RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

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Cannabis-based medicinal products

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POSITION STATEMENT

Position Statement on cannabis-based medicinal products

About this Position Statement

In September 2018, the Advisory Council for the Misuse of Drugs (ACMD)[1] recommended a change in the scheduling of cannabis-based medicinal products (CBMPs) to allow them to be prescribed by clinicians. Following this, the College convened an Expert Reference Group to examine the evidence and consider its position on cannabis relating to medicinal use, as well as recreational use (discussed in a separate, forthcoming statement). This position statement examines the existing evidence on CBMPs and how they relate to mental health.

Context

In November 2018, CBMPs were moved from Schedule 1 to Schedule 2 under the Misuse of Drugs Act[2]. This means it is now possible to prescribe these products under circumstances in which there is an unmet clinical need whereby:

- use is supported by clear clinical evidence or published guidelines
- alternative treatments have been unsuccessful.

This change in scheduling was primarily made to allow the prescription of CBMPs for non-mental health-related conditions such as such as epilepsy and multiple sclerosis. But since this change, prescribing rates of these products have been very low.[3] The possible reasons for this have been the subject of much debate.

There is also a larger global context. The recreational use of cannabis is now legal in Canada and 10 US States, and many other countries preceded the UK in allowing CBMPs to be prescribed, including Australia, Canada, and Germany. It is important to learn from the impact of these policy changes, including health outcomes and whether the prevalence and strength of recreational cannabis has been affected.

This global expansion of CBMPs has not coincided with an expansion of high-quality research into their effects. This paucity of research hampers regulators and governments in providing evidence-based guidance on the prescribing and control of these substances.

Scope

This Position Statement is primarily concerned with issues relating to CBMPs and mental health. It considers both the potential use of CBMPs for treating mental illness and the potential impact on mental health of prescribing CBMPs for non-psychiatric conditions. The statement does not focus specifically on the use of CBMPs for non-psychiatric conditions such as multiple sclerosis or cancer-associated nausea – we defer to bodies with expertise in these conditions for their perspective on the benefits or, otherwise, on CBMPs in these settings.

The College Position

There is a paucity of high-quality evidence supporting the use of CBMPs for any medical indication, as is reflected in the current NICE guidance and a recent meta-analysis and systematic review.[4, 5] When considering psychiatric indications, we are aware of the suggested potential for cannabidiol (CBD) to have some utility in treating psychosis, certain anxiety disorders, post-traumatic stress disorder (PTSD) and addiction to certain substances, but evidence is scarce. We welcome evidence of the potential benefits of CBMPs but caution that most of it comes from small-scale studies and the low rate of use worldwide means that the side effect and risk profile is not adequately evidenced.

There is a pressing need for more high-quality research examining the efficacy of these substances for specific psychiatric indications. Key organisations must act to reduce the barriers that exist to this research. In addition, given the potential adverse psychiatric consequences of CBMPs with tetrahydrocannabinol (THC) as an ingredient, the potential adverse consequences of the mass-prescription of cannabis products must be explored. Data from countries that have already allowed mass prescribing of cannabis or CBMPs will be crucial. If use of CBMPs is to become widespread, clinicians need guidance on how to prescribe these products effectively and safely.

We have received anecdotal claims of a gap between the understanding of the current evidence by some prescribers and patients, which leads to challenging clinical encounters. Without adequate guidance and public education, this gap is only likely to grow and become more common.

Key messages

1. There is a lack of high-quality evidence for the use of CBMPs for the treatment of mental illness.

2. More research is urgently needed on CBMPs in all health settings as the lack of research is the primary barrier to the prescription of CBMPs by health professionals.

3. Clinicians must be supplied with adequate guidance on how to prescribe CBMPs effectively and safely.

4. The propsychotic and anxiogenic properties of THC mean that CBMPs containing THC (other than as a very small proportion) are unlikely to be helpful for any psychiatric condition. If such products are prescribed in other health settings, clinicians must be aware of potential psychiatric complications.

5. Any change in practice of prescribing must be accompanied by a public education campaign in which people are informed of the potential health risks of cannabis use and discouraged from self-medication.

6. Psychiatrists are experienced in prescribing drugs with potential for misuse, dependence and side effects and so are well placed to assist in producing clinical guidance, even if on drugs used exclusively outside the psychiatric profession.

7. Regulators must consider the potential psychiatric implications of increasing prescriptions of CBMPs containing THC.

Current regulatory process system for CBMPs

CBMPs currently fall into three regulatory categories:

1. Licensed products

The synthetic or cannabis-derived products Nabilone, Dronabinol, Epidyolex and Sativex have been individually rescheduled under the Misuse of Drugs Regulations 2001 and have been granted a marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) or equivalent medicines regulatory body. All three products contain THC (Sativex in a 1:1 ratio with CBD) or have THC-like effects.

2. Special products

Unlike licensed medicines, these products have not undergone rigorous tests for quality, safety and efficacy and local medicines governance arrangements will include robust arrangements to safeguard patients where there is a clinical need to use an unlicensed medicine.

3. Food supplements

These products are derived from the cannabis plant but are not scheduled as they do not contain controlled substances. CBD oil sold through health shops is an example from this category.

Existing guidance for clinicians

- Association of British Neurologists statement on use of marijuana (cannabis) related products in the treatment of complex epilepsies
- British Paediatric Neurology Association Guidance on the use of cannabis-based products for medicinal use in children and young people with epilepsy
- Royal College of Physicians' recommendations on cannabis-based products for medicinal use
- NHS England guidance to clinicians: Cannabis-based products for medicinal use
- NICE guidance on cannabis-based medicinal products

Current practice on prescribing

Since the change in regulations, there has been an increase in the prescribing of CBD products, but there has been no increase in NHS prescriptions of THC-containing products. According to NHS England and NHS Improvement[6]:

- 111 patients have accessed Epidyolex through compassionate use and early access programmes ahead of a licensing decision by the European Medicines Agency.
- Intelligence from NHS England Controlled Drugs Accountable Officers indicates that, up until the end to March 2019, five patients had had private prescriptions issued for a CBPM in an independent secondary/tertiary care setting in England.
- Data from the NHS Business Services Authority (March 2019) indicates that there have been fewer than 10 NHS prescriptions for CBPMs issued in primary care since November 2018.

CBMPs used to treat mental illness

Below are the psychiatric disorders for which, following limited research, it has been suggested that CBMPs may be of potential benefit.

- Psychosis
- Social anxiety disorders
- Post-traumatic stress disorder (PTSD)
- Achieving abstinence in the use of addictive substances

Currently, the evidence in all these areas is sparse and in need of improvement through high-quality research. A recent review published in *The Lancet* has found that there 'remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. Further high-quality studies directly examining the effect of cannabinoids on treating mental disorders are needed.'[7]

Apart from the treatment of nightmares in PTSD, suggestion of beneficial effects in psychiatric conditions has only been reported for cannabidiol. Given the propsychotic and anxiogenic effects of THC, this is unsurprising and it seems highly unlikely that future research will find major psychiatric indications for THC-containing preparations.

Future research on CBMPs used to treat mental illness

There is a need for more well-designed and sufficiently-funded research into the efficacy of CBMPs for the treatment of mental illness. CBD is by far the most promising cannabis component and, as discussed above, it seems unlikely that THC-containing agents will have a significant role in psychiatric treatment. Some of the key areas of research we have identified that are needed are as follows.

Randomised control trials

These are the gold standard of scientific research and are the backbone of medical practice and yet there have been very few in the area of CBMPs for mental illness. There is a clear need for a wide availability of these and meta-analyses.

Pathways in and out of CBMP use

There is insufficient UK evidence available on pathways into (legal) use of CBMPs. This is something that needs adequate attention for us to understand the ways in which people can start and stop CBMP treatment(s) and what effects this can have on them.

Other research approaches

Some have argued against the need for RCTs as, given there are various formulations available and each has different effect on an individual, testing one specific formulation against a placebo will rarely succeed. However, a variation of formulations administered through observational and variable trials will show significantly higher effectiveness – sometimes by order of magnitude. Despite this, the College believes that RCTs are necessary and will play an important role in establishing an evidence base.

Barriers to research

A recent NHS review has highlighted that the lack of evidence about the long-term safety and effectiveness of medicinal cannabis has weighed heavily on prescribing decisions and has recommended that further clinical trials are set up.[8] Given the current lack of research, it is important to understand what these barriers are and how they can be overcome.

Scheduling

Barrier to research: In November 2018, Schedule 1 restrictions were lifted only in the context of a clinical trial for CBMPs (i.e. not cannabis in general). Schedule 1 drugs cannot be possessed or prescribed by clinicians, and research on them is only permitted under a Home Office licence that is costly and time-intensive to obtain. These restrictions still apply to other research studies on cannabis-based products/THC such as human and non-human experimental studies.

The research community has expressed concern that Schedule 1 from the Misuse of Drug Regulations (MDR) 2001 acts as a 'barrier to research'[9] and is an issue that has implications not just for cannabis but also for other Schedule 1 drugs for which a potential therapeutic benefit has been proposed.[10]

How to overcome this barrier: Relaxation of Schedule 1 of the Misuse of Drugs Act (MDA) in line with guidelines currently under review from the Advisory Council of the Misuse of Drugs (ACMD) to remove some of the barriers to conducting research with cannabis and THC.[11]

Lack of funding for research

Barrier to research: Given the global precedent of CBMPs being sanctioned without RCTs, many pharmaceutical companies are not keen to invest the large amounts of money needed to run these pieces of research. However, without substantial funding, the evidence for the efficacy of CBMPs won't allow for a change in current practice around prescribing.

How to overcome this barrier: We echo NHSE's recommendation that 'the National Institute for Health Research (NIHR) should support research into the five priority

research areas that have been identified by the draft National Institute for Health and Care Excellence (NICE) clinical guideline on the use of cannabis-based products for medicinal use.'[12]

In addition, it will be necessary for pharmaceutical companies to commission research. Pressure for them to do so could come from top-down pressure from Government and/or from continuous pressure from patient groups.[13]

Difficulty in finding research sponsors

Barrier to research: Most health or academic institutions will have no experience of research on CBMPs. Available regulatory guidelines may not be sufficient.

How to overcome this barrier: Better regulatory processes and encouragement from Government and its agencies.

Guidance on prescribing CBMPs

After sufficient careful research has been conducted, suitable guidance must be developed and provided to clinicians on how to prescribe CBMPs, as this will be essential to ensuring appropriate prescribing.

Misuse/diversion/addiction

Psychiatrists are experienced in prescribing drugs with potential for misuse, dependence and side effects. They are therefore well placed to assist in producing clinical guidance on drugs, even those used exclusively outside the psychiatric profession.

Psychiatrists may also be able to advise on:

- practical measures for prevention and early detection of misuse
- escalating use or diversion where appropriate (e.g. frequent instalment dispensing, a process for detecting if prescriptions are requested early or dose escalation is happening
- monitoring using biomarkers of compliance, safe storage of medication where children and young people are in the home, etc)
- how to help if dependence develops.

Patient information

We have received anecdotal claims of a gap between the understanding of the current evidence between some prescribers and patients, which leads to challenging clinical encounters. Without adequate guidance and public education, this gap is only likely

to grow and become more common. To address this, we welcome the commitment from NHS England, NHS Improvement and the Department of Health and Social Care (DHSC) to work together to develop clear information for patients and patient groups on the prescribing of cannabis-based products for medicinal use.[14]

Public health considerations

Links between CBMPs and recreational use

It is an increasingly common narrative that cannabis has substantial health benefits with a minimum of risks. Along with an increased public awareness of CBMPs, this means we need a greater understanding of the effects of CBMP prescriptions on the prevalence of use of recreational cannabis. To counter any risk, there needs to be a concerted effort to provide a public education programme that makes clear what the risks are to people's health when taking cannabis.

Summary

Although we welcome attempts to establish whether CBMPs could have established benefits in treating mental illness, we are concerned about:

- the current lack of high-quality evidence to guide decision-making
- the risks of CBMPs' potential impact on rising recreational use of cannabis
- the dearth of evidence on the effect of changing practice
- the absence of guidance for clinicians on prescribing.

Conducting high-quality research is a pressing priority. Following this, adequate guidance must be provided for clinicians and patients. This is a complicated area of quick growth and high public interest but it must be treated with the care and attention it deserves.

Appendix A: Glossary

Cannabidiol (CBD) – A key component of cannabis, accounting for up to 40% of the plant's extract, it is without psychoactive properties.

Cannabis for recreational use – The consumption of cannabis products not prescribed medically.

Cannabis-based medicinal products – Also known as cannabis-based products for medicinal use or cannabis derived medicinal products, we follow the definition set out by the UK Government in the 2018 Regulations, summarised as follows: A product that contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers); is produced for medicinal use in humans and is a medicinal product, or a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product.

Randomised control trial (RCT) – A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.

Special products – The MHRA defines a 'special' as a product which "has been specially manufactured or imported to the order of a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber for the treatment of individual patients".

Tetrahydrocannabinol (THC) – A cannabinoid found in cannabis and the primary psychoactive element in cannabis.

References

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3 Independent (2019) https://www.independent.co.uk/life-style/health-and-families/health-news/medicinal-cannabis-legalised-access-marijuana-nhs-a8903051.html

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