A Submission to the Advisory Committee on Medicines and Scheduling on the Down-Scheduling of Low Dose Cannabidiol.

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THE UNIVERSITY OF SYDNEY

LAMBERT INITIATIVE for Cannabinoid Therapeutics

Introduction: The Lambert Initiative

The *Lambert Initiative for Cannabinoid Therapeutics* is a philanthropically funded research program investigating the therapeutic potential of cannabis and the cannabinoids. It was established in July 2015 following an unprecedented donation of $33.7M from Barry and Joy Lambert to the University of Sydney.

Barry and Joy's granddaughter Katelyn Lambert (aged 7) suffers from Dravet syndrome, a severe treatment-resistant form of epilepsy, and the Lambert family have witnessed a remarkable and continuing improvement in Katelyn's condition as a result of her being administered (mostly illicit) cannabis products over the past 4 years. This has engendered a strong desire in Barry and Joy to see others suffering from intractable medical conditions having access to cannabinoid-based medicines.

The Lambert Initiative is developing novel therapeutics derived from the cannabis plant to ameliorate a range of diseases and conditions. It is also involved in education, community outreach, science-based advocacy and policy issues relating to medicinal cannabis. At present the Lambert Initiative supports the research of more than 40 academics, postdoctoral fellows, research assistants and students featuring a number of national and international research collaborations.

Three major areas of research in which the Lambert Initiative is currently active are as follows:

Preclinical Research. This research stream employs cellular and animal models of disease to characterise the therapeutic potential of the more than 140 cannabinoids present in the cannabis plant, and related novel molecules, in treating conditions such as cancer, chronic pain, epilepsy, neurodegenerative conditions, metabolic disorders and mental health conditions. Our medicinal chemistry team synthesises large libraries of cannabinoid molecules as part of this program allowing us to discover and develop new candidate molecules as cannabis-based medicines.

Clinical Trials. This second research stream examines the efficacy and potential side effects of existing cannabis-based medicines in treating patients with a range of different conditions. We are currently involved in clinical trials of existing THC and/or CBD containing products in insomnia, anxiety, Tourette's syndrome and alcohol withdrawal. We are also characterising effects of THC and CBD on driving performance and cognitive function and evaluating the accuracy and validity of current roadside and workplace drug testing procedures. Additional clinical trials planned for 2020 are in the areas of methamphetamine addiction, psychosis, agitation in dementia, excessive daytime sleepiness, and sporting performance. When accessing products for our clinical trials we routinely engage with partners in the local and international medicinal cannabis industry.

Patient Access and Community Use of Medicinal Cannabis. Our third research stream involves surveying patients who are self-medicating with cannabis in Australia, either legally or illegally, to determine their use of official versus unofficial products, perceived efficacy of products, side effects, and preferred models of access in patients. We also conduct surveys of GPs and medical specialists on their attitudes towards, and knowledge of, medicinal cannabis. The Lambert Initiative also uses Freedom of Information requests in an attempt to obtain detailed data on patient approvals from the Therapeutic Goods Administration (TGA) to monitor trends in patient access. We have also conducted international comparisons of cannabis access across different countries.

Statement of support

We write this submission in broad support of the Delegate of the Secretary's Proposal for cannabidiol (CBD) to be included in Schedule 3 (Pharmacist Only Medicine) of the Poisons Standard (SUSMP). This is in keeping with Recommendation 13 of the recent Senate Inquiry into *Current Barriers to Patient Access to Medicinal Cannabis in Australia* that recommended that the Department of Health apply to the *Advisory Committee on Medicines and Scheduling* to consider the down-scheduling or de-scheduling of CBD and other non-psychoactive cannabinoids. The overall sentiment behind this recommendation was to help improve patient access to cannabinoid medicines in Australia. This intent is also shaped by Recommendation 12 of the same Senate Inquiry, which recommended that the TGA conduct a broad public consultation into the scheduling of CBD as a matter of priority.

Deficiencies in current patient access were highlighted in many submissions to the Senate Inquiry, including that of the Lambert Initiative [1]. In our submission we called on lower dose CBD products to be down-scheduled in Australia as a constructive means of meeting community expectations around patient access. Specifically, it would allow patients who believe that medicinal cannabis products might improve their wellbeing to access low risk products without going through the current convoluted and expensive processes involved in procuring unregistered products.

Down-scheduling of lower dose CBD products would also bring Australia in line with many other jurisdictions around the world where CBD products are sold without a prescription. We believe that this can be achieved while upholding Australia's excellent international reputation in the regulation of therapeutic goods. Many countries now allow over-the-counter (OTC) or online access to lower dose CBD products, containing relatively low doses of CBD (e.g. 10-100 mg per recommended daily dose) and low or undetectable Δ^9-tetrahydrocannabinol (THC) concentrations (see Appendix 1). These products, typically marketed as food supplements, are often extracts of the flowering heads of CBD-dominant "industrial hemp" cultivars that are also grown for seed and fibre.

In a recent analysis we found that lower dose CBD products were available without prescription in 7 of the 9 countries we surveyed, including the United States of America, Canada, Germany, Ireland, United Kingdom (UK), Switzerland and Japan [2]. The only two countries where this was not available were Australia and New Zealand. Our analysis of the highest dose products available from the most popular CBD websites for each country (see Appendix 1) suggested that recommended daily doses for orally administered products are generally less than 100 mg of CBD.

The legal and regulatory environment around these products is rather complex in the USA, UK and other EU countries, sometimes as a result of competing State and Federal directives (e.g. in the USA) and different requirements governing CBD products when treated as food rather than medicine [2]. The legislative, regulatory and scientific context around such products continues to evolve internationally.

Recent analyses of actual THC and CBD content of non-prescription products in the UK [3, 4], Germany [5], other EU countries [6] and USA [7] 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) have been detected, with many products in breach of strict THC limits governing hemp-derived products. This would suggest that clarity of

legislative and regulatory oversight as well as product quality control are important issues for Australia to consider.

We agree then that the clarity of regulation afforded by the inclusion of CBD in Schedule 3 of the SUSMP would benefit Australians seeking to utilise a safe CBD medicine of known composition. Our recent research has highlighted the large number of Australians who continue to use Illegal black market medicinal cannabis preparations for health conditions such as epilepsy [8], inflammatory bowel disease [9], anxiety and insomnia [10]. In our recent survey of IBD patients, only 3 out of 212 who were current or previous users of medicinal cannabis preparations source their product through official schemes [9]. In a larger survey of 1388 current Australian users self-medicating with cannabis, often for anxiety and insomnia, only 25 were obtaining official product [10]. The vast majority of these patients would like to be able to access legal, quality-controlled, cannabis-based preparations, including access to CBD dominant products. Current access schemes, however, are perceived as complicated and expensive [10].

Providing high quality CBD products as a Pharmacy Only Medicine should therefore help transition many current medicinal cannabis users from illegal sources to a legal and well-regulated form of supply. This would particularly be the case for patients with mild to moderate forms of anxiety, depression, insomnia and pain who may be currently self-medicating with illicit THC-dominant street cannabis of uncertain composition and origin. Such patients might achieve equivalent or greater forms of relief from a less hazardous down-scheduled CBD-dominant product.

At this point we are in broad agreement with the TGA's recommendation that CBD products be initially limited to forms involving up to 60 mg daily dose. This limit might then be revised as new evidence comes to light on the therapeutic application of CBD for conditions that do not require medical oversight, such as reducing anxiety, improving sleep and diminishing pain. Moreover, high doses might be considered when more safety and efficacy data are made available involving novel and emerging CBD-containing formulations. Our recent analysis (Appendix 1) shows that some higher potency CBD products (e.g. CBD oils of 250 mg/ml, 50 mg CBD capsules, pure crystalline CBD, CBD vape oils) are readily available without a prescription in jurisdictions such as the EU, UK and USA [2].

Commentary on the Proposed Amendment relevant to section 52E of the Therapeutic Goods Act 1989

(a) the risks and benefits of the use of a substance.

We believe the benefits of this proposal far outweigh the risks. Preclinical and clinical studies, including our own studies, have demonstrated efficacy of CBD in the treatment of conditions such as epilepsy [11, 12], anxiety [13-15], psychosis [16, 17] and chronic pain [18]. Our recently completed CAPS (Cannabidiol for Anxiety Pilot Study) trial with ORYGEN Youth Mental Health in Melbourne observed highly significant effects of CBD at 600-800 mg over 12 weeks in reducing severe anxiety and improving occupational and social function in young patients aged 12-25, with minimal side effects (manuscript, in preparation). The new Wellcome Trust-funded CANARY (CANnabidiol for At Risk Youth) trial with ORYGEN will determine whether CBD (1000 mg over 12 weeks) can prevent the development of schizophrenia in young people identified as being at high risk of psychosis.

Clinical trials to date typically show efficacy in conditions such as anxiety, psychosis and epilepsy with higher CBD doses (e.g. 300-1500 mg) [19], yet it remains possible that lower doses do have efficacy. Such dose ranges have often not been explored in a systematic fashion as shown in the TGA's own analysis [20] and also in our own recent analysis provided in Appendix 2. This analysis confirms that few high-quality trials or case series have been completed to test low dose (< 150 mg) CBD effects in clinical conditions, although there are some sporadic signs of efficacy in the studies published to date.

Recent observational studies provide some support for the effectiveness of low dose CBD formulations while preclinical studies broadly confirm anxiolytic, analgesic, sleep-enhancing, anti-inflammatory and antioxidant effects of CBD. A recent paper surveying the first 400 patients that were prescribed CBD products in New Zealand found that 63% reported satisfaction with CBD use, with improvements in quality of life being self-reported by many participants [21]. Patients using between 40 – 300 mg of CBD per day displayed significant improvements in pain, anxiety and depression. The most frequent positive side effect was an improvement in sleep (12% of respondents), while the oils were well-tolerated with a low frequency of side-effects (2% or less for each side-effect), the most common side-effects being sedation, vivid dreams, and emotional disturbance. Obviously, the lack of placebo control and the self-reported nature of improvements means that these conclusions should be treated with caution.

Later this year, the Lambert Initiative in conjunction with the Woolcock Institute for Medical Research and School of Pharmacy at the University of Sydney are planning to launch a clinical trial of a low-dose hemp nutraceutical products (containing 25 mg CBD) in the treatment of insomnia. This will be a community pharmacy study examined 12 weeks of daily treatment with a 50 mg CBD (one capsule, twice daily) *versus* placebo of individuals who attend pharmacies self-reporting sleep problems. The primary outcome will be improved sleep quality, with secondary outcomes including improvements in anxiety, aches and pains, mood and quality of life. In planning this study, the Lambert Initiative is mindful of the current lack of high-quality clinical evidence supporting low dose CBD use, and we hope this study will mark an important advance in backfilling the current gap in evidence.

We also believe that the rescheduling of CBD containing products containing low doses capped at 60 mg per day, as suggested in the draft amendment, would be a welcome step in assisting the community access CBD to improve quality of life and treat medical conditions for which medical oversight is not required. Another benefit might be to help transition many thousands of Australians away from currently popular "wellness products", multivitamins, and other herbal and complementary medicines for the treatment of anxiety, depression and insomnia, products for which there is even less evidence of efficacy than for CBD.

(b) the purposes for which a substance is to be used and the extent of use of a substance;

As described above low-dose CBD preparations could be used to relieve suffering from subclinical ailments including pain, inflammation, insomnia, low mood, and anxiety. We agree with the proposed amendments on the extent of use of CBD, that being it be limited to a 60 mg daily dose with packs containing not more than 30 days of supply. Limiting purchasing to adults aged 18 years and older is also appropriate.

(c) the toxicity of a substance;

We broadly agree with the TGA's report on the safety of low dose CBD products [20]. In January 2019, the World Health Organization (WHO) via its Expert Committee of Drug Dependence (ECDD) recommended to the United Nations that CBD preparations should not be subject to international drug control. This was based on an extensive pre-review and critical review of the evidence which showed that CBD had no intoxicating effects or potential for abuse or dependence. Moreover, it was concluded to be well-tolerated with a good safety profile, with no evidence of problematic recreational use or associated public health problems [22, 23].

Apart from the extensive review of the toxicity conducted by the WHO's ECDD, a very recent paper [24] provides the most scientifically rigorous appraisal of CBD toxicity to date [24] and was published after the TGA's own low dose CBD report [20]. The paper conducted a systematic review and meta-analysis on the adverse effects of CBD across all medical indications using only double-blind and placebo-controlled clinical trial lasting ≥7 days.

Administration of higher dose CBD (10-20 mg/kg), as utilised in trials on childhood epilepsy patients, increased the risk of abnormal liver function tests, somnolence, sedation and pneumonia, which was likely attributed to drug-drug interactions with numerous other anticonvulsant drugs used by these patients. When excluding these high dose studies in childhood epilepsy patients, the only adverse event yielded from adult trials was an increased risk of diarrhoea. Moreover, the study showed than the risk of adverse effects (e.g. inhibition of appetite, somnolence, gastrointestinal upset) was dose-related, with lower doses significantly less likely to give rise to adverse event reports and withdrawal of participants from clinical trials [24].

Overall, it was concluded that high dose CBD was well tolerated with few serious adverse effects, although drug interactions mediated by cytochrome P450 enzymes remain a potential concern, particularly amongst patients dosed with medications that engage CYP3A4, CYP2C9 and CYP2C19 [25]. While we agree in principle with this concern, we observe that problematic pharmacokinetic interactions are largely observed with extremely high doses of CBD in epilepsy trials and may be unlikely to occur at the much lower daily CBD doses proposed by the delegate (60 mg per day). Clearly, systematic evidence is currently lacking on this issue.

So while the collection of more safety data is imperative, this recent review [24] suggests that commonly cited adverse effects of CBD such as sedation and disturbed liver function tests may be restricted to high-dose trials in intractable epilepsy patients and may not apply to the general, adult population, particularly when dosed with CBD products at a lower dose range.

(d) the potential for abuse of a substance;

As noted by the recent WHO reports, purified CBD does not appear to have any addictive or abuse liability. Indeed, our own preclinical research has shown that CBD may serve as an anti-craving agent, as it reduces methamphetamine self-administration in rats [26], and we are currently initiating clinical trials to determine whether CBD is effective in managing alcohol detoxification and treating methamphetamine dependence. There are no reports of purified CBD having habit-forming qualities. A recent study [27], which was published after the TGA report on low dose CBD [20], examined whether abrupt withdrawal from chronically administered CBD induced a withdrawal syndrome in humans. In this placebo-controlled trial, thirty healthy participants were administered purified CBD twice daily at a dose of 750 mg for 28 days before the drug

administration was ceased. The abrupt withdrawal of daily, high-dose CBD administration did not induce any withdrawal symptoms or drug craving, consistent with the view that CBD is not a drug of dependence.

Purified CBD taken orally does not appear to have any THC-like intoxicating effects. A recent paper, that was not captured in the TGA's review, has recently provided very pertinent data using a 100 mg oral dose of purified CBD which is reasonably close to the 60 mg per day dose suggested by the TGA [28]. In this placebo-controlled study, purified CBD was orally administered at a dose of 100 mg to healthy participants and subjective ratings as well as cognitive and psychomotor function were assessed. This 100 mg oral dose had no THC-like intoxicating effects and did not cause any cognitive or psychomotor impairment. There was no evidence of CBD-induced somnolence or sedation and no effects on heart rate or blood pressure.

We have recently completed an on-road driving study in the Netherlands where participants vaporised either CBD-dominant, THC-dominant, or mixed (1:1) THC and CBD containing cannabis, and then drove for 100 km on a normal highway both 30 mins and 4 hours later. Participants were also tested on a range of cognitive tests. While the dose of CBD was low (13.5 mg) the route of administration via vaporization results in a large bolus of CBD reaching the bloodstream very quickly with a rapid spike in plasma CBD concentrations. Results (shown in Appendix 3) showed that while THC and mixed THC/CBD containing cannabis produced clear driving impairment, no such effects were seen with CBD-dominant cannabis. Participants reported feeling very "stoned" after vaporising THC-dominant or THC/CBD-equivalent cannabis but not following CBD-dominant or placebo cannabis. This study is currently being prepared for publication and a manuscript should be available soon on request.

It can therefore be concluded that there is little evidence that CBD has any abuse potential, intoxicating effects, or will cause any driving or cognitive impairment.

(e) the dosage, formulation, labelling, packaging and presentation of a substance;

We generally agree with the proposed dosage, formulation and packaging specifications included in the draft amendment of the SUSMP that will be submitted to the Joint ACMS-ACCS #25 meeting. At present the amendments of CBD being included in Schedule 3 would only be under conditions where CBD "*…comprises 98 per cent or more of the total cannabinoid content of the preparation*" and that "*any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and comprise 2 per cent or less of the total cannabinoid content of the preparation*".

This opens the possibility that 2% of the preparation would comprise THC. We believe this unlikely to pose any health issue with a daily dose limit of 60 mg CBD. The maximal amount of THC ingested with such dosing would be 1.2 mg (or around 0.016 mg/kg in a 60 kg human) although in practice it is likely to be far less. To the best of our knowledge, a 1.2 mg or 0.016 mg/kg dose is well-below the threshold for intoxicating effects of THC (commonly considered to be 5-10 mg oral [29]), or that might impair driving or cognitive function [29, 30]. We also consider that this is a concentration of THC that is unlikely to yield a positive results in currently used roadside drug tests in Australia [31].

Conclusion

We support the draft amendment to include CBD in Schedule 3 of the SUSMP that will be discussed at the upcoming Joint ACMS-ACCS #25 meeting. Low-dose CBD has emerging therapeutic properties and has acceptable safety. A range of cannabis preparations are currently often being accessed illegally by Australian patients thus exposing many vulnerable members of the Australian population to products of unknown composition and quality and possible criminal sanctions. Ready over-the-counter access to low dose CBD preparations as a Pharmacist Only Medication would provide a new, safer access path for the many users who assert these products provide them some symptomatic relief, and also for the many patients who seek to transition from illicit cannabis into quality controlled, pharmacy supplied alternatives.

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APPENDIX 1 Details of highest dose orally administered non-prescription CBD products available on popular websites across seven different countries.

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 99% crystal	- -	- -	10 mL 0.5 g	199.99 GBP 34.99 GBP
	Ice Head Shop[†]	iceheadshop.co.uk	920 mg/mL oil 99% crystal	- -	- -	1 mL 25 g	34.99 GBP 112.50 GBP
Switzerland	Hanfpost[†]	hanfpost.ch	5 mg edible 300 mg/mL oil 99.8% crystal	- - -	- - -	14 edibles 10 mL 1 g	6.90 CHF 129.90 CHF 44.90 CHF
	Marry Jane	marryjane.ch	300 mg/mL oil 99.8% crystal	- -	- -	10 mL 1 g	129.90 CHF 44.90 CHF
	CBD420	cbd420.ch	150 mg/mL oil 99.9% crystal	- -	- -	10 mL 1 g	94.91 EUR 85.17 EUR
Japan	Healthy Tokyo[†]	healthytokyo.com	50 mg capsules 60 mg/mL oil	1-2 capsules 0.5 mL x1-2	50-100 mg 30-60 mg	30 capsules 20 mL	29,160 JPY 19,500 JPY
	CBD Online[†]	cbd-online.jp	240 mg/mL oil 99.6% crystal	5-10 drops x2 -	120-240 mg -	10 mL 1 g	38,000 JPY 14,800 JPY
	Cannapresso Japan	cannapresso-cbd.shop-pro.jp	200 mg/mL oil 99.6% crystal	1-2 drops x2-3 0.1 g	20-60 mg 100 mg	10 mL 1 g	26,900 JPY 9,500 HPY

[††] Recommended daily serving was based on provided recommendations on product page, when available.

[†††] Estimated based on 0.05 mL per drop.

⁻ Information not available.

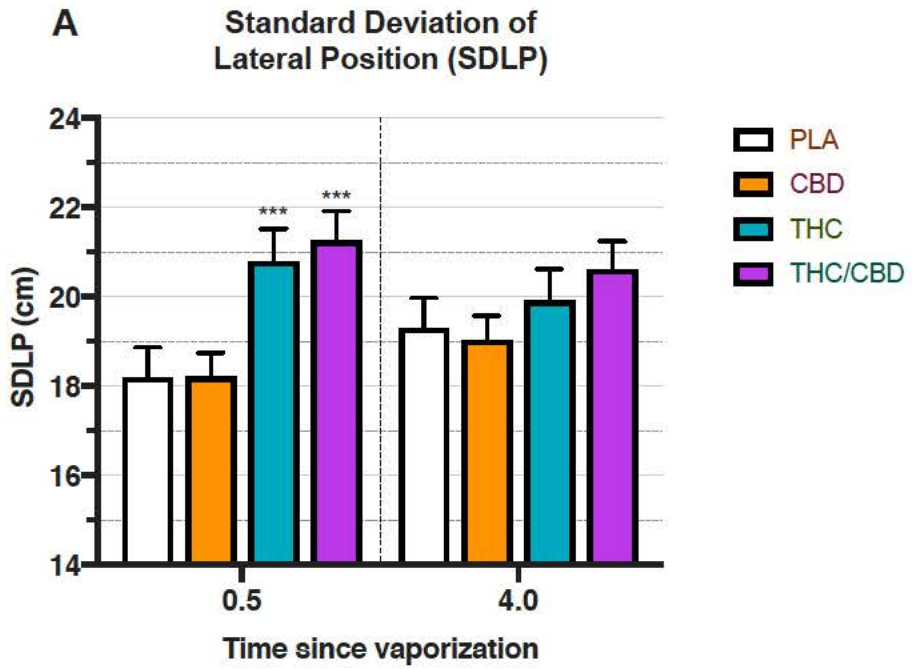
Search Method: To identify readily available CBD products across countries, information on available products was sought from the most popular websites providing CBD products to that country. For this, an internet search engine (Google) was adjusted with region settings to limit searching to each country 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. The highest dose CBD products available on each website were located, and the recommended dose, where such information was available. The websites were originally accessed 27th March 2020 and then updated 20th May 2020. Note that products listed here have not been confirmed as available via actual purchase.

APPENDIX 2 Summary of clinical trials and case series involving low doses (< 150 mg) of oral CBD

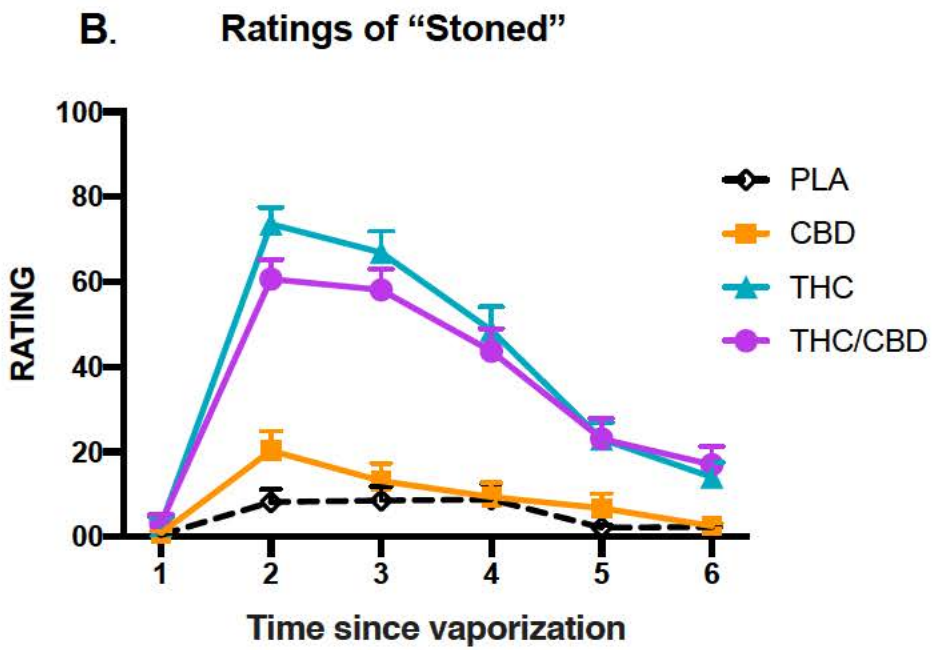
Author	Indication, Task	Design (n)	CBD doses	Outcome	Low dose CBD effect? (i.e. < 150 mg)
Zuardi, Rodrigues [15]	Anxiety, public speaking task	RCT (n=23)	100, 300 or 900 mg (oral)	300 mg CBD decreased anxiety	No
Linares, Zuardi [13]	Anxiety, public speaking task	RCT (n=57)	150, 300 or 600 mg (oral)	300 mg CBD decreased anxiety	No
Karniol, Shirakawa [32]	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, Mechulam [33]	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
Carlini and Cunha [34]	Insomnia	RCT (n=15)	40, 80 or 160 mg (oral)	160 mg CBD increased self-reported sleep duration	No
Tomida, Azuara-Blanco [35]	Intraocular pressure (IOP)	RCT (n=6)	20 or 40 mg (sublingual)	40 mg CBD transiently increased IOP	Yes
Chagas, Eckeli [36]	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, Price [37]	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 [14]	Paediatric anxiety and insomnia	Case report (n=1)	25 mg (oral) per day; 5 months	CBD improved subjective sleep quality	Yes
Shannon, Lewis [38]	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.

APPENDIX 3 Unpublished results from recent on-road driving study in the Netherlands



Standard Deviation of Lateral Position (SDLP) is a standard measure of driving impairment and refers to the extent to which a driver "weaves" from side to side and loses lane position while driving. Alcohol, benzodiazepines and THC cause a dose dependent increase in SDLP. In our recent on-road study in the Netherlands the vaporisation of THC-dominant of THC/CBD equivalent cannabis caused a significant increase in SDLP (relative to placebo cannabis) measured 30 mins but not 4 hours later. Vaporisation of CBD-dominant cannabis had no such effect. The CBD and THC doses were 13.5 mg vaporised N=24 participants tested within-subjects. Arkell et al, manuscript in preparation.



In the same study, participants (n=24) were asked to rate how "stoned" they felt after vaporising THC-dominant, THC/CBD equivalent, CBD-dominant and placebo cannabis on 4 separate occasions. THC-dominant and THC/CBD equivalent cannabis produced major feelings of intoxication that took 5-6 hours to disappear, while CBD-containing cannabis produced few, if any, subject reports of intoxication. The CBD and THC doses were 13.5 mg vaporised. Arkell et al, manuscript in preparation.