CBD THC CBD:THC INSUFFICIENT

Cannabinoid Therapeutics
Clinical Evidence Reference

Non-promotional evidence matrix for UK prescribers mapping 18 indications across 5 evidence levels

VERSION 1.0 WORKING DRAFT 27 REFERENCES

References and regulatory positions require independent verification before external clinical, regulatory, or promotional use. This document does not constitute medical advice.

01 / PURPOSE

This reference maps clinical evidence strength, not prescribing recommendations

Summarises the relative evidence base for CBD, THC, and CBD:THC products across 18 indications. Identifies which molecule has the prevailing evidence and the strength of that evidence for each indication.

01

Evidence mapping

Covers 18 clinical indications across 5 evidence levels, from licensed/strongest (Level 1) to preclinical (Level 5)

02

Molecule identification

For each indication, identifies whether CBD, THC, or a combination has the prevailing evidence base

03

Not a prescribing recommendation

Does not replace patient-specific clinical judgement, product-specific regulatory review, or local governance

04

UK prescriber focus

Intended for clinicians working within licensed-medicine and Specials pathways in UK practice

Five-level evidence grading from licensed/strongest to preclinical

Each indication is assigned a single evidence level based on the strongest available clinical data

1

LICENSED / STRONGEST

Multiple Phase 3 RCTs and/or regulatory approval in the indication

4 indications

2

STRONG RCT

Single adequately powered Phase 3 RCT

1 indication

3

MODERATE

Phase 2 RCT(s) or meta-analysis of moderate-quality trials

6 indications

4

EMERGING

Open-label, observational cohort, or single small RCT

6 indications

5

PRECLINICAL

Preclinical or mechanistic data only

1 indication

Four molecule categories define the colour system throughout this reference

Colour coding reflects which molecule has the prevailing clinical evidence, not clinical superiority

11 **CBD** Cannabidiol

11 OF 18 INDICATIONS

Prevailing evidence across epilepsy, psychiatry, addiction, and emerging indications

3 **THC** Tetrahydrocannabinol

3 OF 18 INDICATIONS

Prevailing evidence in CINV, AIDS-related wasting, and Tourette's syndrome

3 **CBD : THC** Combination

3 OF 18 INDICATIONS

Prevailing evidence in MS spasticity, cancer pain, and neuropathic pain

1 **Insufficient** Evidence

1 OF 18 INDICATIONS

Evidence base too weak to assign a prevailing molecule (TBI sequelae, preclinical only)

The prevailing molecule is an evidence-strength judgement, not a treatment recommendation. Full clinical decision-making must consider patient-specific factors, contraindications, and licensing status.

CBD has the strongest evidence of any cannabinoid in drug-resistant epilepsy

Epidyolex
Cannabidiol oral solution, UK licensed

INDICATION 1

Dravet Syndrome

1 LICENSED / STRONGEST

Pivotal Phase 3 RCT demonstrated significant reduction in convulsive seizure frequency at 10 to 25 mg/kg/day as adjunctive therapy.

Refs: Devinsky 2017 [1], Devinsky 2018 [2]

INDICATION 2

Lennox-Gastaut Syndrome

1 LICENSED / STRONGEST

Two Phase 3 RCTs showed significant reduction in drop seizures. Approved as adjunctive treatment for seizures associated with LGS.

Refs: Devinsky 2018 [2], Thiele 2018 [3]

INDICATION 3

Tuberous Sclerosis Complex

1 LICENSED / STRONGEST

Phase 3 RCT demonstrated significant seizure reduction. Extended the licensed indication for Epidyolex to TSC-associated seizures.

Refs: Thiele 2021 [4]

⚠ **THC contraindicated:** Pro-convulsant risk and absence of paediatric safety data. No role in epilepsy management.

⚠ **Hepatic monitoring required:** Baseline and periodic LFTs per Epidyolex labelling, particularly with concomitant valproate.

Sativex and Nabilone hold Level 1 evidence in their respective indications

The only indications where THC or THC:CBD products reach the highest evidence tier

MS-Related Spasticity

Sativex (nabiximols)

THC:CBD 1:1 oromucosal spray | UK licensed

LEVEL 1 — LICENSED / STRONGEST

KEY EVIDENCE

Two pivotal Phase 3 RCTs and an enriched-design responder trial demonstrate efficacy for MS-related spasticity inadequately responsive to other antispastics. CBD monotherapy has no robust evidence in this indication.

Refs: Collin 2007 [20], Novotna 2011 [21]

Chemotherapy-Induced N&V

Nabilone (Cesamet)

Synthetic THC analogue | UK licensed

LEVEL 1 — LICENSED / STRONGEST

KEY EVIDENCE

Nabilone and dronabinol are both supported by Phase 3 RCTs and meta-analyses. Nabilone is licensed in the UK as Cesamet for CINV. CBD has no licensed CINV indication and limited data in this area.

Refs: Tramer 2001 [17], Whiting 2015 [18]

CBD monotherapy has no robust evidence in either of these indications. THC or THC:CBD products are the prevailing molecules.

Cancer pain and neuropathic pain show evidence signals but mixed Phase 3 results

AIDS-related wasting retains the strongest THC evidence outside licensed indications

INDICATION & LEVEL	MOLECULE & EVIDENCE	UK STATUS & VERDICT
AIDS-Related Wasting 2 STRONG RCT	THC Dronabinol (synthetic THC) supported by Beal 1995/1997 trials demonstrating appetite stimulation and weight stabilisation. FDA-approved as Marinol. CBD has no clinical evidence for appetite stimulation. Refs: 16, 17, 18	**Specials / unlicensed only** Not UK-licensed. Available via Specials import on consultant authorisation. THC analogue has strongest evidence.
Cancer Pain 3 MODERATE	CBD : THC Earlier Phase 2/3 trials positive (Johnson 2010, Portenoy 2012) but subsequent Phase 3 failed primary endpoints (Lichtman 2018). CBD monotherapy not supported in cancer pain. Refs: 18, 22, 23, 24	**Sativex (off-label)** Licensed product used off-label. Evidence signal exists; mixed Phase 3 results. Specialist justification required.
Chronic Neuropathic Pain 3 MODERATE	CBD : THC Whiting 2015 meta-analysis shows modest effects for CBD:THC on central neuropathic pain. CBD monotherapy data weak. THC monotherapy poorly tolerated at therapeutic doses. Refs: 18, 22, 23, 24	**Sativex (off-label)** UK guidance does not support routine cannabinoid prescribing for chronic pain. NICE CAUTION

⚠ PSYCH CAUTION

CBD shows positive psychiatric signals; THC is contraindicated in all psychiatric indications

INDICATION	LEVEL	KEY EVIDENCE	VERDICT
Schizophrenia (Adjunct) CBD monotherapy or adjunct	3 MODERATE	Leweke 2012: CBD vs amisulpride, comparable efficacy. McGuire 2018: CBD adjunct 600-800 mg/day, positive primary endpoint. Boggs 2018: negative at lower dose. Refs 5, 6, 7, 8	CBD has only positive evidence; THC contraindicated
Social Anxiety / Acute Performance Anxiety Acute single-dose studies	3 MODERATE	Bergamaschi 2011, Crippa 2011, Linares 2019: acute-dosing RCTs at 300-600 mg showing reductions in anticipatory and performance anxiety. No chronic Phase 3 data. Refs 9, 10, 11	CBD has small acute-dose RCT support; not licensed
Generalised Anxiety Disorder Chronic dosing extrapolation	4 EMERGING	No chronic-dosing Phase 3 data. Evidence extrapolated from acute social anxiety studies. Chronic GAD efficacy not established. Refs 9, 10, 11	CBD has emerging signal; chronic efficacy not established

⚠ **THC contraindicated across all psychiatric indications.** Anxiogenic at higher doses, associated with psychosis onset. Personal or family history of psychotic disorders, active substance use disorder are absolute contraindications.

Emerging CBD signals in PTSD and addiction; THC for Tourette's under specialist supervision

4 EMERGING CBD

⚠ PSYCH CAUTION

PTSD

Elms 2019 case series (11 patients, oral CBD adjunctive) showed reduced PTSD symptom severity. Bonn-Miller 2021 open-label data provide additional support. Smoked cannabis observational work is methodologically weaker and confounded by THC.

CBD has emerging signal; investigational only

Refs: 12, 25

3 MODERATE CBD

⚠ PSYCH CAUTION

Opioid / Cannabis Use Disorder

Hurd 2019 Phase 2 RCT: CBD reduced cue-induced craving and anxiety in heroin use disorder. Freeman 2020 Phase 2: CBD for cannabis use disorder showed positive Bayesian signal. THC is contraindicated in addiction medicine.

CBD has emerging Phase 2 support; THC contraindicated

Refs: 13, 14

3 MODERATE THC

Tourette's Syndrome

Muller-Vahl small Phase 2 work supports nabilone (THC analogue) for tic reduction. CBD has minimal data in this indication. Off-label use of nabilone under specialist supervision only.

THC analogue has limited supportive data

Refs: 19

PTSD and substance use disorder rows carry PSYCH CAUTION tags. THC is contraindicated in addiction medicine and carries psychosis-onset risk in PTSD populations.

Parkinson's, autism, insomnia, and TBI represent early-stage CBD signals

All four indications are CBD-dominant; THC has no evidence base in any of these areas

4 Parkinson's Disease

EMERGING

CBD (weak signal)

Small RCTs (Chagas 2014; Peball 2020 in REM sleep behaviour disorder) suggest CBD may help non-motor symptoms. Motor evidence is weaker.

Refs: 15

4 Autism (Irritability, Behaviour)

EMERGING

CBD-rich (20:1)

Aran 2019 RCT of CBD-rich extract (CBD:THC 20:1) in children with severe autism showed modest improvements in disruptive behaviour and anxiety.

Refs: 15

4 Insomnia Disorder

EMERGING

CBD (emerging)

Narayan 2024 pilot RCT (150 mg nightly CBD) provides initial controlled data. THC reduces sleep latency acutely but disrupts architecture and shows tolerance. CBD preferred.

Refs: 26

5 Traumatic Brain Injury / TBI Sequelae

PRECLINICAL

CBD (investigational)

Aychman 2023 review supports CBD neuroprotective rationale based on anti-inflammatory and antioxidant mechanisms. No human efficacy data established.

Refs: 27

- **All four indications are CBD-dominant.** THC has no evidence base and is generally unsuitable due to psychiatric risk profiles in these patient populations. Specialist supervision essential for any Specials prescribing.

UK cannabinoid prescribing spans three distinct regulatory categories

Prescribers must explicitly identify the applicable pathway before prescribing

PATHWAY A

Licensed Medicines

Epidyolex | Sativex | Cesamet

Full UK marketing authorisation. Standard prescribing and dispensing pathways apply. These are the only three cannabinoid-based medicines with licensed indications in the UK.

Prescribing: Any registered medical practitioner may prescribe within the licensed indication. Off-label use requires specialist justification.

PATHWAY B

CBPM (Schedule 2)

THC-containing unlicensed products

Cannabis-based products for medicinal use under Misuse of Drugs Regulations 2018. Any product containing THC above trace levels that is unlicensed falls into this category.

Prescribing: Restricted to specialists on the GMC Specialist Register. Prescribers should document treatment details, clinical outcomes, and adverse events, and use local or national registers where available.

PATHWAY C

Pure CBD Specials

Pharmaceutical-grade CBD, negligible THC

Pure CBD-only medicinal products with negligible THC may fall outside the CBPM controlled-drug framework. However, if supplied for a therapeutic indication, they remain medicines under the applicable MHRA licensed or unlicensed/Specials framework.

Prescribing: Not subject to Schedule 2 obligations or Specialist Register restriction. Formal legal/regulatory confirmation should be obtained before external use.

The regulatory classification of a specific product depends on its composition, THC content, and intended use. This summary is for general orientation only and does not constitute legal advice.

Eight mandatory requirements for Specials prescribing in UK practice

All eight conditions must be satisfied before initiating an unlicensed cannabinoid product

01

Particular patient under specialist care

Not for general population prescribing. Patient must be under the direct care of a specialist clinician.

02

Special clinical need not met by a licensed medicine

Documented in the patient record with clinical rationale for why licensed alternatives are unsuitable.

03

Clinical responsibility accepted by prescribing physician

Specials dispensed against the named clinician's judgement. Responsibility cannot be delegated.

04

MHRA reporting and pharmacovigilance compliance

Adverse events reported via **Yellow Card**. Ongoing safety monitoring throughout treatment.

05

Batch traceability maintained

Importer/manufacturer documentation retained per dispensing event for full supply chain audit.

06

Informed consent documented

Patient understands the unlicensed status and consents to the specific product being prescribed.

07

CBD-class hepatic monitoring

Baseline and periodic LFTs per Epidyolex labelling, particularly with **concomitant valproate**.

08

Drug-interaction screening

CBD-CYP3A4 and CYP2C19 interactions; THC-warfarin; common psychotropics. Screen before initiation.

CBD and THC have clinically significant CYP450 and pharmacodynamic interactions

Screen all concomitant medications before prescribing. Full quick-reference card provided separately.

PHARMACOKINETIC (CYP450 MEDIATED)

CBD

CYP3A4 & CYP2C19 inhibitor

CYP3A4 inhibition	**Clobazam** ↑, **midazolam** ↑, **tacrolimus** ↑, **everolimus** ↑ — monitor levels and reduce doses
CYP2C19 inhibition	**Clobazam** (N-desmethyl) ↑, **SSRIs** ↑, **warfarin** ↑, **phenytoin** ↑ — INR and TDM monitoring
UGT pathway	**Valproate** — combined hepatotoxicity risk; baseline and periodic LFTs mandatory

THC

CYP3A4 substrate

Levels increased by	**Ketoconazole**, **ritonavir**, **clarithromycin** ↑ — CYP3A4 inhibitors raise THC exposure; increased CNS effects
Levels decreased by	**Rifampicin**, **carbamazepine**, **phenytoin** ↓ — CYP3A4 inducers reduce THC efficacy
Warfarin	**THC + warfarin** ↑ INR — enhanced anticoagulant effect; close INR monitoring required

PHARMACODYNAMIC INTERACTIONS

CBD + Valproate

Additive hepatotoxicity. Transaminase elevations documented at high CBD doses. LFT monitoring mandatory per Epidyolex labelling.

HIGH SEVERITY

THC + CNS Depressants

Additive sedation with opioids, benzodiazepines, alcohol, gabapentinoids. Dose adjustment and patient counselling required.

HIGH SEVERITY

THC + Sympathomimetics

Additive tachycardia and hypertension risk. Caution with stimulants and decongestants in cardiovascular-risk patients.

MODERATE SEVERITY

Caveats and Limitations

This reference defines explicit boundaries on its scope, accuracy, and intended use. All users must read and accept these limitations before relying on any content.

DOCUMENT STATUS

WORKING DRAFT V1.0

CLASSIFICATION

NON-PROMOTIONAL

01 **Working draft status**

This document is a working draft. It has not been finalised, peer-reviewed, or approved for external distribution. Content may change without notice.

02 **Evidence-strength mapping only**

Maps relative evidence strength across indications. Does not constitute prescribing recommendations, clinical guidelines, or treatment protocols.

03 **Independent verification required**

All references, regulatory positions, and clinical claims require independent verification before any external clinical, regulatory, or promotional use.

04 **Non-promotional and product-neutral**

This document does not promote any specific product, company, or commercial interest. No endorsement is implied by the inclusion of any product name.

05 **Not a substitute for clinical judgement**

Patient-specific treatment decisions remain the responsibility of the prescribing clinician. This reference does not replace local governance or formulary processes.

06 **Regulatory positions may change**

UK regulatory and NICE guidance positions are subject to change. Always check the current MHRA, NICE, and BNF sources before prescribing.

07 **Specials framework classification**

Pure CBD products with negligible THC may fall outside CBPM controlled-drug obligations but remain medicines under the applicable MHRA licensed or unlicensed/Specials framework.

Cannabinoid Therapeutics: Clinical Evidence at a Glance

18

Indications Mapped

Across epilepsy, neurology, psychiatry, pain, oncology, addiction, sleep, and emerging areas

5

Evidence Levels

From Level 1 Licensed/Strongest through to Level 5 Preclinical

3

UK-Licensed Medicines

Epidyolex, Sativex, and Cesamet hold marketing authorisations

27

References Cited

Peer-reviewed trials, meta-analyses, and regulatory sources

RECOMMENDED NEXT STEPS

01

Verify independently

All references, regulatory positions, and evidence grades require independent verification before external clinical, regulatory, or promotional use.

02

Consult product-specific guidance

Review SmPCs, NICE guidance, and local governance frameworks before initiating any cannabinoid prescribing. Patient-specific factors must guide decisions.

03

Report adverse events

All suspected adverse reactions should be reported via the MHRA Yellow Card scheme. Ongoing pharmacovigilance is essential for all cannabinoid products.

Working Draft v1.0 | Non-promotional clinical reference for UK prescribers. Does not constitute medical advice. This document does not replace patient-specific clinical judgement, product-specific regulatory review, or local governance.