis, it is reasonable to ask whether the TGA approval process is protecting patients by ensuring that they are prescribed unapproved therapeutic goods that are clinically justified (Baker, 2022).

The major medical indications for which cannabis was approved for

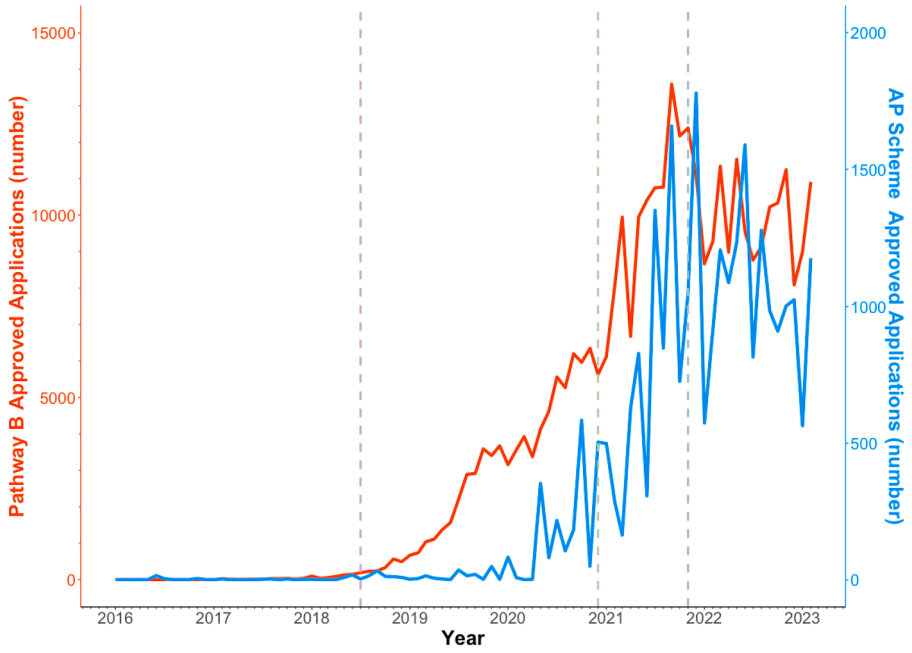

Fig. 1. Medical Cannabis Special Access Scheme (SAS) and Authorized Prescriber (AP) applications
Dashed lines indicate pivotal federal regulatory shifts, including the online application portal (July 2018), low dose CBD announcement (December 2020), and change to AP pathway and medical cannabis category based approvals (November 2021).

prescription via the SAS-B pathway between January 2017 and August 2022 were chronic pain (59 %); anxiety (23 %); sleep disorders (4 %); cancer pain and symptom management (4 %); insomnia (3 %); neuropathic pain (2 %); and post-traumatic stress disorder (2 %). Just over half of the patients (58 %) were male, and half were aged 18–24 years. Around a third (31 %) were aged 45–64 years, 10 % were aged 66–74 years, and 8 % were 74 years and older (Hallinan & Bonomo, 2022).

The SAS data do not include a unique identifier for patients who have been prescribed medical cannabis. This means that it is unclear how many individuals have been prescribed and used specific medical cannabis products. Based on TGA SAS-B medical cannabis dashboard data (exported 3 October 2023) from September 2022 onwards, dried herb and oral liquid (21.80 % (n=29/133) and 59.40 % (n=79/133) of all dosage forms respectively) were the predominant dose forms in the age category 18–44 years. Chronic pain and anxiety (32.33 % (n=43/133) of all indications for each of anxiety and chronic pain) were the leading indications in this age category. For anxiety, 62.50 % (n=10/16) of dried herb and inhalation products were classified as Category 5 THC medical cannabis products (CBD less than 2% and other natural cannabinoids found in cannabis greater than 98% of the total cannabinoid content of the product). For all age categories, most prescribers were based in Queensland (30.56 %; n=114/373) and Victoria (24.93 %; n=93/373) (Therapeutic Goods Administration, 2023b).

A commercial cannabis information company, FreshLeaf Analytics (2021), suggested that there were "blurred lines between adult-use and medical markets with some product companies testing the waters by bringing new product formats to market that are traditionally considered more recreational formats such as bubble hash". Some products available for inhalation have higher THC potency (>30 %) than would be anticipated for a medical market and are in the potency ranges seen in recreational markets (Therapeutic Goods Administration, 2023d). As seen in North America, a shift towards commercialized models of supply may have potentially harmful public health consequences without regulatory provisions to protect vulnerable patient groups.

The proportion of the population accessing medical cannabis via the SAS and Authorized Prescriber pathways has increased over time but according to online surveys of self-identified medical cannabis users, it is still less than the proportion that accesses cannabis for medical conditions outside TGA pathways (e.g. Lintzeris et al., 2022). Australian national household survey data in 2019 indicated that many self-described medical cannabis users were recreational cannabis users who also reported medical use. Less than 1 % of the Australian adult population reported using cannabis exclusively for medical purposes, and nearly all reported doing so without a doctor's prescription (Leung et al., 2022). These low rates of medical cannabis access via TGA channels were before the very large increases in prescriptions in 2020–2022.

Adverse event data

Data on adverse events of prescribed unapproved medical cannabis use relies on health practitioners, suppliers/sponsors, and consumer reports of adverse events to the TGA. Adverse event reports related to registered products (Sativex® and Epidyolex®) and reports involving a combination of products, including other registered medicines or vaccines, are available online via the Database of Adverse Event Notifications (DAEN) platform. Using the search terms "cannabidiol", "tetrahydrocannabinol", and "cannabis", only 27 reports were identified using DAEN up until July 14th, 2023.

Most adverse event reports related to unapproved medical cannabis products are part of an internal adverse event database. Based on an analysis of internal data collected between 29/09/2016 and 21/03/2023 and DAEN data up to 14/07/2023, there were a total of 549 unique adverse event reports (the total excludes 26 records with duplicated ID and nine records with the same date, age, and sex (Therapeutic Goods Administration, 2020b, 2022, 2023e). MedDRA®, the Medical Dictionary for Regulatory Activities terminology (CTCAE version 5.0), were coded as separate binary variables. This is because the reported adverse events are not mutually exclusive. Each report may include more than one adverse event. Additional MedDRA® coding was applied where incomplete coding was identified, and data were analyzed using SAS (version 9.4).

Adverse event reports for females (53.19 %; n = 292/549) were more common than for males (40.07 %; n = 220/549), excluding 37 instances (6.74%) where sex was not noted (see Fig. 2). A large proportion of the reports related to individuals under 18 years of age (17.26 %; n = 87/

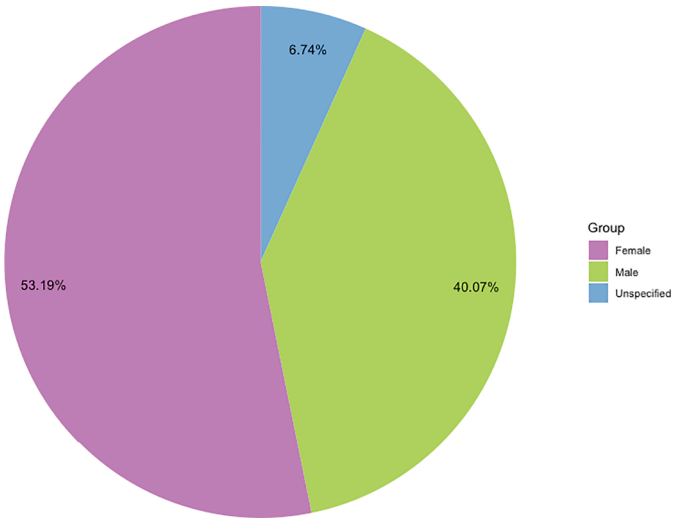

Fig. 2. Unapproved medical cannabis adverse event reports by sex (percentage).

504) and greater than 65 years (26.19 %; $n = 132/504$), excluding 45 instances with missing age (See Fig. 3).

Overall, there were 1297 adverse events reported in the 549 unique reports (see Fig. 4). These adverse events span across 26 MedDRA® System Organ Classes (SOC), with the highest number of conditions related to Nervous System Disorders ($n = 274$), followed by Psychiatric Disorders ($n = 233$) and Gastrointestinal Disorders ($n = 229$) (see Fig. 5). The most frequently reported conditions related to Nervous System Disorders were somnolence (17.15 %; $n = 47/274$), dizziness (16.42 %; $n = 45/274$), and headache (12.77 %; $n = 35/274$). Among conditions related to Psychiatric Disorders, hallucinations (15.45 %; $n = 36/233$), anxiety (10.73 %; $n = 25/233$), and insomnia (6.01 %; $n = 14/233$) accounted for nearly a third of the category. As for Gastrointestinal Disorders, the largest contributions were nausea (24.89 %; $n = 57/229$), diarrhea (19.65 %; $n = 45/229$), and vomiting (13.10 %; $n = 30/229$).

There is potential for cannabinoid–drug interactions in the reported adverse event data, with 37.70 % of the reports ($n = 207/549$) including other medications (Graham et al., 2022). Including medical cannabis products, the average number of medications was 2.66 (SD = 3.50) per report, with a maximum of 30 types of medications used.

Most adverse event reports included a combination of CBD and THC (59.02 %; $n = 324/549$), followed by CBD only (39.53 %; $n = 217/549$) and THC only (1.46 %; $n = 8/549$). There were 205 reports that involved CBD and THC, with no other medications reported. Of these reports, 82 (40.00 %) included an adverse event related to the Nervous System, 60 (29.27 %) related to Psychiatric Disorders, and 53 (25.85 %) involved Gastrointestinal Disorders. Of the 217 reports where CBD only was included, 128 involved CBD without any other medications. A higher proportion of females (60.94 %; $n = 78$) were reported to use CBD only than males (35.16 %; $n = 45$). Among them, the number of reported adverse events ranged from 1 to 12, with 45.31 % ($n = 58/128$) having one adverse event and 31.25 % ($n = 40/128$) having two adverse events. The most common adverse event category was Gastrointestinal Disorders, included in 42 reports (32.81 %). Additionally, 37 reports (28.91 %) had adverse events related to Nervous System Disorders, while in 36 reports (28.13 %), adverse events were categorized as General Disorders and Administration Site Conditions.

The TGA's internal adverse event (AEMS) data up until February 12th, 2023, ($n = 521$) included 11 fatal reports (noting that the fatalities appear to be related to underlying health conditions). There were 16 life-threatening reports, and 77 reports indicating treatment in hospital (Therapeutic Goods Administration, 2023f). A major limitation of these data is that it was not always possible to determine whether the product was accessed via legal (i.e. SAS or Authorized Prescriber) or non-legal pathways. Further research is needed to map the frequency and nature of adverse events related to the use of prescribed medical cannabis compared with cannabis obtained from non-legal pathways, particularly in view of differences in the likely route of administration (i.e. smoking prescribed herbal cannabis products is not recommended but difficult to ensure compliance). Not all health professionals are aware that they are required to report adverse events if they prescribe cannabis as an unapproved medicine, and an adverse event report does not indicate causality. There are also well-known limitations to voluntary adverse event reporting systems for all medications (Graham et al., 2020).

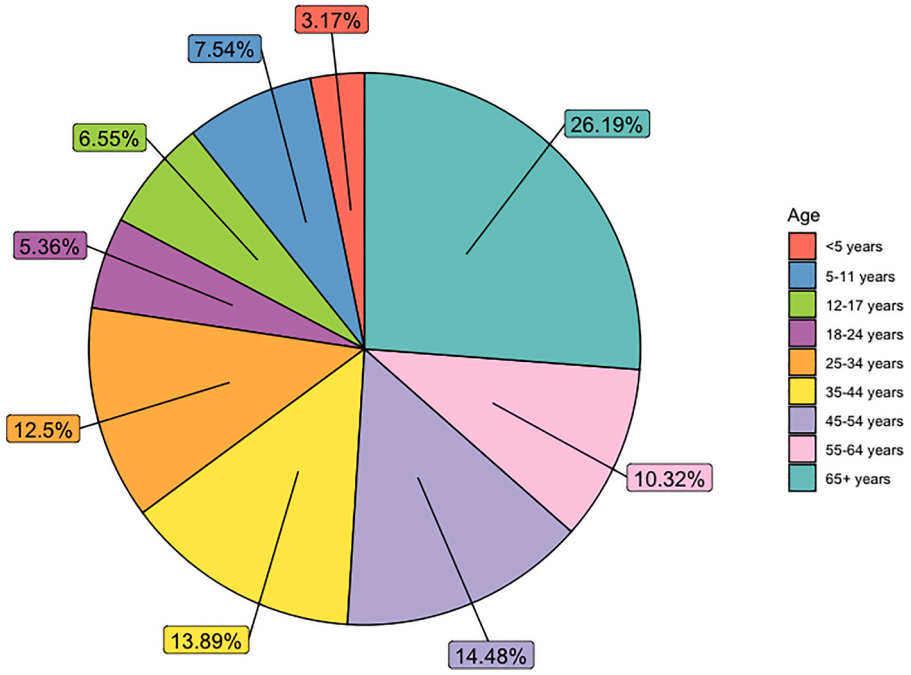

Fig. 3. Overall age distribution for unapproved medical cannabis adverse event reports.

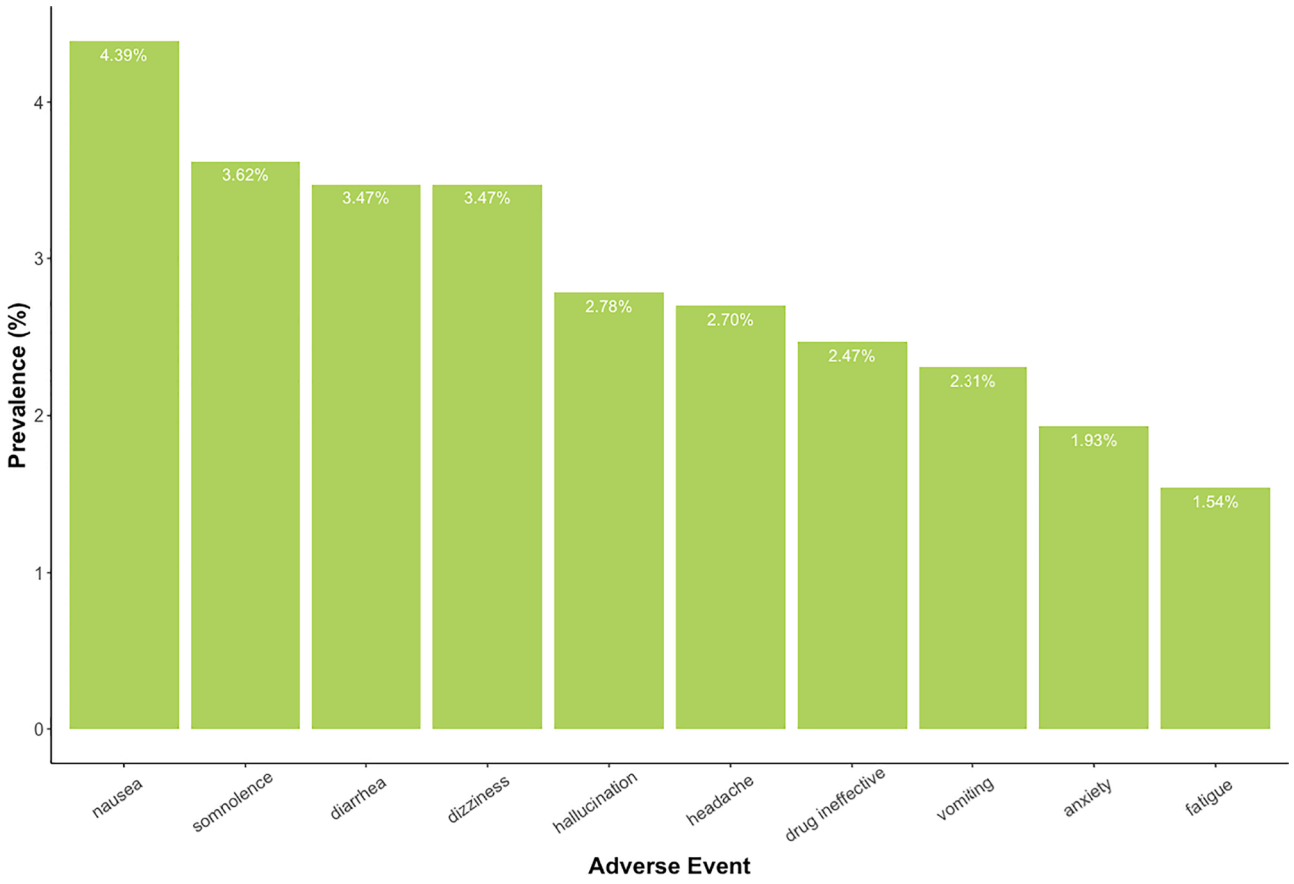

Fig. 4. Top 10 Adverse events for unapproved medical cannabis products.

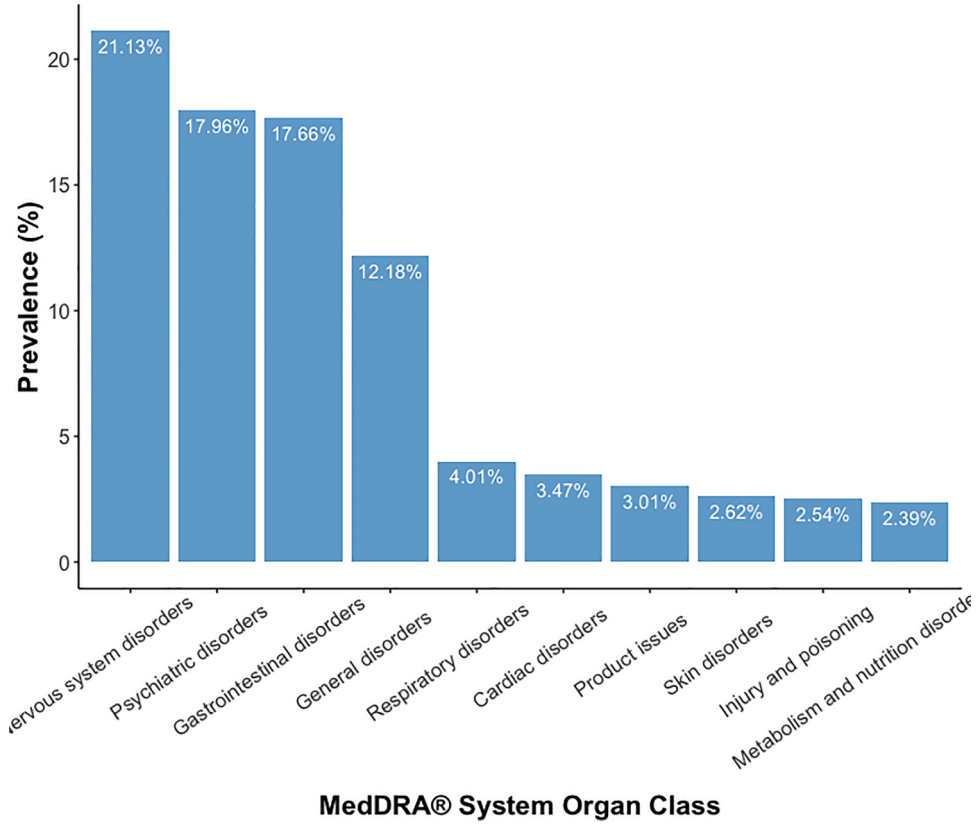

Fig. 5. Top 10 MedDRA SOC adverse events for unapproved medical cannabis products.

Has the Australian program improved the evidence base for medical cannabis use?

When medical cannabis was made legal in Australia, state and federal governments funded clinical trials of medical cannabis in patients who met trial eligibility criteria. In the seven years since a modest number of trials have been completed and published in peer-reviewed journals. It is possible that the increased availability of medical cannabis outside clinical trials, and driving restrictions, have made it more difficult to recruit clinical trial participants. Examples of state-government funded trials that have been completed are Phase I trials in healthy volunteers (Perkins et al., 2020) and Rett syndrome (Hurley et al., 2022), and a Phase II trial in CINV (Grimison et al., 2020). Examples of studies that have been funded at the federal level that have reached completion include a Phase II study in patients with advanced cancer (Hardy et al., 2022), and there are several ongoing studies. Federal funding was also provided for a center of research excellence on cannabinoids (National Health and Medical Research Council (Australia), 2016). State and federal government, along with industry and philanthropic research investment, has been another strength of the Australian system. The investment of funding in this field of research has the potential to improve our understanding of potential therapeutic applications and safety considerations. Whether investment in medical cannabis research will be sustained over the longer term is yet to be determined.

Effects of the medical cannabis program on the pharmaceutical regulation system

Advocates of medical cannabis programs have focused on difficulties reported by patients who want to access medical cannabis and have succeeded in increasing access. An evaluation of the success of the program also requires an examination of the impacts that it has had on the pharmaceutical regulatory system.

The regulatory costs of Australia's medical cannabis program

The cost to the government of Australia's regulatory system has largely not been discussed. These costs could be substantial because they include: the wages of TGA staff involved in the approval of an ever-increasing number of applications to prescribe (now largely routinized but still requiring the approval of a registered medical officer or pharmacist); the approval of applications for licenses to cultivate and produce cannabis, and monitoring compliance with the license conditions by the Office of Drug Control; the costs of auditing products to ensure that these products continue to meet quality control standards; and monitoring compliance with advertising laws (Commonwealth Department of Health, 2023). Adequate cost recovery methods will be essential to ensure the sustainability of the program.

Effects on the SAS

Increased patient access to medical cannabis carries some risks because diverse unapproved cannabis products are prescribed for an equally diverse range of medical conditions in which there are variable levels of safety or efficacy evidence provided by clinical trials. The risk of using unapproved medical products may be justified in the case of patients with life-threatening conditions who are prepared to accept these risks for a possible benefit. More justification is required for the long-term medical use of unapproved products when they are used to treat patients with non-life-threatening conditions and when evidence of their efficacy and safety is weak. These patients may have to live with any potential adverse events occurring from their use (Sansom et al., 2015).

Sansom et al. (2015), who reviewed the TGA's SAS, argued that its capacity to greatly expand access to unapproved medicines can act as a disincentive for companies to register approved medicines, especially when their likely market is small. They were concerned that the SAS could create a de facto market for medical products, including other non-cannabinoid novel therapeutics, that have not met the same regulatory requirements as approved medicines.

Widespread use of the SAS and Authorized Prescriber pathways for medical cannabis has created a precedent for the large-scale, routine medical use of other unapproved drugs. Newly established companies that plan to market therapeutic psychedelic drugs, for example, have successfully campaigned to allow early patient access to these drugs under the Authorized Prescriber Scheme. They used similar advocacy strategies to those in the campaign for access to medical cannabis, e.g. well publicized public lectures and media stories on the benefits of these drugs and personal meetings between politicians and patients who claim to have benefited from using the drugs (Australian Broadcasting Corporation, 2023).

Challenges arising from the expansion of the medical cannabis program

The liberalization of the Australian medical cannabis program has increased access to medical cannabis for a large number of patients who are able to use these products to treat a wide range of medical conditions. Advocates have welcomed this development and campaign for increasing access by removing the barriers of cost and by amending drug driving laws to provide medical cannabis users with an exemption from prosecution. A major challenge in assessing how effective this increase in access has been is the lack of high-quality efficacy evidence for unapproved medical cannabis products for many of the clinical conditions for which they are being prescribed. While there are real-world data and observational studies indicating effectiveness (Banerjee et al., 2022; Graham et al., 2020), these results have not yet been replicated in high-quality trials. Regulatory monitoring of safe and evidence-based prescribing patterns will be essential for the future success of the program.

A potential future challenge for evidence-based medical cannabis use may be the legalization of adult or recreational cannabis use, of which there are a variety of international models (Martin, 2022). Based on the experience in Canada and in U.S. states, patients who use cannabis medically after adult-use legalization have access to a greater diversity of cannabis products, most of which were designed to appeal to daily recreational cannabis users (Hammond et al., 2022; Hawley et al., 2020). Patients often use these products on the advice of medically untrained dispensary employees (i.e. 'budtenders') and in the absence of medical supervision or monitoring of therapeutic or adverse responses (Braun et al., 2022). Adult-use legalization presents both threats and opportunities to research related to the medical use of cannabinoids. North American researchers have faced challenges in evaluating the effectiveness of the diverse range of medical cannabis products typically used.

Conclusions

Australian state and federal governments have responded to demands for greater patient access to medical cannabis by allowing and, more recently, facilitating access to unapproved medical cannabis via the TGA's SAS and Authorized Prescriber Scheme. Patients initially struggled to access medical cannabis because doctors were reluctant to prescribe, and they found it difficult to negotiate the complex approval process and pay the costs of obtaining medical cannabis products. Patient access to medical cannabis products has greatly increased with a relaxation of restrictions on who can prescribe, the products that can be prescribed, and the medical conditions for which they can be prescribed. The implementation of a streamlined application process has ensured rapid and nearly universal approval of applications.

The costs of obtaining a prescription and medical cannabis products

have decreased as cannabis supply has become more dependable, but cost remains a major obstacle to patients of lower socioeconomic status with chronic health conditions in the absence of public subsidies for medical cannabis products. Patient concerns about falling afoul of state laws against cannabis-impaired driving also reportedly discourage medical use, and there is polarized debate about this topical issue.

Australia utilizes a SAS with many features of the traditional pharmaceutical regulatory system. It requires prescription and initially imposed restrictions on which practitioners could prescribe, what medical conditions were eligible, and the type of cannabis products that could be prescribed. Consumer demand, advocacy, and commercial interests, however, have moved practice closer to North American models in which there are few restrictions on prescribers and indications for medical use. One major difference is that the TGA has better regulated the quality of medical cannabis products, although ensuring this is challenging when over 250 unapproved products are available.

Enhanced assessments of how well the Australian regulatory system is operating and how it has affected patient outcomes are critical in guiding future regulatory decisions. Strengths of the Australian approach include public access to SAS and Authorized Prescriber Scheme data that allow for descriptive analysis of approval patterns, observational real-world use studies that provide insights into patient- and clinician-reported outcomes, and government funding of clinical trials. To date, there have been limited comprehensive national assessments of adherence to safe prescribing practices within the current regulatory framework and reported adverse events.

There has also been limited evaluation of the Australian regulatory program compared to a broad spectrum of international regulatory approaches. Longer-term evaluation will also need to consider the impact of the precedent that has been created for other medicines to avoid the traditional pharmaceutical regulatory process that requires clinical trial evidence of efficacy and safety.

Ethics approval

This paper includes data that is publicy available and therefore does not require human ethics approval.

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CRediT authorship contribution statement

Myfanwy Graham: Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization. **Vivian Chiu:** Visualization, Formal analysis, Writing – review & editing. **Daniel Stjepanović:** Writing – original draft, Visualization, Formal analysis, Conceptualization. **Wayne Hall:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Wayne Hall has advised the World Health Organization (WHO) on the health effects of cannabis (2016–2023); reviewed evidence on the medical uses of cannabis for the Australian Government (2017–2018); served as a member of the Australian Advisory Council on the Medical Uses of Cannabis (2017–2020); and served as an unpaid Chair of the International Scientific Advisory Board to the NHMRC-funded center for Excellence in Clinical Research on Medical Uses of Cannabinoids (2019–2022). The views expressed in this paper are his personal views and do not reflect the views of any of these bodies.

Myfanwy Graham contributed to the United Nations Office on Drugs and Crime (UNODC) 2023 World Drug Report chapter on medical cannabis regulation; is a Fulbright Scholar Alumna in medical cannabis public health policy, University of Southern California (2022-2023); an Associate Investigator of the NHMRC-funded Australian Centre for Cannabinoid Clinical and Research Excellence (2019-2023); and received funding from the NSW Clinical Cannabis Medicines Program (2018-2022). The views expressed in this paper are her personal views and do not reflect the views of any of these bodies.

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