



European Monitoring Centre
for Drugs and Drug Addiction

Medical use of cannabis and cannabinoids

Questions and answers for policymaking
December 2018



Cannabis, controversies and challenges: introducing a new series of reports from the EMCDDA

The EMCDDA exists to facilitate a more evidence-informed understanding of issues that are important for developing better drug-related policies and actions across Europe. In a new series of reports, we turn our attention to cannabis, a substance with a long history of use that has recently emerged as a controversial and challenging issue in both European and wider international drug policy debates.

Cannabis is the most commonly used illicit drug in Europe. It is also the drug about which both public attitudes and the political debate are most polarised. Interest in this area is rapidly growing, prompted by some quite dramatic international developments in the ways in which some countries and jurisdictions are now regulating this substance. For Europe, this means that questions on what constitutes an appropriate policy response to cannabis have become both topical and important.

In response, the EMCDDA is producing a set of papers that seek to explore, in an objective and neutral manner, some of the complex issues that exist in this area. We will be publishing a series of reports, each addressing a different aspect of this dynamic and complex policy area. Our aim in this series is to provide an overview of evidence and current practice for those with an interest in the area, to inform debate and not to advocate for any particular policy perspective.

In this report, we examine the evidence for, and practice of, making cannabis or cannabis-based medicines available for therapeutic purposes. This topic is of growing interest, not only because a number of European countries are developing policies in this area but also because the international framework may be changing following the recent review of cannabis by the WHO's Expert Committee on Drug Dependence.



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Luxembourg: Publications Office of the European Union, 2018

Print	ISBN 978-92-9497-361-0	doi:10.2810/41345	TD-06-18-186-EN-C
PDF	ISBN 978-92-9497-362-7	doi:10.2810/979004	TD-06-18-186-EN-N

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Recommended citation:

European Monitoring Centre for Drugs and Drug Addiction (2018), *Medical use of cannabis and cannabinoids: questions and answers for policymaking*, Publications Office of the European Union, Luxembourg.



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Introduction

The medical use of preparations derived from the *Cannabis sativa* plant has a long history. However, by the twentieth century, medical use of cannabis had largely declined, and its consumption for medical purposes was already very limited when in 1961 cannabis was included in the United Nations Single Convention on Narcotic Drugs and classified as a drug that had no medical uses (see 'A brief history of the medical use of cannabis and cannabinoids', on page 7). In the past 20 years, however, there has been a resurgence of patient interest in using cannabis and cannabinoids to treat a variety of conditions, including chronic pain, cancer pain, depression, anxiety disorders, sleep disturbances and neurological disorders, the symptoms of which are reportedly improved by using cannabis (NASEM, 2017).

Increased patient interest in the medical use of cannabis has been accompanied by renewed scientific interest in the medical use of substances found in the cannabis plant, namely cannabinoids. This followed the discovery, in the early 1990s, of a cannabinoid system in the human brain and body that was implicated in the control of important biological functions, such as cognition, memory, pain, sleep and immune functioning. However, the classification of cannabis as a drug without medical uses made it difficult to conduct clinical research (NASEM, 2017).

In the mid-1990s, citizens in several US states responded to patient demand for cannabis by passing referenda that legalised the medical use of cannabis for people with a variety of illnesses, such as chronic pain, terminal cancer and multiple sclerosis. A similar approach was later adopted in many other US states. In 1999, Canada introduced a medical cannabis programme that expanded over the subsequent decades in response to court decisions. In the early 2000s, Israel (2001) and the Netherlands (2003), and later other countries, such as Switzerland (2011), Czechia (2013), Australia (2016) and Germany (2017), legislated to allow the medical use of cannabis under specified conditions. Over a similar period, clinical trials have provided the basis for granting an authorisation for marketing in many EU Member States of a medicinal product, primarily based on cannabis extracts, that has proven effective in the treatment of muscle spasticity due to multiple sclerosis.

Most EU countries now allow, or are considering allowing, the medical use of cannabis or cannabinoids in some form. However, the approaches taken vary widely in terms of both the products allowed and the regulatory frameworks governing their provision. In this context, this report aims to provide a brief overview of current knowledge and the latest developments relating to medical use of cannabis and cannabinoids.

The report is intended to help a broad audience of interested readers, such as policymakers, practitioners, potential patients and the public, to understand the scientific, clinical and regulatory issues that arise when consideration is given to making cannabis or cannabinoids available to treat the symptoms of medical illnesses.

Important caveats when interpreting this report's findings

This report has been prepared to respond to growing policy interest in the issue of the use of cannabis and cannabinoids for medical purposes. Providing a short and clear overview of such a complex topic area is, however, challenging. Importantly, there are a number of caveats that need to be borne in mind when interpreting the findings of this report.

The area of medical use of cannabis and cannabinoids is extremely dynamic. The EMCDDA has endeavoured to ensure that this report is as accurate as possible at the time of writing. However, both the evidence base in this area and policies and practice are evolving rapidly.

There are a number of challenges involved in interpreting the available evidence on the effectiveness of cannabis medications. The review here is based on the evidence available at the time of writing. Until recently, medical interest in this topic was limited, a problem complicated by the large number of conditions for which cannabinoids are purported to be useful. This means that large, well-conducted studies are scarce. In addition, the knowledge base is constantly changing as new studies are conducted.

Reporting on developments in this area is also hampered by the lack of a common or agreed conceptual framework for describing the medical use of cannabis and cannabinoids. In this report, a simple typology is provided to help address this and aid the interpretation of the data. However, it is not always possible to apply this to the information sources on which the report is based.

National regulatory frameworks are also complicated and there may sometimes be a lack of clarity regarding both the details of the various approaches and how they operate in practice. In addition, they evolve over time, and experts sometimes disagree on how such frameworks should be interpreted legally.

| What topics does this report cover?

Part 1 of the report summarises the evidence on the medicinal properties of cannabis and cannabinoids from systematic reviews of randomised controlled clinical trials. It describes the strength of the evidence of medical benefits in various medical conditions, discusses the role that cannabinoid-containing medicines may play in treating these illnesses, and outlines what we know about the possible harms of short- and long-term medical use. A background paper accompanying this briefing provides more detail on the findings of recent systematic reviews of evidence from controlled trials on the effectiveness and safety of cannabis and cannabinoids (Hall, 2018).

Part 2 outlines the legal and regulatory frameworks that are relevant to allowing cannabis and cannabinoids to be used for medical purposes. This section describes the requirements placed on governments by the international drug control treaties. It also describes the type of evidence that pharmaceutical regulators usually require before approving medicines for clinical use in high-income countries. Finally, it considers whether cannabis could be regulated for medical use under special access schemes or as a herbal medicine.

Part 3 gives examples of the various ways in which selected countries have allowed the medical use of cannabis and cannabinoids.

A brief history of the medical use of cannabis and cannabinoids

- In the 19th century, cannabis tinctures were used in Britain and the US to relieve pain and nausea (Grinspoon and Bakalar, 1993; Mechoulam, 1986; Nahas, 1984).
- The medical use of cannabis declined as drugs were developed in the early 20th century that could be given in standardised doses orally or by injection instead of cannabis extracts that varied in quality and content (Kalant, 2001; Pisanti and Bifulco, 2017).
- The inclusion of cannabis in the Single Convention on Narcotic Drugs in 1961 as a drug with no medical uses ended its medical use in the countries that signed the treaty (Grinspoon and Bakalar, 1993).
- A revival of interest in the medical uses of cannabis in the 1970s coincided with widespread recreational cannabis use among young people in the US (Institute of Medicine, 1999).
- Governments feared sending the 'wrong message' to young people by allowing medical use, and the legal classification of cannabis made it difficult to investigate its medical uses in the US (Institute of Medicine, 1999).
- Interest in potential medical uses was revived in the 1990s following the discovery of a cannabinoid system in the brain (Iversen, 2003; Pertwee, 1997), which suggested that cannabinoids could be used to treat chronic pain and neurological disorders such as multiple sclerosis and epilepsy (NASEM, 2017).

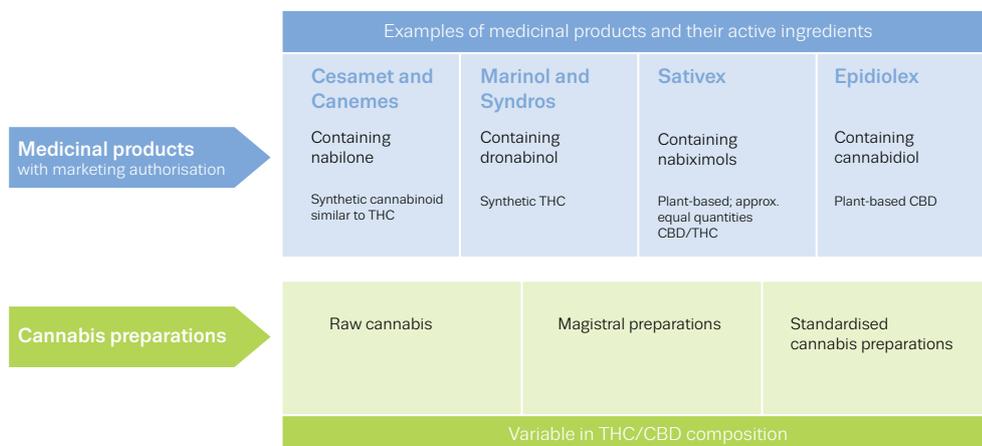
Part 4 summarises the regulatory issues that governments need to address when deciding to allow patients to use cannabis or cannabinoids for medical purposes. This includes making decisions about the types of cannabis products that patients are allowed to use, the medical conditions for which such products can be used, and the type of medical and regulatory supervision under which patients are allowed to use them.

| What do we mean by medical use of cannabis and cannabinoids?

The 'medical use of cannabis and cannabinoids' can refer to a wide variety of preparations and products (see Figure 1) that may contain different active ingredients and use different routes of administration. Although in practice some of the terms in this area have often been used rather loosely, the distinctions between them have both regulatory and medical implications, so it is important to define how we use them in this report.

FIGURE 1

Cannabis and cannabinoids used for medical purposes — a broad typology



One important distinction between different forms of cannabis preparations and cannabinoids for medical use is between those that have a marketing authorisation for medical use and those that do not. Having a marketing authorisation means that an application for a medicinal product was submitted to a regulatory authority and, after evaluating the application, the regulatory authority granted authorisation. This usually implies that the product went through extensive clinical trials and that the drug has been tested for safety, effectiveness and side effects. Regulatory authorities also consider whether the product can be manufactured to a required level of quality.

In this report, we use ‘medicinal product’ to refer to the (plant-derived and synthetic) cannabinoid-containing products with a marketing authorisation. Outside the European Union, other terms, such as ‘product licence’, ‘drug approval’ or ‘registration certificate’, may be used to refer to a ‘marketing authorisation’.

The general term ‘cannabis preparations’ is used in this publication to refer to items derived from the *Cannabis sativa* plant that do not have a marketing authorisation for medical use. These may include the raw cannabis, such as the flowering tops, compressed resin or hash; oils extracted from the plant; concentrated cannabis extracts; and other cannabis preparations, such as soft gels, tinctures or edibles.

The raw cannabis may be transformed by a pharmacist into a magistral preparation for consumption in accordance with a specified medical prescription for an individual patient, or the raw cannabis may already have been transformed by the manufacturer (e.g. into capsules) in larger batches (standardised cannabis preparations). Examples of standardised cannabis preparations include preparations of cannabis flowers, such as Bedrocan; granulates, such as Bediol; and oil extracts, such as Tilray 10:10 Balance.

Cannabis preparations can vary greatly in composition, depending, for example, on the strain of cannabis, the growing conditions and how the preparations are stored. This means that they can be difficult to test for efficacy in clinical trials. In this report, the term ‘medical use of cannabis’ denotes the use of cannabis preparations for medical purposes by smoking, vaporising or oral ingestion (see ‘Medical use of cannabis preparations — modes of consumption’, page 10).

Cannabinoids are substances found in the cannabis plant that act on specific receptors in the human brain and body (NASEM, 2017); they are the main active ingredients in both the medicinal products derived from cannabis and cannabis preparations. The two most

extensively studied are tetrahydrocannabinol (THC) and cannabidiol (CBD), but some of the other 102 cannabinoids and terpenoids in cannabis may also have medical uses (Russo and Marcu, 2017). Cannabinoids are also found in the human body (endocannabinoids), but those consumed for medical use may originate from the cannabis plant (plant-derived cannabinoids, also known as phytocannabinoids) or be synthesised in the laboratory (synthetic cannabinoids). Synthetic cannabinoids may bind to cannabinoid receptors and/or produce similar effects to cannabinoids (Institute of Medicine, 1999; Iversen, 2007). Their chemical structure may not resemble that of any naturally occurring cannabinoids.

THC is the cannabinoid that produces the psychoactive effects sought by recreational users, such as euphoria, relaxation and heightened sensory experiences (NASEM, 2017). There is also evidence to support the medical use of THC in controlling nausea and vomiting, stimulating appetite and reducing pain (see below). CBD may moderate the psychoactive effects of THC, and it has medicinal properties, such as reducing epileptic seizures (NASEM, 2017).

Several cannabinoid-containing medicinal products have been authorised for marketing; the following are those most commonly referred to:

- Marinol and Syndros (active ingredient — dronabinol) ⁽¹⁾: oral capsules or an oral solution containing synthetic THC. Dronabinol is indicated for (1) anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS) and (2) nausea and vomiting associated with cancer chemotherapy, usually after previous treatments have failed.
- Cesamet and Canemes (active ingredient — nabilone): oral capsules containing a synthetic cannabinoid similar to THC. The main indication for their use is nausea and vomiting associated with chemotherapy, usually after previous treatments have failed (Abuhasira et al., 2018).
- Sativex (active ingredient — nabiximols): a medicinal product containing approximately equal quantities of THC and CBD from two cannabis extracts. This product, which is sprayed inside the cheek or under the tongue, has been authorised for the treatment of muscle spasticity resulting from multiple sclerosis (Iversen, 2007; Russo and Guy, 2006).
- Epidiolex (active ingredient — CBD): a plant-derived CBD oral solution indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age or older.

In this publication, we focus on cannabis preparations and products of which medical use is allowed in at least one country.

In the past few years, cannabis-based items (e.g. herbs, hemp and oils) have been offered for open sale in shops in several EU countries, based on the claim that they have little or no psychoactive effect because they contain very low levels of THC and therefore are not controlled under national drug laws. They are sometimes referred to as ‘cannabis light’ products. Many of these, sometimes claiming to be high in CBD, are purported to be good for ‘health and well-being’. These fall outside the scope of the current publication, as they are not made available under any regulatory framework for medical use (see ‘Low-THC products and cannabis products associated with health and well-being’, page 20).

⁽¹⁾ Marinol and Syndros both contain synthetic delta-9-THC (dronabinol). However, ‘dronabinol’ may sometimes refer to plant-derived THC.

Medical use of cannabis preparations — modes of consumption

An important issue in the provision of cannabis preparations for medical use is how they will be consumed.

The fastest route to intoxication, and the traditional mode of consumption for recreational users, is to roll the herbal cannabis or cannabis resin into a cigarette (often mixed with tobacco) and smoke it. As the smoke is absorbed through the lungs into the bloodstream, the effects of THC on the brain are felt in less than a minute.

The harms associated with smoking tobacco are well known. Although it appears from the limited evidence available that smoking cannabis may be somewhat less harmful, it may still damage the lungs. Accurate dosage is also difficult when cannabis is smoked. Safer and more precise methods of administration are available, such as vaporising below the point of combustion, infusing in hot water ('tea') or placing drops of oil in the mouth. Cannabis edibles, such as chocolates and baked goods, have become an important method of administration in the US. Digesting cannabis from edibles, infusion or capsules results in delayed effects — the effects of THC are felt only after 30-60 minutes — but more accurate pharmaceutical dosing is possible.

In the European Union, no country that permits medical use of cannabis preparations recommends smoking as a mode of consumption.

Part 1

What evidence is there that cannabis and cannabinoids have medical uses?

How do we assess the effectiveness of medicinal products?

In most high-income countries, regulatory authorities grant a marketing authorisation after an extensive evaluation of a submitted application for a new medicinal product. Having a marketing authorisation usually implies that the product went through extensive clinical trials⁽²⁾ and that the drug has been tested for safety, effectiveness and side effects (Osakwe, 2016; Rago and Santoso, 2008).

In controlled clinical studies, patients are randomly assigned to receive the drug, a placebo, no treatment or another active treatment for their condition. These trials generally need to show that the drug is more effective than placebo, or another currently used medicine, in relieving the symptoms of the condition (Osakwe, 2016; Rago and Santoso, 2008). There also needs to be evidence that any harms that the medicine causes are outweighed by the benefits of taking it. On the basis of all the evidence, the regulatory authority may grant a marketing authorisation for the medicinal product. The need to take account of both efficacy and potential harms means that in some cases authorisation is given when the new medicine is as effective as or slightly less effective than currently used medicines but has a better safety profile.

Following authorisation, for some medicinal products, clinical guidelines may be drafted to supplement the product information provided by the manufacturer. In this case, an organisation such as the National Institute for Health and Care Excellence in the United Kingdom, and specialist national and international medical colleges and societies, convene expert groups of clinicians to develop such guidelines to advise medical practitioners and patients on how the medicine may be used in clinical practice (Shekelle et al., 2012). The product information and any clinical guidelines summarise the evidence on its safety and efficacy. They provide information on such things as dosage forms and dose ranges, adverse effects,

clinical conditions in which the drug may be contraindicated, and interactions with other commonly used medicines. Clinical guidelines also usually contain advice on where a new medicine fits within established forms of treatment for a condition (e.g. as a first-line treatment or as an adjunctive treatment).

In many countries, and in the European Union, after a medicinal product receives a marketing authorisation, the health authorities are obliged to monitor adverse events among patients who use it. This post-market surveillance aims to detect rare and serious adverse events that may not have been detected during the clinical trials that led to the authorisation. Clinical trials are usually short term and are often conducted in highly selected groups of patients. Rarer adverse events may come to light only when a drug has been used to treat a large number of unselected patients (Osakwe, 2016; Rago and Santoso, 2008).

What is the current evidence on the effectiveness of cannabis and cannabinoids as medicines?

This section summarises the evidence on the medicinal properties of cannabis and cannabinoids from systematic reviews of randomised controlled clinical trials. As noted above, the evidence base is evolving rapidly but is currently quite limited and fragmented, which needs to be borne in mind when considering any evidence review. A particular challenge in interpreting the evidence is that often different cannabis products and preparations have been used, which may have contained quite different active ingredients. For ease of reading, the term 'cannabinoids' has been used in this section when multiple substances were under study. Additional details on the specific cannabinoids involved can be found in the background paper accompanying this report (Hall, 2018).

The evidence from controlled clinical trials that is summarised below (and in Table 1, page 14) suggests that

⁽²⁾ Not all medicinal products with a marketing authorisation have undergone extensive clinical trials; examples are generic drugs and traditional or well-established medicines.

cannabinoids relieve the symptoms of some illnesses. In these cases, cannabinoids are often used as adjunctive treatments, meaning that they are added to other medical treatments rather than used on their own. They are also typically used only after a patient has failed to respond to recommended treatments for these conditions.

| As anti-emetics

Controlled clinical trials have compared the anti-emetic effects of THC (taken orally) with those of either a placebo or another anti-emetic drug in patients with nausea and vomiting related to cancer chemotherapy. Systematic reviews of the trials (e.g. NASEM, 2017; Smith et al., 2015; Tramer et al., 2001; Whiting et al., 2015) have concluded that THC and other cannabinoids that produce similar effects (known as cannabinoid agonists) were more effective than placebo and often had levels of effectiveness similar to those of the anti-emetic drugs with which they were compared.

The most recent comprehensive reviews differed in their evaluations of the strength of the evidence for the efficacy of cannabinoids as anti-emetics. Whiting et al. (2015) rated the quality of these trials as 'low' because the majority of authors failed to include patients who discontinued treatment in their analyses of outcomes. A Cochrane review (Smith et al., 2015) also concluded that the evidence was weak because of limitations in the study designs and the use of outdated comparison treatments. However, the US National Academies of Sciences, Engineering, and Medicine (NASEM) found that there was 'conclusive evidence' that oral cannabinoids were effective in treating chemotherapy-induced nausea and vomiting (NASEM, 2017).

These clinical trials have major limitations, as noted in all reviews. First, newer cancer chemotherapy regimens produce less nausea and vomiting than the treatments used in trials conducted between 1975 and 1991 (Smith et al., 2015). Second, the active treatment with which THC and other cannabinoids were most often compared was prochlorperazine, and newer anti-emetic drugs provide much better control of nausea and vomiting than prochlorperazine (Institute of Medicine, 1999; Navari, 2009). There have been very few clinical trials comparing the anti-emetic effects of cannabinoids with those of these newer agents in cancer patients treated with current chemotherapy regimens (NASEM, 2017; Navari, 2009). Such trials are required to clarify the role of cannabinoids in managing nausea and vomiting in cancer patients. There is very limited evidence on the role of cannabinoids in

treating nausea and vomiting caused by other medical conditions (NASEM, 2017).

| For stimulating appetite

Marinol was approved in the United States in 1999 for use as an appetite stimulant in patients with AIDS-related wasting. This approval was based on very few small clinical trials (Beal et al., 1995; Lutge et al., 2013; Tramer et al., 2001). Systematic reviews concluded that these trials provided weak evidence for the use of THC as an appetite stimulant because there was substantial risk of bias (Lutge et al., 2013; NASEM, 2017; Whiting et al., 2015). There is now much less need to stimulate appetite in AIDS patients because very few people infected with human immunodeficiency virus (HIV) develop AIDS-related wasting if they are treated with highly active antiretroviral drugs (NASEM, 2017). There is insufficient evidence to assess the value of dronabinol in stimulating appetite in people with other disorders, such as anorexia nervosa and cancer cachexia (NASEM, 2017).

| For neuropathic pain and spasticity in multiple sclerosis

Clinical trials have evaluated the efficacy of cannabinoids in treating muscle spasm and neuropathic pain in patients with the neurodegenerative disorder multiple sclerosis. The product most often trialled has been nabiximols (Sativex), a standardised cannabis extract with approximately equal quantities of THC and CBD delivered as an oromucosal spray.

In randomised clinical trials, some patients who received nabiximols (in addition to their existing treatment) reported less muscle spasticity than patients who were given a placebo (Collin et al., 2010; Novotna et al., 2011; Wade et al., 2004). Clinician ratings of the patients' muscle spasticity, however, showed only marginal reductions (e.g. Koppel et al., 2014; NASEM, 2017; Whiting et al., 2015; Zajicek et al., 2003). Whiting et al. described the evidence for efficacy as 'moderate' in quality. The NASEM review concluded that cannabinoids were 'probably effective' in reducing patient-reported muscle spasticity but described their clinical effects as 'modest'.

| For chronic non-cancer pain

One of the most commonly reported reasons patients use cannabis for medical purposes in the United States is to treat chronic pain that is not caused by cancer (chronic

non-cancer pain, CNCP) (NASEM, 2017). This includes neuropathic pain, arthritis, back pain, neck and shoulder pain, and headaches.

Andreae et al. (2015) reported a Bayesian meta-analysis of data from 178 patients with various types of neuropathic pain in five randomised controlled trials (RCTs) of inhaled, vaporised herbal cannabis. The patients were assessed for up to 2 weeks. The authors found that patients vaporising herbal cannabis were three times more likely (odds ratio (OR) = 3.2) to report a 30 % reduction in pain than those given a placebo.

A Cochrane review assessed studies that compared the efficacy of cannabinoids (herbal, plant-based, synthetic) with that of placebo for reducing chronic neuropathic pain in adults (Mucke et al., 2018a). It included 16 studies with 1 750 participants who received a cannabinoid medicine (nabiximols or THC and its analogues) or a placebo for 2-26 weeks. The authors rated the study quality as low in 2 studies, moderate in 12 studies and high in 2 studies. They found that cannabinoids increased the percentage of patients who achieved a 50 % reduction in pain compared with placebo from 17 % to 21 %. The number who needed to be treated to benefit was 20. The percentage who achieved a 30 % reduction in pain was 39 % compared with 33 % and the number who needed to be treated to benefit was 11. There were more withdrawals from treatment because of adverse events in the cannabinoid condition than in the placebo condition (10 % vs. 5 %).

Stockings et al. (2018a) reported a comprehensive review of controlled clinical trials and observational studies comparing cannabinoids and placebo for treating various types of CNCP. They included 91 publications that involved 9 958 participants in 47 RCTs (24 parallel group studies and 23 crossover trials) and 57 observational studies. Forty-eight studies included patients with neuropathic pain (16 in patients with multiple sclerosis and 32 in patients with neuropathic pain from other conditions). They also included 7 studies of patients with fibromyalgia, 1 study of patients with rheumatoid arthritis and 48 studies of patients with other types of CNCP (13 in patients with multiple sclerosis-related pain, 6 in patients with visceral pain and 29 in samples of patients with mixed or undefined CNCP). The percentage of CNCP patients who achieved a 30 % reduction in pain intensity, when averaged across RCTs, was 29 % for patients treated with cannabinoids, compared with 26 % for those who received a placebo. This difference was statistically significant. However, a higher proportion of patients treated with cannabinoids reported adverse events. Stockings et al. concluded that the evidence for the effectiveness of cannabinoids in treating CNCP was limited. There was

limited evidence of benefit in other pain-related domains, such as sleep.

| For palliative cancer care

Media discussions of the potential medical uses of cannabis often mention palliative care for patients with terminal cancer. Medical use of cannabis and cannabinoids has been advocated for managing a broad range of symptoms reported by terminally ill cancer patients, by controlling pain, stimulating appetite, reducing anxiety and improving sleep.

Mucke et al. (2018b) conducted a systematic review and meta-analysis of the efficacy, tolerability and safety of cannabinoids in palliative medicine. They found nine studies with 1 561 participants, all of which were judged to be at moderate risk of bias. They did not find any significant differences between cannabinoids and placebo in improving calorie intake, appetite, nausea or vomiting, pain, or sleep in terminally ill cancer patients. They also found no high-quality evidence that cannabinoids were of value for treating anorexia or cachexia in cancer patients. The strength of these conclusions was limited by the small number of high-quality studies and their small sample sizes, which reduced the chance of finding any differences in favour of cannabinoids. Larger, better-designed trials are needed to assess the value of cannabis and cannabinoids in palliative cancer care.

| For intractable childhood epilepsy

Parents of children with intractable epilepsy have reported that oils rich in CBD reduce the frequency and severity of their children's seizures (Devinsky et al., 2016; Hussain et al., 2015; Press et al., 2015). These parental reports have been supported by a large, open-label trial and a large, multisite RCT (Devinsky et al., 2016; Devinsky et al., 2017; Dos Santos et al., 2014; Friedman and Devinsky, 2015). Early systematic reviews (e.g. Gloss and Vickrey, 2014) concluded that no reliable conclusions could be drawn about the efficacy and safety of CBD. A systematic review of clinical trials conducted since then (Stockings et al., 2018b) found that adding CBD to conventional anti-epileptic drugs significantly reduced seizure frequency in children with Dravet syndrome or Lennox-Gastaut syndrome. The review concluded that more controlled clinical trials were needed to specify the doses of CBD that reliably produce anti-epileptic effects with a minimum of adverse events and minimal interaction with other anti-epileptic medications, such as benzodiazepines. Clinical pharmacological studies are needed to better define drug

doses and interactions with other anti-epileptic medications. Clinical trials may then be required to assess whether CBD is useful in treating other types of intractable epilepsy in children and adults (Stockings et al., 2018b).

Other medical uses of cannabinoids

Patient groups and some doctors have advocated using cannabis and cannabinoids to treat a variety of conditions in addition to those described so far. These conditions include anxiety disorders, such as post-traumatic stress disorder; depressive disorders; sleep disorders; types of chronic pain not included in the clinical trials to date; degenerative neurological conditions; and inflammatory bowel diseases such as Crohn’s disease. Some patients with these conditions have reported clinical benefits from using cannabis or cannabinoids.

For the great majority of these medical conditions, there is either no evidence of effectiveness from controlled clinical trials or limited evidence from studies that are rated as susceptible to bias because they used small patient samples, were poorly controlled or did not compare cannabis or cannabinoids with placebo or active drug

treatments (NASEM, 2017; Whiting et al., 2015). Medical professionals who treat these conditions may be reluctant to use cannabinoids outside clinical trials in the absence of such evidence (e.g. Martin et al., 2018). Patients nonetheless use cannabis and cannabinoids to treat these symptoms in countries where they are able to do so. This highlights the need to expand the evidence base by undertaking robust studies that cover the full range of cannabis preparations being used, including addressing the issue raised by some patients who report greater benefit from using the whole plant than from using single extracts of cannabinoids, the so-called entourage effect (Russo, 2011).

Summary

Table 1 provides an overview of the current evidence for the medical use of cannabis and cannabinoids as well as highlighting the limitations of and important gaps in the evidence. This emphasises the need for additional research and clinical studies, including larger and better-designed trials, studies looking at dosage and interactions between medicines, and studies with longer-term follow-up of participants.

TABLE 1
Summary of the evidence for the medical use of cannabis and cannabinoids

Disease/symptoms	Products tested	Strength of evidence	Limitations
Nausea and vomiting associated with cancer chemotherapy	Cannabinoids	Weak	Few studies testing against newer, more effective anti-emetics. Newer chemotherapy regimens produce less nausea. Little evidence available about use in other types of nausea.
Appetite stimulant in patients with AIDS-related wasting	Dronabinol/THC	Weak	Fewer AIDS-related cases available to treat now. Little evidence available about use to stimulate appetite in people with other conditions.
Muscle spasm in patients with multiple sclerosis	Nabiximols	Moderate	Patients report reductions, but more limited impact on clinician ratings.
CNCP, including neuropathic pain	Cannabis and cannabinoids	Moderate	Small (but statistically significant) effect compared with placebo.
Palliative care for cancer	Cannabinoids	Insufficient	Larger, better-designed trials are needed.
Intractable childhood epilepsy	CBD	Moderate	Evidence for use in adjunctive therapy in people with Dravet or Lennox-Gastaut syndrome. More studies are needed to look at dosage, interactions and use in people with other forms of epilepsy.
Other medical uses, such as sleep disorders, anxiety disorders, depression, degenerative neurological disorders, and inflammatory bowel disease	Cannabis or cannabinoids	Insufficient	Some evidence for short-term effects in some conditions (e.g. sleep disorders) but larger, better-designed trials are needed, with longer follow-up.

What health risks are associated with the medical use of cannabis and cannabinoids?

What are the short-term risks?

The short-term adverse effects of medical cannabinoids and cannabis have been evaluated in the randomised controlled clinical trials summarised above. Follow-up in trials of THC for nausea and vomiting ranged from 1 to 6 days, and in trials of cannabinoids to stimulate appetite and reduce pain and muscle spasticity it ranged from 8 to 15 weeks (Whiting et al., 2015). In general, the short-term adverse events reported were similar to those of other commonly used medicines and related to symptoms such as dizziness, dry mouth, disorientation, nausea, euphoria, confusion and somnolence. Serious adverse events were rare.

A 1999 review by the Institute of Medicine, US National Academies of Science (now the Health and Medicine Division, NASEM) concluded that the short-term adverse effects of cannabinoids were similar to those of other commonly used medicines (Institute of Medicine, 1999). Wang et al.'s (2008) review of these trials did not find an increased risk of serious adverse events in patients using cannabinoid drugs (whether plant extracts or THC preparations) compared with placebo. They cautioned, however, that many of these trials had a limited ability to detect rare but serious adverse events because of their small sample sizes and their failure to follow up patients who discontinued.

Whiting et al. (2015) conducted a meta-analysis of short-term adverse events in 79 randomised trials that evaluated the effectiveness of cannabinoids in treating nausea and vomiting, chronic pain, spasticity due to multiple sclerosis, depression, anxiety, sleep disorders, psychosis, glaucoma and movement disorders, and in stimulating appetite. The incidence of these adverse events did not differ between cannabinoids. Patients receiving cannabinoids were more likely than those receiving a placebo to report an adverse event (OR = 3.03) and slightly more likely to report a serious adverse event (OR = 1.41). Patients receiving cannabinoids were also more likely than those receiving a placebo to withdraw from a study because of adverse events (OR = 2.94). The adverse events most commonly reported by patients receiving cannabinoids were dizziness, dry mouth, disorientation, nausea, euphoria, confusion and somnolence. Serious adverse events were much rarer.

They included confusion, hallucinations, paranoia and symptoms of psychosis.

What are the long-term risks?

There is less evidence about the risks of long-term medical use of cannabinoids, but in general those reported are similar to those reported for short-term use. Over time, more people report adverse events, but these are generally mild to moderate. More research is needed, however, including on the long-term use of CBD to treat intractable childhood epilepsy.

There is some research on adverse events reported by people using cannabinoids daily for months or years to treat chronic pain or muscle spasticity related to multiple sclerosis (Wang et al., 2008). Serpell et al. (2013) reported the longest follow-up of adverse events in multiple sclerosis patients treated with nabiximols for spasticity. They assessed adverse events in patients who participated in a 6-week RCT of nabiximols and who then received the drug in an open-label phase for up to 3 years. Eighty-four percent ($n = 145$) continued in the open-label trial; 35 used nabiximols for up to 1 year, 43 used them for up to 2 years, and 4 used them for up to 3 years. Ninety-five percent of patients experienced an adverse event during the follow-up, but the majority were mild to moderate. The most common were dizziness, fatigue and headache. Twenty-three patients (16 %) withdrew from the study because of adverse events.

Two observational studies have reported on adverse effects in cancer patients (Bar-Lev Schleider et al., 2018) and elderly patients (Abuhasira et al., 2018) treated in a leading Israeli cancer hospital between January 2015 and October 2017. Adverse events were assessed in a telephone interview conducted 6 months after treatment started. Among cancer patients, 31 % reported an adverse event; these most commonly related to dizziness (8.0 %), dry mouth (7.3 %), increased appetite (3.6 %), sleepiness (3.3 %) and psychoactive effects (2.8 %) (Bar-Lev Schleider et al., 2018). The prevalence and type of adverse events were very similar in older patients treated with cannabis for more varied medical conditions (Abuhasira et al., 2018).

There have not yet been any studies of adverse events associated with the regular use of CBD in children treated for intractable epilepsy. This should be a research priority given concerns about the possible effects of long-term medication use on brain development in children and adolescents.

What can be learned about potential risks from studies of long-term recreational cannabis use?

Some of the harms reported among long-term users of recreational cannabis could possibly occur among long-term medical users of cannabis or cannabinoids. These include the development of dependence as well as a range of possible physical and mental health problems. A brief summary of the risks of long-term recreational cannabis use is given in this section; details are available in the background paper (Hall, 2018).

Cannabis dependence

Cannabis dependence or cannabis use disorders are potential consequences of long-term use (Hall, 2015). These disorders are characterised by a difficulty in controlling use or an inability to stop using when an individual wishes to do so. As a result, that person may continue to use cannabis despite its harming their health or well-being or impairing their performance of social roles.

Cannabis dependence has been studied primarily in recreational cannabis users who typically begin in adolescence and smoke potent cannabis products daily over months and years. In the early 1990s, recreational cannabis users' lifetime risk of developing dependence was estimated to be 9 % in the United States (Anthony, 2006), compared with 32 % for nicotine, 23 % for heroin, 17 % for cocaine, 15 % for alcohol and 11 % for stimulants (Anthony et al., 1994; Hall et al., 1999).

Other risks

Epidemiological studies of recreational cannabis users have examined the effects of sustained, daily recreational cannabis use in adolescence and early adulthood on psychosocial outcomes in young adulthood (Hall et al., 2016; NASEM, 2017). There has been only a small number of well-controlled studies of adverse health effects, such as cancers and heart diseases, among long-term cannabis smokers (Aldington et al., 2008; Hall et al., 2016; Hashibe et al., 2006; NASEM, 2017). These indicate that long-term cannabis smoking is associated with an increased risk of chronic bronchitis (Hall et al., 2016; NASEM, 2017). Long-term recreational cannabis use has also been

associated with impaired memory, attention, decision-making and planning (Crean et al., 2011; Solowij et al., 2002), as well as with psychological disorders (Hall et al., 2016; NASEM, 2017), although there are few prospective studies of these disorders (Hall et al., 2016; NASEM, 2017).

Recent reviews of the epidemiological evidence on cardiovascular outcomes suggest that cannabis smoking may trigger myocardial infarction (Franz and Frishman, 2016; Hall et al., 2016; NASEM, 2017) and stroke in younger recreational users (Hall et al., 2016). It is uncertain whether cannabis smoking increases the risks of cancers. There have been inconsistent findings in epidemiological studies: some have failed to find an increased cancer risk; a few case-control studies have found a modest elevation of risk in very heavy long-term cannabis smokers (Aldington et al., 2008; Hall et al., 2016; Hashibe et al., 2006).

It can be difficult to estimate the extent to which the risks associated with long-term recreational cannabis use would apply to long-term, medically supervised cannabis use. In general, there is an absence of studies, and the risks are influenced by a number of factors, such as the type of product and mode of consumption, which may be different when cannabis or cannabinoids are used for medical purposes. For example, if a patient consumes cannabinoids in a capsule or dissolved in oil, the respiratory risks associated with cannabis smoking would be avoided. Similarly, the use of vaporisers would also reduce the risk, but to what extent is not clear.

Summary

The short-term health risks associated with the medical use of cannabis and cannabinoids, as reported in trials, were similar to those of other commonly used medicines and related to symptoms such as dizziness, dry mouth, disorientation, nausea, euphoria, confusion and somnolence. Serious adverse events were rare. There is less evidence about the health risks of long-term medical use of cannabinoids, but in general those reported are similar to those reported for short-term use. Some of the harms reported among long-term users of recreational cannabis could possibly apply to the long-term medical use of cannabis and cannabinoids, but more research is needed to draw evidence-based conclusions.

Part 2

What regulatory frameworks are relevant to the medical use of cannabis and cannabinoids?

This section outlines the requirements for medical use of cannabis and cannabinoids under the international drug control treaties and the approaches that are generally used to evaluate and approve medicines in European and other high-income countries. It describes schemes that are designed to allow seriously ill patients to use unauthorised medicines in certain circumstances. It also briefly describes approaches to the regulation of herbal medicines.

Is medical use of cannabis and cannabinoids allowed under the international drug control treaties?

Under the international drug control treaties, the use of cannabis is limited to scientific and medical purposes (UNODC, 2013). The treaties impose requirements on signatory countries that permit the medical use of cannabis and other drugs that are under international control (INCB, 2017). The treaties require tighter regulation of cannabis than medicines that are not under international control. For example, they require that governments establish a national agency that controls cannabis production and supply for medical use. This agency has to report to the International Narcotics Control Board (INCB) on the quantities of cannabis that are used for medical purposes and on the number of patients who are treated using cannabis-based medicines.

The treaties also require that the medical use of cannabis and cannabinoids be supervised by medical practitioners and that these drugs be dispensed by prescription. The drugs should be used only if there is evidence of their quality, safety and efficacy for medical use. At national level, the medical use of cannabis and other controlled drugs may involve monitoring the behaviour of prescribers and patients to ensure that cannabis-based medicines are appropriately prescribed and that they are not diverted to non-medical use or abused by patients.

In a recent development, the World Health Organization Expert Committee on Drug Dependence (WHO-ECDD) dedicated a special session to cannabis and undertook a critical review of CBD (June 2018). The WHO-ECDD recommended that preparations considered to be pure CBD should not be placed under international drug control because the substance does not have psychoactive properties, and no case reports of abuse or dependence have been reported. In addition, the WHO-ECDD undertook a critical review of cannabis and cannabis-related substances in November 2018⁽³⁾. The decision on whether or not to adopt the recommendations will be subject to a vote by the UN Commission on Narcotic Drugs, which next meets in March 2019 (WHO, 2018).

What are the regulatory frameworks within which cannabis or cannabinoids are authorised for medical use at European level?

Medicines regulation in Europe is based on a network of 50 medicines regulatory authorities in 31 European Economic Area (EEA) countries (comprising the 28 EU Member States, Iceland, Liechtenstein and Norway). This system ensures that there is consistent regulation of pharmaceuticals across the European Union in order to protect public health and ensure that EU citizens have access to high-quality, safe and effective medicines (EMA, 2016).

Medicines can be authorised in the European Union by one of three routes. The first is a centralised procedure under the responsibility of the European Medicines Agency (EMA) that allows a single EU-wide authorisation for marketing of a pharmaceutical drug. The use of the centralised authorisation procedure is compulsory for

⁽³⁾ For WHO-ECDD recommendations see the WHO website: https://www.who.int/medicines/access/controlled-substances/ecdd_41_meeting/en/

most innovative medicines, including biotechnology-derived medicinal products, advanced therapy medicinal products, medicines with a new active substance indicated for major therapeutic areas (AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases) and medicines for rare diseases (orphan medicinal products).

The second is a decentralised procedure in which companies can apply for simultaneous authorisation of a medicine in more than one EU Member State. This applies if the medicine has not yet been authorised in any EU country and does not fall within the scope of the centralised procedure.

The third is a mutual recognition route in which companies that have a medicine authorised in one EU Member State can apply for this authorisation to be recognised by other EU countries. All regulatory processes require companies to present evidence of a medicine's quality, efficacy and safety, based mostly on evidence from controlled clinical trials for the medical condition for which authorisation is sought (EMA, 2016).

The EMA is responsible for the scientific assessment of new medicines submitted through the centralised procedure, and the European Commission grants an EU-wide marketing authorisation to medicines for which the benefit-to-risk ratio is positive on the basis of these evaluations. Decisions on pricing and reimbursement are made by Member States in the light of the role that the medicine may play in each of their health systems. The EMA, through the pharmacovigilance system, also conducts routine monitoring of the safety of centrally and nationally authorised medicines, imposes risk management measures and maintains a database on suspected adverse drug reactions.

To date, except for Acomplia, an inverse agonist at the CB₁ receptor, which was withdrawn from the market in 2008, no EU-wide marketing authorisation has been granted for cannabinoid-containing medicinal products. However, nabiximols has received approval in several countries using the decentralised and mutual recognition procedures. A marketing authorisation application is currently under review at the EMA for a product the active substance of which is CBD. This product is intended to be used in adjunctive therapy for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome.

What regulatory frameworks are used to authorise cannabis or cannabinoids for medical use at national level?

National regulatory authorities license the use of a medicinal product based on the European requirements for marketing authorisations, that is, when there is good evidence that it can be manufactured to a required level of quality and there is evidence from clinical trials that it is safe and effective when used to treat patients with specified medical disorders (Osakwe, 2016; Rago and Santoso, 2008). Evidence of quality is ensured by a specific chemical or biological evaluation and requires the use of standards of good manufacture. Evidence of safety and efficacy requires preclinical pharmacological and toxicological research as well as clinical trials. It is confirmed usually by randomised controlled clinical trials that compare the effects of the medicinal product with those of a placebo, or an active treatment, in patients with the specified medical condition.

After a medicine has been licensed by national authorities, its safety is monitored through the national pharmacovigilance system, or at European level when it has been authorised in more than one Member State. This monitoring allows the detection of rare and sometimes unexpected serious adverse events that may not have been detected in the relatively short time frame of the clinical trials (conducted in selected patient populations) conducted to obtain authorisation for medical use.

What other regulatory approaches are used to make cannabis or cannabinoids available for medical use without formal marketing authorisation?

Many pharmaceutical regulatory systems include schemes that allow patients to access unapproved medicines under medical supervision. These schemes are usually used by patients who have serious illnesses, such as terminal cancer or degenerative neurological diseases, that have not responded to conventional treatments. They often provide early access to medicines that are undergoing clinical trials or that have been approved for use in other countries (Martinalbo et al., 2016).

Under these schemes, access to unapproved medicines usually requires a prescription by a licensed medical practitioner and approval by the pharmaceutical regulator for the patient to obtain and use the medicine. Patients

often pay the costs of obtaining it; sometimes the pharmaceutical company provides it at no cost to the patient on compassionate grounds. The prescriber may be required to report patient outcomes and any adverse events. A minority of patients in developed countries use this method to access unapproved medicines, usually to treat serious illnesses that have not responded to the standard treatments.

Many EU Member States have some type of compassionate access programme for unauthorised pharmaceuticals (Balasubramanian et al., 2016). These are known by various names depending on the country, such as early-access programmes, special access programmes, named patient programmes and managed access programmes. Regardless, all these programmes make a medicine available to a patient before its authorisation and commercial launch in the country (Balasubramanian et al., 2016).

In Europe, access to cannabis preparations, including magistral preparations, where allowed, appears to be provided primarily through compassionate or exceptional use programmes (HPRA, 2017). In countries where access to cannabis preparations is given in this way, it is usually granted for the treatment of a narrow range of medical conditions. One common feature of these access programmes is a specialised prescriber who has a specific licence to prescribe non-authorised cannabis preparations (HPRA, 2017; Krcevski-Skvarc et al., 2018). Other European countries allow access to cannabis preparations through expanded access programmes. These programmes use country-specific regulatory tools that allow patients with unmet medical needs access to a medicine in clinical development before its official launch (HPRA, 2017; Krcevski-Skvarc et al., 2018).

There is wide variation in how these programmes are implemented at national level, and each country has its own rules and procedures for allowing cannabis preparations to be provided to patients.

Could cannabis be sold as a herbal medicine?

Most pharmaceutical regulatory systems allow the use of herbal medicines that do not meet the same requirements as those for pharmaceutical medicines (Ekor, 2014; WHO, 2015). For example, manufacturers of traditional herbal medicines with well-established uses are not usually

required to provide evidence of efficacy and safety from clinical trials. Instead, they are required only to show evidence of product quality and consistency to ensure that consumers receive standardised doses of herbal products that are free from contaminants and adulterants. These herbal medicines are distinct from health foods and similar products, which are outside the scope of this report (see 'Low-THC products and cannabis products associated with health and well-being', page 20).

The justification for this minimal regulatory approach is that herbal medicines have histories of traditional or well-established use, generally in the absence of reports of serious adverse events. Critics of herbal medicines point out that there is a lack of evidence to support many of the therapeutic claims made for these traditional herbal medicines. Moreover, many herbal medicines are used in addition to (rather than instead of) conventional medicines and may interact with pharmaceutical medicines in sometimes unknown ways that may harm patients (Ekor, 2014; Sammons et al., 2016).

The preference among some patients for the medical use of herbal preparations of the whole cannabis plant rather than pharmaceutical products has strong similarities to the reasons people give for using traditional herbal medicines. Herbal cannabis is sometimes preferred because of the hypothesised entourage effect, meaning that the combination of cannabinoids and other substances in the whole plant has a greater medical effect than single cannabinoids extracted from it (Russo, 2011).

Under the European Union's medicinal products directive (European Parliament and Council, 2001), drugs under international control must be distributed on prescription, whereas herbal medicines, with a simplified registration procedure (based on traditional use), are usually non-prescription. On this basis, cannabis would be difficult to regulate as a traditional herbal medicine in the European Union while it remains a drug under international control or while the national legislation in many countries classifies cannabis as a drug that has no medical uses. Major challenges in regulating cannabis products as herbal medicines would remain even if these obstacles were removed. These would include characterising and standardising the cannabinoid and other chemical constituents of herbal cannabis (Martin and Bonomo, 2016), assessing their stability in stored medicines (Martin and Bonomo, 2016), and ensuring that herbal cannabis products were free of contamination by microbes (e.g. fungi and moulds), heavy metals and pesticides (Dryburgh et al., 2018).

Low-THC products and cannabis products associated with health and well-being

This publication focuses on the regulation of cannabis preparations and cannabinoid products for medical use. However, in the past few years a range of items derived from cannabis (herbs, hemp, oils) have been offered for open sale in shops in several EU countries based on the claim that they have little or no psychoactive effect because they contain less than the legal minimum level of THC and therefore are not controlled under drug laws. These and other products may claim to be high in CBD, which is not controlled under drug laws in most countries (e.g. in Finland it is classed as a medicinal product).

CBD may help to control the symptoms of epilepsy, but there are also claims that it is useful for treating a wide range of other illnesses or symptoms for which there is currently insufficient evidence to make a proper assessment. Any claims that they prevent or treat disease, or relieve symptoms, would bring these products under medicines law, which requires a licence for sale. The marketing of these products therefore often contains non-specific words or phrases, such as 'health and well-being', 'wellness', 'nutraceuticals', etc. Food safety and other regulations may be required to regulate these products to ensure that they contain what it is claimed that they do. These products fall outside the scope of this publication.

Summary

The regulation of cannabis and cannabinoids for medical purposes is a complex patchwork of approaches. At international level, the UN drug control treaties, under which the medical use of cannabis is very strictly limited, provide a backdrop to the regulatory frameworks for the medical use of cannabis and cannabinoids in all signatory countries. In addition, at EU level, the EMA is responsible for the scientific evaluation, supervision and safety monitoring of medicines, and it coordinates a network of national regulatory authorities.

There are three ways for medicines to receive cross-national authorisation within Europe. One grants EU-wide access, and the other two can lead to authorisation in more than one EU country. To date, there have been no EU-wide marketing authorisations for cannabinoid-containing medicines, although, for example, nabiximols has received approval in several EU countries using the alternative procedures. Medicines may also be authorised at national level. Regulatory procedures for new medicines consider evidence of both clinical effectiveness and safety. Regulatory authorities also undertake post-market monitoring of adverse events. Many of these pharmaceutical regulatory systems also have schemes that allow doctors to prescribe unapproved medicines under certain circumstances, often called compassionate use programmes. In many cases, these programmes are used to provide access to medicines for which trials are under way or the evidence is under evaluation.

Part 3

What approaches to allowing the medical use of cannabis and cannabinoids have countries used?

This part of the report gives some examples of how various countries have made some form of cannabis or cannabinoids available for medical use, which products or preparations they have allowed and what legal and regulatory instruments they have used. These illustrate the variety of approaches taken and how these have evolved. A selection of European and international case studies are presented. The case studies have been selected to illustrate the range of regulatory frameworks applied, such as expanded versus exceptional access programmes, and the various products and preparations authorised. The North American schemes are described in some detail because they have been in operation the longest.

How is the medical use of cannabis and cannabinoids regulated in the United States and Canada?

North America was the first region to introduce the medical use of cannabis. This happened first in several states in the United States that passed citizen-initiated referenda to legalise medical use of cannabis in the mid-1990s. In 1999, the Canadian courts ordered the federal government to develop a national approach to the medical use of cannabis. The resulting programme was initially very restrictive but its operation was extended in response to a series of court challenges from patients who were dissatisfied with the access allowed under the initial scheme.

Medical use of cannabis and cannabinoids in the United States

Types of products and preparations available for medical use

In the United States, the Food and Drug Administration (FDA) has approved various cannabinoids for medical use

using the pharmaceutical regulatory path, namely on the basis of evidence from clinical trials that cannabinoids are safe and effective for medical use. Marinol was approved in 1985 by the FDA as an anti-emetic drug for cancer patients undergoing chemotherapy. Cesamet was approved in 1992 as an appetite stimulant in patients with AIDS-related wasting (Institute of Medicine, 1999).

Neither of these cannabinoids has been widely used in the United States. When taken orally, THC has a delayed onset of effect and patients often either do not achieve a therapeutic effect or experience adverse side effects that make them discontinue the drug (Grotenhermen, 2004; Iversen, 2007). This narrow therapeutic window (whereby blood concentrations that are effective are close to or overlap with those that produce symptoms of toxicity) is common to many other centrally acting medicines.

For a number of reasons, US pharmaceutical companies stopped developing new cannabinoids from the 1990s onwards. First, it is costly to develop and test new drugs, and it is difficult to recoup these costs for cannabinoids when many of the medical conditions for which they would be used are uncommon (Institute of Medicine, 1999). Chronic pain is more common but, as indicated in the review above, in clinical trials cannabinoids have proven to be only modestly effective analgesics. Second, the legal status of cannabis made it difficult to conduct research on the safety and effectiveness of cannabinoids. Third, there would be restrictions on the medical use of any approved cannabinoids, which might discourage physicians from prescribing them (Bostwick, 2012; Cohen, 2008; Institute of Medicine, 1999). However, in June 2018, the FDA approved Epidiolex, a CBD-based product developed by a company based in the United Kingdom, to treat patients 2 years of age or older with epilepsy resulting from Lennox-Gastaut or Dravet syndrome (US FDA, 2018). These are rare conditions and it is too early to know how widely this product will be used.

In the United States, patient advocates used citizen-initiated referenda to legalise the medical use of herbal

cannabis (known in North America as 'medical marijuana'). They argued that patients' reports of the medical benefits of using cannabis gave them a legal right to use cannabis for medical purposes, very broadly defined. Proposals to legalise the medical use of cannabis were put to the popular vote in citizen-initiated referenda, a procedure available in nearly half of US states that allows a proposition to be put on a ballot if it secures the signatures of a specified percentage of voters. If the proposition receives the majority of the vote, then the state legislature must enact legislation to make it state law.

An initiative to legalise the medical use of cannabis was passed in California in 1996 when voters supported Proposition 215 by 56 % to 44 %. This initiative allowed the medical use of cannabis for a broad set of indications that included nausea, weight loss, pain and muscle spasm, and any 'serious medical condition' for which cannabis might provide relief (Conboy, 2000). Over the next two decades, initially citizen-initiated referenda, and later legislation by state governments, allowed the medical use of cannabis in 29 US states and the District of Columbia at the time of writing.

Availability issues

US states have varied in their definitions of the indications for the medical use of cannabis and in whether or not they have allowed patients to obtain cannabis from commercial dispensaries (Pacula and Smart, 2017; ProCon.org, 2017). The most restrictive state provisions only allow medical necessity as a defence against prosecution if a patient is arrested for using cannabis. Other states allow the medical use only of CBD-based cannabis preparations. Still other states allow the medical use of cannabis to be defined by doctors and patients, and permit medical cannabis to be sold in retail dispensaries to anyone with a medical recommendation (Pacula and Smart, 2017).

State-based laws on the medical use of cannabis have created regulatory issues for state and federal governments in the United States. State laws on the medical use of cannabis conflict with the US Federal Controlled Substances Act, which prohibits all uses of cannabis, including medical. Under the US Constitution, federal laws take precedence over state laws when the two conflict (Bostwick, 2012; Conboy, 2000; Hoffmann and Weber, 2010). The Bush administration enforced federal laws against cannabis sellers in states that allowed medical use. In 2009, the Obama administration announced that it would give a low priority to enforcing federal law in these states if they regulated the medical use of cannabis in ways that protected public health and order (Hoffmann and Weber, 2010). The

administration continued to enforce federal laws against the cultivation and supply of cannabis on a commercial scale but refrained from prosecuting patients and doctors who complied with state laws (Eddy, 2009).

In many US states with laws allowing the medical use of cannabis, some physicians were reluctant to recommend it. They argued that in the absence of good evidence they found it difficult to decide who should be prescribed cannabis, in what doses and for how long (Barnes, 2000; Cohen, 2006; Hall and Degenhardt, 2003). Physicians were also concerned that they would be legally liable for any harms that patients experienced (Hoffmann and Weber, 2010; Pacula et al., 2004).

Patients often found it difficult to legally obtain cannabis in states that allowed medical use. In some states, they had to use the black market and in others they were allowed to grow their own, or have a carer grow it for them. State laws that allowed carers to grow for more than one patient enabled the development of cannabis buyers' clubs that grew and sold cannabis to patients with a doctor's recommendation. These clubs were not licensed to produce cannabis and so obtained it from the illicit market (Hoffmann and Weber, 2010). The Obama administration's decision not to enforce federal law in states that had authorised medical use effectively meant that states with liberal laws and dispensaries (California, Colorado and Washington State) had a quasi-legal market in which cannabis could be sold to any user who had a doctor's recommendation (Cohen, 2010; Regan, 2011; Samuels, 2008).

Medical use of cannabis and cannabinoids in Canada

In Canada, some cannabinoid medicines have been authorised for use, but cannabis has also been made available for medical use under special access schemes that have changed over time in response to patient pressure and court decisions.

With respect to authorised medicines, Sativex is approved for use for multiple sclerosis-associated spasticity under certain conditions. Additional indications include adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis, and adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain while on the highest tolerated dose of strong opioid therapy for persistent background pain. Nabilone is available for the treatment of severe nausea and vomiting associated with cancer therapy. Marinol was approved for AIDS-related anorexia associated with weight loss and for severe nausea and vomiting

Potential unintended consequences of the medical use of cannabis and cannabinoids

When considering the outcomes of regulatory changes to allow access to cannabis and cannabinoids for medical use, in addition to considering health risks and benefits for patients it is important to take into account the potential broader social and public health impacts. There is now a growing number of studies, primarily from the US, investigating these wider impacts. However, as with the evidence concerning the clinical effectiveness of various cannabis products and preparations, variations in approaches, definitions and data sources make drawing firm conclusions difficult, with studies often having contradictory outcomes or inconclusive results.

The EMCDDA is preparing a report that will provide an overview of evaluations of new regulatory models in the Americas, where some of these issues will be covered. In this box, we highlight some of the issues addressed in medical cannabis studies to date to illustrate the types of potential unintended consequences, both positive and negative, that may need to be considered when making cannabis or cannabinoids available for medical use. More details about the individual studies can be found in the background paper accompanying this report (Hall, 2018).

- **Impact on recreational use.** Data from US household drug surveys suggest that cannabis use among adults over the age of 21 years may have increased between 2004 and 2012 after laws on the medical use of cannabis were passed (Wen et al., 2015). There were no differences in the prevalence of cannabis use among adults in states with and without laws on the medical use of cannabis, but adults in states with these laws were more likely to have used cannabis in the past 30 days, to be daily cannabis users and to report symptoms of cannabis abuse/dependence than adults who lived in states that had not passed laws on the medical use of cannabis.
- **Use among young people.** There is some concern that if medical cannabis laws make cannabis more available and send the message that cannabis use is not risky, use among young people might increase. However, comparisons of adolescent cannabis use in household and school-based surveys have generally not found any difference in use between US states that do and those that do not have laws on the medical use of cannabis (e.g. Ammerman et al., 2015; Cerda et al., 2012; Choo et al., 2014; Harper et al., 2012; Lynne-Landsman et al., 2013; Schuermeyer et al., 2014; Wall et al., 2011, 2012).
- **Accidental poisonings.** Studies into cannabis poisonings among young children and acute healthcare contacts raise concerns about the potential for increases in accidental poisonings (Wang et al., 2016, 2017). The accidental poisonings of very young children highlight the importance of child-proof packaging and regulations around sales to minors when establishing these programmes.
- **Cannabis-related motor vehicle fatalities.** There have been mixed results from studies of the effects of laws on the medical use of cannabis on cannabis-related motor vehicle fatalities. Some studies (e.g. Masten and Guenzburger, 2014) have found increased involvement of cannabis-impaired drivers in fatal crashes in states that have passed laws on the medical use of cannabis. Other studies have not (e.g. Anderson et al., 2013).
- **Suicides.** Anderson et al. (2014) reported steeper declines in suicides among males aged 20 to 30 years in US states that legalised medical use of cannabis than in those that had not, but other studies that took account of differences between states (Grucza et al., 2015) or looked at the association between suicide rates and the number of patients using cannabis for medical purposes did not support this finding (Rylander et al., 2014).
- **Substitution of medical cannabis for other substances.** An important issue is whether medical cannabis may be substituted for other, potentially more risky, substances. An analysis of opioid overdose deaths in the US found smaller increases in these deaths in states with laws on the medical use of cannabis than in those without such laws, and the difference appeared to increase over time (Bachhuber et al., 2014). Better evidence is needed that cannabis has been substituted for opioids in this way and that the association cannot be explained by other policy differences between states that have and have not passed laws on the medical use of cannabis (e.g. rates of imprisonment of opioid users and provision of methadone-assisted treatment) (Campbell et al., 2018; Hayes and Brown, 2014).

associated with cancer chemotherapy. It was withdrawn from the Canadian market by the manufacturer in February 2012, but this was not for safety reasons (Abuhasira et al., 2018).

In addition, Canada was one of the first countries to establish a national programme for the medical use of cannabis. In 1999, the federal government established an exceptional access scheme that required the minister to approve each patient. Court actions by patients who complained that the system was too restrictive ensured that the programme evolved over the next two decades from an exceptional access scheme to an expanded access programme like that in California (Freckelton, 2015; Ries, 2016).

In 1998, a patient with HIV argued in court that he should be exempted from criminal prosecution to allow him to use cannabis to treat his illness and in June 1999, the health minister published guidance on allowing exemptions from criminal prosecution in exceptional cases. However, these exemptions were based on ministerial discretion. In 2000, the Ontario Superior Court of Justice ruled that the federal prohibition on cannabis use, without a well-defined and functioning exemption for medical use, violated the rights of a patient with intractable epilepsy under the Canadian Charter of Rights and Freedoms. The court ruled that the government should allow patients to use cannabis for medical purposes and that it should provide a legal supply of cannabis so that doctors could prescribe cannabis to their patients.

In April 2001, the Canadian government legislated to allow patients to access cannabis for medical purposes (Bogdanoski, 2010; Lucas, 2008) if they (1) had a terminal illness and a life expectancy of less than 12 months; (2) had multiple sclerosis, a spinal cord injury or disease, cancer pain, AIDS, arthritis or epilepsy; or (3) had another 'serious medical condition' that had failed to be relieved by 'conventional treatments' (Lucas, 2012; Moffat, 2002). Patients with these conditions (or a carer) could obtain cannabis from the government, or obtain a licence to grow cannabis for their own medical use or have a carer grow it on their behalf.

Relatively few patients used this scheme. There were, for example, an estimated 290 000 patients using cannabis for medical purposes in British Columbia in 2007 (Lucas, 2008), but only 1 816 had approved access to medical cannabis and only 356 obtained cannabis from the government (Fischer et al., 2015). The remainder were licensed to grow cannabis because they were dissatisfied with the quality and cost of the government cannabis (Lucas, 2008). This regulatory system was also successfully challenged in court in 2008. New legislation in March 2014 licensed more cannabis producers, allowed doctors greater latitude in prescribing, removed federal oversight of prescribing and permitted patients to receive cannabis directly from licensed producers

(Ablin et al., 2016). The cost of herbal cannabis (estimated to be CAD 500 (approximately EUR 330) a month) was not covered by health insurance (Ablin et al., 2016).

Under all variations of Canadian policy, doctors have been reluctant to prescribe cannabis (Ablin et al., 2016; Lucas, 2012). The Canadian Medical Association and the Canadian Medical Protective Association advised physicians against doing so (Abraham, 2002; Lucas, 2008; Ries, 2016) because there was a lack of evidence that cannabis was effective for most of the requested indications and prescribers could be sued if their patients experienced adverse effects (Lucas, 2012). The fact that most physicians were reluctant to prescribe cannabis created a market niche for doctors who were prepared to prescribe cannabis for a fee (Ablin et al., 2016).

What approaches have been used to allow the medical use of cannabis or cannabinoids in the European Union?

Novel policy approaches to the medical use of cannabis in the United States and Canada have prompted other countries, including some in Europe, to allow patients to use cannabis and cannabinoids for medical purposes⁽⁴⁾. The most common initial approach has been to use some form of special access scheme, typically by creating a system that provides medical approval and oversight, limits medical use to a restricted set of medical conditions, and often restricts the cannabis preparations that patients can use. The decision to subsidise or reimburse patient costs, or expect them to pay full price, for the medicine or preparation will also have an impact on the extent of use.

Medicinal products containing cannabinoids are authorised for use in many EU countries (Abuhasira et al., 2018; Bramness et al., 2018; Krceviski-Skvarc et al., 2018). Table 2 shows that medicinal products containing nabiximols are available in the majority of EU countries. Medicinal products containing dronabinol and nabilone are less widespread, available in around one third of EU countries. In some of these countries, national health insurance systems will reimburse the cost under certain conditions, such as prior approval or prescription by a specialist. Epidiolex has not been authorised for use in Europe; the EMA's decision on this was under review in 2018.

⁽⁴⁾ National regulatory frameworks are complicated and there may sometimes be a lack of clarity on both the details of the different approaches and how they operate in practice. In addition, they evolve over time and experts sometimes disagree on how frameworks should be legally interpreted.

TABLE 2

Availability of cannabinoid-containing medicinal products in the European Union, Turkey and Norway

	Medicinal products containing			Comment
	dronabinol	nabilone	nabiximols	
Belgium	No	No	Yes	
Bulgaria	No	No	No	
Czechia	No	No	Yes	Sativex has a marketing authorisation but is not traded.
Denmark	Yes	Yes	Yes	Medicinal products containing nabilone and dronabinol on compassionate grounds.
Germany	No	Yes	Yes	There is no marketing authorisation for medicinal products containing dronabinol, but dronabinol is available in magistral preparations.
Estonia	No	No	Yes	The Estonian State Agency of Medicines (ESAM) may authorise use based on an application by a doctor for a specific patient. A medicines wholesaler needs to submit an application for the import of the medicinal product, which is evaluated by the ESAM. Three applications for Sativex have been submitted (two were approved).
Ireland	Yes	Yes	Yes	Medicinal products containing nabilone and dronabinol are not authorised for marketing, but can be prescribed and imported.
Greece	No	No	No	
Spain	Yes	Yes	Yes	Medicinal products containing dronabinol and nabilone in exceptional cases (imported).
France	Yes	No	Yes	Medicinal product containing dronabinol by temporary authorisation. A marketing authorisation was granted for Sativex in January 2014, but it has not been marketed yet.
Croatia	Yes	Yes	Yes	No marketing authorisation for medicinal products, but they can be imported based on individual prescriptions.
Italy	No	No	Yes	
Cyprus	No	No	No	
Latvia	No	No	No	
Lithuania	No	No	Yes	Nabiximols for clinical trials only.
Luxembourg	No	No	Yes	
Hungary	No	No	No	
Malta	No	No	Yes	Sativex has a marketing authorisation but is not traded.
Netherlands	No	No	Yes	
Austria	No	Yes	Yes	There is no marketing authorisation for medicinal products containing dronabinol, but dronabinol is available in magistral preparations.
Poland	Yes	Yes	Yes	Sativex has a marketing authorisation. The other two products do not, but they can be made available to patients through a special permit (named-patient import).
Portugal	No	No	Yes	
Romania	No	No	No	

TABLE 2 (continued)

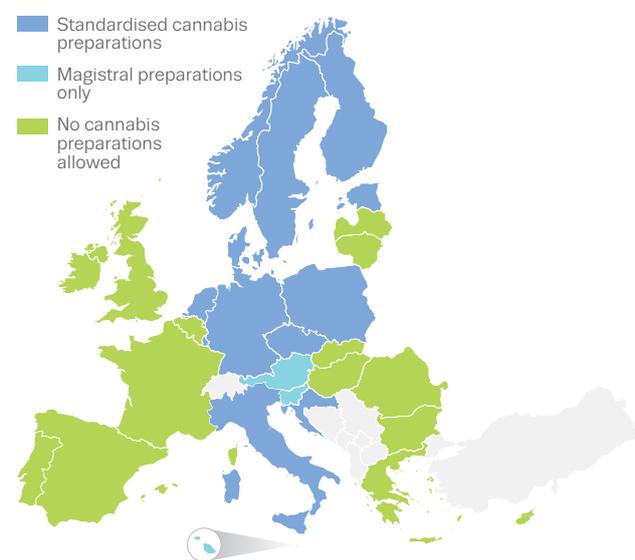
	Medicinal products containing			Comment
	dronabinol	nabilone	nabiximols	
Slovenia	Yes	Yes	Yes	Sativex, Marinol and Cesamet have no marketing authorisation, but they can be made available to patients through special permit (named-patient import).
Slovakia	No	No	No	Sativex was authorised but the marketing authorisation expired in June 2017.
Finland	No	No	Yes	
Sweden	Yes	No	Yes	Dronabinol: special permission on a named-patient basis. No legal objections for nabilone (if for a medicinal purpose and for personal use), but no special permission on a named-patient basis has been applied for in the last 3 years.
United Kingdom	No	Yes	Yes	
Turkey	No	No	Yes	
Norway	Yes	Yes	Yes	Medicinal products containing dronabinol and nabilone: compassionate use for a named patient.

NB: In several countries, cannabinoid-containing medicinal products have no marketing authorisation, but are available through a variety of schemes (under medical supervision) that allow patients to access medicines that have no formal marketing authorisation (see Part 2). This table is based on Abuhasira et al. (2018), Bramness et al. (2018), Krcevski-Skvarc et al. (2018) and feedback from the EMCDDA network of legal and policy correspondents. Epidiolex (CBD) has not been included in this exercise, but may be available in some countries through compassionate use programmes.

It is uncommon in the European Union for the use of raw herbal cannabis for medical purposes to be permitted. Some countries allow patients to access standardised cannabis preparations (either imported or cultivated domestically). Other countries give patients access to cannabis for medicinal purposes in the form of magistral preparations (i.e. raw cannabis transformed into final consumption format by a pharmacist) (Figure 2).

Several European countries have established some form of exceptional/compassionate use programme or other special access scheme to allow access to cannabis preparations for the treatment of a narrow range of medical conditions. Countries that currently have such programmes include Croatia, Denmark, Finland, Norway, Poland and Sweden. Four European countries have an established access programme: Czechia, Germany, Italy and the Netherlands. Both Luxembourg and Portugal passed laws on the medical use of cannabis in 2018, but details on implementation were not available at the time of writing.

FIGURE 2
Availability of cannabis preparations for medical use in the European Union and Norway



NB: In the majority of countries where standardised cannabis preparations are available, magistral preparations are also permitted: Estonia, applications for standardised preparations need to be submitted to the Estonian State Agency of Medicines; Finland, medical use partially allowed; Sweden and Norway, only a small number of patients have been granted permission to use cannabis preparations; Poland, at the time of writing, standardised cannabis preparations are not available, but approval was given to a supplier. In the case of Portugal, at the time of writing, no details were available on the implementation of the Portuguese law on the medical use of cannabis, which was adopted in July 2018. Similarly, the UK situation was under review at the time of writing. This figure is based on Abuhasira et al. (2018), Bramness et al. (2018), Krcevski-Skvarc et al. (2018) and feedback from the EMCDDA network of legal and policy correspondents.

Medical use of cannabis and cannabinoids in the Netherlands

The Dutch framework is an example of a long-established system that allows relatively broad access to cannabinoid medicines and cannabis preparations, with any doctor allowed to prescribe.

In the Netherlands, nabiximols-containing medicinal products are available as authorised medicines. However, since 2003, Dutch law has also permitted any doctor to prescribe herbal cannabis to treat symptoms of medical conditions including, but not limited to, multiple sclerosis, HIV, cancer, pain and Tourette syndrome. Guidelines from the Office of Medicinal Cannabis in the Ministry of Health, Welfare and Sport recognise that there have been positive experiences with many other indications, and allow the doctor to judge if cannabis will help a patient's condition. A doctor should prescribe cannabis only if the standard treatments and registered medicines have not had the desired effect or are causing too many side effects.

Under the Dutch scheme, cannabis is produced under licence by a private company, Bedrocan, to meet quality standards. It is dispensed by a pharmacist to patients with a medical prescription (Bogdanoski, 2010). The company manufactures five products, with various THC and CBD levels, in dried flower and granulated form. This company has also been supplying several other European countries that have started new programmes for the medical use of cannabis.

Patient characteristics have been reported in two studies. Hazekamp and Heerdink (2013) reported the characteristics of 5 540 patients who were prescribed cannabis for medical purposes in the Netherlands between 2003 and 2010. The incidence of new users peaked at 5 per 100 000 in the first 2 years of the scheme and declined thereafter to 3 per 100 000. The annual prevalence of the medical use of cannabis varied between 8 and 10 per 100 000 between 2005 and 2010. The drugs co-prescribed to the Dutch patients suggested that cannabis was used primarily to treat chronic pain. More recently, de Hoop et al. (2018) have provided information on the patients who accessed cannabis under the scheme between 2013 and 2016. The prevalence of the medical use of cannabis increased from 6.9 per 100 000 in 2010 to 24.6 per 100 000 in 2016. The proportion of female patients marginally declined (from 57% to 51%) but there was no change in age, mean daily dose of cannabis (0.64 g vs. 0.73 g) or average duration of use (251 and 254 days). The authors attributed the increased prevalence to the fact that cannabis oils have also been permitted since 2015.

Medical use of cannabis and cannabinoids in Czechia

Czechia operates a policy that illustrates how a country may permit cannabinoid medicines and cannabis for medicinal purposes in a strictly limited way. In Czechia, medicinal products containing dronabinol or nabilone are not available as authorised medicines. Sativex is an authorised medicine, but it is not reimbursed by the national health system or social insurance companies and it is currently not traded.

Czechia does allow patients to use cannabis preparations for medical purposes. A law allowing individuals to use herbal cannabis for medicinal purposes was passed in December 2013. Only a limited number of medical indications qualify for prescription (cancer, Parkinson's disease, multiple sclerosis and psoriasis), as set out in a ministerial notice of 2015. Prescription is limited to specially qualified doctors (currently 57), such as oncologists and psychiatrists. Dispensing is limited currently to 41 pharmacies. Since 2018, the maximum amount that can be prescribed to a patient has been 180 g per month. The supply initially came from Bedrocan in the Netherlands, but domestic cultivation by a monopoly producer now provides defined varieties of cannabis to the government for distribution. The first domestic harvest was delivered to pharmacies in March 2016. The final price to the patient is approximately EUR 3.70 per gram, which is not reimbursed by the national health system or social insurance companies.

Medical use of cannabis and cannabinoids in Croatia

The policy in Croatia provides greater access to medical cannabinoids and cannabis than in Czechia, but less than in Germany or the Netherlands.

In Croatia, medicinal products containing dronabinol, nabiximols and nabilone are available, with the former prescribed for symptoms of cancer and AIDS. Neither is reimbursed by national health or social insurance companies. There is no marketing authorisation for these products, but they can be imported based on prescriptions for individual patients issued by selected primary healthcare physicians following the recommendation of a specialist physician.

As a result of media and public pressure in support of some patients, in October 2015 the national law was changed to permit medicines that contain THC to be prescribed, including preparations of plant material. Only a limited number of medical indications qualify for prescription, namely multiple sclerosis, cancer, epilepsy

and AIDS. Although an initial recommendation is needed from a neurology, infectious disease or cancer specialist, it is possible for any general or family practitioner to write the prescription. The prescription should state the amount of THC in a single dose, the number of individual doses, drug form, dosage and method of use and, if applicable, also specify the type of herbal drugs and herbal preparation that should be used. The quantity prescribed may be sufficient for up to 30 days' use, up to a maximum allowable amount of 7.5 g of THC. Tilray products are imported to Croatia and are not reimbursed.

Medical use of cannabis and cannabinoids in Germany

The German legal framework developed over several years as a result of court challenges to the state ⁽⁵⁾. The result is a policy that provides broad access to cannabinoids and cannabis for medical purposes.

In Germany, medicinal products containing nabilone and nabiximols are available on prescription; they may be reimbursed by national health or social insurance companies.

In March 2017, the 'Cannabis as Medicine' Act created a mechanism for quality-controlled cannabis supply, including domestic production. Patients for whom all other treatment options have been exhausted can get a medical prescription for dried cannabis flowers and extracts of standardised quality at a pharmacy. The prescription of cannabis preparations is not limited to certain specialists, nor is their use limited to specific medical indications.

The 2017 Act allows cannabis to be prescribed for any life-threatening illness, or one that will affect the patient's quality of life permanently because of severe health problems. It allows for up to a maximum of 100 g per month, and insurance companies must cover these costs for chronically and terminally ill patients.

To establish domestic production and to ensure that the cannabis preparations supplied are of standardised quality, a government 'cannabis agency' was set up. In April 2017, a tender went out for 10 companies to grow approximately

2 000 kg of cannabis for medicinal purposes, but production is unlikely to start before 2019.

Medical use of cannabis and cannabinoids in Italy

The policy in Italy shows how a country may limit medicinal products while investing in the production of standardised cannabis preparations. Medicinal products containing dronabinol or nabilone are not authorised; the only authorised cannabinoid medicinal product is Sativex, which is reimbursed under the national health insurance scheme.

In 2007, a Decree of the Ministry of Health scheduled natural and synthetic cannabinoid derivatives in the list of substances with therapeutic activity, allowing them to be prescribed. In 2013, cannabis plant extracts and active compounds of plant origin were added to the list, allowing doctors to prescribe cannabis preparations for medical use. In 2015, the medical indications were clarified as including multiple sclerosis pain, chronic pain resistant to conventional treatment, and nausea, vomiting and cachexia associated with cancer or HIV. Any doctor can prescribe for medical use and the preparations can be made in any pharmacy, in accordance with a medical prescription for an individual patient. Cannabis extracts should be administered only orally, by infusion or in oil, or by inhalation, not by smoking. Currently, it is estimated that 9 000-10 000 patients receive cannabis for medical use. Initially, Bedrocan products were imported from the Netherlands, and in 2017 280 kg was imported. However, domestic growing started in 2014 at a secure state pharmaceutical facility under the supervision of the Ministry of Health, with an expected yield of 100 kg per year. Distribution started at the end of 2016.

The cannabis is cultivated from two plant varieties and is certified for good agricultural practice and good manufacturing practice. The standardised cannabis preparations are available in two formulations, FM1 (13-20 % THC and <1 % CBD) and FM2 (6 % THC and 8 % CBD), with both products priced at approximately EUR 42 for 5 g.

⁽⁵⁾ In 2000, eight patients with different medical conditions won their cases before the Federal Constitutional Court to get legal access to cannabis plant material. By 2007, the Federal Ministry of Health's Federal Institute for Drugs and Medical Devices was allowing local pharmacies to sell imported cannabis flowers and extracts. Around 900 patients received an approval, but they claimed that imported cannabis was not affordable.

Examples of approaches taken by some other countries to allow the medical use of cannabis and cannabinoids

Medical use of cannabis and cannabinoids in Israel

The case of Israel offers an example of a system in which one cannabinoid medicine is authorised and reimbursed, and policies on the use of herbal cannabis as medicine have evolved over time. Health professionals have played an important role in the development of the medical use of cannabis and cannabinoids in Israel. The number of medical indications for which herbal cannabis is allowed is limited, but Israel, unlike EU countries, permits patients to smoke it. New regulations in 2016 aimed to raise and standardise the quality of the supply, prescription and clinical practices. They have led to an increase in the number of patients registered, by requiring only standard rather than special prescriptions and by permitting the distribution of cannabis by pharmacies rather than growers as before.

In Israel, medicinal products containing dronabinol and nabilone are not available as authorised medicines. Sativex is authorised for treating moderate to severe spasticity in multiple sclerosis and as an adjunctive treatment for cancer pain. It is reimbursed by health insurance companies or the state social security system.

Israel was one of the first countries outside North America to allow the medical use of cannabis, under the approval and oversight of what is now the Israeli Medical Cannabis Agency (IMCA) within the Ministry of Health. The IMCA authorises growers to produce cannabis (nine growers as at February 2018). For some years it was sold directly to patients, but following the 2016 regulations the growers supply it to registered pharmacies. The cannabis is supplied as an oil or as dried flowers for smoking or vaporisation. It contains 12 % THC and an amount of CBD specified by the physician. Also following the 2016 regulations, cultivators and processors should follow the IMCA 'Medical Grade Cannabis Cannacopeia' guide to good agricultural, manufacturing, distribution, security, and clinical practices. Only 30 physicians are authorised to prescribe cannabis, though the 2016 regulations have proposed a standardised training course that should increase this number. Herbal cannabis is not publicly subsidised, and patients pay approximately 30 EUR for 10 grams.

Since July 2014, permits to use cannabis have been allowed for a short list of medical indications, and only when a physician has indicated that a patient has failed to

respond to recognised treatments. The approved indications include cancer treatment; inflammatory bowel disease; neuropathic pain after more than a year of treatment in a pain clinic; AIDS-related cachexia; neurological diseases such as multiple sclerosis, Parkinson's disease and Tourette syndrome; post-traumatic stress disorder; and terminal illnesses. The Israeli programme also lists the following contraindications for the medical use of cannabis: congestive heart failure, psychosis, anxiety disorder, having a first-degree relative with a psychiatric disorder (especially one with onset under the age of 30 years), and a personal history of drug abuse or addiction.

In exceptional circumstances, Israeli patients can use cannabis for other medical conditions if an expert physician requests an 'exceptional approval'. The physician must make a detailed case to the medical cannabis unit, describe how they would assess the patient's response to cannabis and indicate that they would report any adverse events (Ablin et al., 2016).

There are limited data on the number of patients receiving cannabis in Israel. The Ministry of Health indicated in 2013 that 8 713 patients had been granted a licence to use cannabis for medical purposes, including 1 518 with cancer and 4 864 with chronic pain. Waissengrin et al. (2015) presented data on cancer patients treated with cannabis in a major Israeli cancer hospital. These included 270 patients who had obtained a permit to use cannabis for medical purposes out of an estimated 17 000 patients who were treated at the hospital in 1 year (1.7 % of patients). They received cannabis to treat pain, loss of appetite and nausea. Nearly half (46 %) died within 6 months of initiating treatment. Among those still alive at 6 months, 46 % renewed their medical cannabis permits. The authors attributed the low rate of uptake in this hospital to physicians' reluctance to prescribe cannabis and patients' reluctance to use an illicit substance; such physician reluctance has also been reported elsewhere. However, attitudes may be changing with experience in prescribing cannabis (Sharon et al., 2018) and as the new training programme for physicians is implemented. The number of licensed medical cannabis patients has increased in recent years, reaching 28 000 patients with valid licences in March 2017 (Zarhin et al., 2017).

Medical use of cannabis and cannabinoids in Switzerland

The Swiss model, dating from 2011, is an example of a system that restricts the prescriber's choice to either an approved medicinal cannabinoid product or a magistral

cannabis preparation and restricts prescriptions to applicants on a named-patient basis. Although the qualifying medical conditions are not individually identified, they are specified as 'potentially life-threatening'.

In Switzerland, dronabinol (by special permit) and nabiximols are available as authorised medicines. Reimbursement for nabiximols is on a case-by-case basis on request to the insurance company.

In 2011, Switzerland legislated to allow the medical use of cannabis in exceptional circumstances under the supervision of the Swiss Federal Office of Public Health (Kilcher et al., 2017). Doctors must request a licence for each patient that enables the patient to use either a commercially available synthetic THC (dronabinol) or a tincture of *Cannabis sativa* containing 5 % of THC prepared by a pharmacist. The prescriber has to document that the patient has a potentially life-threatening condition, describe the likely benefit from THC and include evidence that the patient has provided informed consent to using the cannabis product.

Kilcher et al. (2017) reported data on patients treated under this scheme in 2013 and 2014. Only 8 of 1 656 requests were rejected, and 1 193 patients were treated (542 in 2013 and 825 in 2014) by 332 internal medicine specialists (55 %) and neurologists (14 %). Most patients (91 %) paid USD 400-500 per month because these drugs were not covered by insurance. Just over half (57 %) were female, with a mean age of 57 years. The main diagnoses were neurological disorders (49 %), musculoskeletal disorders (25 %) and cancers (10 %), and the main reasons for use were chronic pain (49 %) and spasticity (40 %). Most patients (62 %) took no other medication. When they did, analgesics were the most commonly used medicines. Licences were given for 6 months but could be extended and the proportion that were extended increased from 26% in 2013 to 39% in 2014.

In July 2018, the Federal Office of Public Health announced its intention to broaden access to the scheme, with a new law to be proposed by summer 2019.

Medical use of cannabis and cannabinoids in Australia

In 2016, the Australian federal government legislated to enable patients to obtain unapproved cannabis products for medical use under the special access provisions of the Therapeutic Goods Act (Freckelton, 2015). State governments in New South Wales, Queensland and

Victoria have also made legislative changes that permit medical cannabis use and the cultivation of cannabis for medical use.

The Australian programme for the medical use of cannabis met with considerable resistance from oncologists, neurologists and pain specialists, who are the only medical practitioners who can initiate treatment. These specialists argue that there is little evidence to support the medical use of cannabis and that much better treatments are available for chemotherapy-induced nausea and vomiting, neuropathic pain, muscle spasticity and epilepsy (see, for example, ANZCA Faculty of Pain Medicine, 2015; Cancer Council Australia and Clinical Oncology Society of Australia, 2016; Martin et al., 2018). Prescribers' legal liability for any harm caused to patients is also a concern. Patients have therefore found it difficult to obtain a prescription for cannabis. Patients also complain about the complex approval process produced by overlapping federal and state/territory requirements. Critically for many patients, the Australian healthcare system does not cover the costs of importing cannabis products. Patients therefore have to pay the substantial costs of importing the drug, for example AUD 400 (around EUR 250) per month for pharmaceutical-grade CBD to treat epilepsy.

Summary and discussion

It is clear that no standard regulatory framework for cannabis preparations and cannabinoid products has been developed and that there is considerable variation between countries in the approaches taken, reflecting a variety of historical and cultural factors. In most countries, the provision of cannabis and cannabinoid products and preparations for medical purposes has evolved over time, often in response to patient demand or product developments, and the situation continues to change rapidly. Nevertheless, in general three broad types of approach can be seen, although often countries will use more than one of these in parallel.

Allowing the use of medicinal products containing cannabinoids

As described above, several pharmaceutical cannabinoids have been approved for medical use (e.g. Marinol and Cesamet), but in general these are not widely used because patients find it difficult to achieve the desired therapeutic benefits without also experiencing unwelcome psychoactive effects. In addition, some of these drugs resulted in limited financial returns for the companies that marketed them, and this may have slowed down product

development. Sativex and Epidiolex have since been developed and approved for medical use in neuropathic pain and intractable epilepsy, respectively, on the basis of evidence of their effectiveness from RCTs. In addition, clinical trials of some standardised cannabis preparations are under way, so in the future some of these may also receive market authorisation as pharmaceutical products.

However, many governments are faced with demand from patients who want to use cannabis and cannabinoids to treat symptoms of illnesses for which there is currently little or no evidence of efficacy or safety. This includes many of the conditions for which cannabis is reportedly used in countries that have schemes that provide wide access, namely anxiety disorders, depression, sleep problems, other neurological conditions, cancers and inflammatory bowel diseases. Currently, there are insufficient clinical trial data on which to base approval of their use in treating these conditions, which may cause patients to resort to black market cannabis products. This has led to the development in some countries of alternative methods of providing access to cannabis and cannabinoids.

Allowing the medical use of unauthorised products or preparations

Special access schemes to allow the medical use of unauthorised products or preparations take a number of forms. In some cases, the medical use of cannabis may be allowed under some variation of a special access scheme for unapproved medicines as an interim measure while awaiting the results of clinical trials or pending authorisation. This approach has been taken in, for example, Australia, Israel and the Netherlands. These schemes allow doctors to prescribe cannabis and cannabinoids as unapproved medicines for various medical purposes.

Other schemes allow cannabis and cannabinoids to be supplied to patients on prescription, often on compassionate grounds. Some schemes restrict use to medical conditions for which there is evidence of efficacy (e.g. nausea and vomiting, muscle spasticity and chronic pain). Sometimes access is approved on a case-by-case, named-patient basis. Some schemes restrict the cannabis products that can be used to pharmaceutical-quality cannabinoids or standardised plant extracts. Others allow the use of herbal cannabis products that have been standardised and quality controlled. In general, these schemes still parallel the regulatory approach for medicinal products.

A major challenge in many of these approaches has been physicians' reluctance to prescribe cannabis for ethical and medico-legal reasons. Patients also complain about cumbersome approval processes, the quality and the cost of the cannabis and cannabinoids that are available, and restrictions on the cannabis products that they are allowed to use.

De novo stand-alone medical cannabis programmes

Some stand-alone medical cannabis programmes have been established outside the medicines regulatory systems. For example, in the United States, the regulatory requirements for medicines have been avoided by passing citizen-initiated referenda that allow patients to smoke cannabis and use other cannabis products for very broadly defined medical reasons. Physicians have sometimes been reluctant to 'recommend' cannabis under such schemes because of uncertainty about clinical indications and fear of being held legally liable for any harm that patients may experience. In some US states, this issue has been circumvented by legalising the commercial supply of cannabis through dispensaries.

In general, these stand-alone schemes do not facilitate the conduct of clinical trials and the establishment of an evidence base on which to assess the benefits and harms of medical use of cannabis and cannabinoids. Other methods, which might include large-scale cohort studies using record linkage or the establishment of registries for medical cannabis users to monitor rates of continuation and adverse events, are needed. Government funding of such studies may be required.

Part 4

What are the regulatory challenges in allowing the medical use of cannabis and cannabinoids?

Many EU countries now allow, or are considering allowing, the medical use of cannabis or cannabinoids in some form. However, the approaches taken to making these available are very variable, in terms of both the medicinal products and preparations allowed and the regulatory frameworks governing their provision. Consideration of these diverse approaches highlights a number of key issues that need to be addressed as part of any process for making cannabis or cannabinoid-containing products or preparations available for medical use.

Medicinal products that have followed the pharmaceutical regulatory path (including Cesamet, Marinol, Sativex and Epidiolex) will have had many decisions predetermined by that process, such as doses, indications and routes of administration. However, when countries are considering allowing cannabis preparations for medical use, these and a number of other regulatory issues need to be considered. Key issues include:

- What types of medicinal products or cannabis preparations should be allowed? Governments can decide to allow only medicinal products that have followed the pharmaceutical regulatory path and are authorised for marketing in the country. Governments can also consider giving access to unauthorised products and preparations through a range of other mechanisms, such as exceptional use, compassionate use and named-patient or expanded access programmes (see Part 2 of this report).
- What forms of cannabis preparations should be allowed? Governments might consider allowing raw cannabis; magistral preparations made by a pharmacist; other cannabis preparations, such as standardised cannabis extracts; cannabis oils; and/or other forms of cannabis.
- What routes of administration for cannabis preparations should be allowed? Cannabis can be manufactured as oral preparations, such as capsules or oils; as preparations that can be vaporised; or in other forms.
- For which medical conditions should treatment with cannabis preparations or medicinal products be permitted? Governments could consider authorising cannabis preparations to treat only medical conditions for which there is evidence of efficacy (e.g. nausea and vomiting, muscle spasticity and chronic pain) or they might consider, under certain preconditions, approval for any condition in which some patients have reported benefits.
- If cannabis preparations were to be made available, would they require a prescription? If so, who would be authorised to prescribe (e.g. only specialist physicians, any medical practitioner and/or nurse prescribers)?
- If cannabis is made available for medical use, how will governments address the possible reluctance of physicians to prescribe cannabis for ethical or medico-legal reasons and uncertainty about clinical indications and dosing, particularly where any physician is authorised to prescribe cannabis preparations? Would guidelines and training be provided, and, if so, by whom?
- For any scheme proposed, how much of the cost will be met by patients? Will medicinal products or cannabis

preparations be reimbursed to patients? Will the cost of these medicinal products or cannabis preparations be covered by the national healthcare system or health insurance schemes?

- How should cannabinoids fit into existing treatment for those medical conditions for which they may be used (e.g. as an adjunctive treatment or as a first-line treatment)?
- How might prescriptions be limited? How should monitoring of patient outcomes and adverse events be carried out, and by whom?
- What type of quality standards should be applied? If cannabis is to be grown at home for medicinal purposes, will any standards be applicable, and how will they be enforced?
- If cannabis is to be an active substance in the manufacture of cannabis preparations such as oils or capsules, will the manufacturer comply with the relevant quality standards, such as EU good manufacturing practice and good distribution practice standards?
- How might governments permit the manufacturing and distribution of cannabis for medical purposes? Should governments contract private companies? Might patients be allowed to grow their own cannabis for medical purposes? How should cannabis be distributed to patients? Could this be done through any pharmacy, specific pharmacies or other distribution channels?
- How will the necessary pharmacovigilance schemes and data collection for reporting to the INCB be organised?
- Will data systems be established to collect evidence on the wider public health and societal outcomes of the regulatory changes and to help in strengthening the evidence base? How will this be organised and what roles might government, research bodies and industry play in this (e.g. by facilitating or conducting large-scale cohort studies or establishing patient registries)?
- In the European Union, consideration may need to be given to potential cross-border patient access issues that might arise where neighbouring countries have different national schemes.

The above list is not exhaustive. It highlights the complexity of any decision-making about making cannabis or cannabinoids available for medical use. Consideration needs to be given to multiple issues along the whole chain of events from product development through production and distribution to monitoring outcomes for both safety and effectiveness. In what is a very fast-moving field characterised by an often hotly contested debate, this report has sought to provide an objective look at current evidence, practice and experience. It illustrates the diversity of approaches currently being taken and points to the importance of developing an agreed conceptual framework and terminology to assist in building a base for assessing the medical use of cannabis and cannabinoids.

Glossary

AIDS — acquired immune deficiency syndrome.

Cannabinoids — substances found in the cannabis plant that act on specific receptors in the human brain and body; they are the main active ingredients in both the medicinal products derived from cannabis and cannabis preparations. The two most extensively studied cannabinoids are THC and CBD. Cannabinoids are also found in the human body (endocannabinoids), but those consumed for medical use may originate from the cannabis plant (plant-derived cannabinoids, also known as phytocannabinoids) or be synthesised in the laboratory (synthetic cannabinoids).

Cannabis magistral preparation — raw cannabis transformed by a pharmacist for consumption, in accordance with a specified medical prescription for an individual patient.

Cannabis preparations — in this report, items derived from the *Cannabis sativa* plant that do not have a marketing authorisation for medical use. These may include the raw cannabis, such as the flowering tops, compressed resin or hash; oils extracted from the plant; concentrated cannabis extracts; and other cannabis preparations, such as soft gels, tinctures or edibles.

CBD — cannabidiol; see *cannabinoids*.

CNCP — chronic non-cancer pain.

Dronabinol — synthetic THC; active ingredient of authorised medicinal products such as Marinol and Syndros. However, 'dronabinol' may sometimes be used to refer to plant-derived THC.

EEA — European Economic Area.

EMA — European Medicines Agency.

EMCDDA — European Monitoring Centre for Drugs and Drug Addiction.

Endocannabinoids — see *cannabinoids*.

EU — European Union.

FDA — US Food and Drug Administration.

GP — general practitioner.

HIV — human immunodeficiency virus.

INCB — International Narcotics Control Board.

Nabilone — synthetic cannabinoid similar to THC; active ingredient of authorised medicinal products such as Cesamet and Canemes.

Nabiximols — plant-based cannabis extract containing approximately equal quantities of THC and CBD; active ingredient of authorised medicinal products such as Sativex.

NASEM — National Academies of Sciences, Engineering, and Medicine.

OR — odds ratio.

Phytocannabinoids — see *cannabinoids*.

RCT — randomised controlled trial.

Standardised cannabis preparations — raw cannabis transformed by the manufacturer (e.g. into capsules) in larger batches, containing a constant composition of cannabinoids (examples of standardised cannabis preparations include preparations of cannabis flowers, such as Bedrocan; granulates, such as Bediol; and oil extracts, such as Tilray 10:10 Balance).

Synthetic cannabinoids — cannabinoids synthesised in the laboratory.

THC — tetrahydrocannabinol; see *cannabinoids*.

UN — United Nations.

WHO — World Health Organization.

WHO-ECDD — WHO Expert Committee on Drug Dependence.

References

- Ablin, J., Ste-Marie, P. A., Schafer, M., Hauser, W. and Fitzcharles, M. A. (2016), 'Medical use of cannabis products: lessons to be learned from Israel and Canada', *Schmerz* 30, pp. 3-13.
- Abraham, C. (2002), 'Medicinal-marijuana harvest on hold', *The Globe and Mail*, 22 April 2002, p. A4.
- Abuhasira, R., Schleider, L. B.-L., Mechoulam, R. and Novack, V. (2018), 'Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly', *European Journal of Internal Medicine* 49, pp. 44-50.
- Aldington, S., Harwood, M., Cox, B., Weatherall, M., Beckert, L., Hansell, A., et al. (2008), 'Cannabis use and risk of lung cancer: a case-control study', *European Respiratory Journal* 31, pp. 280-286.
- Ammerman, S., Ryan, S. and Adelman, W. P. (2015), 'The impact of marijuana policies on youth: clinical, research, and legal update', *Pediatrics* 135, e769-785.
- Anderson, D. M., Hansen, B. and Rees, D. I. (2013), 'Medical marijuana laws, traffic fatalities, and alcohol consumption', *Journal of Law and Economics* 56, pp. 333-369.
- Anderson, D. M., Rees, D. I. and Sabia, J. J. (2014), 'Medical marijuana laws and suicides by gender and age', *American Journal of Public Health* 104, pp. 2369-2376.
- Andraea, M. H., Carter, G. M., Shaparin, N., Suslov, K., Ellis, R. J., Ware, M. A., et al. (2015), 'Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data', *Journal of Pain* 16, pp. 1221-1232.
- Anthony, J. (2006), 'The epidemiology of cannabis dependence', in Roffman, R. A. and Stephens, R. S. (eds.), *Cannabis dependence: its nature, consequences and treatment*, Cambridge University Press, Cambridge, pp. 58-105.
- Anthony, J., Warner, L. and Kessler, R. (1994), 'Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey', *Experimental and Clinical Psychopharmacology* 2, pp. 244-268.
- ANZCA Faculty of Pain Medicine (2015), 'Statement on "medicinal cannabis" with particular reference to its use in the management of patients with chronic non-cancer pain', Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists, Melbourne (<http://fpm.anzca.edu.au/documents/pm10-april-2015.pdf>).
- Bachhuber, M. A., Saloner, B., Cunningham, C. O. and Barry, C. L. (2014), 'Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010', *JAMA Internal Medicine* 174, pp. 1668-1673.
- Balasubramanian, G., Morampudi, S., Chhabra, P., Gowda, A. and Zomorodi, B. (2016), 'An overview of Compassionate Use Programs in the European Union member states', *Intractable and Rare Diseases Research* 5, pp. 244-254.
- Bar-Lev Schleider, L., Mechoulam, R., Lederman, V., Hilou, M., Lencovsky, O., Betzalel, O., et al. (2018), 'Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer', *European Journal of Internal Medicine* 49, pp. 37-43.
- Barnes, R. E. (2000), 'Reefer madness: legal and moral issues surrounding the medical prescription of marijuana', *Bioethics* 14, pp. 16-41.
- Beal, J. E., Olson, R., Laubenstein, L., Morales, J. O., Bellman, P., Yangco, B., et al. (1995), 'Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS', *Journal of Pain and Symptom Management* 10, pp. 89-97.
- Bogdanoski, T. (2010), 'Accommodating the medical use of marijuana: surveying the differing legal approaches in Australia, the United States and Canada', *Journal of Law and Medicine* 17, pp. 508-531.
- Bostwick, J. M. (2012), 'Blurred boundaries: the therapeutics and politics of medical marijuana', *Mayo Clinic Proceedings* 87, pp. 172-186.
- Bramness, J. G., Dom, G., Gual, A., Mann, K. and Wurst, F. M. (2018), 'A survey on the medical use of cannabis in Europe: a position paper', *European Addiction Research* 24, pp. 201-205.

- ▮ Campbell, G., Hall, W. D., Peacock, A., Lintzeris, N., Bruno, R., Larance, B., et al. (2018), 'Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study', *Lancet Public Health* 3, e341-e350.
- ▮ Cancer Council Australia, Clinical Oncology Society of Australia (2016), 'Position statement — medical use of cannabis' (<https://www.cosa.org.au/media/332295/medical-use-of-cannabis-position-statement-17052016.pdf>).
- ▮ Cerda, M., Wall, M., Keyes, K. M., Galea, S. and Hasin, D. S. (2012), 'Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence', *Drug and Alcohol Dependence* 120, pp. 22-27.
- ▮ Choo, E. K., Benz, M., Zaller, N., Warren, O., Rising, K. L. and McConnell, K. J. (2014), 'The impact of state medical marijuana legislation on adolescent marijuana use', *Journal of Adolescent Health* 55, pp. 160-166.
- ▮ Cohen, P. J. (2006), 'Medical marijuana, compassionate use, and public policy: expert opinion or vox populi?', *Hastings Center Report* 36, pp. 19-22.
- ▮ Cohen, P. J. (2010), 'Medical marijuana 2010: it's time to fix the regulatory vacuum', *Journal of Law, Medicine and Ethics* 38, pp. 654-666.
- ▮ Cohen, S. P. (2008), 'Cannabinoids for chronic pain', *BMJ* 336, pp. 167-168.
- ▮ Collin, C., Ehler, E., Waberzinek, G., Alsindi, Z., Davies, P. and Powell, K., et al. (2010), 'A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis', *Neurological Research* 32, pp. 451-459.
- ▮ Conboy, J. R. (2000), 'Smoke screen: America's drug policy and medical marijuana', *Food and Drug Law Journal* 55, pp. 601-617.
- ▮ Crean, R. D., Crane, N. A. and Mason, B. J. (2011), 'An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions', *Journal of Addiction Medicine* 5, p. 1.
- ▮ de Hoop, B., Heerdink, E. R. and Hazekamp, A. (2018), 'Medicinal cannabis on prescription in the Netherlands: statistics for 2003-2016', *Cannabis Cannabinoid Res* 3, pp. 54-55.
- ▮ Devinsky, O., Marsh, E., Friedman, D., Thiele, E., Laux, L., Sullivan, J., et al. (2016), 'Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial', *Lancet Neurology* 15, pp. 270-278.
- ▮ Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., et al. (2017), 'Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome', *New England Journal of Medicine* 376, pp. 2011-2020.
- ▮ Dos Santos, R. G., Hallak, J. E., Leite, J. P., Zuardi, A. W. and Crippa, J. A. (2014), 'Phytocannabinoids and epilepsy', *Journal of Clinical Pharmacy and Therapeutics* 40, pp. 135-143.
- ▮ Dryburgh, L. M., Bolan, N. S., Grof, C. P. L., Galettis, P., Schneider, J., Lucas, C. J. and Martin, J. H. (2018), 'Cannabis contaminants: sources, distribution, human toxicity and pharmacologic effects', *British Journal of Clinical Pharmacology*, pp. 2468-2476.
- ▮ Eddy, M. (2009), *Medical marijuana: review and analysis of federal and state policies*, Congressional Research Service, Washington, DC.
- ▮ Ekor, M. (2014), 'The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety', *Frontiers in Pharmacology* 4, p. 177.
- ▮ EMA (European Medicines Agency) (2016), *The European regulatory system for medicines: a consistent approach to medicines regulation across the European Union*, EMA, London (http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2014/08/WC500171674.pdf).
- ▮ European Parliament and Council (2001), Directive 2001/83/EC of the European Parliament and of the Council, of 6 November 2001, on the Community code relating to medicinal products for human use, *Official Journal of the European Communities* L 311/67.
- ▮ Fischer, B., Kuganesan, S. and Room, R. (2015), 'Medical marijuana programs: implications for cannabis control policy — observations from Canada', *International Journal of Drug Policy* 26, pp. 15-19.

- Franz, C. A. and Frishman, W. H. (2016), 'Marijuana use and cardiovascular disease', *Cardiology in Review* 24, pp. 158-162.
- Freckelton, I. (2015), 'Medicinal cannabis law reform: lessons from Canadian litigation', *Journal of Law and Medicine* 22, pp. 719-738.
- Friedman, D. and Devinsky, O. (2015), 'Cannabinoids in the treatment of epilepsy', *New England Journal of Medicine* 373, pp. 1048-1058.
- Gloss, D. and Vickrey, B. (2014), 'Cannabinoids for epilepsy', *Cochrane Database of Systematic Reviews* 3, CD009270.
- Grinspoon, L. and Bakalar, J. (1993), *Marihuana: the forbidden medicine*, Yale University Press, New Haven.
- Grotenhermen, F. (2004), 'Cannabinoids for therapeutic use: designing systems to increase efficacy and reliability', *American Journal of Drug Delivery* 2, pp. 229-240.
- Grucza, R. A., Hur, M., Agrawal, A., Krauss, M. J., Plunk, A. D., Cavazos-Rehg, P. A., et al. (2015), 'A reexamination of medical marijuana policies in relation to suicide risk', *Drug and Alcohol Dependence* 152, pp. 68-72.
- Hall, W. D. (2015), 'What has research over the past two decades revealed about the adverse health effects of recreational cannabis use?', *Addiction* 110, pp. 19-35.
- Hall, W. D. (2018), *A summary of reviews of evidence on the efficacy and safety of medical uses of cannabis and cannabinoids* (http://www.emcdda.europa.eu/publications_en).
- Hall, W. D. and Degenhardt, L. D. (2003), 'Medical marijuana initiatives: are they justified? How successful are they likely to be?', *CNS Drugs* 17, pp. 689-697.
- Hall, W. D., Teesson, M., Lynskey, M. and Degenhardt, L. (1999), 'The 12-month prevalence of substance use and ICD-10 substance use disorders in Australian adults: findings from the National Survey of Mental Health and Well-being', *Addiction* 94, pp. 1541-1550.
- Hall, W. D., Renström, M. and Poznyak, V. (2016), *The health and social effects of nonmedical cannabis use*, World Health Organization, Geneva (http://www.who.int/substance_abuse/publications/msb_cannabis_report.pdf).
- Harper, S., Strumpf, E. C. and Kaufman, J. S. (2012), 'Do medical marijuana laws increase marijuana use? Replication study and extension', *Annals of Epidemiology* 22, pp. 207-212.
- Hashibe, M., Morgenstern, H., Cui, Y., Tashkin, D. P., Zhang, Z.-F., Cozen, W., et al. (2006), 'Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study', *Cancer Epidemiology, Biomarkers and Prevention* 15, pp. 1829-1834.
- Hayes, M. J. and Brown, M. S. (2014), 'Legalization of medical marijuana and incidence of opioid mortality', *JAMA Internal Medicine* 174, pp. 1673-1674.
- Hazekamp, A. and Heerdink, E. R. (2013), 'The prevalence and incidence of medicinal cannabis on prescription in the Netherlands', *European Journal of Clinical Pharmacology* 69, pp. 1575-1580.
- Hoffmann, D. E., Weber, E. (2010), 'Medical marijuana and the law', *New England Journal of Medicine* 362, pp. 1453-1457.
- HPRA (Health Products Regulatory Authority) (2017), *Cannabis for medical use — a scientific review* (<https://www.hpra.ie/docs/default-source/publications-forms/newsletters/cannabis-for-medical-use---a-scientific-review.pdf?sfvrsn=7>).
- Hussain, S. A., Zhou, R., Jacobson, C., Weng, J., Cheng, E., Lay, J., et al. (2015), 'Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox-Gastaut syndrome', *Epilepsy and Behavior* 47, pp. 138-141.
- INCB (International Narcotics Control Board) (2017), *Alert on control of narcotic drugs: the therapeutic use of cannabis*, INCB, Vienna (https://www.incb.org/documents/News/Alerts/Alert_on_Control_of_Narcotic_Drugs_June_2017.pdf).
- Institute of Medicine (1999), *Marijuana and medicine: assessing the science base*, National Academy Press, Washington, DC.

- | Iversen, L. (2003), 'Cannabis and the brain', *Brain* 126, pp. 1252-1270.
- | Iversen, L. (2007), *The science of marijuana*, Oxford University Press, Oxford.
- | Kalant, H. (2001), 'Medicinal use of cannabis: history and current status', *Pain Research and Management* 6, pp. 80-91.
- | Kilcher, G., Zwahlen, M., Ritter, C., Fenner, L. and Egger, M. (2017), 'Medical use of cannabis in Switzerland: analysis of approved exceptional licences', *Swiss Medical Weekly* 147, w14463.
- | Koppel, B. S., Brust, J. C., Fife, T., Bronstein, J., Youssof, S., Gronseth, G. and Gloss, D. (2014), 'Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology', *Neurology* 82, pp. 1556-1563.
- | Krcevski-Skvarc, N., Wells, C. and Hauser, W. (2018), 'Availability and approval of cannabis-based medicines for chronic pain management and palliative/supportive care in Europe: a survey of the status in the chapters of the European Pain Federation', *European Journal of Pain* 22, pp. 440-454.
- | Lucas, P. G. (2008), 'Regulating compassion: an overview of Canada's federal medical cannabis policy and practice', *Harm Reduction Journal* 5, p. 5.
- | Lucas, P. G. (2012), 'It can't hurt to ask: a patient-centered quality of service assessment of Health Canada's medical cannabis policy and program', *Harm Reduction Journal* 9, p. 2.
- | Lutge, E. E., Gray, A. and Siegfried, N. (2013), 'The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS', *Cochrane Database of Systematic Reviews* 4, CD005175.
- | Lynne-Landsman, S. D., Livingston, M. D. and Wagenaar, A. C. (2013), 'Effects of state medical marijuana laws on adolescent marijuana use', *American Journal of Public Health* 103, pp. 1500-1506.
- | Martin, J. H. and Bonomo, Y. A. (2016), 'Medicinal cannabis in Australia: the missing links', *Medical Journal of Australia* 204, pp. 371-373.
- | Martin, J. H., Bonomo, Y. and Reynolds, A. D. B. (2018), 'Compassion and evidence in prescribing cannabinoids: a perspective from the Royal Australasian College of Physicians', *Medical Journal of Australia* 208, pp. 107-109.
- | Martinalbo, J., Bowen, D., Camarero, J., Chapelin, M., Demolis, P., Foggi, P., et al. (2016), 'Early market access of cancer drugs in the EU', *Annals of Oncology* 27, pp. 96-105.
- | Masten, S. V. and Guenzburger, G. V. (2014), 'Changes in driver cannabinoid prevalence in 12 U. S. states after implementing medical marijuana laws', *Journal of Safety Research* 50, pp. 35-52.
- | Mechoulam, R. (1986), 'The pharmacohistory of cannabis sativa', in Mechoulam, R. (ed.), *Cannabinoids as therapeutic agents*, CRC Press, Boca Raton, FL., pp. 1-9
- | Moffat, A. C. (2002), 'The legalisation of cannabis for medical use', *Science and Justice* 42, pp. 55-57.
- | Mucke, M., Phillips, T., Radbruch, L., Petzke, F. and Hauser, W. (2018a), 'Cannabis-based medicines for chronic neuropathic pain in adults', *Cochrane Database of Systematic Reviews* 3, CD012182.
- | Mucke, M., Weier, M., Carter, C., Copeland, J., Degenhardt, L., Cuhls, H., et al. (2018b), 'Systematic review and meta-analysis of cannabinoids in palliative medicine', *Journal of Cachexia, Sarcopenia, and Muscle* 9, pp. 220-234.
- | Nahas, G. G. (1984), 'Toxicology and pharmacology', in Nahas, G. G. (ed.), *Marihuana in science and medicine*, Raven Press, New York, pp. 102-247.
- | NASEM (2017), *The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research*, National Academies Press for the National Academies of Sciences Engineering and Medicine, Washington, DC.
- | Navari, R. M. (2009), 'Pharmacological management of chemotherapy-induced nausea and vomiting: focus on recent developments', *Drugs* 69, pp. 515-533.
- | Novotna, A., Mares, J., Ratcliffe, S., Novakova, I., Vachova, M., Zapletalova, O., et al. (2011), 'A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis', *European Journal of Neurology* 18, pp. 1122-1131

- Osakwe, O. (2016), 'Pharmaceutical regulation: the role of government in the business of drug discovery', in Osakwe, O. and Rizvi, S. A. A. (eds.), *Social aspects of drug discovery, development and commercialization*, Elsevier, London, pp. 3-27.
- Pacula, R. L. and Smart, R. (2017), 'Medical marijuana and marijuana legalization', *Annual Review of Clinical Psychology* 13, pp. 397-419.
- Pacula, R. L., Chriqui, J. and King, J. (2004), *Marijuana decriminalization: what does it mean in the United States?*, RAND, Santa Monica, CA, http://www.rand.org/pubs/working_papers/WR126/.
- Pertwee, R. G. (1997), 'Pharmacology of cannabinoid CB1 and CB2 receptors', *Pharmacology and Therapeutics* 74, pp. 129-180.
- Pisanti, S. and Bifulco, M. (2017), 'Modern history of medical cannabis: from widespread use to prohibitionism and back', *Trends in Pharmacological Sciences* 38, pp. 195-198.
- Press, C. A., Knupp, K. G. and Chapman, K. E. (2015), 'Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy', *Epilepsy and Behavior* 45, pp. 49-52.
- ProCon.org (2018), *31 legal medical marijuana states and DC*, ProCon.org, Santa Monica, CA, <http://medicalmarijuana.procon.org/view.resource.php?resourceID=00881>.
- Rago, L. K. and Santoso, B. (2008), 'Drug regulation: history, present and future', in van Baxtel, C. J., Santoso, B. and Edwards, I. R. (eds.), *Drug benefits and risks: an international textbook of clinical pharmacology*, OIS Press and Uppsala Monitoring Centre, pp. 65-77.
- Regan, T. (2011), *Joint ventures: inside America's almost legal marijuana industry*, Wiley, New York.
- Ries, N. M. (2016), 'Prescribe with caution: the response of Canada's medical regulatory authorities to the therapeutic use of cannabis', *McGill Journal of Law and Health* 9:2, pp. 215-254.
- Russo, E. B. (2011), 'Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects', *British Journal of Pharmacology* 163, pp. 1344-1364.
- Russo, E. B. and Guy, G. W. (2006), 'A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol', *Medical Hypotheses* 66, pp. 234-246.
- Russo, E. B. and Marcu, J. (2017), 'Cannabis pharmacology: the usual suspects and a few promising leads', *Advances in Pharmacology* 80, pp. 67-134.
- Rylander, M., Valdez, C. and Nussbaum, A. M. (2014), 'Does the legalization of medical marijuana increase completed suicide?', *American Journal of Drug and Alcohol Abuse* 40, pp. 269-273.
- Sammons, H. M., Gubarev, M. I., Krepkova, L. V., Bortnikova, V. V., Corrick, F., Job, K. M., et al. (2016), 'Herbal medicines: challenges in the modern world. Part 2. European Union and Russia', *Expert Review of Clinical Pharmacology* 9, pp. 1117-1127.
- Samuels, D. (2008), 'Dr Kush: how medical marijuana is transforming the pot industry', *The New Yorker* (<https://www.newyorker.com/magazine/2008/07/28/dr-kush>).
- Schuermeyer, J., Salomonsen-Sautel, S., Price, R. K., Balan, S., Thurstone, C., Min, S.-J. and Sakai, J. T. (2014), 'Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003-11', *Drug and Alcohol Dependence* 140, pp. 145-155.
- Serpell, M. G., Notcutt, W. and Collin, C. (2013), 'Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis', *Journal of Neurology* 260, pp. 285-295.
- Sharon, H., Goldway, N., Goor-Aryeh, I., Eisenberg, E. and Brill, S. (2018), 'Personal experience and attitudes of pain medicine specialists in Israel regarding the medical use of cannabis for chronic pain', *Journal of Pain Research* 11, pp. 1411-1419.
- Shekelle, P., Woolf, S., Grimshaw, J. M., Schunemann, H. J. and Eccles, M. P. (2012), 'Developing clinical practice guidelines: reviewing, reporting, and publishing guidelines; updating guidelines; and the emerging issues of enhancing guideline implementability and accounting for comorbid conditions in guideline development', *Implementation Science* 7, p. 62.
- Smith, L. A., Azariah, F., Lavender, V. T., Stoner, N. S. and Bettiol, S. (2015), 'Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy', *Cochrane Database of Systematic Reviews* 11, CD009464.

- | Solowij, N., Stephens, R. S., Roffman, R. A., Babor, T., Kadden, R., Miller, M., et al. (2002), 'Cognitive functioning of long-term heavy cannabis users seeking treatment', *JAMA* 287, pp. 1123-1131.
- | Stockings, E., Campbell, G., Hall, W. D., Nielsen, S., Zagic, D., Rahman, R., et al. (2018a), 'Cannabis and cannabinoids for the treatment of people with chronic non-cancer pain conditions: a systematic review and meta-analysis of controlled and observational studies', *Pain* 159, pp. 1932-1954.
- | Stockings, E., Zagic, D., Campbell, G., Weier, M., Hall, W. D., Nielsen, S., et al. (2018b), 'Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence', *Journal of Neurology, Neurosurgery, and Psychiatry* 89, pp. 741-753.
- | Tramer, M. R., Carroll, D., Campbell, F. A., Reynolds, D. J. M., Moore, R. A. and McQuay, H. J. (2001), 'Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review', *British Medical Journal* 323, pp. 16-21.
- | UNODC (United Nations Office on Drugs and Crime) (2013), *The International Drug Control Conventions: Single Convention on Narcotic Drugs of 1961 as amended by the 1972; Protocol Convention on Psychotropic Substances of 1971; United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988; with final acts and resolutions*, United Nations, New York (https://www.unodc.org/documents/commissions/CND/Int_Drug_Control_Conventions/Ebook/The_International_Drug_Control_Conventions_E.pdf).
- | US FDA (US Food and Drug Administration)(2018), 'FDA news release: FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy', US Food and Drug Administration, Silver Spring, MD, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm611046.htm>.
- | Wade, D. T., Makela, P., Robson, P., House, H. and Bateman, C. (2004), 'Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients', *Multiple Sclerosis* 10, pp. 434-441.
- | Waissengrin, B., Urban, D., Leshem, Y., Garty, M. and Wolf, I. (2015), 'Patterns of use of medical cannabis among Israeli cancer patients: a single institution experience', *Journal of Pain and Symptom Management* 49, pp. 223-230.
- | Wall, M. M., Poh, E., Cerda, M., Keyes, K. M., Galea, S. and Hasin, D. S. (2011), 'Adolescent marijuana use from 2002 to 2008: higher in states with medical marijuana laws, cause still unclear', *Annals of Epidemiology* 21, pp. 714-716.
- | Wall, M. M., Poh, E., Cerda, M., Keyes, K. M., Galea, S. and Hasin, D. S. (2012), 'Do medical marijuana laws increase marijuana use? Replication study and extension', *Annals of Epidemiology* 22, pp. 536-537.
- | Wang, T., Collet, J.-P., Shapiro, S. and Ware, M. A. (2008), 'Adverse effects of medical cannabinoids: a systematic review', *CMAJ: Canadian Medical Association Journal* 178, pp. 1669-1678.
- | Wang, G. S., Le Lait, M. C., Deakne, S. J., Bronstein, A. C., Bajaj, L. and Roosevelt, G. (2016), 'Unintentional pediatric exposures to marijuana in Colorado, 2009-2015', *JAMA Pediatrics* 170, e160971.
- | Wang, G. S., Hall, K., Vigil, D., Banerji, S., Monte, A. and VanDyke, M. (2017), 'Marijuana and acute health care contacts in Colorado', *Prevention Medicine* 104, pp. 24-30.
- | Wen, H., Hockenberry, J. M. and Cummings, J. R. (2015), 'The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances', *Journal of Health Economics* 42, pp. 64-80.
- | Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., et al. (2015), 'Cannabinoids for medical use: a systematic review and meta-analysis', *JAMA* 313, pp. 2456-2473.
- | WHO (2015), *National policy on traditional medicine and regulation of herbal medicines: report of a WHO global survey*, WHO, Geneva (<http://apps.who.int/medicinedocs/pdf/s7916e/s7916e.pdf>).
- | WHO (2018), 'Q&A: WHO Expert Committee on Drug Dependence review of cannabis' (http://www.who.int/medicines/access/controlled-substances/Cannabis_Review_QA_26July2018.pdf?ua=1).

- | Zajicek, J., Fox, P., Sanders, H., Wright, D., Vickery, J., Nunn, A. and Thompson, A. (2003), 'Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial', *Lancet* 362, pp. 1517-1526.
- | Zarhin, D., Negev, M., Vulfsons, S. and Szintman, S. (2017), 'Medicalization of cannabis: What does it mean?', *International Journal of Drug Policy* 49, pp. 54-57.

Acknowledgements

External peer reviewers: Jørgen Bramness (Norwegian Centre for Addiction Research, University of Oslo), Anne Line Bretteville-Jensen (Norwegian Institute of Public Health), Mary-Ann Fitzcharles (Division of Rheumatology, McGill University), Ian Freckelton (University of Melbourne), Eva Hoch (Ludwig Maximilian University of Munich), Jenny Martin (School of Medicine and Public Health, University of Newcastle), Rosalie Liccardo Pacula (RAND Drug Policy Research Center, RAND Corporation).

EMCDDA peer review and other contributions: Danilo Ballotta, Joanna De Morais, Roumen Sedefov, Anna Wcislo.

The EMCDDA national policy and legal correspondents contributed to the publication.

Sarah Yeates and Daniel Stjepanovic provided assistance in undertaking research for this review.

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About this publication

This report examines the evidence for, and practice of, making cannabis or cannabis-based medicines available for therapeutic purposes. This topic is of growing interest, not only because a number of European countries are developing policies in this area but also because the international framework may be changing following the recent review of cannabis by the WHO's Expert Committee on Drug Dependence.

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