National Institute for Health and Care Excellence

Final

# Cannabis-based medicinal products

## Appendix 1 – Expert witness report - Cannabinoid Psychopharmacology - Tom Freeman, Addiction and Mental Health Group (AIM), Department of Psychology, University of Bath

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*Evidence reviews*

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*These evidence reviews were developed by NICE Guideline Updates Team*

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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# Cannabinoid Psychopharmacology

The cannabis plant produces at least 144 cannabinoids, but most clinical research has focused on THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol). Biosynthesis of THC and CBD differs across cannabis plants with three main chemotypes: THC dominant, CBD dominant, and mixed THC/CBD. This means that plants producing high concentrations of THC typically produce minimal CBD, and vice versa. The chemotype (and therefore THC/CBD profile) of cannabis-based products for medicinal use may contribute to their therapeutic indications and safety. Terpenoids (e.g. limenene, α-pinene, β-myrcene, linalool) may also contribute to efficacy and safety, although evidence is limited at present.

Cannabinoids such as THC and CBD act on the endocannabinoid system which includes cannabinoid receptors (e.g. CB1Rs and CB2Rs), endocannabinoids (e.g. anandamide, 2-AG), and enzymes (e.g. Fatty Acid Amide Hydrolase; FAAH). Endocannabinoids are synthesised on demand and play a modulatory role in several key biological processes. CB1Rs are primarily located in the central nervous system and CB2Rs in the peripheral nervous system. THC is a partial agonist at CB1Rs and CB2Rs, whereas CBD has a broad range of targets. Within the endocannabinoid system, CBD has minimal direct activity at CB1Rs and CB2Rs, but it acts as a negative allosteric modulator at CB1Rs, preventing other ligands from binding to these receptors. CBD inhibits FAAH, which increases endocannabinoid levels. CBD has several targets beyond the endocannabinoid system, e.g. agonist at 5-HT1ARs, and partial agonist at D2highRs.

Systematic reviews with Grading of Certainty of Evidence have found low to moderate certainty evidence assessing cannabinoids for the treatment of chronic pain, spasticity in multiple sclerosis, treatment resistant epilepsy, and nausea and vomiting due to chemotherapy. The primary products tested in these studies are Sativex (THC+CBD), Epidiolex (CBD), and Dronabinol (synthetic THC). Adverse effects of THC include disorientation, dizziness, euphoria, confusion and drowsiness; there is some evidence of withdrawals from clinical trials due to adverse events. CBD is safe and well tolerated; adverse events include sedation, diarrhoea, abdominal discomfort and headache. Possible drug-drug interactions include mania following THC with fluoxetine (potentially due to a CYP2D6 mechanism), and delirium and hypomania following THC with disulfiram (unknown mechanism). Plasma CBD concentrations may be decreased by CYP3A4 inducers (e.g. rifampicin) and increased by CYP3A4 inhibitors (e.g. ketoconazole). CBD can inhibit CYP2C19 enzymes, which may increase plasma concentrations of drugs such as clobazam and their associated side effects. THC and CBD may exacerbate the effects of central nervous system depressants such as alcohol. CBD is not dependence forming, but clinicians should monitor for the possible development of dependence on THC. Withdrawal symptoms can occur following cessation of THC in dependent cannabis users. These peak at four days of cessation, reduce by seven days, and remit at 14 days. Tolerance and withdrawal to THC may be accompanied by downregulation of cannabinoid receptors, which can be rapidly reversed (e.g. after two days of abstinence).

Cannabis-based products for medicinal use can be administered using a vaporizer. The use of ground cannabis flower may require care in order to achieve standardised dosing. A Dutch study indicated that patients reported using 0.3 grams cannabis per dose regardless of its THC/CBD profile. After intrapulmonary administration, bioavailability is 10-35% for THC and 11-45% for CBD. Peak plasma concentrations occur 6-10 minutes after onset. THC is metabolised by cytochrome P450 enzymes, primarily in the liver. THC rapidly penetrates vascularised tissues and then accumulates in body fat (THC and 11-OH-THC). THC has a

fast initial half-life (6 minutes) followed by a slow terminal half-life (22 hours) due to prolonged release from lipid stores.

Subjective effects following intrapulmonary administration peak at 15-30 minutes and decrease progressively up to 4 hours. Experimental psychopharmacology studies have used dosing schedules such as 6mg THC followed by 1mg THC every 30 minutes, or 8mg THC followed by 4 mg THC 90 minutes later, to maintain stable subjective effects over time. Cannabinoids for oral administration can be formulated in capsules or oils, providing fixed doses for patients (e.g. 10mg THC or 10mg THC + 10mg CBD). Bioavailability for oral administration is 2-14% for THC and 13-19% for CBD, with significant first pass metabolism in the liver. Peak THC plasma concentrations occur at 1-2 hours and subjective effects can last from 1-8 hours, peaking from 2-4 hours. Oral administration can require fewer repeated doses to maintain clinical benefit when compared to intrapulmonary administration.

Experimental psychopharmacology studies have found that people with and without psychosis respond differently to THC. Additionally, adolescents respond in a contrasting way to adults. Specific considerations may be necessary for people with mental health disorders and in different age groups. CBD may offset some of the acute effects of THC such as paranoia and memory impairment. However, these findings are not entirely consistent and dose-response effects are unclear. Functional impairment of driving may occur at plasma concentrations of 5ng/ml THC, while 2ng/ml THC is a driving offence in the UK. For people with low exposure to THC (1-2 days per week) a single intrapulmonary dose of 16mg THC may result in plasma concentrations of ≤5 ng/ml THC at 2 hours and ≤1 ng/ml THC at 7 hours. Among people with daily THC exposure, 11 out of 22 participants had plasma concentrations of ≥1ng/ml THC by 24 hours abstinence; none had concentrations indicative of functional driving impairment (≥5ng/ml THC). By seven days of cessation, all participants reached ≤1 ng/ml THC. THC can be detected in plasma for as long as 30 days of abstinence following daily use, but only in a minority (2 out 22 participants) and at very low levels that are not associated with driving impairment (0.25 ng/ml THC). THC readily crosses the placenta; fetal plasma concentrations may be 1/3$^{rd}$ of those in maternal plasma (intrapulmonary administration) or 1/10$^{th}$ of those in maternal plasma (oral administration). THC passes into breast milk and accumulates after long-term administration; a nursing infant might consume 0.01-0.1mg THC daily from a mother using cannabis every day.

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