Cannabis Scheduling Review
Part 1

The therapeutic and medicinal benefits of Cannabis based products – a review of recent evidence

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1   Summary

1.1   Interest is growing across the United Kingdom, and indeed the world, into the therapeutic benefit of 'cannabis based medicinal products'* in the treatment of illness. In this review I summarise the evidence for the Home Secretary as a "review of contemporary reviews".

1.2   As the Chief Medical Advisor to the UK Government, I have examined evidence of the medicinal benefit of cannabis based products to advise on the appropriateness of their place within Schedule 1 of the Misuse of Drugs Regulations 2001 and subject to designation under s7(4) of the Misuse of Drugs Act 1971.

1.3   This evidence review is specifically for medicinal use, on prescription; it does not address recreational use of these products. Cannabis has many active chemicals and only cannabis or derivatives produced for medical use can be assumed to have the correct concentrations and ratios. Using other forms, such as grown or street cannabis, as medicine for therapeutic benefit is potentially dangerous. The evidence that cannabis and some of its derivatives can be addictive and harmful has been known for some time and is not disputed by recent science, so I believe the reasons it is a controlled drug in the UK stand.

1.4   There is now however, conclusive evidence of the therapeutic benefit of cannabis based medicinal products for certain medical conditions and reasonable evidence of therapeutic benefit in several other medical conditions. This evidence has been reviewed in whole or part, and considered robust, by some of the leading international scientific and regulatory bodies, as well as the World Health Organization (WHO). As Schedule 1 drugs by definition have little or no therapeutic potential, it is therefore now clear that from a scientific point of view keeping cannabis based medicinal products in Schedule 1 is very difficult to defend. Moreover, I believe that it would not make sense to move cannabis and its derivatives out of Schedule 1 whilst leaving synthetic cannabinoids, which the evidence suggests have potentially greater therapeutic benefit and less potential for harm, in Schedule 1. **I therefore recommend that the whole class of cannabis based medicinal products be moved out of Schedule 1.**

1.5   Moving these drugs out of Schedule 1 would allow them to be prescribed under controlled conditions by registered practitioners for medical benefit. In addition, moving the whole class of cannabis based medicinal products out of Schedule 1, will allow the evidence base on the therapeutic benefits associated with using this class of drugs to be improved through research, maximising benefits to patients.

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*   This definition encompasses cannabis; cannabinoids; and synthetic compounds (see paragraph 3.1).

2   The Review

2.1   I have been asked to review evidence on the therapeutic benefits of cannabis based medicinal products and advise if this class of drugs should be considered for being moved out of Schedule 1.

2.2   This review considers only cannabis based medicinal products that could be prescribed by a registered medical practitioner. There are serious sanctions, including from the General Medical Council, for inappropriate prescription of controlled drugs without medical indication. **This review does not consider the use of these products for non-medicinal or recreational purposes, or where those wishing to provide cannabis based medicinal products are not registered medical practitioners.**

2.3   There are well known harms from cannabis and some of its derivatives including addiction and mental health disorders. As with all other medicines, when taking prescribing decisions doctors must balance the potential for harm against the potential for benefit for individual patients.

2.4   This review covers only medical cannabis and cannabis based medicinal products designed specifically for medicinal use. Grown cannabis has over 100 active drugs, which can have a wide variety of concentrations and ratios creating different and often severe side effects. Most important are two drugs: tetrahydrocannabinol usually shorted to THC, and cannabidiol. THC has the great majority of the effect including harmful effects on the brain; cannabidiol to some extent counteracts this. Because different forms of grown cannabis have different concentrations and ratios of these drugs, grown or street cannabis cannot safely be substituted for medicinal cannabis.

3   Definitions

3.1   This review uses the terminology 'cannabis based medicinal products', this
        encompasses:

   a) **cannabis** - a broad term used to describe organic products (e.g., cannabinoids,
      marijuana, hemp) derived from the Cannabis genus of plants;

   b) **cannabinoids** - a class of diverse chemical compounds that act on cannabinoid
      receptors (CB1) in cells that alter neurotransmitter release in the brain, spinal
      cord and peripheral nerves. Cannabinoids can be naturally derived from the
      cannabis plant, or manufactured. Non-psychoactive examples currently within
      Schedule 1 include **cannabinol and** cannabidiols. It does not include **cannabidiol
      (CBD) as this is not a controlled drug and therefore is not in Schedule 1.**

   c) synthetic compounds with chemical structures similar to cannabinoids that have
      little or no effect on the brain and are unlikely to have addictive potential. These
      are sometimes included in Schedule 1 in current generic definitions.

4   Background

4.1   Controlled drugs are assigned a Class, and a Schedule. The Class (A, B and C) broadly relates to potential for harm, and has legal implications, and potential penalties for inappropriate possession. Cannabis and many of its derivatives are assigned to Class B under the Misuse of Drugs Act 1971 based on the potential for harm. This review does not consider evidence in relation to the Class of cannabis and its derivatives.

4.2   Recognising that potentially addictive and harmful drugs also have medical benefit in specific cases, they are also assigned a Schedule, which defines the conditions under which they may be prescribed and stored. The Misuse of Drugs Regulations 2001 defines the categories of people authorised to supply and possess drugs under the Act. Drugs in Schedule 1 are considered to have little or no therapeutic value. By definition they are therefore not available to be prescribed or held legally with a prescription. Drugs with some potential medical indication are categorised into Schedule 2, 3, 4 or 5, in descending order of restrictions. It is only legal to possess a drug in one of these Schedules with a valid prescription from a registered medical practitioner.

4.3   Under these regulations cannabis and the majority of cannabis like products are categorised as Schedule 1. This only makes medical and scientific sense if there is no or very little evidence of potential therapeutic benefit in a treatment setting.

4.4   For any (new) medicine there is a requirement to demonstrate that the benefits outweigh its potential for harm. There is clear evidence that cannabis is a harmful drug which can damage peoples' mental and physical health. However since cannabis based products were initially given a Schedule 1 designation, evidence has steadily accumulated about the role of cannabis based medicinal products in therapeutic use for particular medical conditions.

4.5   There have been a number of recently published good quality evidence reviews on the health effects of cannabis based medicinal products and so this paper represents a 'review of reviews'. This review draws evidence primarily from a recent report by the US National Academies of Sciences, Engineering, and Medicines (NASEM)[1] on the health effects of cannabis and cannabinoids; a scientific review by the Health Products Regulatory Authority (HPRA)[2] of the Republic of Ireland on the medical use of cannabis; reviews published or in progress from WHO[3-7]; and a review on medicinal cannabis recently completed by the Australian Government Department of Health.[8]

4.6   The UK has already registered a cannabis-derived drug (nabiximols, with the trade name Sativex) for spasticity in MS; this is currently controlled under Schedule 4. Other regulators have also recognised a shift in evidence for cannabis-derived drugs - on 25 June 2018 the US Food and Drug Administration (FDA) has licenced the GW drug Epidiolex, or purified cannabidiol, to treat Lennox-Gastaut syndrome and Dravet syndrome, rare forms of childhood epilepsy.

4.7   Evidence of harm has been extensively covered by the Advisory Committee on Misuse of Drugs (ACMD). I see no reason to revisit this; cannabis is an addictive and harmful drug. The evidence of harm from cannabis is also covered by the NASEM Report which finds clear evidence of harm including increased risk of schizophrenia, respiratory symptoms, increased risk of road traffic accidents and heightened probability of substance abuse. As there is a broad consensus on harms I have not included consideration of these in this review, which focuses solely on current evidence, or not, of potential beneficial medical uses.

5   The Health Effects of Cannabis and Cannabis-Like Products: Current State of Evidence

5.1   NASEM is equivalent to our Royal Society and Academy of Medical Sciences: a government-recognised but fully independent body of the most eminent scientists, including medical scientists, in the country. NASEM has international credibility as one of the leading scientific academies in the world.[†]

5.2   In 2016, in response to changes to the cannabis policy landscape in the USA, NASEM convened a committee of experts to conduct an evidence review of the short and long term health effects (harms and benefits) of cannabis and/or its constituents. The 'Committee on the Health Effects of Marijuana' brought together experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, respiratory disease, paediatric and adolescent health, immunology, toxicology, pre-clinical research, epidemiology, systematic review and public health. The Committee reported in 2017. I have used many of their original words to ensure the meaning remains consistent, but have added additional information, or points relevant to the UK context.

5.3   The Committee considered recently published systematic reviews and good quality primary research identified and assessed using published criteria; only fair- and good-quality reviews were considered. In my opinion the review of this committee can be considered the most rigorous and wide ranging to date. I therefore base most of what follows on their report. Findings published since NASEM's report do not, in my view, undermine their findings.

5.4   The committee considered therapeutic uses of cannabis and cannabinoids for the treatment of: chronic pain; cancer; chemotherapy-induced nausea/vomiting; anorexia and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis or spinal cord injury; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; dementia; glaucoma; traumatic brain injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia and other psychoses. There are potential indications not covered in this list and the number of potentially useful applications grows every year.

[†]   Declaration: I am a fellow of the Royal Society and Academy of Medical Sciences and an elected member of the National Academies of Sciences, Engineering and Medicine.

5.5   The Committee used **standard language on the weight of evidence** regarding whether cannabis or cannabinoid for therapeutic purposes is an effective or ineffective treatment.

a) **Conclusive evidence** - strong evidence from randomised control trials to support the conclusion that cannabis or cannabinoids are/are not an effective treatment.

b) **Substantial evidence** - several supportive findings from good quality studies with very few or no credible opposing findings.

c) **Moderate evidence** - several supportive findings from good- to fair-quality studies with very few or no credible opposing findings.

d) **Limited evidence** - supportive findings from fair-quality studies or mixed findings with most favouring one conclusion.

e) **No or insufficient evidence to support the association** - there are mixed findings, a single poor study, or a health endpoint has not been studied at all.

6 Conclusions on Cannabis or Cannabinoids with Potentially Psychoactive Components from NASEM's Report

6.1 **Conclusive or substantial evidence** that cannabis or cannabinoids are effective:
a) for the treatment of chronic pain in adults (cannabis);
b) as treatment for chemotherapy-induced nausea and vomiting (oral cannabinoids)
c) for improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

6.2 There is **moderate evidence** that cannabis or cannabinoids are effective for:
a) Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnoea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols)

6.3 There **is limited evidence** that cannabis or cannabinoids are effective for:
a) Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids)
b) Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids)
c) Improving symptoms of Tourette syndrome (THC capsules)
d) Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol[‡])
e) Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial)

6.4 There is **limited evidence** of a statistical association between cannabinoids and:
a) Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial haemorrhage.

6.5 NASEM found **no or insufficient evidence** to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:
a) Cancers, including glioma (cannabinoids)
b) Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids)
c) Symptoms of irritable bowel syndrome (dronabinol)
d) Epilepsy (cannabinoids)
e) Spasticity in patients with paralysis due to spinal cord injury (cannabinoids)
f) Symptoms associated with amyotrophic lateral sclerosis (cannabinoids)
g) Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids)
h) Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids)
i) Dystonia (range of movement disorders that cause muscle spasms and contractions) (nabilone and dronabinol)

[‡] Cannabidiol is not a controlled substance and is therefore not included in Schedule 1.

j) Achieving abstinence in the use of addictive substances (cannabinoids)
k) Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol)[§]

6.6 For many of the indications in (6.5) above, and other indications the Committee did not consider, there are individual case reports or case series implying benefit. There are therefore strong reasons to undertake double-blind randomised trials, and several of these indications are biologically plausible. The fact that cannabis is controlled and in Schedule 1, explains in part why such trials have not been undertaken. It is likely that some would be demonstrated to have therapeutic benefit, while some would be shown to have no benefit or benefit only in a definable subgroup.

[§] Cannabidiol is not a controlled substance and is therefore not included in Schedule 1.

7   HPRA Cannabis For Medical Use – A Scientific Review

7.1   In 2017 the HPRA (Irish equivalent of the Medicines and Healthcare Regulatory Authority) published a review of the potential medical uses of cannabis, in response to a request by the Republic of Ireland's Minister for Health. They found, at best, 'moderate benefits' from using cannabis in a small number of conditions and conflicting evidence, or no evidence at all for a large number of other medical conditions. The report concluded that based on the compelling anecdotal evidence and the (limited) scientific evidence, cannabis has potential therapeutic benefits, but that they need to be defined through peer-reviewed clinical research.

7.2   Should cannabis be permitted for medical purposes, the HPRA advised that cannabis should only be made available for the treatment of patients with specific medical conditions including:

   a)   spasticity associated with multiple sclerosis resistant to all standard therapies and interventions whilst under expert medical supervision;

   b)   intractable nausea and vomiting associated with chemotherapy, despite the use of standard anti-emetic regimes whilst under expert medical supervision; and

   c)   severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications whilst under expert medical supervision.

7.3   The restrictions advised by the HPRA are similar to those that are in place in some of the other countries where cannabis has been legalised for medicinal use.

8 WHO Expert Committee on Drug Dependence

8.1 In June 2018 the WHO Expert Committee on Drug Dependence (ECDD) convened a special a session dedicated to discuss a "critical[**]" review of cannabidiol and carry out several pre-reviews of cannabis and cannabis-related substances.

8.2 The WHO "critical" review of cannabidiol found that the most advanced clinical use of cannabidiol is for the treatment of some forms of epilepsy, with one pure cannabidiol product currently in Phase III clinical trials and multiple other smaller clinical studies demonstrating efficacy.[††]

[**] The "critical" review is an in-depth analysis that includes up to date evidence.
[††] Cannabidiol is not a controlled substance and therefore is not included in Schedule 1.

9   Australian Government Department of Health – Medicinal Cannabis Review

9.1   The Australian Government Department of Health commissioned the University of Sydney, University of New South Wales, and the University of Queensland under the coordination of the National Drug and Alcohol Council (NDARC) to review the available evidence for the use of medicinal cannabis for treating epilepsy, multiple sclerosis, nausea and vomiting, chronic pain and palliative care. This review was published in 2018 and informed by a systematic review of other systematic reviews and found:

a)   **Epilepsy** - limited but high quality evidence for the use of medicinal cannabis products in epilepsy;

b)   **Multiple sclerosis** - low to moderate quality evidence for treating symptoms of pain (pharmaceutical grade THC) and some evidence for treating spasticity (cannabidiol[‡‡]);

c)   **Nausea and vomiting** – some evidence of effective treatment but likely inferior to other treatment options;

d)   **Chronic pain** – some moderate evidence that patients using cannabinoids for MS related pain and for non-MS neuropathic pain experienced a decrease in their pain scores;

e)   **Palliative care** - some limited evidence but from a low number of generally poor quality studies.

[‡‡]   Cannabidiol is not a controlled substance and therefore is not included in Schedule 1.

10   Synthetic Cannabinoids Without Psychoactive Effects

10.1   The 2016 amendment to the Misuse of Drugs Act 1971, added a new generic structure definition to synthetic cannabinoids that captured within Schedule 1 a wide variety of compounds structurally similar to cannabinoids but not known to have any neurological implications.

10.2   As these compounds do not affect cannabinoid receptors in the brain and so are not considered to have the potential for addictive harm of cannabis they were outside the scope of the reviews considered here (the NAS report; the HPRA review; the WHO reviews; and the Australian Government Department of Health Review). Therefore, the evidence base around the potential benefits of these compounds cannot be summarised for this report.

10.3   Many pharmaceutical companies have cannabis-chemical-like drugs in their portfolio that now fall under the Misuse of Drugs Act but cause no known psychoactive effects. Compounds are routinely screened by pharmaceutical companies for cannabinoid CB1 activity and are usually not progressed if they are found to be active. The range of potentially useful drugs is constantly expanding and our research community have anecdotally reported multiple instances where research on potential new medicines has been blocked by the 2016 amendment of the Misuse of Drugs Act 1971.

10.4   It is scientifically difficult to defend moving cannabis and its immediate derivatives out of Schedule 1 yet to leave in Schedule 1 the potentially much more medically useful and likely less harmful drug classes captured within the generic definition of synthetic cannabinoids.

11   Recommendation

11.1   Schedule 1 drugs by definition have little or no therapeutic potential. As summarised in this review, there is now conclusive evidence of medicinal benefit of cannabis based products for certain medical conditions, and reasonable evidence of benefit for indications that they may be useful under restricted circumstances.

11.2   **My recommendation is that cannabis based medicinal products are moved out of Schedule 1 of the Misuse of Drugs Regulations 2001.** It may be pragmatic for them all to be moved to Schedule 2 pending a fuller review by ACMD that can differentiate different products into the appropriate different Schedules.

References

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2   Health Products Regulatory Authority, *Cannabis for Medical Use - A Scientific Review*, 2017. Available at https://www.hpra.ie/docs/default-source/publications-forms/newsletters/cannabis-for-medical-use---a-scientific-review.pdf?sfvrsn=7, (Accessed on 20 June 2018).

3   World Health Organization Expert Committee on Drug Dependence, *Cannabidiol (CBD) Critical Review Report*, 2018. Available at http://www.who.int/medicines/access/controlled-substances/WHOCBDReportMay2018-2.pdf?ua=1, (Accessed on 20 June 2018).

4   World Health Organization Expert Committee on Drug Dependence, *Cannabidiol (CBD) Expert Peer Review 1*, 2018. Available at http://www.who.int/medicines/access/controlled-substances/Cannabidiolpeerreview1.pdf?ua=1, (Accessed on 20 June 2018).

5   World Health Organization Expert Committee on Drug Dependence, *Cannabidiol (CBD) Expert Peer Review 2*, 2018. Available at http://www.who.int/medicines/access/controlled-substances/CannabidiolPeerreview2.pdf?ua=1, (Accessed on 20 June 2018).

6   World Health Organization Expert Committee on Drug Dependence, Pre-review: Cannabis plant and resin, 2018. Available at http://www.who.int/medicines/access/controlled-substances/ecdd_40_meeting/en/, (Accessed on 20 June 2018).

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8   Australian Government Department of Health Therapeutic Goods Administration, *Medicinal cannabis - guidance documents*, 2018. Available from https://www.tga.gov.au/medicinal-cannabis-guidance-documents, (Accessed on 20 June 2018).

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