thebmj

BMJ 2019;365:l1141 doi: 10.1136/bmj.l1141 (Published 4 April 2019)

PRACTICE

CLINICAL UPDATE

Medicinal use of cannabis based products and cannabinoids

Tom P Freeman *senior lecturer*[1 2 3 4], Chandni Hindocha *research fellow*[3 4 5], Sebastian F Green *academic foundation doctor*[4], Michael A P Bloomfield *UCL excellence fellow and consultant psychiatrist*[3 4 5 6 7]

[1]Addiction and Mental Health Group (AIM), Department of Psychology, University of Bath, UK; [2]National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK; [3]Clinical Psychopharmacology Unit, Research Department of Clinical, Educational & Health Psychology, University College London, UK; [4]Translational Psychiatry Research Group, Research Department of Mental Health Neuroscience, Division of Psychiatry, Faculty of Brain Sciences, University College London, UK; [5]NIHR University College London Hospitals Biomedical Research Centre, University College Hospital, London, UK; [6]Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Imperial College London, UK; [7]The Traumatic Stress Clinic, St Pancras Hospital, Camden & Islington NHS Foundation Trust, London, UK

What you need to know

- Cannabis based products for medicinal use contain cannabinoids derived from the cannabis plant, including Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), or a combination of THC and CBD. Synthetic cannabinoids for medicinal use typically mimic the effects of specific cannabinoids such as THC
- THC is the constituent of cannabis that causes the "high," whereas CBD is not intoxicating at typical doses. THC and CBD have contrasting mechanisms of action and therapeutic indications; THC carries a higher risk of adverse events compared with CBD
- Rescheduling on 1 November 2018 permits some unlicensed cannabis based products to be prescribed for the first time in the UK, but only by doctors on the relevant Specialist Register of the General Medical Council
- Indications for treatment, supported by evidence of low to moderate certainty, include chronic pain, some treatment resistant epilepsies, and nausea and vomiting caused by chemotherapy (table 2)
- Non-medicinal CBD products are legal and widely available on the internet and from health food retailers, but they lack quality standards and should not be used for medicinal purposes

Until recently, cannabis and its derivatives were widely restricted under legislation which stated they had no medical value and carried a substantial risk of misuse. Policy is rapidly changing, and cannabis can now be prescribed for medicinal use in many countries, including the UK. This provides important new opportunities for treating patients although these need to be weighed up against potential risks. Several different medicinal products exist, with contrasting mechanisms of action, efficacy, and safety. Use of these products may increase as new evidence arises and policy changes occur. Here we review this emerging field.

What are the latest developments in regulation, in the UK and internationally?

In the UK, drugs perceived by policy makers to have no medical value and a high risk of misuse, such as MDMA (3,4-methylenedioxy-methamphetamine, common street name "ecstasy") are placed in Schedule 1 of the Misuse of Drugs Regulations 2001. These drugs cannot be prescribed, and research can only be conducted under a Home Office licence.

On 1 November 2018, unlicensed cannabis based products were moved from Schedule 1 to Schedule 2 in the UK, enabling them to be prescribed for the first time.[1] This amendment of UK legislation affected some but not all products, as some were already listed in Schedule 2 or 4 (table 1). Non-medicinal synthetic cannabinoids (which are found in products such as "Spice") were not rescheduled and remain in Schedule 1. Cannabidiol (CBD) has minimal risk of misuse[5] and was never scheduled in the UK.

At the time of writing, in the US cannabis is available for medicinal use in 33 US states and for non-medicinal use in 10 US states, although both remain illegal under federal law. Other recent developments include the legalisation of cannabis for non-medicinal use in Canada on 17 October 2018. The World Health Organization has proposed that cannabis should be rescheduled within international law because of growing evidence of its medicinal applications.[6]

Correspondence to T Freeman t.p.freeman@bath.ac.uk

What types of product are available and where?

The cannabis plant can produce at least 144 naturally occurring compounds known as cannabinoids.[7] The most widely researched cannabinoids are Δ^9-tetrahydrocannabinol (THC) and CBD. THC is the primary constituent of cannabis that causes the "high" whereas CBD is not intoxicating at typical doses. Several different products exist for medicinal use and these differ in THC/CBD profile, formulation, licensed indications, and conditions for prescribing (table 1). See the glossary of terms (box 1) for accepted definitions.

Box 1: Key terms

- **Cannabinoid**—a drug that acts on the endocannabinoid system. The cannabis plant synthesises many cannabinoids such as THC and CBD
- **THC**—Δ^9-tetrahydrocannabinol, a cannabinoid used for medicinal purposes and non-medicinally for its intoxicating effects
- **CBD**—cannabidiol, a cannabinoid with contrasting mechanisms of action and therapeutic indications to THC. Not intoxicating at typical doses
- **Cannabis based products for medicinal use**—medicinal products containing cannabis or cannabinoids derived from the cannabis plant (eg, THC and/or CBD)
- **Synthetic cannabinoids for medicinal use**—medicinal products containing synthetically produced cannabinoids which typically mimic the effects of THC
- **Non-medicinal CBD products**—products containing CBD that are widely sold as herbal remedies but are not regulated as medicinal products
- **Non-medicinal cannabis**—material from the cannabis plant that is not regulated as a medicinal product, widely used for its intoxicating effects
- **Non-medicinal synthetic cannabinoids**—synthetic cannabinoids that are not structurally related to naturally occurring cannabinoids and are not currently recognised for medicinal use (eg, synthetic cannabinoid receptor agonists, which are found in products such as "Spice")

Cannabis based products for medicinal use

Cannabis based products that were previously listed in Schedule 1 can now be prescribed by doctors on the General Medical Council Specialist Register in the UK, on a named patient basis. Currently, general practitioners in the UK cannot prescribe them.

These products are not licensed for specific medical indications but are used off licence for medicinal purposes in many countries, and are certified for quality according to good manufacturing practice. Examples include herbal cannabis (floral material from the cannabis plant). The recommended route of administration is through a medical vapouriser device[9] and smoking is currently prohibited under NHS guidance.[10] Extracts from the cannabis plant (such as cannabis oils containing THC) are also available for oral administration.

Some cannabis based products were already available for medicinal use before rescheduling in 2018. Sativex, an oral spray derived from the cannabis plant containing THC and CBD in a 1:1 ratio, is licensed for the treatment of spasticity in multiple sclerosis in 29 countries, including the UK, Israel, Canada, Brazil, and Australia. However, meta-analysis suggests its effectiveness may be limited[11] and it is not recommended by the UK's National Institute for Health and Care Excellence (NICE) because of poor cost effectiveness.[12] Epidiolex, an oral CBD solution derived from the cannabis plant, was licensed by the US Food and Drug Administration in June 2018 for the treatment of seizures in two rare and severe forms of childhood epilepsy—Lennox-Gastaut syndrome and Dravet syndrome. At the time of writing, an application for the same indication is under review by the European Medicines Agency, and it can currently be prescribed on a named patient basis in the UK.

Synthetic cannabinoids for medicinal use

Dronabinol and nabilone are synthetically produced medicinal products that mimic the effects of THC. Dronabinol has an identical structure to THC, while nabilone has a related structure and is more potent than dronabinol, requiring lower doses to achieve clinical efficacy. Countries including the US, the Netherlands, Germany, Austria, and Croatia have licensed the use of both products. They are licensed for the treatment of weight loss in patients with AIDS and of nausea and vomiting in people receiving chemotherapy who have failed to respond adequately to conventional anti-emetics. Nabilone is licensed in the UK while dronabinol is not licensed but can be prescribed on a named patient basis.

Non-medicinal products

CBD products are also widely available in health food shops and on the internet in the UK and elsewhere (fig 1) and are not scheduled or regulated as medicines. Their THC or psychoactive content is legally controlled not to exceed 0.2% in the EU.[8] As with other herbal remedies, the declared contents of non-medicinal CBD preparations is variable, and often inaccurate,[2 13] and these products sometimes exceed the legal limit of THC.[13] Moreover, the amount of CBD in these products is typically far lower[14 15] than in clinical trials[16] (eg, 25 mg in a non-medicinal product versus 150-1500 mg/day in clinical trials). Advise patients that these widely available CBD products lack quality assurance and should not be treated as medicines.

Other products include non-medicinal cannabis and non-medicinal synthetic cannabinoids, which are both currently illegal in the UK.

Why and how are cannabis based products and cannabinoids therapeutic (or harmful)?

THC and CBD have contrasting mechanisms of action on the endocannabinoid system,[17 18] which is widely expressed in the mammalian central and peripheral nervous systems. These actions may account for their therapeutic effects. For example, CBD increased plasma endocannabinoid levels in a clinical trial in schizophrenia, which correlated with the degree of symptom improvement.[19] When taken together with THC, CBD may offset some of the adverse effects of THC, such as memory impairment and paranoia.[20 21] Therefore, the balance of THC and CBD may contribute to safety as well as therapeutic effects. CBD has an excellent safety profile and is well tolerated, even at high doses.[22] THC carries an increased risk of adverse events (including serious adverse events). In a systematic review and meta-analysis, cannabinoids (primarily THC) were associated with a fivefold increase in rates of disorientation and dizziness, compared with placebo or active comparators.[11]

What is the evidence underpinning medicinal use of cannabis based products and cannabinoids?

Table 2 summarises evidence from systematic reviews of cannabis based products and cannabinoids for the treatment of chronic pain, multiple sclerosis, treatment resistant epilepsy, and nausea and vomiting associated with chemotherapy.[11 23 24] There is less available evidence to estimate the effectiveness of these products for other indications, such as appetite and weight loss associated with HIV/AIDS, Tourette syndrome, anxiety, post-traumatic stress disorder, and schizophrenia.[11 26 27]

The limited number of randomised trials for unlicensed cannabis based products is partly attributable to the regulatory challenges of conducting research on drugs in Schedule 1.[28] Removing these barriers is an important benefit of rescheduling, which should lead to a stronger evidence base to guide clinical decision making. At the time of writing, the UK National Institute for Health Research (NIHR) has pledged dedicated funding and has called for grant proposals to investigate cannabis based products for medicinal use.

Limitations of current evidence include the inappropriate handling of withdrawals from treatment, selective reporting of outcomes, and inadequate descriptions of randomisation, allocation concealment, and blinding.[11] Heterogeneity in the types of product tested, including differences in pharmacokinetics and the balance of THC and CBD content, makes it difficult to establish optimal therapeutic formulations and dosing regimens. More larger and rigorous clinical trials are needed, including further exploration of dose-response and interactions with other medicines.[27] For example, both nabilone (THC) and epidiolex (CBD) may increase the effects of central nervous system depressants such as alcohol.[29 30] Epidiolex is metabolised by cytochrome P450 enzymes and may increase the risk of adverse effects from other medicines metabolised by this pathway, such as clobazam and valproate.[29]

How should doctors manage requests for cannabis based products and cannabinoids? (box 2)

Box 2: Managing requests for cannabis based products and cannabinoids

Consider

- Is this indication supported by evidence from randomised clinical trials? (table 2)
- What is the cannabinoid profile of the medicinal product being requested (THC, CBD, THC+CBD?)
- Is this medicinal product available, and who can prescribe it? (table 1)
- Might this medicinal product interact with other prescribed drugs?
- Are specific considerations necessary for young people, children and babies, older people, people with mental health problems, people with a learning disability, pregnant women, and women who are breastfeeding?
- If a prescription is not offered, might this patient seek or use a non-medicinal product lacking safety and quality assurance?

Guidelines are currently being prepared by NICE, which will initially focus on the indications listed in table 2. Interim guidance from England's Chief Medical Officer states that unlicensed cannabis based products can only be prescribed by doctors on the General Medical Council Specialist Register.[10] The same guidance also stipulates that doctors should prescribe products only for disorders within their specialty; when there is clear published evidence or UK guidelines to support treatment; when clinical need cannot be met by a licensed medicine; and when established treatment options have been exhausted. Additional guidance has been provided by the Royal College of General Practitioners[31] and NHS England.[32]

Within this framework, specialists in the UK will need authorisation from their medical director and agreement from the multidisciplinary team, using existing protocols on controlled drugs. Therefore, use of unlicensed cannabis based products in the UK may be limited initially, even in specialist settings. Active, compassionate, and fully informed engagement with patients requesting treatment remains important, and questions to consider are given in box 2. As this is a rapidly evolving field, seek confirmation from the relevant statutory authorities before changing practice.

Education into practice

- To what extent might it be stigmatising for a patient to request and use a cannabis based product, and how can this be managed?
- Are patients fully aware of the difference between medicinal and non-medicinal products, their legal status, and the risk of harm or prosecution associated with them?
- How can I record and share information from my practice on requests for, uses of, and responses to cannabis based products to ensure that future regulations and guidance better meet the needs of patients?

How this article was created

We used the most up to date and relevant information available to us from systematic reviews, meta-analyses, and key clinical trials. Summary statistics and grading of evidence were obtained from systematic reviews for indications included in forthcoming NICE guidelines. We referred to NICE, the Department for Health & Social Care, NHS England, the UK Home Office, and the Advisory Council for the Misuse of Drugs (ACMD). We discussed our article with clinicians, researchers, and patients.

How patients were involved in the creation of this article

We discussed our article with patients who had health conditions for which there is evidence that cannabis based products or cannabinoids may be effective. We conducted interviews with them asking what they thought would be helpful for patients and clinicians to learn from this article. We showed them drafts of this article and invited them to provide feedback which was incorporated into subsequent versions of the article. On the basis of this feedback, we adapted the structure of the article such that recent policy developments were presented first. We expanded our discussion of the differences between medicinal products and health food supplements, and added a new table to provide an accessible overview of these different products. We highlighted that some patients may seek unlicensed or illegal products if they are unavailable on prescription, and that requesting cannabis based products from a doctor and using them could be stigmatising.

Provenance: commissioned, peer reviewed.

Competing interests *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests:

TPF was funded by a senior academic fellowship from the Society for the Study of Addiction (SSA). MAPB is funded by a UCL Excellence Fellowship. MAPB, SFG, and CH are supported by the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre. The views expressed here are those of the authors, and do not reflect those of the SSA, the University of Bath, UCL, or NIHR. The funders had no role on the planning, researching, or writing of this report or in the decision to submit it for publication.

Further details of *The BMJ* policy on financial interests is here: https://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests

Contributorship statement and guarantor TPF had the idea for this article and wrote the first draft. All authors provided substantial contributions to the design of the work. CH, SFG, and MAPB wrote additional sections. Two anonymous patients suggested additional changes. All authors revised the article and approved the final version. As the guarantor, TPF affirms that the manuscript provides an honest, accurate, and transparent account of the issues covered, that there are no important omissions, and that there are no discrepancies between what was planned and the final version. All authors accept full responsibility for the work and the decision to publish.

Acknowledgments We thank two patients for their feedback on previous versions of this article. Both preferred to stay anonymous.

1 The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018 http://www.legislation.gov.uk/uksi/2018/1055/pdfs/uksi_20181055_en.pdf

2 Pavlovic R, Nenna G, Calvi L, etal . Quality traits of "cannabidiol oils": cannabinoids content, terpene fingerprint and oxidation stability of European commercially available preparations. *Molecules* 2018;23:1230. 10.3390/molecules23051230 29783790

3 Niesink RJ, Rigter S, Koeter MW, Brunt TM. Potency trends of Δ9-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005-15. *Addiction* 2015;110:1941-50. 10.1111/add.13082 26234170
4 Kalk NJ, Boyd A, Strang J, Finch E. Spice and all things nasty: the challenge of synthetic cannabinoids. *BMJ* 2016;355:i5639. 10.1136/bmj.i5639 27777237
5 Schoedel KA, Szeto I, Setnik B, etal . Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. *Epilepsy Behav* 2018;88:162-71. 10.1016/j.yebeh.2018.07.027 30286443
6 Mayor S. WHO proposes rescheduling cannabis to allow medical applications. *BMJ* 2019 https://www.bmj.com/content/364/bmj.l574.
7 Hanuš LO, Meyer SM, Muñoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. *Nat Prod Rep* 2016;33:1357-92. 10.1039/C6NP00074F 27722705
8 European Monitoring Centre for Drugs and Drug Addiction. Cannabis legislation in Europe: an overview. Publications Office of the European Union, Luxembourg, 2018. http://www.emcdda.europa.eu/publications/adhoc/cannabis-legislation-europe_en
9 Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther* 2007;82:572-8. 10.1038/sj.clpt.6100200 17429350
10 Department of Health & Social Care. Cannabis-based products for medical use. London, 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/753444/letter-with-guidance-on-cannabis-based-products-for-medicinal-use.pdf
11 Whiting PF, Wolff RF, Deshpande S, etal . Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015;313:2456-73. 10.1001/jama.2015.6358 26103030
12 National Institute for Health and Care Excellence. Do Not Do Recommendations: Sativex to treat spasticity in people with MS because it is not a cost effective treatment. 2014. https://www.nice.org.uk/donotdo/do-not-offer-sativex-to-treat-spasticity-in-people-with-ms-because-it-is-not-a-cost-effective-treatment.
13 Hazekamp A. The trouble with CBD oil. *Med Cannabis Cannabinoids* 2018;1:65-7210.1159/000489287.
14 Shannon S, Opila-Lehman J. Effectiveness of cannabidiol oil for pediatric anxiety and insomnia as part of posttraumatic stress disorder: a case report. *Perm J* 2016;20:16-005.27768570
15 Shannon S, Opila-Lehman J. Cannabidiol oil for decreasing addictive use of marijuana: a case report. *Integr Med (Encinitas)* 2015;14:31-5.26807069
16 Devinsky O, Patel AD, Thiele EA, etal. GWPCARE1 Part A Study Group. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology* 2018;90:e1204-11. 10.1212/WNL.0000000000005254. 29540584
17 Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol* 2008;153:199-215. 10.1038/sj.bjp.0707442 17828291
18 Curran HV, Freeman TP, Mokrysz C, Lewis DA, Morgan CJ, Parsons LH. Keep off the grass? Cannabis, cognition and addiction. *Nat Rev Neurosci* 2016;17:293-306. 10.1038/nrn.2016.28 27052382
19 Leweke FM, Piomelli D, Pahlisch F, etal . Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012;2:e94. 10.1038/tp.2012.15 22832859
20 Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. *Br J Psychiatry* 2010;197:285-90. 10.1192/bjp.bp.110.077503 20884951
21 Englund A, Morrison PD, Nottage J, etal . Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol* 2013;27:19-27. 10.1177/0269881112460109 23042808
22 Taylor L, Gidal B, Blakey G, Tayo B, Morrison G. A phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in healthy subjects. *CNS Drugs* 2018;32:1053-67. 10.1007/s40263-018-0578-5 30374683
23 Stockings E, Campbell G, Hall WD, etal . Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain* 2018;159:1932-54. 10.1097/j.pain.0000000000001293 29847469
24 Stockings E, Zagic D, Campbell G, etal . Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *J Neurol Neurosurg Psychiatry* 2018;89:741-53. 10.1136/jnnp-2017-317168 29511052
25 Guyatt GH, Oxman AD, Vist GE, etal. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. 10.1136/bmj.39489.470347.AD 18436948
26 The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. National Academies of Sciences E, Medicine. National Academies Press 2017.
27 European Monitoring Centre for Drugs and Drug Addiction. Medical use of cannabis and cannabinoids: questions and answers for policymaking. Publications Office of the European Union, Luxembourg, 2018. http://www.emcdda.europa.eu/system/files/publications/10171/20185584_TD0618186ENN_PDF.pdf
28 Freeman TP, Mehta MA, Neill JC, Nutt DJ, Tunbridge EM, Young AH. Restrictions on drugs with medical value: Moving beyond stalemate. *J Psychopharmacol* 2018;32:1053-5. 10.1177/0269881118798609 30278146
29 Highlights of prescribing information: EPIDIOLEX. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf.
30 emc. Nabilone 1mg capsules. 2014. https://www.medicines.org.uk/emc/product/6176/smpc.
31 Royal College of General Practitioners. Cannabis-based medicines: an interim desktop guide 2018. https://www.rcgp.org.uk/clinical-and-research/resources/a-to-z-clinical-resources/cannabis-based-medication.aspx
32 NHS England. Cannabis-based products for medicinal use. https://www.england.nhs.uk/medicines/support-for-prescribers/cannabis-based-products-for-medicinal-use/.

Tables

Table 1| An overview of cannabis based products and cannabinoids

	Medicinal products						Non-medicinal products		
	Cannabis based products for medicinal use				Synthetic cannabinoids for medicinal use		Non-medicinal CBD products	Non-medicinal cannabis	Non-medicinal synthetic cannabinoids
Example	**Bedrocan**	**Tilray**	**Sativex**	**Epidiolex**	**Dronabinol**	**Nabilone**	**CBD oil[2]**	**White Widow[3]**	**Spice[4]**
Cannabinoid profile	THC +/−CBD	THC +/−CBD	THC:CBD ratio 1:1	CBD	THC	THC	High CBD, low THC	High THC, low CBD	Synthetic cannabinoid receptor agonists
Formulation	Herbal cannabis	Oil	Oromucosal spray	Oral solution	Capsule or liquid	Capsule	Varied; capsule and oil	Varied; herbal cannabis	Herbal, liquid, or powder
Licensed indications (UK)	None	None	Multiple sclerosis	None	None	Chemotherapy induced nausea and vomiting	Not medicinal products		
Quality standards	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	No quality assurance		
Affected by rescheduling (UK) on 1 November 2018?	Yes	Yes	No	No	No	No	No	No	No
Pre-amendment Schedule (UK)	1	1	4	Not scheduled	2	2	Not scheduled (if THC does not exceed 0.2%)	1	1
Post-amendment Schedule (UK)	2	2	4	Not scheduled	2	2	Not scheduled (if THC does not exceed 0.2%)	1	1
Can be prescribed in the UK?	Doctors on General Medical Council specialist register; named patient basis	Doctors on General Medical Council specialist register; named patient basis	Specialist doctors with expertise in treating multiple sclerosis	No restrictions on prescribing; named patient basis. Likely to be a specialist prescribing due to the proposed indications	No restrictions on prescribing; named patient basis	No restrictions on prescribing. Preferably administered in a hospital setting. GPs may prescribe once treatment initiated	No	No	No

Table 2| Summary of evidence for medicinal use of cannabis based products and cannabinoids.

Indication	Number of studies (participants)	Primary products tested	Comparator	Outcome	Summary estimate (95% confidence interval)	GRADE certainty rating
Chronic pain[23]	9 (1734)	Sativex (THC+CBD)	Placebo	30% reduction in pain	Odds ratio: 1.46 (1.16 to 1.84). More effective than placebo	⊕⊕⊕◯ Moderate
Multiple sclerosis[11]	5 (1244)	Sativex (THC+CBD)	Placebo	Ashworth spasticity scale	Weighted mean difference: −0.12 (−0.24 to 0.01). Not more effective than placebo	⊕⊕⊕◯ Moderate
Treatment resistant epilepsy[24]	2 (291)	Epidiolex (CBD)	Placebo	50% reduction in seizure frequency	Relative risk: 1.74 (1.24 to 2.43). More effective than placebo	⊕⊕◯◯ Low
Nausea and vomiting due to chemotherapy[11]	3 (102)	Dronabinol (THC)	Placebo	Complete response in nausea and vomiting	Odds ratio: 3.82 (1.55 to 9.42). More effective than placebo	⊕⊕◯◯ Low

Grading of recommendations, assessment, development, and evaluations (GRADE)[25]

⊕⊕⊕⊕ High, the authors have a lot of confidence that the true effect is similar to the estimated effect

⊕⊕⊕◯ Moderate, the authors believe that the true effect is probably close to the estimated effect

⊕⊕◯◯ Low, the true effect might be markedly different from the estimated effect

⊕◯◯◯ Very low, the true effect is probably markedly different from the estimated effect

Figure

Fig 1 Non medicinal CBD products are widely available