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# Access to cannabidiol without a prescription: A cross-country comparison and analysis

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ABSTRACT

*Background:* Recent legislative change has allowed increased access to cannabis products in many jurisdictions. In some locations, this includes over-the-counter (OTC) and/or online access to products containing cannabidiol (CBD), a non-intoxicating cannabinoid with therapeutic properties. Here we compared the availability of CBD products and the associated legislative and regulatory background in nine selected countries.

*Methods:* Accessibility of CBD products was examined in the USA, Canada, Germany, Ireland, United Kingdom, Switzerland, Japan, Australia, and New Zealand as of May 2020. Regulatory and other relevant documents were obtained from government agency websites and related sources. Relevant commercial websites and some physical retailers were visited to verify access to CBD-containing products and the nature of the products available.

*Results:* A range of CBD products appeared to be accessible without prescription in seven out of nine countries reviewed. Australia and New Zealand were the exceptions where clinician prescription was required to access any CBD-containing product. CBD products commonly available without prescription included oils, gel capsules, purified crystal and topical products. The daily recommended doses with orally administered non-prescription products were typically well below 150 mg and substantially lower than the doses reported to have therapeutic effects in published clinical trials (e.g., 300-1500 mg). The legal foundations enabling access in several countries were often unclear, with marketed products sometimes failing to meet legal requirements for sale. There was an obvious disparity between federal directives and available products in both the USA and European countries examined.

*Conclusions:* There are a variety of approaches in how countries manage access to CBD products. Many countries appear to permit OTC and online availability of CBD products but often without legislative clarity. As consumer demand for CBD escalates, improved legislation, guidelines and quality control of CBD products would seem prudent together with clinical trials exploring the therapeutic benefits of lower-dose CBD formulations.

## Introduction

Cannabidiol (CBD) is a non-intoxicating cannabinoid found in the *Cannabis sativa* plant. Scientific and community interest in CBD has expanded dramatically in recent times (Leas, et al., 2019) with pre-clinical and clinical studies demonstrating efficacy in the treatment of conditions such as epilepsy (Devinsky, et al., 2017; Thiele, et al., 2018), anxiety (Linares, et al., 2019; Zuardi, et al., 2017), psychosis (Leweke, et al., 2012; McGuire, et al., 2018) and chronic pain (Costa, Trovato, Comelli, Giagnoni, & Colleoni, 2007). Despite their striking chemical similarity, CBD lacks the distinctive psychotropic and intoxicating effects of $\Delta^9$-tetrahydrocannabinol (THC), and serious side effects involving CBD appear rare (Chesney, et al., 2020; Larsen & Shahinas, 2020; Millar, et al., 2019; Spindle, et al., 2020;

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**Table 1**
Most popular websites by country allowing online access to CBD products without a prescription

| Region | Online availability | Top search engine items in region of interest | Website URL | No. CBD products | Type of CBD-only product available | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Oil/ tincture | Capsule | Topical | Edible | Plant | Vaping oil | Crystals | Pet product |
| **USA** | Yes, many | Pure Kana | purekana.com | 51 | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| | | Direct CBD Online† | directcbdonline.com | >100 | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ |
| | | Premium Jane | premiumjane.com | 24 | ✓ | ✓ | ✓ | ✓ | | | | |
| **Canada** | Yes, few | Ontario Cannabis Store† | ocs.ca | >100 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| | | CBD Oil Canada† | cbd-oil-canada.ca | >100 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | Herb Approach† | herbapproach.com | >100 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Germany** | Yes, few | CBD Shop 24† | cbdshop24.de | 80 | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | CBD Welt† | cbdwelt.de | 34 | ✓ | | ✓ | | | ✓ | | |
| | | CBD Deal 24† | cbd-deal24.de | >100 | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ |
| **Ireland** | Yes, few | CBD Store† | cbdstore.ie | 39 | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| | | The CBD Store† | thecbdstore.ie | 32 | ✓ | ✓ | | ✓* | | ✓ | | |
| | | CBD Ireland Online† | cbdirelandonline.ie | 9 | ✓ | | ✓ | | | | | |
| **United Kingdom** | Yes, few | CBD.co.uk† | cbd.co.uk | >100 | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| | | Flawless CBD Shop† | flawlesscbd.co.uk | >100 | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ |
| | | Ice Head Shop† | iceheadshop.co.uk | >100 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| **Switzerland** | Yes, few | Hanfpost† | hanfpost.ch | >100 | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | Marry Jane | marryjane.ch | 29 | ✓ | | | | ✓ | | ✓ | |
| | | CBD420 | cbd420.ch | 25 | ✓ | | ✓ | | ✓ | ✓ | ✓ | |
| **Japan** | Yes, limited | Healthy Tokyo† | healthytokyo.com | 20 | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| | | CBD Online† | cbd-online.jp | 25 | ✓ | | ✓ | ✓ | | ✓ | ✓ | |
| | | Cannapresso Japan | cannapresso-cbd.shop-pro.jp | 11 | ✓ | | | | | ✓ | ✓ | |
| #**Australia** | No | | | | | | | | | | | |
| #**New Zealand** | No | | | | | | | | | | | |

For search methods used, please see Methods section. Note that products listed here have not been confirmed as available via actual purchase.
† Store is a distributor.
* Only total phytocannabinoid content reported.
# CBD products available on prescription only.

Taylor, Crockett, Tayo, Checketts, & Sommerville, 2020; Therapeutic Goods Administration, 2020). The various therapeutic actions of CBD reported in clinical trials are typically seen at oral doses of 300-1500 mg (Millar, et al., 2019) with doses of up to 6000 mg reasonably well-tolerated (Taylor, Gidal, Blakey, Tayo, & Morrison, 2018).

Many countries now permit over-the-counter (OTC) or online access to a variety of CBD products. These products are often extracts of the flowering heads of CBD-dominant "industrial hemp" cultivars that are also grown for seed and fibre. These products come in multiple forms and commonly include CBD oils and tinctures, gel capsules, purified CBD crystal, and balms and lotions for topical application. Other accessible CBD products include chewing gum, lozenges, "gummy bears", sports drinks and pet products. Some European countries also have retail outlets selling CBD-dominant cannabis plant material known as "light cannabis" that is smoked or vaporised in the same way as traditional cannabis (Pichini, et al., 2019). High concentration CBD "vape oils" for use in e-cigarette devices are also available in some countries (Table 1). It should be noted that these CBD-containing products are distinct from hemp seeds, hemp seed protein and hemp seed oil, which usually contain negligible THC/CBD concentrations, reflecting the absence of cannabinoids in cannabis seed (although cannabinoid contamination of hemp seed products from the surrounding hull can sometimes occur (Ross, Mehmedic, Murphy, & Elsohly, 2000)).

Non-prescription CBD products appear to involve relatively low daily doses of CBD as would be obtained with products such as capsules containing 10-50 mg CBD or oils of 50-100 mg/mL concentration that are dosed at a few drops per day. This would suggest that use of non-prescription products produces doses that are well below those identified as effective in clinical trials (Millar, et al., 2019). However, it is also worth noting that the accuracy of the labelling of such products has been called into question by several recent analyses meaning that the actual CBD doses taken by patient may sometimes be larger (or smaller) than intended, and that other cannabinoids, particularly THC, may be present in greater quantities than labelling suggests (Bonn-Miller, et al., 2017; Hazekamp, 2018; Lachenmeier, et al., 2019; Liebling, Clarkson, Gibbs, Yates, & O'Sullivan, 2020; Pavlovic, et al., 2018).

At the same time as non-prescription products have proliferated, the prescription-only CBD medication Epidiolex™ has received marketing approval by regulatory agencies worldwide including the Food Drug Administration (FDA) and European Medicines Agency (EMA). Epidiolex™ is an oil containing 100 mg/mL CBD and is approved for the treatment of various rare forms of paediatric epilepsy following successful Phase 3 trials (Devinsky et al., 2017; Thiele et al., 2018). Epidiolex™ is typically administered at doses of around 20 mg/kg/day (e.g., 800 mg total daily dose of CBD in a 40 kg child) (Thiele, et al., 2018). Many countries also have the THC/CBD containing buccal spray nabiximols (Sativex™) available on prescription for the treatment of spasticity in Multiple Sclerosis (MS). This is a 1:1 ratio formulation of CBD and THC and a typical daily dose for MS includes 8 - 16 sprays, delivering only around 20-40 mg CBD in total (Rice & Cameron, 2018).

In January 2019, the World Health Organization (WHO) via its Expert Committee of Drug Dependence proposed changes to the scheduling of CBD-containing and other non-THC containing cannabis preparations (Adhanom, 2019; WHO, 2019). Specifically, it was stated that CBD preparations should not be subject to international drug control as CBD is not intoxicating, is generally well tolerated, with no evidence of problematic use or associated public health concerns (WHO, 2017b; WHO, 2019). The therapeutic value of CBD in childhood epilepsy was also recognised (WHO, 2019). Clarification regarding the absence of scheduling of CBD is proposed to be achieved through a footnote to the "Cannabis and Cannabis Resins" section of the International Drug Control Conventions as follows: *"preparations containing predominately cannabidiol and not more than 0,2 percent of delta-9-tetrahydrocannabinol are not under international control"*. This proposal was later further clarified to state that "*the percentage of CBD to be used in practice could be left to individual Member States*". The United Nations

(UN) has delayed voting on the recommendation (Somerset, 2019), while acknowledging that CBD products are available in many countries, and that "*Member States can regulate its availability using their own national legislation*".

There has been an obvious transition in the regulation and availability of CBD products in many countries. In a WHO survey of member states published in 2017 (WHO, 2017a), only four of 45 respondents (countries unspecified) reported that CBD was being used as a non-medical product (e.g., dietary supplement or food product) in their country. Three years later, it is evident that a wide variety of OTC and online CBD products can be accessed in many jurisdictions, although the legality of such products is not always clear. For example, at the time of writing, the website of well-known health food and nutraceutical retailer *Holland and Barrett* allowed the instant online purchase and delivery of numerous CBD products to 29 different European countries. A cross-country policy analysis of CBD has been lacking, despite the obvious worldwide escalation in CBD use (Brightfield Group, 2019; Gibbs, Yates, & Liebling, 2019), with forecasts of a global market worth $US17 billion by 2026 (Fior Markets, 2019). Here we systematically investigated between-country variations in the legislative approach to CBD and its availability without prescription. Our focus was on a number of developed countries selected from the European, North American and Asia-Pacific regions. We also examined the nature of available products, the likely dose that they supply, and the evidence supporting therapeutic benefits of such doses.

## Methods

We identified developed countries, representative of specific geographic regions, where information around consumer access to CBD products was available. Some countries were chosen because of visits by the authors confirming availability of CBD products without prescription in retail outlets. Other countries included were the authors' home countries (Australia, United Kingdom (UK) and New Zealand). The countries included were: the United States of America (USA) and Canada (North America); Germany, Ireland and the UK (European Union (EU) countries); Switzerland (European non-EU country); Japan, Australia and New Zealand (Asia-Pacific). In the USA a single state, Kansas, was used to explore state-federal variation in legislative approaches.

Information on the regulatory status of CBD was sought primarily from regulatory websites and other information in the public domain. Regulators were sometimes contacted to clarify the information. To identify readily available CBD products, information on available products was sought from the most popular websites providing CBD products to that country (see Tables 1 and 2). For this, an internet search engine (Google) was adjusted with region settings to limit searching to each country of interest with the search term "CBD online". The top three online shopping search results with available items for purchase were included for each country in Tables 1 and 2. Table 2 also includes information on the highest dose CBD products available on each website, and the recommended dose, where such information was available. The websites were originally accessed 27$^{th}$ March 2020 and then updated 20$^{th}$ May 2020. Physical retailers were visited in Germany, UK, Switzerland and Japan, although these visits were not undertaken in a systematic fashion. A summary overview of CBD availability via prescription and non-prescription sources for the nine countries of interest is presented in Table 3.

In considering the therapeutic benefits of lower doses of CBD we defined a low dose of CBD as 150 mg CBD/day, or 2.5 mg/kg in a 60 kg adult, based on our initial understanding of the likely maximal daily doses provided by currently available non-prescription products. A recent analysis of dosing in clinical trials with CBD showed successful therapeutic outcomes at dosing of around 14-23 mg/kg/day (Millar, et al., 2019). We conducted a literature review of studies involving lower doses of CBD, informed by the recent analysis by the Therapeutic Goods Administration of Australia (Therapeutic Goods Administration, 2020), to assess the available evidence that CBD doses $<$ 150 mg have therapeutic efficacy. This analysis is presented in Table 4.

## Results

### *USA*

In the USA, both federal and state legislation affect the availability of CBD and other cannabis products, with legislation in both domains having evolved significantly in recent years. There is currently legal access to medicinal cannabis products (including both THC and CBD-containing products) in 33 states and the District of Columbia while 15 states have medical programs permitting access to CBD products only (FDA, 2019b). Eleven states and the District of Columbia have also legalised cannabis for non-medical use while a further 16 have decriminalised the possession of non-medical cannabis.

Epidiolex™ is the only CBD product that is currently marketed as a prescription medication in the USA (Table 3), after being approved by the FDA in 2018 for the treatment of Dravet Syndrome and Lennox-Gastaut Syndrome. Sativex™, on the other hand, has yet to obtain FDA approval.

Non-prescription products are readily available in drug stores in many USA states and online purchases with home delivery are also widely available. For example, Walgreens, a major pharmacy chain, has CBD patches, sprays and creams available in more than 1500 stores in 9 states across the USA (LaVito, 2019). In addition, CBD-containing strains of cannabis are widely available in dispensaries in States with non-medical and medicinal cannabis availability. Examples of online products are presented in Tables 1 and 2: these include capsules, edibles, oils, CBD crystal, vaping oils and pet products. Even the highest strength orally administered products identified tended to involve daily CBD doses of less than 100 mg.

The legal status of non-prescription CBD products in the USA is not entirely clear. At a federal level, the Drug Enforcement Agency (DEA) still defines cannabis as a Schedule 1 controlled substance (a drug with high potential for abuse and no acknowledged medical use). In 2018, however, they made an exception for "finished dose formulations" of CBD that contain $<$ 0.1% THC and are approved by the FDA. These products are now captured by the less restrictive Schedule V of the Controlled Substances Act, allowing Epidiolex™ to be marketed for medical use and prescribed (Drug Enforcement Agency, 2018). At the same time Federal and State-level legislative changes were made with an intent to restore traditional agricultural and commercial activity involving hemp products (FDA, 2019b). The *Agriculture Improvement Act* (2018) removed hemp (the plant, parts of the plant or cannabis derivatives with $<$ 0.3% of THC by dry weight) from controlled substance status, making broad commercial cultivation, production and sale of hemp-derived products legal across the USA. Despite these developments, confusion and complexity around the legality of CBD as a non-prescription product continues (Corroon & Kight, 2018; Grinspoon, 2018). This largely arises because the FDA retains legal authority over hemp-derived CBD products available without a prescription.

Food additives need to be approved by the FDA unless exempted via a "generally recognised as safe" (GRAS) classification: but this has only occurred for hulled hemp seeds, hemp seed protein, and hemp seed oil (FDA, 2019b). The FDA has stated that "*CBD and THC cannot lawfully be added to a food or marketed as a dietary supplement*" (FDA, 2019b) and asserts jurisdiction where compounds derived from cannabis, including CBD, are "*added to a food or cosmetic, marketed as a drug, or otherwise added to an FDA-regulated product in interstate commerce*" (Sharpless, 2019). This was reiterated in November 2019 when the FDA stated "*It is currently illegal to market CBD by adding it to a food or labeling*

**Table 2**
Details of the highest dose, orally-administered, CBD products available on most popular websites.

| Region | Top search engine items in region of interest | Website URL | Highest Dose Oral Products | | | | |
|---|---|---|---|---|---|---|---|
| | | | Product | Recommended daily serving[††] | CBD amount in rec. serving[†††] | Unit size | Price |
| **USA** | Pure Kana | purekana.com | 25 mg capsule/edible | 1-2 edible | 25-50 mg | 20 edibles | 40.00-83.00 USD |
| | | | 83.3 mg/mL oil | 0.5 dropper x 1-2 | 41.7-83.3 mg | 60 mL | 390.00 USD |
| | Direct CBD Online[†] | directcbdonline.com | 50 mg capsule | - | - | 10-200 edibles | 1.79-2.50 USD/ edible |
| | | | 250 mg/mL oil | - | - | 30 mL | 339.99 USD |
| | | | "100%" crystal | - | - | 5-200g | 74.99-2,399.99 USD |
| | Premium Jane | premiumjane.com | 25 mg capsule/edible | 2 edibles | 50 mg | 30 units | 55.00-75.00 USD |
| | | | 33.3 mg/mL oil | 0.5 dropper x 1-2 | 25-50 mg | 30 mL | 124.00 USD |
| **Canada** | Ontario Cannabis Store[†] | ocs.ca | 20 mg capsule | - | - | 15 units | 42.95 CAD |
| | | | 26 mg/mL oil | - | - | 20 mL | 75.50 CAD |
| | CBD Oil Canada[†] | cbd-oil-canada.ca | 50 mg capsule | - | - | 10 capsules | 60.00 CAD |
| | | | 300 mg/mL oil | - | - | 1 mL | 60.00 CAD |
| | Herb Approach[†] | herbapproach.com | 200 mg/mL oil | 5-10 mg x 2 | 10-20 mg | 1 mL | 40.00-60.00 CAD |
| | | | 99% isolate crystal | 5-10 mg x 2 | 10-20 mg | 1 g | 80.00 CAD |
| **Germany** | CBD Shop 24[†] | cbdshop24.de | 5 mg edible | 1 edible | 5 mg | 14 edibles | 4.10-4.35 EUR |
| | | | 250 mg/mL oil | 1-3 drops x 3 | 37.7-112.5 mg | 10 mL | 104.99 EUR |
| | | | 99% crystal | - | - | 1g | 38.99 EUR |
| | CBD Welt[†] | cbdwelt.de | 270 mg/mL oil | - | - | 10 mL | 118.90 EUR |
| | CBD Deal 24[†] | cbd-deal24.de | 270 mg/mL oil | - | - | 10 mL | 118.90 EUR |
| | | | 500 mg/mL paste | - | - | 5 mL | 137.00 EUR |
| | | | 99% crystal | - | - | 1 g | 69.99 EUR |
| **Ireland** | CBD Store[†] | cbdstore.ie | 50 mg capsule | - | - | 30 capsules | 116.10 EUR |
| | | | 150 mg/mL oil | - | - | 10 mL | 116.10 EUR |
| | The CBD Store[†] | thecbdstore.ie | 50 mg/mL oil | 2 drops x 2 | 10 mg | 30 mL | 109.00 EUR |
| | CBD Ireland Online[†] | cbdirelandonline.ie | 200 mg/mL oil | 1-3 drops x 2-3 | 20-90 mg | 10 mL | 99.00 EUR |
| **United Kingdom** | CBD.co.uk[†] | cbd.co.uk | 25 mg edible | 1-2 edibles | 25-50 mg | 5-20 edibles | 12.50-34.99 GBP |
| | | | 33 mg/mL oil | 1 mL | 33 mg | 30 mL | 100.00 GBP |
| | Flawless CBD Shop[†] | flawlesscbd.co.uk | 30 mg edible | 1 edible x 1-2 | 30-60 mg | 25 edibles | 40.00 GBP |
| | | | 400 mg/mL oil | - | - | 10 mL | 199.99 GBP |
| | | | 99% crystal | - | - | 0.5 g | 34.99 GBP |
| | Ice Head Shop[†] | iceheadshop.co.uk | 920 mg/mL oil | - | - | 1 mL | 34.99 GBP |
| | | | 99% crystal | - | - | 25 g | 112.50 GBP |
| **Switzerland** | Hanfpost[†] | hanfpost.ch | 5 mg edible | - | - | 14 edibles | 6.90 CHF |
| | | | 300 mg/mL oil | - | - | 10 mL | 129.90 CHF |
| | | | 99.8% crystal | - | - | 1 g | 44.90 CHF |
| | Marry Jane | marryjane.ch | 300 mg/mL oil | - | - | 10 mL | 129.90 CHF |
| | | | 99.8% crystal | - | - | 1 g | 44.90 CHF |
| | CBD420 | cbd420.ch | 150 mg/mL oil | - | - | 10 mL | 94.91 EUR |
| | | | 99.9% crystal | - | - | 1 g | 85.17 EUR |
| **Japan** | Healthy Tokyo[†] | healthytokyo.com | 50 mg capsules | 1-2 capsules | 50-100 mg | 30 capsules | 29,160 JPY |
| | | | 60 mg/mL oil | 0.5 mL x1-2 | 30-60 mg | 20 mL | 19,500 JPY |
| | CBD Online[†] | cbd-online.jp | 240 mg/mL oil | 5-10 drops x2 | 120-240 mg | 10 mL | 38,000 JPY |
| | | | 99.6% crystal | - | - | 1 g | 14,800 JPY |
| | Cannapresso Japan | cannapresso-cbd.shop-pro.jp | 200 mg/mL oil | 1-2 drops x2-3 | 20-60 mg | 10 mL | 26,900 JPY |
| | | | 99.6% crystal | 0.1 g | 100 mg | 1 g | 9,500 JPY |

For search methods used, please see Methods section. Note that products listed here have not been confirmed as available via actual purchase.
⁻ Information not available.
[††] Recommended daily serving was based on provided recommendations on product page, when available.
[†††] Total CBD daily serving. Estimated based on 0.05 mL per drop.

*it as a dietary supplement*" (FDA, 2019b).

Furthermore, the FDA has noted the marketing of some CBD products with unproven medical claims and of unknown quality and a potential for harm. Accordingly the FDA has issued warning letters to manufacturers for marketing CBD as a dietary supplement when it does not meet the criteria for a dietary supplement, and/or makes unsubstantiated therapeutic claims for CBD products (FDA, 2019a). Despite this, the CBD "gold rush" continues apace in the USA, with a profusion of products and State-level legislation seeming to conflict with federal legislative imperatives, although, in some cases, causing considerable confusion.

The state of Kansas provides an example of this. Cannabis laws in Kansas have historically been amongst the most restrictive in the USA. In mid-2018 a law was passed to exclude CBD from the definition of "marijuana", so that it was no longer a controlled substance, while THC remained illegal (Kansas State, 2018). Products purporting to be pure CBD quickly proliferated throughout Kansas. Additional legislation to create a commercial industrial hemp program came into effect on 1 July 2019, easing restrictions on hemp cultivation and the processing of CBD from hemp (Kansas State, 2019). This legislation appeared to permit

**Table 3**
Summary of Current Regulatory and Legal Status of CBD across Relevant Countries

| Country | Medical Cannabis Scheme? | CBD-Containing Prescription Medicines Available? Epidiolex™ | Sativex™ | Other | Non-prescription CBD products? | THC limits in non-prescription CBD products |
|---|---|---|---|---|---|---|
| **USA** | ✓[1] | ✓ | - | Varies by state | ✓[2] | Varies by state[1]. Hemp federally defined as <0.3% w/w THC. |
| **Canada** | ✓ | - | ✓ | Multiple CBD-containing products can be accessed with authorisation | ✓ | 1 g THC/package, 10 mg THC/serving. |
| **Germany** | ✓ | ✓ | ✓ | Multiple CBD-containing products can be prescribed | ✓ | Hemp defined as <0.2% w/w THC.[3] |
| **Ireland** | ✓ | - | ✓ | Multiple CBD-containing products can be prescribed | ✓ | Hemp defined as <0.2% w/w THC.[3] |
| **United Kingdom** | ✓ | ✓ | ✓ | Multiple CBD-containing products can be prescribed | ✓ | Hemp defined as <0.2% w/w THC.[3] |
| **Switzerland** | ✓ | - | ✓ | Compounding pharmacy CBD formulations can be prescribed | ✓ | 1.0% THC total. |
| **Japan** | - | - | - | - | ✓ | NO THC permittedo THC is listed as a narcotic. None permitted. |
| **Australia** | ✓ | - | ✓ | Multiple CBD-containing products can be prescribed | -[4] | - |
| **New Zealand** | ✓ | - | ✓ | Multiple CBD-containing products can be prescribed | - | - |

[1] Medicinal cannabis not federally legal, legality varies by state. See USA section.
[2] Not explicitly federally legal, legality varies by state. See USA section.
[3] The European Food Safety Authority has set the acute reference dose of THC at 1 μg/kg body weight, stating as highest dose that can be consumed without adverse effect (EFSA, 2015); however, this is not an official limit.
[4] Currently under review by Therapeutic Goods Administration, subject to change.



**Table 4**
Clinical trials and case studies including low dose range (< 150 mg) CBD treatment

| Author | Indication, Measure | Design (n) | CBD doses | Outcome | Low dose CBD effect? (i.e. < 150 mg) |
|---|---|---|---|---|---|
| Zuardi et al. (2017) | Anxiety, public speaking task | RCT (n=23) | 100, 300 or 900 mg (oral) | 300 mg CBD decreased anxiety | No |
| Linares et al. (2019) | Anxiety, public speaking task | RCT (n=57) | 150, 300 or 600 mg (oral) | 300 mg CBD decreased anxiety | No |
| Karniol, Shirakawa, Kasinski, Pfeferman, and Carlini (1974) | Cognitive function, Time estimate | RCT (n=40) | 15, 30 or 60 mg (oral) | CBD attenuated THC-induced pulse rate acceleration and other effects. CBD alone had no effect | No |
| Naftali et al. (2017) | Crohn's Disease, Crohn's Disease Activity Index | RCT (n=19) | 10 mg (sublingual; 2 mL of 5 mg/mL in olive oil) twice per day; 56 days | 20 mg CBD had no effect on Crohn's Disease Activity Index | No |
| Lopez et al. (2020) | Multiple outcomes | RCT (n=68) | 15 mg (oral) per day; 42 days | 15 mg CBD increased HDL cholesterol | Yes |
| Carlini and Cunha (1981) | Insomnia | RCT (n=15) | 40, 80 or 160 mg (oral) | 160 mg CBD increased self-reported sleep duration | No |
| Tomida et al. (2006) | Intraocular pressure (IOP) | RCT (n=6) | 20 or 40 mg (sublingual) | 40 mg CBD transiently increased IOP | Yes |
| Chagas et al. (2014) | Parkinson's disease | Case series (n=4) | 75 or 300 mg (oral) per day; 42 days | 300 mg CBD reduced symptoms of rapid eye movement sleep behaviour disorder | No |
| Notcutt et al. (2004) | Chronic Pain; visual analogue scale, quality and quantity of sleep | Case series (n=34) | Repeated 2.5 mg oral sprays titrated per individual. Median dose 18.25 mg. 7 days, twice. | CBD alone was not significantly better than placebo at reducing pain, but improved self-reported quality of sleep | Yes (sleep) |
| Shannon and Opila-Lehman (2016) | Paediatric anxiety and insomnia | Case report (n=1) | 25 mg (oral) per day; 5 months | CBD improved subjective sleep quality | Yes |
| Shannon, Lewis, Lee, and Hughes (2019) | Anxiety and sleep, Hamilton Anxiety Rating Scale and Pittsburg Sleep Quality Index | Case series (n=72) | 25-175 mg/day (oral) | Anxiety and sleep improved for most patients, but no statistical analysis was presented | Uncertain |

*Abbreviations:* RCT = randomised placebo-controlled trial with parallel groups.

"*the production, use or sale of any hemp product that is otherwise not prohibited by state or federal law*" with prohibition maintained for cigarettes, cigars, teas, and vaping products (Kansas State, 2019). The press reported conflicting opinions of a Kansas state senator who insisted the legislative intent of the July 2019 laws was to make "full spectrum" CBD oils (i.e. hemp extracts containing CBD in conjunction with other phytocannabinoids and terpenes) lawfully available, whereas senior Kansas law enforcement officials issued warnings on social media that this was not the case. Despite these uncertainties in legislative frameworks, there is an ongoing proliferation of CBD products (both with and without THC) across Kansas retail stores with such products readily obtained by consumers (Llopis-Jepsen, 2019).

*Canada*

Legislation governing access to medicinal cannabis in Canada was first introduced in 1999 and has evolved through many stages, culminating in the legalisation of cannabis for both medical and non-medical uses in October 2018 via the *Cannabis Act*. Canada is the second country in the world, following Uruguay, to legalise the non-medical use of cannabis, with persons over the age of 18 legally permitted to possess and share up to 30 grams of cannabis (Department of Justice (Canada), 2020). Additional minimum age-related restrictions have a been implemented at a Provincial level that range from 18 (e.g., Alberta) to 21 (e.g., Quebec).

All cannabis products, including those containing CBD, are legally controlled, with the production, distribution and sale of such products requiring a federal licence (Health Canada, 2018, 2019a). Licensees must adhere to stringent production, testing, packaging and promotional standards, that are enforced by Health Canada (Health Canada, 2019b). Compliance and enforcement tools include inspections (whether scheduled or ad hoc), audits, product recalls, as well as administrative monetary penalties and licence suspension or removal. An update to the *Cannabis Act* that came into effect 17 October 2019 extended the range of available non-medical products from dried and fresh cannabis and oils, to include edibles (including food products and drinks), topicals, and extracts (Health Canada, 2019b).

Cannabis and cannabinoid products involve three different categories. The first category, "Health Products with Cannabis", involves conventional prescribed cannabinoid products such as the THC/CBD buccal spray nabiximols (Sativex™;Table 3). These are regulated under both the *Food and Drugs Act* and *Cannabis Act*, and require a prescription for access. Such products undergo pre-market review for safety, efficacy and quality, as with any conventional prescription medication, and this is the only category that enables marketing of cannabis products with authorised health claims.

The second category, "Cannabis for Medical Purposes", includes the medicinal cannabis products that have been available to Canadian patients for many years through the previous federal medicinal cannabis legislation (*Access to Cannabis for Medical Purpose Regulations*). This scheme allows health practitioners to authorise a patient to access a range of products directly from licenced producers, not all of which are available through the legal non-medical access schemes described below. Many relatively high-dose CBD products are available through this scheme, including a range of THC/CBD containing dried cannabis and oils with various THC/CBD ratios. For example, a brief overview of a few "medical" licenced producer websites found oils featuring THC:CBD ratios of 1:50 (Green Relief, 2020), 5:20 (Tilray, 2020a), 2:100 (Tilray, 2020b) and 4:110 (James E. Wagner Cultivation, 2020).

The third category is "Non-Medical" and includes a large array of products that can be acquired from legal provincial and territorial authorized retailers (e.g., Ontario Cannabis Store, 2019). A brief review of "non-medical" licensed producer websites found that these include several CBD-dominant extracts (e.g., 10-30 mg/mL CBD with < 1 mg/mL THC). The "Non-Medical" scheme imposes an age restriction (18-21 years of age, depending on the province/territory) that does not apply to the "Health Products with Cannabis" or "Cannabis for Medical Purposes" schemes. The same products can be sold under "Non-Medical" and "Cannabis for Medical Purposes" schemes but producers require separate licensing for each scheme. There currently appears to be a greater range of products available under the "Non-Medical" scheme.

No matter the relevant access scheme, all CBD-containing products fall under the *Cannabis Act*, and therefore involve the same stringent production, distribution and quality controls (described above) that apply to THC-containing products (Government of Canada, 2019). Nonetheless, internet searches (Tables 1 and 2), reveal several non-licensed companies selling apparently illegal CBD products for purchase (Hager, 2019) as well as reports of Canadian storefronts selling unregulated products (Hager & Pellegrini, 2019). Available products include the entire array of orally administered products (e.g., capsules, oils, crystals), vaping oil and pet products (Table 1) with oral products tending to be dosed at typical low doses < 150 mg/day.

Retailer and consumer confusion surrounding the legality of CBD products may stem from the widespread online marketing of CBD products in the USA spilling over into Canadian markets with Canadians often unaware that CBD remains federally regulated to a different standard as compared to the USA (The Canadian Press, 2019). At least one store owner has been charged for selling unlicensed CBD products since legalization of cannabis in Canada, and police have been shutting down unlicensed retail websites (Maimann, 2019).

*Germany*

Germany enacted legislation in March 2017 to allow for medical cannabis to be made available via prescription by a doctor (Stöver, Michels, Werse, & Pfeiffer-Gerschel, 2019). While non-medical cannabis remains illegal in Germany, this new legislation allows for any doctor to prescribe imported cannabis products, including THC and CBD-dominant cannabis flowers (Grotenhermen & Göttsche, 2020), and a variety of oils/extracts, to patients with a legitimate diagnosis for a serious medical condition and where conventional means of treatment have been exhausted (Prohibition Partners, 2019). Notably, German legislation also allows for many patients to obtain insurance reimbursement for cannabis products. More than 95,000 prescriptions were issued in 2018 (Pascual, 2020).

The CBD prescription medicine Epidiolex™ (known in EU countries as Epidyolex™), received approval from the EMA in September 2019 for adjunctive therapy of seizures associated with Lennox-Gastaut Syndrome or Dravet Syndrome. This provides marketing authorisation for all 28 EU countries, including Germany, as well as Iceland, Liechtenstein and Norway (European Medicines Agency, 2019). German patients have also been able to access the THC/CBD product nabiximols (Sativex™) on prescription since 2011 for the treatment of MS (Table 3). Both Epidiolex™ and Sativex™ can be marketed in the EU with claims around efficacy in their approved indications, epilepsy and MS respectively.

In EU countries, including Germany, CBD products that are not prescription medicines, but intended for consumption, are defined as foods. In January 2019 CBD was reclassified by the European Food Safety Authority (EFSA) who created a new entry in their Novel Food Catalogue entitled "Cannabinoids" stating that "*products containing cannabinoids are considered novel foods as a history of consumption has not been demonstrated*" (European Commission, 2019). As a result of this, CBD became considered an unauthorised novel food, imposing the requirement of pre-market authorisation of products. Although this is not a binding document, EU members, when considering such CBD products, should heed this EFSA directive. Hemp seed products are unaffected given their low cannabinoid content and widespread use prior to 1997: foods that were widely available prior to 1997 are not considered "novel".

The German Federal Office for Consumer Protection and Food Safety (BVL, *Bundesamt für Verbraucherschutz und Lebensmittelsicherheit*)

has asserted that CBD-containing extracts fall under EU novel food criteria, that CBD has pharmacological actions, and consequently CBD in food or in supplements should not be marketed. Their website concludes that [English translation] "*From the point of view of the BVL, before placing products containing CBD on the market, either an application for authorisation of a medicinal product or a request for authorisation of a novel food must be made. Under these procedures, the safety of the product must be demonstrated by the applicant.*" The authority also reports that where extraction methods result in targeted increases or decreases of certain substances, particularly cannabinoids, these would generally be novel foods (BVL, 2019). As of July 2019 the agency was reportedly unaware of any authorisation granted for a CBD food product and clarity on the governmental position on CBD was sought in July 2019 by the Free Democratic Party, a liberal opposition party (Pascual, 2019).

Despite the new EU directives and their assertion by German authorities, pharmacies, kiosks, specialist shops and online vendors sell a range of CBD products in Germany (Tables 1 and 2), including CBD capsules, oils, crystals, pastes and pet products. Highest strength available products include 50 mg capsules and 270 mg/mL oils that are dosed at a few drops per day leading to likely daily CBD doses of < 150 mg/day. Overall, there remains considerable confusion around the legal status of CBD leading to repression in some jurisdictions but not others. For example, Cologne banned CBD products in June 2020, following the EU novel food directive (**Müllenberg, 2020**).

*Ireland*

Ireland, a member of the EU, introduced a Medicinal Cannabis Access Scheme in June 2019 that allows patients with a highly circumscribed set of specific conditions (refractory epilepsy, MS spasticity, chemotherapy-induced nausea and vomiting) to obtain this "treatment of last resort" as part of a five year pilot program (Office of the Irish Minister for Health, 2019). The non-medical use of cannabis remains illegal. The prescription CBD-containing products Epidiolex™ and nabiximols (Sativex™) are not currently marketed in Ireland, despite both prescription products having EU marketing approval.

Non-prescription CBD-containing products in food or supplements can be marketed in Ireland on the proviso that they do not make any medicinal or health claims (Food Safety Authority of Ireland, 2020). As a member of the EU, Ireland is subject to the EFSA novel food directive for cannabinoids as discussed above in relation to Germany. Hemp seed products are broadly permissible, given their minimal cannabinoid content, and on the basis of the EU "non-novel" status arising from the widespread use of such products prior to 1997. This is in contrast to CBD oral products, which require novel food authorisation under the EFSA in order to be sold (Food Safety Authority of Ireland, 2020). Obtaining such authorisation is a lengthy and complex process that includes safety assessments. There is no legal level set for THC in food, but a requirement that food is safe, and a reference to the EFSA acute reference dose of THC of 1 μg/kg body weight, implying that consumption of a daily dose of THC above this level may not be safe.

Despite the EU directives, there is widespread availability of CBD products to Irish customers online at the time of writing. This includes 16 CBD-containing products from the well-known Boots pharmacy chain (Ireland) including oils containing 3 - 11.1% CBD (The Boots Company, 2020a). Holland and Barrett online (Ireland) had 35 oral CBD products, including CBD oils or sprays with 1 - 8.1 mg of CBD per dose, other oils labelled as 0.2 - 5% in strength, capsules containing 5 - 25 mg CBD (including capsules developed specifically for sports/athletes), and lozenges containing 10 mg CBD (Holland and Barrett, 2020b). Other examples of available online products are provided in Tables 1 and 2 and include capsules, oral oils, vaping oils and edibles. The likely doses obtained with recommended use of such products would be < 150 mg/day CBD.

*The United Kingdom*

The UK enacted legislative change on 1st November 2018 which defined a new category of "cannabis-based products for medicinal use in humans", allowing these products to be moved from Schedule 1 to Schedule 2 of the *Misuse of Drugs Regulations*, and for specialist doctors to prescribe such products in cases of exceptional need (Home Office, 2018b). Non-medical use of cannabis remains illegal.

The licensed THC/CBD medicine nabiximols (Sativex™) has been available in the UK since 2010 after the approval by the Medicines and Healthcare Regulatory Agency (MHRA) for treatment of MS. Epidiolex™ was also approved in November 2019 for use in the National Health Service (NHS) in the UK, with associated subsidy to patients, by the National Institute on Clinical Excellence (NICE) (Epilepsy Action, 2019). Aside from Sativex™ and Epidiolex™, no other CBD-containing products have marketing approvals as prescription medicines in the UK (Table 3), although some unlicensed CBD products can be obtained on prescription by specialists through the government's current Schedule 2 legislation . The recently announced "Project Twenty21" intends to follow the first 20,000 UK patients to receive such unregistered products on prescription (Drug Science, 2019).

Most CBD products sold in the UK are classified as food and are therefore marketed without efficacy claims and are subject to regulation by the Food Standards Agency (FSA). More than 100 retailers offer non-prescription CBD products under the FSA with major players including the Boots pharmacy chain (77 products online at the time of writing) and Holland and Barrett (35 products). Products include oils (0.2 - 33% CBD), oral sprays (around 1-8.3 mg per spray), capsules (5-25 mg CBD) and lozenges (10 mg) (Holland and Barrett, 2020a; The Boots Company, 2020b). Other online vendors captured in Tables 1 and 2 supplied a wide range of non-prescription CBD products. These likely produce maximal daily doses < 150 mg day, although some very high concentrations oils (e.g. 400 and 920 mg/mL sold in 10 ml and 1 ml volumes respectively) could conceivably lead to higher dosing (Table 2).

Despite widespread availability, there is a somewhat confusing intersection of differential regulation imposed on non-prescription CBD products by the Home Office, FSA, the MHRA and (while the UK remains in the EU) the EFSA (Tallon, 2020). For example the MHRA states that *"products containing CBD, when used for a medical purpose, should be regulated as medicinal products"* (MHRA, 2020) and any product making a medicinal claim, including testimonials and promotional material, is considered a medicinal product. A product is also considered a medicinal product if it may be used in humans with a view to restoring, correcting or modifying physiological functions through pharmacological, immunological or metabolic action (MHRA, 2020). Suggesting that CBD modifies, stimulates or enhances the endocannabinoid system, for example, could be regarded as a medical claim.

The Home Office advises that CBD products are controlled under the *Misuse of Drugs Act* and *Misuse of Drugs Regulations* because controlled substances may be present in these products (Home Office, 2018a). For CBD to be lawfully consumed, it needs to meet the Exempted Product Criteria in the *Misuse of Drugs Regulations*, or be approved as a medicine. Such criteria include that the preparation is not designed to administer a controlled drug (e.g., THC) to a human or animal, the controlled drug cannot be recovered by readily applicable means, or in a yield which provides a risk to health, and that the container of the product or preparation does not contain more than 1 mg of the controlled drug. The Home Office also suggests a necessity for independent testing and regulation to demonstrate that there is no intent to administer the controlled drugs (Home Office, 2018a). Meanwhile, the FSA states that it "*accepts the clarification from the EU that CBD extracts are considered novel foods*" and will "*work with local authorities, businesses and consumers to clarify how to achieve compliance in the marketplace in a proportionate manner*" (FSA, 2019). With this clarification in June 2019, a

window has been given until 31 March 2021 to give current producers of non-prescription products on the UK market time to apply for novel food authorization (FSA, 2020).

In practice, some distributors do sometimes make health claims about their products and the MHRA has issued urgent notices to companies about making medicinal claims for CBD products under regulation 165 of *The Human Medicines Regulations* (MHRA, 2019). Furthermore, two recent analyses demonstrated that many non-prescription CBD products, both OTC and via online purchase, contain concentrations of THC higher than those legally permitted (Gibbs, et al., 2019; Liebling, et al., 2020) making their sale and possession illegal under the *Misuse of Drugs Act 1971* (Home Office, 2018a). This has led to pharmacy governing bodies advising that supply of OTC CBD food products may not be legal, requesting further clarification on regulations from the Home Office (Ridley, 2019), and advising pharmacists to check legality of the products before supplying them (Robinson, 2019).

There is also the departure of the UK from the European Union to consider. EU membership implies that CBD must be considered a novel food as discussed for Germany and Ireland above (Gibbs, et al., 2019), and hence be subject to EFSA guidelines. Departure from the EU allows the UK to develop, similar to Switzerland, its own legislation around the importation, sale and quality control of CBD products.

### *Switzerland*

Cannabis-based medical products that can currently be prescribed in Switzerland include nabiximols (Sativex™) for treating MS muscle spasticity (Table 3). With FDA approval of Epidiolex™ in 2018, CBD met the requirement for Swiss classification as an active pharmaceutical substance for a preparation of formula-based medicinal products under the Therapeutic Products Ordinance (Swiss Confederation, 2019). As a result, magistral (i.e., compounding-pharmacy prepared) CBD formulations can be prescribed for the treatment of Dravet Syndrome, Lennox-Gastaut Syndrome, or other treatment-resistant epilepsies, or other conditions in exceptional justified cases, and when preparations meet specific conditions including Good Manufacturing Practice (Bundesamt für Gesundheit, 2019; Swiss Confederation, 2020a). Additionally, medicinal cannabis and other cannabis-based medical products are currently available with authorised access (Swiss Confederation, 2020a), but laws surrounding this are currently undergoing review, with a public consultation completed at the end of 2019 (Bundesamt für Gesundheit, 2020).

Switzerland is a non-EU country within Europe and has its own legislation around non-prescription CBD products. Cannabis preparations with a total THC content < 1.0% are not controlled under the Narcotics Act (Swiss Confederation, 2020b). This limit was revised upwards from 0.2% in 2011, reflecting the practical reality that industrial hemp cultivars sometimes contain THC above the 0.2% limit (Zobel, 2019). This legislative change, coupled to the development of low-THC, high-CBD cannabis cultivars, has provided an opportunity for new products to enter the market. This includes low-THC, high-CBD "light cannabis" products, often sold as tobacco substitutes, that became legally available in 2016, as well as the usual CBD oils, topicals and other products obtained in other countries. There are some restrictions: CBD-containing products can only be marketed if they meet the legislated criteria described in an implementation guide published in November 2018 by the Federal Office of Public Health (FOPH), Federal Food Safety and Veterinary Office (FSVO), and Federal Office for Agriculture and Swissmedic (the Swiss Agency for Therapeutic Products) (Bundesamt für Gesundheit, 2019). This includes the requirement that imported products must show evidence of THC content < 1%.

Foods enriched with CBD are considered novel foods and must be authorised by the Federal Food Safety and Veterinary Office of Switzerland, or the EU. CBD-containing liquids for e-cigarettes are only permitted if the CBD is not in pharmacologically effective doses, and without therapeutic claims (Bundesamt für Gesundheit, 2019). In general, CBD can be used in cosmetics, or as a tobacco substitute, providing total THC content is < 1.0% and no therapeutic claims are made (e.g., anxiolytic or sedative effects). The distributor has self-supervision and registers the product with the Federal Office of Public Health (Bundesamt für Gesundheit, 2019).

CBD products have become increasingly available in Switzerland from pharmacies, retailers and online without a prescription, particularly since the permitted concentration of THC was increased to < 1%. Examples provided in Tables 1 and 2 include edibles, plant material, purified crystals and oral oils. Survey research indicates CBD use by a range of people, with flower-based "light cannabis" products used by younger groups who were often also consuming illegal cannabis (Zobel, Notari, Schneider, & Rudmann, 2019). The other major segment of users are typically an older group (average age of 45 years) who use CBD oil for medical purposes or well-being, but do not consume illegal cannabis (Zobel, et al., 2019).

### *Japan*

Unlike the countries considered to this point, Japan has no legislation to enable the prescription of medical cannabis and cannabis-based medical products to patients. Indeed, the Japanese laws against cannabis are generally considered to be more severe than their European or North American counterparts. The *Cannabis Control Act* (1948) explicitly prohibits the distribution and use of cannabis-derived products, including medicines. Nonetheless, the Act excludes grown stalk and seed (which usually have negligible cannabinoid content), and their products, from the definition of cannabis (Government of Japan, 1948). This has given some companies the opportunity to market non-prescription CBD products provided that they claim to derive only from the stalk and seed of the plant. Notably, however, the Australian-based importer Elixinol Global and its Japanese subsidiary recently fell afoul of the strict Japanese requirements for "stalk and seeds" (**Elixinol Global Ltd, 2019**).

Companies entering the Japanese market report receiving approval from authorities before their products are marketed or advertised (Direct Selling News, 2019; The Newswire, 2017). Minimal information exists in the public domain on the pathways for gaining such approval, with the Ministry of Health, Labour and Welfare having expressed concern about potential increased distribution of products containing prohibited ingredients (Ministry of Health, Labour and Welfare, 2018). Before exporting CBD products to Japan, each business operator needs to contact the Monitoring Guidance and Narcotics Countermeasures Division through local importers.

Unlike many European countries, CBD-containing products are not widely available in physical stores in Japan. However, retailers selling health and wellness products also sometimes stock CBD products, including skin preparations, and oils or tinctures (e.g., 1-4% CBD) and capsules that are suggested to help with anxiety, sleep and pain. Capsules in stores visited by one author contained 5 mg to 25 mg CBD and sometimes also other ingredients (e.g., omega-3 fatty acids, or caffeine and vitamins). These products available appear to be imported, for example from the USA or the Netherlands, rather than locally produced. There are also some online sellers (Tables 1 and 2) providing capsules, crystals and oils, with maximal daily doses usually < 150 mg, although one example of a recommended daily dose of an oil of 240 mg CBD was noted (Table 2).

### *Australia*

In 2016, Australia introduced legal medicinal cannabis availability through an amendment to the *Narcotic Drug Act* (1967). This allowed the local cultivation of medicinal cannabis and the manufacture of cannabis-based medical products according to strict security and quality requirements. This includes CBD-dominant hemp strains and

related products. Further legislative changes enabled patient access under existing Therapeutic Goods Administration (TGA) schemes that allow access to unregistered medicines (the Special Access Scheme B (SAS-B) and Authorised Prescriber (A-P) schemes). Access to unregistered CBD products on prescription under these schemes is tightly restricted, and requires that the patient find a clinician to write an application on their behalf. This is often achieved in practice by patients attending one of the many "cannabis access clinics" that have opened in major capital cities. Cannabis use for non-medical purposes remains illegal at a federal level in Australia, although individual states and territories employ various forms of *de facto* or *de jure* decriminalisation.

A range of more than 100 unregistered products (oils, capsules, cannabis flower and buccal sprays), with varying CBD/THC content, are currently available for prescription under the SAS-B and A-P schemes, while nabiximols (Sativex™) is the only registered cannabis-based medicine in Australia and can currently be marketed with health claims (Table 3). Freshleaf Analytics (2019) report that 29 of 100 available products have ≥ 98% CBD content, and a further 18 have greater CBD than THC content. CBD-dominant products seem to be preferentially accessed by patients suffering from epilepsy. Around 38,000 approvals under the SAS-B scheme have been granted as of March 2020 (Australian Government, 2020), but surveys suggest that this is far less than the number of Australians who continue to use cannabis products illegally to self-medicate conditions such as chronic pain and anxiety (Benson & Cohen, 2019; Lintzeris, et al., 2020). Officially obtained products tend to be quite expensive presenting a significant barrier to access, as was described in a recent federal Senate Inquiry into patient access (Community Affairs References Committee, 2020).

Unlike the countries discussed so far, CBD products are not legally available in Australia without a prescription. CBD was rescheduled by the TGA in 2015 following a rescheduling application by the States of Victoria and Western Australia. This removed CBD from the highly restrictive Schedule 9 where CBD was classified as "Prohibited Drug" and placed it into Schedule 4 as a "Prescription-only Medicine". The current Schedule 4 requirement mandates that CBD comprises ≥ 98% of the total cannabinoid content of a product and must be prescribed by a doctor (Australian Government, 2019).

To allow Australian consumers access to non-prescription CBD products equivalent to that of the EU or USA will require further rescheduling of such products into the less restrictive Schedule 2 ("Pharmacy Medicine") or Schedule 3 ("Pharmacist Only") categories. A proposal to downschedule CBD products has been prepared by the TGA and was considered at its own dscheduling committee meeting in June 2020: a final decision is expected by November 2020 following additional public consultation. This proposal supports consideration of downscheduling to Schedule 3 when the CBD product contains a daily dose of 60 mg CBD or less, the total CBD content is ≥ 98% of the total cannabinoid content, the pack contains a maximum 30 days' supply, and the purchaser is aged 18 or over. This proposal follows a recent review by the TGA of the safety of low-dose CBD which concluded that there was good safety and tolerability of CBD in doses of up to 60 mg/day, although noting the possibility of drug-drug interactions and an absence of evidence for clinical efficacy with lower CBD dose ranges (TGA, 2020).

Current medicinal cannabis legislation in Australia has been recently subjected to a formal Parliamentary Review that has made many recommendations (McMillan, 2019) including deletion of the definition of *"cannabidiol (including all its isomers and salts)"* as a narcotic drug to allow better harmonisation with the UN Single Convention. This change to the law would require a Bill passed by parliament. Another recommendation calls for the ongoing governmental monitoring of the *"options (if any) for altering the operation of the Act to remove any obstacles to the cultivation and sale of low-THC Hemp under State and Territory law."* (McMillan, 2019). The Australian government has confirmed that all 26 of the Recommendations made by the Review will be implemented although the time line for achieving this is unclear (Office of Drug Control, 2019).

Given the strong public demand for CBD products in Australia (Australian Financial Review, 2019), the regulation of CBD in Australia is an issue that will continue to stimulate public debate. Given current developments, it appears likely that access to non-prescription CBD products may be a reality for Australian consumers by 2021-2022.

### *New Zealand*

New Zealand passed legislation in December 2018 to enable the broader prescribing of medical cannabis and cannabis-based medicines, something previously requiring written approval from the Minister of Health. Importantly, these laws removed CBD products (containing up to 2% of "specified substances" such as THC) from the *Misuse of Drugs Act*, but retained controls under the *Medicines Act*. A new Medicinal Cannabis Agency (MCA) became operational 1 April 2020 to oversee a new *Medicinal Cannabis Scheme,* the intent of which is to improve access to quality cannabis medicines for patients.

The MCA is responsible for regulating local cultivation and manufacture, and setting quality standards for products and their assessment (New Zealand Government, 2020). It does not assess safety or efficacy. Medical cannabis or cannabis-based products assessed by the MCA as meeting the quality standards can be prescribed by any doctor (i.e., General Practitioner or Specialist), while CBD products similarly assessed by the MCA may be prescribed by any doctor or nurse practitioner (Clark, 2018). Pharmacies can import, procure and dispense CBD products that have been assessed as meeting the quality standards or any medicinal cannabis product approved as medicines (e.g., Sativex™). CBD products that have not yet been assessed as meeting the quality standards by the MCA can still be supplied by a medical practitioner to a named patient or by a pharmacy to a named patient with a doctor's prescription (Medsafe, 2020; New Zealand Government, 2020). A recent manuscript describing self-reported health outcomes for the first 400 New Zealand patients to obtain CBD on prescription noted significant improvements in anxiety, pain and quality of life (Gulbransen, Xu, & Arroll, 2020).

A non-binding referendum on legalising cannabis for personal adult use will be held concurrently with a scheduled general election in New Zealand on 17th October 2020. Government documents note a likely overlap between the Medicinal Cannabis Scheme discussed above and a regulatory model for the personal adult use of cannabis, should the referendum bring about broader lawful access to products (irrespective of intended use). Production quality and approvals for medicinal cannabis under the Scheme are envisaged to remain unchanged.

At present, as in Australia, no CBD-containing products can be obtained in pharmacies or other physical stores in New Zealand without a prescription. One website marketing to New Zealanders from overseas advises consumers to include a copy of their prescription or letter from a doctor or nurse practitioner as an attachment to their online order (The Good Earth, 2019). The company does not guarantee delivery without a prescription but suggests they have been supplying successfully without covering prescriptions or letters. Another website states all parcels are declared "skin care" when shipped, being only sold for external use in Australasia, and taking no responsibility for meeting local laws (CW Online NZ, 2019).

## Discussion

The global CBD market is rapidly expanding, with a pace that many jurisdictions are struggling to adapt to. We have established that consumer access to CBD products without prescription varies across the nine countries examined as does the legality of, and guidance surrounding, the distribution and selling of such products. While some countries have relatively unambiguous requirements that clearly regulate (e.g., Switzerland, Canada) or prevent (e.g., Australia and New

Zealand) access to non-prescription CBD products, others lack clarity in official information as to what can be marketed, with competing or conflicting advice from different regulatory agencies. This is seen, for example, in the UK where CBD is subject to multiple laws and regulations, with involvement of multiple authorities causing challenges in interpreting the various guidelines, and confusion in the marketplace despite widespread product availability. Disparity is also evident between the EU regulations around novel foodstuffs and the widespread availability of non-prescription CBD products in Germany, Ireland, the UK and other EU member countries. A similar disconnection of official advice is apparent in the USA where widespread state-sanctioned access to CBD products, and recently enacted Federal regulations supporting hemp-derived products, are in conflict with FDA and DEA imperatives. Within individual states of the USA there is also uncertainty and contradiction in legislative intent, as the case study of Kansas illustrates, where both within-state and state/federalregulation appear incongruent. Taken together, this serves to paint a rather confusing picture that is at odds with the unambiguous prohibition and stiff sanctions traditionally associated with non-medical cannabis.

All countries studied, except Australia and New Zealand , have CBD products available without a prescription in varying forms and strengths, although Japan appears to have fewer products available in bricks and mortar retailers. The Japanese requirement that CBD be derived from “stalks and seed” is unique from other countries. The low to negligible cannabinoid content in these plant constituents would appear to represent an insurmountable *a priori* hurdle for CBD consumer products to cross (Mead, 2017). Nonetheless, some appear to do so, with vendors advertising oils with CBD doses as high as 240 mg/mL, as well as pure isolated crystal (Tables 1 and 2). Japan is also unusual in requiring all CBD products to be specifically authorised through the medicines regulator.

Switzerland allows a significant amount of THC at 1.0% in non-prescription products, a concentration that when smoked in the form of “light cannabis” could well induce intoxicating effects and positive effects on roadside drug tests (Arkell, et al., 2019; Pacifici, et al., 2019). In contrast, in EU countries, non-prescription products usually come from plants containing < 0.2% THC by dry weight, while most states of the USA have an apparent THC limit of < 0.3% by dry weight.

The dramatic variation between what is ostensibly legal and what is actually marketed in some countries may reflect liberal interpretation of legislation by some companies distributing CBD products. Such opportunism is not unexpected when there is poor legal clarity in the marketplace, enormous consumer demand, high potential earnings, and a perceived lack of regulatory enforcement. This uncertainty contrasts to the situation where pharmaceuticals are accessed without prescription: here the legislative intent and requirements for non-prescription supply are very clear (Gauld, Kelly, Emmerton, Bryant, & Buetow, 2012; Gauld, et al., 2014). The CBD market is growing rapidly, providing a fertile ground for entrepreneurs and financial investors who are often selling product into an uncertain legislative and regulatory environment. Failure of these legislatures to rapidly adapt to such entrepreneurship and consumer demand has contributed to the present uncertainty.

Canada is in some ways the most permissive country in terms of allowing legal and transparent access to a wide range of non-medical cannabis products to the community. But in other ways it is the most restrictive around retailing of CBD-containing health products, given that these are captured in the quality control requirements of the new legislative instruments governing all cannabis products. This means that quality requirements are much stricter than other countries in which CBD is available without prescription. Other countries may wish to follow this example if it ensures quality control and certainty around the cannabinoid content of non-prescription CBD products. On the other hand, CBD products of seemingly illegal provenance are finding their way into Canadian storefronts and online vendors regardless of current legislation (Hager, 2019; Hager & Pellegrini, 2019).

*Do non-prescription products deliver therapeutic doses?*

The current analysis suggests that within the most popular websites presented in Table 2 almost all of the “maximum dose” products yielded daily doses well below those shown to be effective in clinical trials (Millar, et al., 2019). While effective doses in clinical trials range from 300-1500 mg/day or 14-23 mg/kg/day (Chesney, et al., 2020; Millar, et al., 2019) the recommended daily doses provided by non-prescription products were, with one exception, below 150 mg (Table 2). As access to these predominantly low-dose CBD products increases internationally, high quality evidence supporting their therapeutic benefits in conditions such as pain, anxiety and sleep is scarce at best. Available clinical trials, and case studies are shown in Table 4, and show little evidence of efficacy of CBD doses < 150 mg. Additional to Table 4, are various observational studies. One retrospective survey of users found self-reported benefits of CBD products in conditions including pain, anxiety and insomnia (Corroon & Phillips, 2018), while a single-arm prospective cohort study of a CBD hemp oil extract (usual daily dose 31.4 mg CBD, 1 mg THC and other cannabinoids) reported improved quality of life and reduced opioid use (Capano, Weaver, & Burkman, 2019). The recent survey of New Zealand patients receiving CBD products on prescription from a general practitioner suggested beneficial effects of CBD at doses of 40-300 mg on anxiety and pain, with improved quality of life and no major adverse effects (Gulbransen, et al., 2020). A very recent clinical trial of a hemp product containing 15 mg CBD showed beneficial effects on high-density lipoprotein (HDL) in an overweight population over a 6 week period with trends towards improvements in sleep and quality of life (Lopez, et al., 2020). However, other randomised controlled trials and case series conducted to date have not discerned any clinically relevant effects of CBD at dose ranges of 10-150 mg with the exception of a single case report reporting a clinically relevant action of CBD dosed repeatedly at 25 mg/day (Table 4).

This is not so say that non-prescription CBD products are ineffective, merely that high quality scientific studies around the potential benefits of low CBD doses are yet to be conducted and so efficacy at these doses remains to be demonstrated. This represents a significant opportunity for scientists, clinicians and commercial interest to backfill the evidence that may validate a global consumer phenomenon, or alternatively, illustrates the magnificent folly of the entire enterprise. Absence of quality scientific evidence clearly does not deter consumer demand, with a recent analysis showing exponential growth in USA Google searches around CBD across the years up to 2019 (Leas, et al., 2019).

*Safety of non-prescription CBD products*

Despite the absence of compelling evidence for efficacy, it can be argued that restriction on the availability of CBD products, such as in Australasian countries, is disproportionate to the high margins of safety and low levels of risk inherent in CBD consumption. Reviews have found a favourable safety profile of CBD in humans (Bergamaschi, Queiroz, Zuardi, & Crippa, 2011; Chesney, et al., 2020; Iffland & Grotenhermen, 2017; TGA, 2020) and in Phase 1 studies CBD was generally well-tolerated at doses up to 6000 mg in single doses or 1500 mg in multiple doses (Taylor, et al., 2018). The 6000 mg dose represents forty times the 150 mg low dose threshold we have set in the markets we have studied. Likewise, Epidiolex™ is dosed at 20 mg/kg/day, equating to 1200 mg per day for a 60 kg adult, approximately 8-fold higher than a typical “high” non-prescription dose. A recent meta-analysis suggests few serious adverse events in clinical trials involving high doses of CBD but also that non-serious adverse events (e.g. somnolence, decreased appetite, gastrointestinal upset) appear significantly lessened at lower CBD doses ranges. Outside of clinical trials involving epilepsy, the only adverse event more prominent with CBD over placebo is diarrhea (Chesney, et al., 2020). Pharmacokinetic interactions between CBD and prescription medications remain possible

(Morrison, Crockett, Blakey, & Sommerville, 2019; Qian, Gurley, & Markowitz, 2019) but the likelihood of such interactions at the low CBD doses obtained from non-prescription products remains to be established. There is little information available on long-term effects of CBD consumption outside of the (up to) 1-14 week time interval involved in recent clinical trials (Chesney, et al., 2020), and the occasional pre-clinical study where rodents have been dosed long-term without any obvious adverse consequences (Schleicher, et al., 2019). Obviously, then, there remains the possibility that hitherto unrecognised and problematic side effects may emerge in the future when patients using CBD over many months or years are studied.

Other potential hazards relate to observations of the inaccuracy of the labelling of non-prescription products. Recent analyses of actual THC and CBD content of available products in the UK (Gibbs, et al., 2019; Liebling, et al., 2020), Germany (Lachenmeier, et al., 2019), other EU countries (Pavlovic, et al., 2018) and USA (Bonn-Miller, et al., 2017) suggest a worrying lack of accuracy in product labelling. Both over-labelling (the product provides lower cannabinoid content than stated on the pack) and under-labelling (the product provides higher cannabinoid content than started on the pack) were detected, with many products in breach of strict THC limits. This would suggest that regulatory oversight in these jurisdictions is inconsistent at best.

Problems in enforcement in the EU and USA could reflect the rapid transition in laws (e.g. hemp-related laws in the USA and novel food classification in the EU) leading to a grey zone in which producers operate in a somewhat ambiguous legal and regulatory framework (Tozser, 2020). These inaccuracies in labelling have implications for the efficacy and safety of products, and also the potential for the user to inadvertently fail a roadside or workplace drug test, highlighting the importance of sufficient regulatory oversight and enforcement of both testing and product labelling. Another concern is the excessive health claims made on some websites, such as anti-cancer effects, and efficacy in schizophrenia and depression. These are particularly concerning should they encourage vulnerable patients to eschew proven treatments in favour of unproven ones. However, policing such disingenuous claims is extremely difficult in current online retail environments.

### *Future developments*

Notwithstanding the above, it is apparent that quality-controlled CBD products have a very large margin for safety and this is in reflected in the recommendation of the WHO Expert Committee on Drug Dependence that CBD products not be scheduled in international drug control treaties (WHO, 2019). Such a recommendation, while yet to be ratified by the UN, appears to be driving legislative and regulatory change in more CBD-restrictive jurisdictions such as Australia. The high levels of consumer demand for CBD products will inevitably be met with illegal activity until such time as government legislative approaches are harmonised with community expectations around ease of access.

Clear legislation and guidelines of what can be marketed, and an authorisation process that includes independent analysis of products, would help ensure the quality of marketed products for the consumer and limit entrance of companies which do not have the necessary standards. This would engender greater confidence in the sector currently supplying non-prescription CBD products. Some have proposed that cannabis product taxes be used to fund the high quality research needed to validate the therapeutic actions of currently available products (Zobel, 2019). Others have also suggested a “listing” process for CBD products to enable greater safety and product quality, recognising deficiencies of existing legislation (Cohen & Sharfstein, 2019). The current lack of clarity around the efficacy of low CBD products, as noted above, is not uncommon for a herbal medicine and it is expected that greater clarity around CBD efficacy will come to hand as the numerous current clinical trials involving CBD start to report results, and as commercial interests seek to register CBD products with authorities such as the EMA, FDA and TGA for specific indications.

While low regulatory barriers to bringing low dose CBD nutraceutical products to market appear desirable, these need to be coupled with safety and quality assurance for consumers. Mandating pharmacovigilance reporting by manufacturers and distributors would also assist in the collection of evidence around safety with long-term CBD use.

## Limitations

This paper provides a current snapshot of CBD availability in different countries based on readily available guidance from government websites, online searches of retailers, and non-systematic visits to some brick and mortar retailers. The authors found challenges in interpreting the available information, particularly when it was from different government agencies within the same country. The study is not designed to be comprehensive, and legal views on what can be marketed in the different countries could differ from our findings. In searching for information about products on the market, we looked online, and visited small numbers of retailers in most countries. The resulting information provides an indication of available products, but is not a definitive list. This is a rapidly moving field and we acknowledge that our analysis may be quickly superseded by legislative developments and changes in guidance issued by government agencies.

## Conclusions

Countries vary considerably in how they manage prescription-free access to CBD, and also in the variety of existing CBD products that are currently available on the market. In some countries, CBD fits comfortably into existing medicine, food and controlled drug legislation and there is little ambiguity. In other countries there is contradictory or confusing information around legal availability. A substantial and increasing array of CBD products are readily available in many different countries, most of which lack compelling evidence for medical benefits, although such evidence may accrue over time. CBD access is a rapidly evolving global phenomenon and clearer legislation, guidelines and scientific evidence around CBD products will hopefully emerge in the near future.

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## Author contribution

NG, RC and IM provided conceptualisation and decided on methods. NG, DC, IM, EC and SA collected and analysed data. IM and NG wrote the manuscript with assistance from EC, RC, JA, DC, MH and SA. All co-authors reviewed and contributed to the final version of the paper.

## Declaration of Competing Interests

IM has acted as a consultant to Kinoxis Therapeutics, is on the

Medical Advisory Board of BOD Australia, and has received honoraria from Janssen. His research is funded by the Lambert Initiative and the Australian National Health and Medical Research Council (NHMRC). He, together with JA, are inventors on several patents relating to novel cannabinoid therapeutics. JA has served as an expert witness in various medicolegal cases involving cannabis and in 2018 was a temporary advisor to the World Health Organization (WHO) on their review of cannabis and the cannabinoids. His research is funded by the Lambert Initiative and the Australian National Health and Medical Research Council (NHMRC). RC provides consultancy to the medical cannabis industry. DC is the Medical Lead for the Centre for Medicinal Cannabis (UK), an organization that is funded by manufacturers of cannabinoid medical products, and has received funding in undertaking this work. NG provides consultancy on prescription to non-prescription reclassification of medicines, and, since this paper has been written has provided consultancy on CBD availability without prescription. Other authors report no competing interests.

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