Reviews #4 and #5

A rapid evidence summary of the literature evidencing the relationship between cannabis use and health benefits/deficits

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Context. This review was limited to existing systematic reviews of the literature, given the volume of material in the area. The review was intended to be broad, with the purpose of informing debate among attendees at a Cannabis-specific conference. Searches were conducted in Web of Science in December 2022 (see page 20 for search strategy). Of note, this review is not intended to be used as a reference point for scientific writing. It is purposively written for a broad audience in particular, those not accustomed to reviewing the scientific literature.

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> *Variability in the methodologies used in cannabis research makes it challenging to draw conclusions about dosing, routes, and frequency of administration. Most of the existing evidence suggests that medical cannabis use is effective, but this efficacy has been demonstrated only when either there is no comparator, or cannabis is compared with placebo. Studies using an active comparator have not demonstrated efficacy.*
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> Madden et al., 2019[1]

> *The evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis, or CBM (cannabis-based medicines) in the management of pain.*
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> Fisher et al., 2021[2]

> *Results from the included reviews were mixed, with most reporting an inability to draw conclusions due to inconsistent findings and a lack of rigorous evidence. Mild harms were frequently reported, and it is possible the harms of cannabis-based medicines may outweigh benefits.*
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> Pratt et al., 2019[3]

> *Evidence shows a clear association between cannabis use and psychosis, affective disorders, anxiety, sleep disorders, cognitive failures, respiratory adverse events, cancer, cardiovascular outcomes, and gastrointestinal disorders. Moreover, cannabis use is a risk factor for motor vehicle collision, suicidal behaviour, and partner and child violence…There is still little data on the dose-dependency of these effects; evidence is essential in order to define, from a public health perspective, what can be considered risky use of cannabis.*

[1] Madden, K., et al. (2019). Cannabis for pain in orthopaedics: a systematic review focusing on study methodology. *Canadian Journal of Surgery, 62*, 369-380.
[2] Fisher, E., et al. (2021). Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomized controlled trials. *Pain, 162*, S1, S45-S66.
[3] Pratt, M., et al. (2019). Benefits and harms of medicinal cannabis: a scoping review of systematic reviews. *Systematic Reviews, 8(1).*

Campeny et al., 2020[4]

> *…the report concluded that there was conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of pain in adults; chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis. Moderate evidence was found for secondary sleep disturbance. The evidence supporting improvement in appetite, Tourette syndrome, anxiety, PTSD, cancer, irritable bowel syndrome, epilepsy and a variety of neurodegenerative disorders was described as limited, insufficient, or absent.*
>
> Abrams, 2018[5]

Background.

The two main compounds of cannabis with analgesic and anti-inflammatory properties are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). Cannabidiol is a non-psychotropic cannabinoid that has recently drawn attention of clinicians and researchers for its potential therapeutic applications. These cannabinoids bind to the endocannabinoid system receptors in the human brain.

In the UK, Cannabis is currently classified (Misuse of Drugs Act, 1971) as a class B drug, with few exceptions. In many Western countries, the legal status of Cannabis is being considered, with widespread discussion about the potential benefits of more liberal Cannabis-specific legislation. One issue currently is the availability of increasing numbers of cannabis-based products, which can make potential side-effects of use in medical settings more unpredictable. Over time, changes in the strength of available cannabis have been observed. In one review, authors reported that for herbal cannabis, THC concentrations had increased by 0.29% each year (statistically significant $p < .001$) based on 66,747 samples from eight studies between 1970 and 2017[6]. For Cannabis resin, THC concentrations increased by 0.57% each year ($p = 0.017$) based on 17,371 samples from eight studies between 1975 and 2017. There was no evidence for changes in CBD in herbal cannabis, or in cannabis resin[6].

Overall, the evidence for the use of cannabidiol as a treatment for non-seizure-related health conditions has been inconsistent. In a review of health professionals' knowledge, beliefs and concerns about medical cannabis published in 2019, Gardiner et al.[7] indicated that the general impression of these professionals was in support of the use of medical cannabis, yet at the same time, there was a unanimous self-perceived lack of knowledge surrounding all aspects of medical cannabis.

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[4] Campeny, E., et al. (2020). The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms. *European Neuropsychopharmacology, 33*, 1-35.
[5] Abrams, D. (2018). The therapeutic effects of Cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report. *European Journal of Internal Medicine, 49*, 7-11.
[6] Freeman, T., et al., (2021). Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. *Addiction, 116*, 1000-1010.
[7] Gardiner, K., et al. (2019). Health professional beliefs, knowledge, and concerns surrounding medicinal cannabis – A systematic review. *Plos ONE, 14(5).*

Abbreviations

AE = Adverse event
CI = Confidence intervals
CBD = Cannabidiol
CNCP = Chronic non-cancer pain.
NNT = Number needed to treat
NNH = Number needed to harm
OR = Odds ratio
RCT = Randomised Controlled Trial
THC = Tetrahydrocannabinol

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There now follows some extracted information on a range of health-related conditions or topics.

Erectile dysfunction. Pizzol et al. (2019) reported that the overall prevalence of erectile dysfunction in cannabis users was 69.1% (38.0-89.1), whilst the corresponding figure in controls was 34.7% (20.3-52.7). The odds of having erectile dysfunction in cannabis users was higher than in controls (Odds ratio = 3.83, 1.30-11.28, p = .02)[8].

Cannabinoids have been suggested to potentially help with some symptoms of **autism spectrum disorder** such as problem behaviours, sleep problems, and hyperactivity, with limited cardiac and metabolic side effects. The use of cannabinoids generally allowed for a reduction in the number of prescribed medications and lead to a decreased frequency of seizures in patients with comorbid epilepsy[9].

The use of cannabinoids is a developing area in **Urology**. Here, some evidence has been presented for the therapeutic potential of cannabinoids in the management of specific benign urological diseases, notably neurogenic bladder dysfunction (clinical studies), renal disease (animal studies) and interstitial cystitis (animal studies). However, whilst increasingly used, they cannot currently be considered reliable alternatives to more recognised treatments[10].

Multiple Sclerosis (MS). Cannabis and cannabinoids have been used among MS patients to treat spasticity (muscle stiffness) and pain. There is some preliminary evidence for the role of psychological interventions, and cannabis extract in the treatment of insomnia in MS patients[11]. Five reviews in this area concluded that there was sufficient evidence that cannabinoids may be effective for symptoms of pain and/or spasticity in MS, with few reviews reporting positive conclusions for other symptoms. In summary, recent high-quality reviews find that cannabinoids may have modest effects in MS for pain and spasticity[12]. In addition, and in terms of cost, some review work has suggested that prescribed cannabis-

[8] Pizzol, D., et al. (2019). Relationship between Cannabis use and Erectile Dysfucntion: A systematic review and meta-analysis. *American Journal of Men's Health, 13(6).*
[9] Fusar-Poli, L., et al. (2020). Cannabinoids for people with ASD: A systematic review of published and ongoing studies. *Brain Science, 10,* 572.
[10] Taylor, C., & Birch, B. (2021). Cannabinoids in Urology. Which benign conditions might they be appropriate to treat: A systematic review. *Urology*, 148, 8-25.
[11] Bacaro, V., et al. (2021). Efficacy of interventions for improving health in patients with multiple sclerosis on insomnia symptoms and sleep quality: A systematic review of randomized controlled trials. *Journal of Behavioral and Cognitive Therapy, 31,* 137-145.
[12] Nielsen, S., et al. (2018). The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews. *Current Neurology and Neuroscience Reports, 18(2).*

based medicines are a potentially cost-effective add-on treatment for MS spasticity, however the evidence is uncertain, and further RCTs with economic analyses built-in are required[13].

Lennox-Gastaut syndrome (LGS). This is a severe development epileptic encephalopathy accompanied by seizures. A number of trials have reported potential benefits of cannabinoid use. For example, patients reporting a ≥ 50% drop in seizures were 40.3% with CBD, and 19.3% with placebo (Risk ratio = 2.12, 95% CI = 1.48-3.03). Adverse events (AEs) included somnolence, decreased appetite, diarrhoea, and increased serum aminotransferases. It was concluded that CBD resulted in a greater reduction in seizure frequency and a higher rate of AEs than placebo in patients with LGS presenting seizures uncontrolled by concomitant antiepileptic drugs[14]

Cannabis and violence. Studies have examined the relationship between cannabis use and 'harm-to-others' involving violence and aggression. A moderately positive association between cannabis use and perpetration of physical (including intimate partner) violence risk may be elevated by intense use patterns[15].

One systematic review suggested that cannabidiol had an anorexigenic effect, correlated with a decrease in body weight. However, most of the studies examined came with a risk of bias, and the authors suggested that further research was needed to clarify potential mechanisms involved in the effect of cannabidiol on feeding/appetite[16].

Parkinson's Disease (PD). The positive effects on motor (5 studies) and non-motor symptoms (4 studies) described in uncontrolled studies have not been confirmed by the few and small-sized Randomised Controlled Trials (RCTs) undertaken. Only one RCT found a reduction of levodopaininduced dyskinesias, another a reduction in anxiety and tremor amplitude in an anxiogenic situation, while the remaining three reported no effect on motor/non-motor symptoms. Authors concluded that there is insufficient evidence to reform international legislation regarding cannabis use in PD practice[17]. Based on the available data, others concluded that there is currently insufficient data to support the administration of cannabinoids to PD patients, with a call for larger RCTs[18]. Again, elsewhere authors suggested that no compelling evidence had been found to recommend the use of Cannabis in PD patients. However, a potential benefit was identified with respect to alleviation of PD related tremor, anxiety, pain, improvement of sleep quality, and quality of life. Authors again highlighted the need for well-designed trials[19].

Bowel disease. Cannabinoids/cannabis were not found to be effective in inducing remission in studies of irritable bowel disease (RR = 1.56, 95% CI 0.99-2.46), and no effect on inflammatory biomarkers was observed[20]. However, clinical symptoms (abdominal pain,

[13] Herzog, S., et al. (2018). Systematic review of the costs and benefits of prescribed cannabis-based medicines of the management of chronic illness: Lessons from multiple sclerosis. *Pharmacoeconomics, 36*, 67-78.
[14] Lattanzi, S., et al. (2018). Efficacy and safety of adjunctive cannabidiol in patients with Lennox-Gastaut Syndrome: A systematic review and meta-analysis. *CNS Drugs, 32*, 905-916.
[15] Daldegan-Bueno, D., et al. (2022). Conceptualizing and considering cannabis-related "harm-to-others": The role of cannabis-related violence. *Substance use and misuse, 57*, 1488-1491.
[16] Pinto, J. (2022). Effects of cannabidiol on appetite and body weight: A systematic review. *Clinical Drug Investigatio*n, 42, 909-919.
[17] Bougea, A.. et al., 2020). Medical cannabis as an alternative therapeutics for Parkinson's Disease: Systematic review. *Complimentary Therapies in Clinical Practice, 39*.
[18] Figura, M., et al. (2022). Cannabis in Parkinson's Disease – the patient's perspective versus clinical trials: a systematic literature review. *Neurologia (Neurochirurgia Polska), 56*, 21-27.
[19] Urbi, B., et al. (2022). Effects of cannabis in Parkinson's Disease: A systematic review and meta-analysis. *Journal of Parkinson's Disease, 12*, 495-508.
[20] Doeve, B., et al. (2021). A systematic review with meta-analysis of the efficacy of cannabis and cannabinoids for Inflammatory Bowel Disease, what can we learn from randomized and nonrandomized studies? *Journal of Clinical Gastroenterology, 55*, 798-809.

general well-being, nausea, diarrhoea, and poor appetite) all improved with cannabinoids/cannabis use. Cannabis/oids not found to induce clinical remission or affect inflammation in irritable bowel disease patients. However, they do significantly improve patient-reported symptoms and quality of life[23].

Male fertility. In-depth research on studies concluded that cannabis seems to have specific adverse effects on sperm parameters, namely sperm count, concentration, motility, morphology, capacitation, and viability, thus affecting fertility in men. It is also noted that these studies are observational only and are conducted in small groups in multicentre geographical locations where lifestyle patterns could be a confounder. Further human trials are suggested to be needed[21].

Preterm birth. Parental cannabis exposure was found to be associated with an increased risk of preterm birth (OR = 1.35, 95% CI 1.24-1.48). Authors called for greater public awareness of this issue[22]. Relatedly, Significant increases in adverse neonatal outcomes among women who were exposed to cannabis during pregnancy vs those who were not. These included risk of low birth weight, small for gestational age, preterm delivery, and ICU admission[23]. Some evidence also for the additive effect of co-use of cannabis and tobacco in terms of head circumference, weight and length at birth, prematurity, gestational age, and deficits in the new-born, among others[24].

Effects of cannabis use on puberty. Authors attempted a systematic review but ultimately had to exclude all possible papers[25]. Insufficient literature to draw a conclusion..

Insomnia. Among patients with chronic pain, moderate certainty evidence was found that medical cannabis probably results in a small improvement in sleep quality (versus placebo). Moderate to high certainty evidence shows that medical cannabis vs placebo results in a small improvement in sleep disturbance for chronic non-cancer pain, and a very small improvement in sleep disturbance for chronic cancer pain. Moderate to high certainty evidence showed that medical cannabis (v placebo) resulted in an increased in the risk of dizziness, and a small increase in the risk of somnolence, dry mouth, fatigue, and nausea. Medical cannabis and cannabinoids might improve impaired sleep among people living with chronic pain, but the magnitude of the difference is very small[26]. Elsewhere, positive association reported for relationship between cannabis (among other drugs) and sleep disturbances in the domains of regularity, timing, efficiency, and duration[27].

In another review results suggested that CBD alone or with equal quantities of THC may be beneficial in alleviating the symptoms of insomnia. Future research assessing CBDs effectiveness in population of patients specifically with insomnia utilizing validated

[21] Srinivasan, M., et al. (2021). The effect of marijuana on the incidence and evolution of male infertility: A systematic review. *Cureus Journal of Medical Science, 13(12).*
[22] Duko, B., et al. (2022). The effect of prenatal cannabis exposure on offspring preterm birth: a cumulative meta-analysis. *Addiction*, early online.
[23] Marchand, G., et al. (2022). Birth outcomes of neonates exposed to marijuana in utero: A systematic review. *JAMA Network Open, 5(1).*
[24] Gonzales-Sala, F., et al. (2020). Effects of dual cannabis-tobacco consumption on pregnancy and offspring: a systematic review. *Revista Iberoamericana de Psicologia y Salud, 11*, 68-81.
[25] Sims, E., et al. (2018). The effect of cannabis exposure on pubertal outcomes: a systematic review. *Adolescent Health Medicine and Therapeutics, 90*, 137-147.
[26] AminiLari, M., et al., (2022). Medical cannabis and cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized controlled trials. *Sleep, 45(2).*
[27] Kwon, M., et al. (2019). Adolescent substance use and its association to sleep disturbances: A systematic review. Sleep Health, 5, 382-394.

subjective and objective measures is necessary before definitive inferences can be made[28]. Again, a review of RCTs showed that pharmaceutical THC (nabilone, dronabinol) did not affect sleep or appetite. In contrast there was moderate evidence that CBD decreased appetite, with no effect on sleep. Thus, it appears that approved cannabinoids can decrease appetite as a negative side effect, an effect that seems to be driven by CBD. Approved cannabinoids do not negatively affect sleep in somatic and psychiatric patients[29]. In a review where the authors suggested that there were "some possible signals for efficacy" in terms of the potential for some cannabinoids to positively impact insomnia, the following was also stated:

> "*…the heterogeneity of participants, interventions, efficacy outcomes and results, and the high risk of bias across included trials, (these studies) do not reliably inform evidence-based practice. The review highlights shortcomings in the existing literature, including lack of diagnostic clarity, poorly defined participant groups, non-standardised interventions, and studies of appropriate design, duration and power to detect clinically meaningful outcomes*"[30].

In a further review, sleep improvements were reported in 7 out of 19 randomised studies and in 7 out of 12 nonrandomised studies. There were no significant differences between the effects of THC and CBD. Cannabis showed most promise at improving sleep in patients with pain-related disorders, compared with neurologic, psychiatric, or sleep disorders, and showed no significant effects on healthy participants' sleep. Some AEs included headaches, sedation, and dizziness, occurring more frequently at higher doses. Authors concluded that high quality evidence remains limited[31].

Cancer. Regarding head or neck cancer, authors reported a very limited literature, heterogenous in terms of administration and forms of cannabis. No meta-analysis was possible. Authors concluded that a lack of evidence does not disprove, but equally, there is no strong evidence of efficacy[32]. Additional cancer-related evidence will be described in the **Pain** section below.

Conflicting articles regarding the risk of exposure to cannabis in **breast milk**[33]. Women should be advised to abstain, or reduce, and to abstain from breastfeeding within one hour of inhaled use to reduce exposure to the highest concentrations of cannabis in breast milk. More research needed[33]. Use of cannabis among pregnant women frequent but has not been extensively researched. Prenatal exposure to cannabis may be associated with affective symptoms and ADHD[34].

Occupational Injury. Positive association seen in 7 studies, negative association in 1 study, and no association in 8 studies. Not sufficient evidence that cannabis users are at increased risk of occupational injury. Study quality, bias, confounding variables, selection of

[28] Ranum, R. M., et al. (2022). Use of Cannabidiol in the management of insomnia: A systematic review. *Cannabis and Cannabinoid Research*, early online.
[29] Spanagel, R., & Bilbao, A. (2021). Approved cannabinoids for medical purposes: Comparative systematic review and meta-analysis for sleep and appetite. *Neuropharmacology, 196*.
[30] Bhagavan, C., et al. (2020). *CNS Drugs, 34*, 1217-1228.
[31] Velzeboer, R., et al. (2022). Cannabis dosing and administration for sleep: a systematic review. *Sleep, 45*.
[32] Caputo, M., et al. (2021). Medical cannabis as an adjunctive therapy for head and neck cancer patients. *Cureus, 13(9)*.
[33] Ordean, A., & Kim, G. (2020). Cannabis use during lactation: Literature review and clinical recommendations. *Journal of Obstetrics and Gynaecology Canada, 42*, 1248-1253.
[34] Roncero, C., et al. (2020). Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review. *Reproductive Health, 17(1)*.

participants, and assessment of exposures and outcomes all potentially problematic[35]. Elsewhere, cannabinoid use was significantly associated with self-injurious behaviours at the cross-sectional and longitudinal levels. Chronic use, presence of mental disorders, depressive symptoms, emotional dysregulation, and impulsive traits might further increase the likelihood of self-harm in cannabis users[36].

Diabetes. Recreational cannabis use may negatively impact diabetes metabolic factors and self-management behaviours in people with Type 1 diabetes. In people with Type 2 diabetes, recreational cannabis use may increase risks for peripheral arterial occlusion, myocardial infarction, and renal disease. However, the evidence in this rapid review was from 6 observational studies of poor to fair methodological quality. More research needed[37]. Elsewhere, looking at substances more generally, a review reported a non-significant association between substance use and blood sugars. Again, authors called for more and better quality studies[38].

Arthritis. Cannabis and cannabis-derived products and synthetic cannabinoids may slightly reduce disease activity in patients with rheumatoid arthritis. Its use may result in little or no difference in pain reduction and may slightly increase nervous system adverse events. The evidence is very uncertain about the effect of cannabis, cannabis-derived products, and synthetic cannabinoids on serious adverse events risk[39].

Voice disorders. The findings suggest that cannabis-only smoking is associated with changes in vocal fold appearance, respiratory symptoms, and negative lung function changes, especially in heavy smokers[40].

Huntingdon Disease. Strong evidence reported for significant improvement in the neurologic symptoms of spasms, tremors, spasticity, chorea, and quality of sleep following treatment with medical cannabis. Regarding specific motor symptoms, significant improvement in tremors and rigidity. Also, significant increase in number of hours slept. Call for larger studies[41].

Oral health. Qualitative analysis showed that cannabis consumption has been correlated to a higher risk of gingival and periodontal disease, oral infection, and cancer of the oral cavity, while the physico-chemical activity has not been completely clarified. Further investigation needed[42].

[35] Biasutti, W., et al. (2020). Systematic review of cannabis use and risk of occupational injury. *Substance Use and Misuse, 55*, 1733-1745.
[36] Escelsior, A., et al. (2021). Cannabinoid use and self-injurious behaviours: A systematic review and meta-analysis. *Journal of Affective Disorders, 278*, 85-98.
[37] Porr, C., et al. (2020). The effects of recreational cannabis use on glycemic outcomes and self-management behaviours in people with type 1 and type 2 diabetes: a rapid review. *Systematic Reviews, 9(1)*.
[38] Ojo, O., et al. (2018). The effects of substance abuse on blood glucose parameters in patients with diabetes: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health, 15(12)*.
[39] Schulze-Schiappacasse, C., et al. (2022). Are cannabis, cannabis-derived products, and synthetic cannabinoids a therapeutic tool for rheumatoid arthritis? A friendly summary of the body of evidence. *Journal of Clinical Rheumatology, 28*, E563-E567.
[40] Meehan-Atrash, J., et al. (2019). Cannabis inhalation and voice disorders: A systematic review. *JAMA Otolaryngology – Head and Neck Surgery, 145*, 956-964.
[41] Akinyemi, E., et al. (2020). Medical marijuana effects in movement disorders, focus on Huntington Disease: A literature review. *Journal of Pharmacy and Pharmaceutical Sciences, 23*, 389-395.
[42] Bellocchio, L., et al. (2021). Cannabinoids drugs and oral health – from recreational side-effects to medicinal purposes: A systematic review. *International Journal of Molecular Sciences, 22(15).*

Inflammation. Review showed that CBD, CBG (cannabigerol), and CBD+THC combination exerted a predominantly anti-inflammatory effect in vivo, whereas THC alone did not reduce pro-inflammatory or increase anti-inflammatory cytokines[43].

Fibromyalgia. Cannabis found to be safe and well tolerated in fibromyalgia. The main AEs were feeling high, dizziness/vertigo, dry mouth, cough, red eyes, and drowsiness, with no serious AEs. Medical cannabis may be beneficial for some people with fibromyalgia, but further research required in order to determine efficacy by cannabis form, and also how to assess efficacy[44].

Low-strength evidence suggests that smoking cannabis is associated with cough, sputum production, and wheezing. Evidence on the association between cannabis use and **obstructive lung disease and pulmonary function** is insufficient[45].

Brain toxicity and cognitive functioning. Wieghorst et al. (2022) reviewed 23 studies where 15 reported non-significant findings, 6 reported cognitive impairments, one reported cognitive improvement, and a single study found improvement following withdrawal. Large heterogeneity and methodological limitations… not possible to make definitive conclusions on the impact of cannabis-based medicines on cognitive functioning. Majority of higher quality evidence points in the direction that negative impact of cannabis-based medicines on cognitive functioning is minor, provided that the doses of THC are low to moderate[46]. Scott et al. (2019) reviewed 26 studies reporting on medical and recreational use in a range of populations. Modest reductions in cognitive performance were generally detected with higher doses and heavier lifetime use (although issues with cannabis products used, outcomes assessed, and study quality were all confounders). Authors called for additional high-quality research "***using standardised, validated assessments of cannabis exposure and cognitive outcomes***"[47].

Lorenzetti et al. (2019) reviewed 30 studies. Regular cannabis use pointing to smaller volumes of hippocampus, orbitofrontal cortex, and lateral brain, relative to controls. Volumes of hippocampus and orbitofrontal cortex were not significantly associated with duration and dosage. Results point to commonality in neurobiological abnormalities between regular users of cannabis and of other substances[48]. Hammond et al. (2022) looked at 45 fMRI studies. They observed differences in neuronal response between cannabis using and non-using typically developing youth during executive control, emotion processing, and reward processing in cortical and subcortical brain regions that varied as a function of sex, cannabis use disorder severity, psychiatric comorbidity, and length of abstinence. Further investigations called for[49].

[43] Henshaw, F. R., et al. (2021). The effects of cannabinoids on pro- and anti-inflammatory cytokines: A systematic review of in vivo studies. *Cannabis and Cannabinoid Research, 6,* 177-195.
[44] Kurlyandchik, I., et al. (2021). Safety and efficacy of medicinal cannabis in the treatment of Fibromyalgia: A systematic review. *Journal of Alternative and Complimentary Medicine, 27,* 198-213.
[45] Ghasemiesfe, M., et al. (2018). Marijuana use, respiratory symptoms, and pulmonary function: A systematic review and meta-analysis. *Annals of Internal Medicine, 169,* 106.
[46] Wieghorst, A., et al. (2022). The effect of medical cannabis on cognitive functions: A systematic review. *Systematic Reviews, 11(1).*
[47] Scott, E., et al. (2019). A systematic review of the neurocognitive effects of cannabis use in older adults. *Current Addiction Reports, 6,* 443-455.
[48] Lorenzetti, V., et al. (2019). Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies. *European archives of Psychiatry and Clinical Neuroscience, 269,* 59-71.
[49] Hammond, C. J., et al. (2022). A meta-analysis of fMRI studies of youth cannabis use: Alterations in executive control, social cognition/emotion processing, and reward processing in cannabis using youth. *Brian Sciences, 12(10).*

Lovell et al. (2020) reported that cannabis was associated with significant but small-magnitude deficits in executive function, learning and memory, and global cognition, while decision-making had moderate deficits. Overall results suggested that long-term regular cannabis use was associated with small to moderate deficits in some cognitive domains:

> "*Our meta-analysis found minor deficits in decision-making related to long-term, regular cannabis consumption, which were largely uninfluenced by age of onset, cannabis use duration, and prolonged abstinence. Individuals who use cannabis regularly over many years may experience difficulties with some cognitive skills that underlie everyday tasks such as driving, and the ability to cease substance use*"[50].

Scopetti et al. (2022) reviewed 30 papers and reported that consumption of cannabinoids was associated with the development of psychiatric, neurocognitive, neurological disorders, and in some cases, of acute consumption, even death. In this sense the greatest risks have been related to the consumption of high-potency synthetic cannabinoids, although the consumption of phytocannabinoids is not devoid of risks[51].

Nader et al. (2018) reviewed Neuropsychological studies and reported evidence for subtle cognitive deficits at least 7 days after heavy cannabis use. Neuroimaging studies showed growing evidence of abnormalities in hippocampus volume and gray matter density of cannabis users relative to controls. Functional neuroimaging studies suggested an altered pattern of brain activity associated with cannabis use. However, the authors claimed that uncertainty remains about whether the identified alterations are as a consequence of or precede cannabis use[52]. Finally, significant effects for the association between frequent or dependent cannabis use in youth and intelligence quotient (IQ) change. Authors reported that this translated to an average decline of approximately 2 IQ points following exposure to cannabis in youth[53].

Cardiac health and physical activity. Cannabis use results in elevation of heart rate and blood pressure immediately after use. Cannabis use has been suggested to be related to increased risk of cardiac dysrhythmia, which is rare but may be life-threatening. Authors called for increased awareness raising of this. In those with underlying heart conditions[54]. Recent cannabis use has elsewhere been listed as one factor for sudden cardiac death, however, it was lowest of all listed risks (including physical exertion, cocaine use, influenza infection etc)[55]. Yang et al. (2022) reported a decrease in perceived risk despite increased use. Cannabis use was found to be associated with increased risk of myocardial infarction within 24 hours in 2 studies, and stroke in 6 studies. There was a suggested increased risk of angina, particularly for those with history of a cardiovascular event. There was a wide variation in the types of studies used here (RCT, Case-control, Cohort etc[56]).

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[50] Lovell, M. E., et al. (2020). Cognitive outcomes associated with long-term, regular, recreational cannabis use in adults: A meta-analysis. *Experimental and Clinical Psychopharmacology, 28*, 471-494.
[51] Scopetti, M., et al. (2022). Cannabinoids and brain damage: A systematic review on a frequently overlooked issue. *Current Pharmaceutical Biotechnology*.
[52] Nader, D. A., et al. (2018). Effects of regular cannabis use on neurocognition, brain structure, and function: a systematic review of findings in adults. *American Journal of Drug and Alcohol Abuse, 44*, 4-18.
[53] Power, E., et al. (2021). Intelligence quotient decline following frequent or dependent cannabis use in youth: a systematic review and meta-analysis of longitudinal studies. *Psychological Medicine, 51*, 194-200.
[54] Richards, J. R., et al. (2020). The association of cannabis use and cardiac dysrhythmias: a systematic review. *Clinical Toxicology, 58*, 861-869.
[55] Culic, V., et al. (2021). Public health impact of daily life triggers of sudden cardiac death: A systematic review and comparative risk assessment. *Resuscitation,162*, 154-162.
[56] Yang, P. K., et al. (2022). Nonmedical marijuana use and cardiovascular events: A systematic review. *Public Health Reports, 137*, 62-71.

In a different review, Kramer et al. (2020) reported that in four studies, resting heart rate was the only variable of difference, and only in one of the studies. Chronic cannabis use appeared to show no significant effect on athletic performance. Recovery or endurance not assessed. In short, the review revealed verry little by way of deleterious effects[57]. Jivanji et al. (2020) suggested that the long-term cardio effects of cannabis remain largely unknown. In a study of 56,742 people, there was reduced prevalence of cardiovascular disease in cannabis users, but when adjusted for age, gender, ethnicity etc the result became non-significant[58]

Epilepsy. Stockings et al. (2018) reported CBD (20mg/kg/day) more effective than placebo at reducing seizure frequency. Number needed to treat for one person using CBD to experience >50% seizure reduction was 8. CBD more effective than placebo at achieving complete seizure freedom and at improving quality of life. However, CBD was associated with increased risk of AEs. Overall pharmaceutical-grade CBD as adjuvant treatment in paediatric onset drug-resistant epilepsy may reduce seizure frequency, however, more RCTs needed[59]. Lattanzi et al. (2018). Reported on four trials involving 550 patients. Results were in favour of CBD over placebo (Pooled average difference in change in seizure frequency during treatment period results 19.5 (8.1 – 31.0, $p < .001$) between CBD 10mg and placebo…. and 19.9 (11.8 – 28.1, $p < .001$) percentage points between 20mg and placebo)[60].

Reis et al. (2020) reviewed 16 papers for descriptive analysis, and 4 for meta-analysis. Statistically meaningful effect of CBD compared to placebo found ($p < .00001$). Comparing treatment with CBD or medicinal cannabis, significance not found for the AE profile ($p = .74$). As AEs for CBD were more common under short-term than under long-term treatment ($p < .00001$), this approach was favourable in the long-term. Cannabidiol more effective than placebo regardless of etiology of epileptic syndromes and dosage. Overall, the AE profile did not differ across treatments with cannabidiol or medicinal cannabis, though it did differ favorably for long term than for short term treatment[61].

Elliott et al. (2019) reported on four RCTs and 19 non-RCTs. Primarily using CBD. RCTs found to have a low bias risk, while non-RCTs all had a high bias risk. In RCTs, NO statistically significant difference between CBD and placebo in seizure freedom, quality of life, sleep disruption, or vomiting. There was a statistically significant reduction in median frequency of monthly seizures with CBD compared to placebo and an increase in the number of participants with at least a 50% reduction in seizures and diarrhoea. Significance evidence from high-quality RCTs suggests that CBD probably reduces seizures among children with drug-resistant epilepsy (moderate certainty). Evidence base primarily limited to CBD, so findings should not be extended to all Cannabis-based products[62]. In an up-to-date summary (35 studies, inc 4 RCTs) – NO statistically significant difference between CBD and placebo for seizure freedom, quality of life, or sleep disruption. Data from RCTs and non-RCTs suggests CBD reduces seizure frequency and increases treatment response, however, there is an increased risk of gastrointestinal AEs. Newly available evidence continues to support

[57] Kramer, A., et al. (2020). Chronic cannabis consumption and physical exercise performance in healthy adults: a systematic review. *Journal of Cannabis Research, 2(1)*.
[58] Jivanji, D., et al. (2020). Association between marijuana use and cardiovascular disease in US adults. *Cureus, 12(12)*.
[59] Stockings, E., et al. (2018). Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *Journal of Neurology, Neurosurgery, and Psychiatry, 89*, 741-753.
[60] Lattanzi, S., et al. (2018). Efficacy and Safety of Cannabidiol in Epilepsy: A systematic review and meta-analysis. *Drugs, 78*, 1791-1804.
[61] Reis, R.. et al. (2020). Efficacy and adverse event profile of cannabidiol and medicinal cannabis for treatment-resistant epilepsy: Systematic review and meat-analysis. *Epilepsy and Behavior, 102*.
[62] Elliott, J., et al. (2019). Cannabis-based products for pediatric epilepsy: A systematic review. *Epilepsia, 60*, 6-19.

earlier findings that CBD probably reduces the frequency of seizures among children with drug-resistant epilepsy[63].

Suicide. Schmidt et al. (2020), in an examination of 12 papers focussing on adolescents, there was a variety of study types, but there was an association between cannabis use and suicidal thoughts, behaviour, and attempts[64]. Armoon et al. (2021) reported that substance use disorder was significantly associated with suicidal ideations. Among those with substance use disorder, cannabis use was also associated with suicide attempts. Should be said that cannabis one of many factors here[65].

Carvalho et al. (2022) reviewed 22 articles with some studies showing greater cannabis use and greater association with suicidal thoughts and behaviours, but a very complex review and a very complex area. Issue around self-reported cannabis use, what does that mean? Also, frequency of cannabis use issue, and a lack of consistency of confounders[66]. Fresan et al. (2022) reviewed 20 studies (people aged 11-21). Increased suicide attempts attempt in cannabis smokers versus non-smokers (OR = 2.33, 1.78-3.05), cannabis smoking and suicide ideation (OR = 2.04, 1.64-2.53), and suicide planning (OR = 1.67, 1.55-1.80). Meta-regression showed age negatively associated to attempt, planning, or ideation in this group of 11–21-year-olds. Concern raised about the sample specific nature of these analyses and need for more and further work[67].

Rioux et al. (2021) In a review of prospective studies they reported that substance use disorders predicted suicidality, and suicidality predicted substance use disorders. So, while the majority of studies look at the secondary psychiatric disorder hypothesis (substance use disorder -> suicide), attention needs also to be paid to the secondary substance use disorder hypothesis (suicidality -> substance use/substance use disorder)[68].

Psychiatry. This area is relatively large, and results will be presented in bullet points.

- Majority of studies revealed an association between cannabis use and anxiety, but the strength of association, and study design variability requires further work be undertaken. Only 5 studies met criteria that used brain imaging techniques, and findings are non-conclusive[69].
- Study looking at clinically high-risk people for dev of psychosis. 128 studies with 26 factors were examined. No factors showed class 1 convincing evidence. Overall finding – despite the large number of putative risk factors investigated in the literature, only attenuated positive psychotic symptoms, global functioning, and negative psychotic

[63] Elliott, J., et al. (2020). Cannabis-based products for pediatric epilepsy: An updated systematic review. *Seizure, 75*, 18-22.
[64] Schmidt, K., et al. (2020). A systematic review: Adolescent cannabis use and suicide. *Addictive Disorders and their Treatment, 19*, 146-151.
[65] Armoon, B., et al. (2021). Prevalence, sociodemographic variables, mental health condition, and type of drug use associated with suicide behaviors among people with substance use disorders: a systematic review and meta-analysis. *Journal of Addictive Diseases, 39*, 550-569.
[66] Carvalho, J. V., et al. (2022). Association between cannabis use and suicidal behavior: A systematic review of cohort studies. *Psychiatry Research, 312*.
[67] Fresan, A., et al. (2022). Cannabis smoking increases the risk of suicide ideation and suicide attempt in young individuals of 11-21 years: A systematic review and meta-analysis. *Journal of Psychiatric Research, 153*, 90-98.
[6868] Rioux, C., et al. (2021). Substance use disorders and suicidality in youth: A systematic review and meta-analysis with a focus on the direction of the association. *Plos ONE, 16(8)*.
[69] Cancilliere, M. K., et al. (2018). Effects of co-occurring marijuana use and anxiety on brain structure and functioning: A systematic review of adolescent studies. *Journal of Adolescence, 65*, 177-188.

symptoms show suggestive evidence or greater for association with transition to psychosis[70].

- Study precisely examining link of cannabis to psychosis when taking account of confounders. Evidence confirms an overarching negative impact on psychotic outcomes of cannabis intake in psychosis populations, even when accounting for confounders[71].
- Significant log-linear dose-response relationship. Risk of psychosis significantly increasing for weekly or more frequent cannabis use (RR 1.01, 95% CI 0.93-1.11 yearly; RR = 1.10, 95% CI 0.97-1.25 monthly; RR = 1.35, 95% CI 1.19-1.52 weekly; and RR = 1.76 95% CI 1.47-2.12 daily). Increased frequency of cannabis use brings increased risk of psychosis[72].
- Literature suggests that cannabis use linked to onset and poorer clinical outcomes in bipolar disorder, PTSD, but that this is not as clear in depression or anxiety disorder. Limitation to conclusions of a lack of well-controlled longitudinal studies[73].
- Psychosis – all but one study found that earlier cannabis use was generally associated with higher risks. For depression or anxiety 6 of 11 studies reported data indicating an association between earlier cannabis use and higher symptom levels. In persons <25 years old, greater cannabis use associated with more psychological symptoms, especially among those with a predisposition, or existing vulnerability to such outcomes[74].
- General findings – cannabis use not generally associated with neurocognitive functioning in patients with first episode psychosis. However, it highlights the deleterious effects of low doses of cannabis in some patients. Also stresses the importance of type of antipsychotic prescription and cannabis dose as moderator variables in the neurocognitive functioning of cannabis use with first episode psychosis[75].
- Overall, use of higher potency cannabis, relative to lower potency cannabis was associated with an increased risk of psychosis and cannabis use disorder. Evidence varied for depression and anxiety[76].
- Limited evidence supporting antipsychotic efficacy for CBD and none supporting its benefits for cognition or functioning. Cannabidiol treatment had an advantageous side effect profile compared to other antipsychotics and was well tolerated across studies. Factors potentially contributing to variability in results included: dosage of CBD, treatment duration, use as adjunctive treatment, and participant inclusion criteria[77].
- Non parametric tests showed highly statistically significant difference in odds ratios for schizophrenia between both high- and low-cannabis users. Both high and low frequency

[70] Oliver, D., et al. (2020). What causes the onset of psychosis in individuals at clinical high risk? A meta-analysis of risk and protective factors. *Schizophrenia Bulletin, 46*, 110-120.
[71] Athanassiou, M., et al. (2021). A systematic review of longitudinal studies investigating the impact of cannabis use in patients with psychotic disorders. *Expert Review of Neurotherapeutics, 21*, 779-791.
[72] Robinson, T., et al. (2022). Risk thresholds for the association between frequency of cannabis use and the development of psychosis: a systematic review and meta-analysis. *Psychological Medicine, 24*, 1-11.
[73] Botsford, S. L., et al. (2020). Cannabis and Cannabinoids in Mood and Anxiety Disorders: Impact on illness onset and course, and assessment of therapeutic potential. *American Journal on Addictions, 29*, 9-26.
[74] Hosseini, S., & Oremus, M. (2019). The effect of age of initiation of cannabis use on psychosis, depression, and anxiety among youth under 25 years. *Canadian Journal of Psychiatry, 64*, 304-312.
[75] Sanchex-Gutierrez, T., et al. (2020). Cannabis use and nonuse in patients with first-episode psychosis: A systematic review and meta-analysis of studies comparing neurocognitive functioning. *European Psychiatry, 63*.
[76] Petrilli K., et al. (2022). Association of cannabis potency with mental ill health and addiction: a systematic review. *Lancet Psychiatry, 9*, 736-750.
[77] Ghabrash, M. F., et al. (2020). Cannabidiol for the treatment of psychosis among patients with schizophrenia and other primary psychotic disorders: A systematic review with a risk of bias assessment. *Psychiatry Research, 286*.

cannabis use were associated with increased risk of schizophrenia compared to non-users[78].

- All studies had medium to high risk of bias and were of low quality. Fount that cannabinoids may decrease PTSD symptomatology, in particular sleep disturbances and nightmares. Most studies to date are small and of low quality. Therefore, more and better quality studies needed[79].
- Odds ratio for depression among cannabis users in young adulthood was 1.37 (1.16 – 1.62). Pooled odds ratio for anxiety was not significant 1.18 (0.84-1.67). Pooled odds ratio significant for suicidal ideation = 1.50 (1.11-2.03) and for suicide attempt OR = 3.46 (1.53-7.84). Individual risk remains moderate to low, need future adequately powered prospective studies[80].
- Sarris et al., 2022. Isolated individual studies have revealed tentative support for cannabinoids (namely cannabidiol CBD) for reducing social anxiety with mixed (mainly positive) effects evidence for adjunctive use in schizophrenia. Case studies (evidence weak) suggest that medical cannabis might be beneficial for improving sleep and PTSD. No benefit for depression from THC, or from CBD for mania. Currently the evidence is embryonic for benefit of medical cannabis in the treatment of a range of psychiatric disorders. Clinicians need to be aware of potential dose-specific negative effects at high dose[81].
- Psychotic-like experiences (PLEs) and substance use children/adolescents $\leq$ 17 years. Around 2/5 substance users reported PLEs and one in 5 with PLEs reported using substances. Substance users nearly twice as likely report PLEs than non-users (moderate quality evidence), and those with PLEs were twice as likely to use substances than those not reporting PLEs (very low-quality evidence). Younger age associated with higher likelihood of PLEs in substance users compared to non-users. Young substance users may present a subclinical at-risk group for psychosis[82].
- Cross sectional associations between cannabis use and aggression/violence in samples with PTSD were found. Longitudinal association between cannabis use and violence/aggression observed with psychotic spectrum disorders. Methodological limitations preclude the drawing of causal conclusions. Well-controlled and longitudinal studies are needed[83].
- Cannabis use significantly associated with the development of any anxiety condition (overall) but use not significantly associated with generalised anxiety disorder, panic disorder, or social anxiety disorder specifically. Cannabis use likely associated with increased risk of anxiety in the long term, but variability of study designs precludes declaration of a causal relationship[84].

[78] Godin, S-L., & Shehata, S. (2022). Adolescent cannabis use and later development of schizophrenia: A updated systematic review of longitudinal studies. *Journal of Clinical Psychology, 78*, 1331-1340.
[79] Hindocha, C., et al. (2020). The effectiveness of Cannabinoids in the treatment of posttraumatic stress disorder (PTSD): A systematic review. *Journal of Dual Diagnosis, 16*, 120-139.
[80] Gobbi, G., et al. (2019). Association of Cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: A systematic review and meta-analysis. *Jama Psychiatry, 76*, 426-434.
[81] Sarris, J., et al. (2020). Medicinal cannabis for psychiatric disorders: a clinically focused systematic review. *BMC Psychiatry, 20*.
[82] Matheson, S. L., et al. (2022). Substance use and psychotic-like experiences in young people: a systematic review and meat-analysis. *Psychological Medicine*, early online.
[83] Sorkhou, M., et al. (2022). Does cannabis use predict aggressive or violent behaviour in psychiatric populations? *American Journal of Drug and Alcohol Abuse*, early online.
[84] Xue, S., et al. (2020). Cannabis use and prospective long-term association with anxiety: A systematic review and meta-analysis of longitudinal studies. *Canadian Journal of Psychiatry, 66*, 126-138.

- Adverse effects of cannabis/cannabinoids found on 30/32 studies reporting psychotic symptoms, 13/18 studies reporting depressive symptoms, and 4/4 studies reporting (hypo)manic symptoms. Evidence robust for psychotic and (hypo)manic results, but results for depression were mixed. Risk of developing symptoms influenced by age of onset, THC potency, and frequency of use. Cannabis use increases risk of developing (hypo)manic and psychotic symptoms, with mixed effects for depression, in healthy individuals. Effects are in a dose-dependent manner and are dependent on THC potency[85].
- There is currently limited safety evidence for use of CBD in treatment of psychiatric disorders. Available trials did report evidence for effects in specific psychopathological conditions such as substance use disorders, chronic psychosis, and anxiety. Further work needed[86].
- Studies on CBD and nabiximols (whole plant extract from Cannabis sativa L. that has been purified into 1:1 ratio of CBD and delta-9-THC). CBD and CBD-containing compounds such as nabiximols were helpful in alleviating psychotic symptoms and cognitive impairment in patients with a variety of conditions and several studies provided evidence of effectiveness in the treatment of cannabis withdrawal and moderate to severe cannabis use disorders with Grade B recommendation. Again, call for large scale RCTs[87].
- THC component can be the main culprit causing psychosis and schizophrenia in the at-risk population. THC can also be the culprit in exacerbating symptoms and causing an adverse prognosis in already diagnosed patients. Even though CBD shows therapeutic effects and THC opposing effects, the data is minimal and low safety and efficacy warrants more research. Again, call for more research[88].
- Limited evidence found for the effectiveness of cannabinoid-based products (CBP) to acutely treat a narrow range of psychiatric symptoms. No evidence reported supporting mid- to long-term range effectiveness of any currently available CBP. In general, quality of evidence was on the low side. None of the studies endorsed the use of cannabis flower as a method of treatment for any recognised psychiatric disorder[89].
- Positive association between cannabis and depression (OR = 1.29, 95% CI 1.10-1.51), and anxiety (OR = 1.36, 95% CI 1.02-1.81). Unidirectional relationship between cannabis -> depression (OR = 1.33, 95% CI 1.19-1.49)[90].
- There is very low-quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions. There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. Further high-quality studies needed[91].

[85] Polkosnik, G. L., et al. (2021). Effects of cannabis use on psychotic and mood symptoms: A systematic review. *Canadian Journal of Addiction, 12*, 10-21.
[86]Bonaccorso, S., et al. (2019). Cannabidiol (CBD) use in psychiatric disorders: A systematic review. *Neurotoxicology, 74*, 282-298.
[87] Khan, R., et al. (2020). The therapeutic role of Cannabidiol in mental health: a systematic review. *Journal of Cannabis Research, 2(1).*
[88] Patel, S., et al. (2020). The association between cannabis use and schizophrenia: causative or curative? A systematic review. *Cureus, 12(7).*
[89] McKee, K. A., et al. (2021). Potential therapeutic benefits of cannabinoid products in adult psychiatric disorders: A systematic review and meta-analysis of randomised controlled trials. *Journal of Psychiatric Research, 140*, 267-281.
[90] Esmaeelzadeh, S., et al. (2018). Examining the association and directionality between mental health disorders and substance use among adolescents and young adults in the U.S. and Canada: A systematic review and meta-analysis. *Journal of Clinical Medicine, 7(12)*.
[91] Black, N., et al. (2019). Cannabinoids for the treatment of mental disorders and symptoms of mental health disorders: a systematic review and meta-analysis. *Lancet Psychiatry, 6*, 995-1010.

- Majority of studies provided evidence of recreational cannabis use and PTSD. Findings provide evidence for self-medication. Association between recreational cannabis use and PTSD likely bidirectional[92].
- Call for more research on use of CBD for the treatment of mood disorders… "***the current state of research in this field does not seem reassuring***"[93].
- THC (v placebo) significantly increased total psychiatric symptom severity (OR = 1.10, 95% CI 0.92-1.28), positive symptom severity (OR = 0.91, 95% CI 0.68-1.14) and negative symptom severity (OR = 0.78, 95% CI 0.59-0.97). Of the studies (4) examining CBDs effects on THC-induced symptoms, only one identified a significant reduction in symptoms. A single THC administration induces psychotic, negative, and other psychiatric symptoms with large effect sizes. There is no consistent evidence that CBD induces symptoms or moderates the effects of THC. Findings highlight potential risks associated with use of cannabis and other cannabinoids that contain THC for recreational or therapeutic purposes[94].

Pain. This area was very large, and results will be presented in bullet points.

- Across RCTs pooled events rates (PERs) for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo) – significant effect for cannabinoids, number needed to treat/benefit = 24 (95% CI = 15-61). For 50% reduction in pain PERs were 18.2% vs 14.4% (no sig difference). In summary, effects suggest that number needed to treat/benefit is high, and number needed to treat/harm is low – with limited impact on other domains. It seems unlikely that cannabinoids are highly effective medicines for chronic non-cancer pain[95].
- Meta-analysis of 15 RCTs found more patients taking cannabinoids attained at least a 30% pain reduction (RR = 1.37 (1.14-1.64), number needed to treat = 11). Sensitivity analyses on type of study found sig effect – larger and longer RCTs finding no benefit. Meta-analysis of RCTs found positive global impression of change in spasticity RR = 1.45 (1.08-1.95; NNT = 7). Meta-analysis of RCTs found effect for control of vomiting after chemotherapy (RR = 3.60, 2.55-5.09; NNT = 3). Individual adverse effects were very common dizziness (NNH = 5), sedation (NNH = 5), confusion (NNH = 15), and dissociation (NNH = 20). Reasonable evidence that cannabinoids improve nausea and vomiting after chemotherapy. They might improve spasticity (primarily in MS). Some uncertainty about pain improvement, but if cannabinoids improve pain, it is neuropathic pain, and the benefit is likely small. Adverse effects are very common meaning that benefits would need to be considerable to warrant trials of therapy[96].
- All the included publications provided a recommendation supporting medical cannabis for chronic non-cancer pain in general, and for the specific conditions of neuropathic

[92] Hicks, T. A., et al. (2022). The association between recreational cannabis use and posttraumatic stress disorder: A systematic review and methodological critique of the literature. *Drug and Alcohol Dependence, 240*.
[93] Bartoli, F. (2021). Cannabidiol for mood disorders: A call for more research. *The Canadian Journal of Psychiatry, 66*, 182-183.
[94] Hindley, G., et al. (2020). Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. *Lancet Psychiatry, 7*, 344-353.
[95] Stockings, E., et al. (2018). Cannabis and Cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain, 159*, 1932-1954.
[96] Allan, G., et al. (2018). Systematic review of systematic reviews for medical cannabinoids. Pain, nausea, and vomiting, spasticity, and harms. *Canadian Family Physician, 64*, E78-E94.

pain, chronic pain for people living with HIV, and chronic abdominal pain. Currently only weak recommendations are available for medical cannabis in patients with CNCP[97].

- Paucity of evidence on orofacial pain. Application of topical dermal cannabinoid formulation has shown positive findings such as reducing pain and improving muscle function in patients suffering from myofascial pain. Conversely two orally administered synthetic cannabinoid receptor agonists (AZD1940 and GW842166) failed to demonstrate significant analgesic effects following surgical third molar removal[98].
- Both significant and nonsignificant impacts were observed on lower back pain. Contradicting evidence observed for anxiety and insomnia, two comorbidities or lower back pain. The existing literature suggests that cannabis may be used in the management of lower back pain and comorbid symptoms, but more research needed[99].
- The studies generally suggest that medical cannabis is a safe and effective treatment for Fibromyalgia pain, several limitations regarding dosage, length of treatment, adverse effects, long-term follow up, and dependence need further investigation[100].
- 16 studies on gynaecologic pain. Cohort studies reported evidence for pain relief and the average reduction in pain after 3 months of treatment was 3.35 (+/- 1.39) on the 10-point visual analog scale. Survey data showed that most women reported that cannabis improved pain from numerous gynaecologic conditions. Cohort studies reported pain reduction. Interpretation limited due to varying cannabis formulations, delivery methods, and dosage that preclude a definitive statement about cannabis for gynaecologic pain relief[101].
- Primary outcomes were 30% to 50% reduction in pain intensity and AEs. Evidence for benefit was found for cannabis <7 days (risk difference 0.33, 0.20-0.46; very low quality evidence in 2 trials), and nabiximols >7 days (risk difference 0.06, 0.01-0.12, very low quality evidence, 6 trials). Cannabis, nabiximols, and delta-9-THC had more AEs than control. Authors reported low confidence in the estimates of effect and cited poor to low quality evidence. *"The evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis, or CBM in the management of pain*".
- Concluded that based on the literature, cannabis use in Sickle Cell Disease patients either worsened their painful crises or offered little to no help compared to opioids or hydroxyurea usage. There were limited RCTs. Call and hope for more data to be gathered[102].
- Overall, there was a small but statistically significant treatment effect favouring the use of cannabinoids over placebo (-0.90, -1.69—0.01). When stratified by route of administration, intramuscural cannabinoids were found to have a significant reduction in pain relief relative to placebo (-2.98, -4.09—1.87). No difference in effect between oral cannabinoids and placebo. Serious AEs were rare and similar across the cannabinoid and placebo groups. There is low quality evidence indicating that cannabinoids may be a safe

[97] Chang, Y., et al. (2021). Medical cannabis for chronic noncancer pain: A systematic review of health care recommendations. *Pain Research and Management*.
[98] Grossman, S., et al. (2022). Cannabis and orofacial pain: a systematic review. *British Journal of Oral and Maxillofacial Surgery, 60*, e677-e690.
[99] Senderovich, H., et al. (2022). The effectiveness of cannabis and cannabis derivatives in treating lower back pain in the aged population: A systematic review. *Gerontology, 68*, 612-624.
[100] Khurshid, H., et al. (2021). A systematic review of Fibromyalgia and recent advancements in treatment: Is medicinal cannabis a new hope? *Curues, 13(8)*.
[101] Liang, A., et al. (2022). Medical cannabis for gynecologic pain conditions: A systematic review. *Obstetrics and Gynecology, 139*, 287-296.
[102] Paulsingh, C. N., et al. (2022). The efficacy of Marijuana use for pain relief in adults with Sickle Cell Disease: A systematic review. *Cureus Journal of Medical Science, 14*(5).

alternative for a small but significant reduction in the subjective pain score when treating acute pain, with intramuscular administration resulting in a greater reduction relative to oral. Higher quality long-term RCTs are required[103].

- There was a 64-75% reduction in in opioid dosage when used in combination with medical cannabis. Use of medical cannabis for opioid substitution was reported by 32-59% of patients with non-cancer chronic pain. While the review indicated the likelihood of reducing opioid dosage when used in combination with medical cannabis, a causal inference cannot be made. The evidence from this review cannot be relied upon to promote medical cannabis as an adjunct to opioids in treating non-cancer chronic pain. More research needed[104].
- Moderate to high certainty evidence shows that non-inhaled medical cannabis or cannabinoids results in a small to very small improvement in pain relief, physical functioning, and sleep quality among patients with chronic pain, along with several transient adverse side effects, compared with placebo[105].
- In each study there was a quantifiable advantage of cannabis therapy for alleviating back pain with an acceptable side effect profile. However, long-term follow-up is lacking. As medicinal cannabis is being used more commonly for analgesic effect and patients are 'self-prescribing' cannabis for back pain, additional studies are needed for healthcare providers to confidently recommend cannabis therapy for back pain[106].
- This study found evidence for pain relief but also a call for more specific studies looking at specific routes of administration for some cannabinoids[107].
- Review of 13 RCTs – 5 demonstrated moderate analgesic effects of cannabis for chronic pain, and 8 concluded that there were no significant impacts on pain in the cannabis-treated group, versus the control group. Evidence on the efficacy of cannabinoids for chronic pain shows patient-perceived-benefit but inconsistent other-treatment effects. These findings indicate that cannabinoids may have a modest analgesic effect for chronic neuropathic pain conditions, and that the use of cannabinoids is relatively safe, with few adverse events. Need for more studies on a larger scale[108].
- Of the 106 articles read, 57 were self-declared systematic reviews, most published since 2010. They included any type of cannabinoid, cannabis, or CBM, at any dose, however administered, in a broad range of pain conditions. No review examined the effects of a particular cannabinoid, at a particular dose, using a particular route of administration, for a particular pain condition, reporting a particular analgesic outcome. Confidence in the results in the systematic reviews using AMSTAR-2 definitions was critically low (41), low (8), moderate (6), or high (2). Meta-analyses typically pooled widely disparate studies, and, where assessable, were subject to potential publication bias. Systematic reviews with positive or negative recommendation for use of cannabinoids, cannabis, or CBM in pain typically rated critically low or low (24/25 [96%] positive; 10/12 [83%]

[103] Gazendam, A., et al. (2020). Cannabinoids in the management of acute pain: A systematic review and meta-analysis. *Cannabis and Cannabinoid Research, 5(4),* 290-297.
[104] Okusanya, B. O., et al. (2020). Medical cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: A systematic review. *Systematic Reviews, 9(1).*
[105] Wang, L., et al. (2021). Medical cannabis or cannabinoids for chronic non-cancer and cancer-related pain: A systematic review and meta-analysis of randomized clinical trials. *BMJ-British Medical Journal, 374*.
[106] Price, R. L., et al. (2022). The efficacy of cannabis in reducing back pain: A systematic review. *Global Spine Journal, 12(2),* 343-352.
[107] Rabgay, K., et al. (2020). The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: A systematic review and network meta-analysis. *Journal of the American Pharmacists Association, 60,* 225.
[108] Longo, R., et al. (2021). Cannabis for chronic pain: A rapid systematic review of randomized control trials. *Pain Management and Nursing, 22(2),* 141-149.

negative). Current reviews are mostly lacking in quality and cannot provide a basis for decision-making. A new high-quality systematic review of randomised controlled trials is needed to critically assess the clinical evidence for cannabinoids, cannabis, or CBM in pain[109].

- The search of databases up to 2/1/2021 yielded 379 records with 17 RCTs included (861 patients with NP). Meta-analysis showed that there was a significant reduction in pain intensity for THC/CBD by -6.624 units ($p < .001$), THC by -8.681 units ($p < .001$), and dronabinol by -6.0 units ($p = .008$) compared to placebo on a 0-100 scale. CBD, Cannabidivarin (CBDV), and CT-3 showed no significant differences. Patients taking THC/CBD were 1.756 times more likely to achieve a 30% reduction in pain ($p = .008$) and 1.422 times more likely to achieve a 50% reduction ($p = .37$) than placebo. Patients receiving THC had a 21% higher improvement in pain intensity ($p = .005$) and were 1.855 times more likely to achieve a 30% reduction in pain than placebo ($p < .001$). Although THC and THC/CBD interventions provided a significant improvement in pain intensity and were more likely to provide a 30% reduction in pain, the evidence was of moderate-to-low quality. Further research is needed for CBD, dronabinol, CT-3, and CBDV[110].
- Meta-analysis was performed for 33 studies that compared cannabinoids to placebo and showed a mean pain score (scale 0-10) reduction of -0.70 ($p < 0.001$, random effect). Meta-regression showed that analgesic efficacy was similar for neuropathic and non-neuropathic pain (Difference = -0.14, $p = 0.262$). Inhaled, oral, and oromucosal administration all provided statistically significant, but small reduction in mean pain score (-0.97, -0.85, -0.45, all $p < 0.001$). Incidence of serious adverse events was rare, and non-serious adverse events were usually mild to moderate. Heterogeneity was moderate. The grade level of evidence was low to moderate. Pain intensity of chronic non-cancer patients was reduced by cannabinoids consumption, but effect sizes were small. Efficacy for neuropathic and non-neuropathic pain was similar[111].
- This systematic review of the literature reveals a lack of clinical research investigating cannabis by routes other than oral and inhalation as a potential treatment for neuropathic pain and highlights the need for further investigation with well-designed clinical trials. There is a significant lack of evidence indicating that cannabinoids administered by routes other than oral or inhaled may be an effective alternative, with better tolerance and safety in the treatment of neuropathic pain. Higher quality, long-term, randomized controlled trials are needed to examine whether cannabinoids administered by routes other than inhalation and oral routes may have a role in the treatment of neuropathic pain[112].
- Data Synthesis: Eighteen randomized, placebo-controlled trials (n = 1740) and 7 cohort studies (n = 13 095) assessed cannabinoids. Studies were primarily short term (1 to 6 months); 56% enrolled patients with neuropathic pain, with 3% to 89% female patients. Synthetic products with high THC-to-CBD ratios (>98% THC) may be associated with moderate improvement in pain severity and response (>= 30% improvement) and an

[109] Moore, R. A., et al. (2021). Cannabinoids, cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews. *Pain, 162*(Suppl 1), S67-S79.
[110] Sainsbury, B., et al. (2021). Efficacy of cannabis-based medications compared to placebo for the treatment of chronic neuropathic pain: a systematic review and meta-analysis. *Journal of Dental Anesthesia and Pain Medicine, 21*, 479-506.
[111] Wong, S. S. C., et al. (2020). Analgesic effects of Cannabinoids for chronic non-cancer pain: a Systematic review and meta-analysis with meta-regression. *Journal of Neuroimmune Pharmacology, 15(4)*, 801-829.
[112] Quintero, J-M., et al. (2022). A systematic review on cannabinoids for neuropathic pain administered by routes other than oral or inhalation. *Plants-Basel, 11(10)*.

increased risk for sedation and are probably associated with a large increased risk for dizziness. Extracted products with high THC-to-CBD ratios (range, 3:1 to 47:1) may be associated with large increased risk for study withdrawal due to adverse events and dizziness. Sublingual spray with comparable THC-to-CBD ratio (1.1:1) probably is associated with small improvement in pain severity and overall function and may be associated with large increased risk for dizziness and sedation and moderate increased risk for nausea. Evidence for other products and outcomes, including longer-term harms, were not reported or were insufficient. Limitation: Variation in interventions; lack of study details, including unclear availability in the United States; and inadequate evidence for some products. Conclusion: Oral, synthetic cannabis products with high THC-to-CBD ratios and sublingual, extracted cannabis products with comparable THC-to-CBD ratios may be associated with short -term improvements in chronic pain and increased risk for dizziness and sedation. Studies are needed on long-term outcomes and further evaluation of product formulation effects[113].

- Compared with placebo, cannabinoids showed a significant reduction in pain which was greatest with treatment duration of 2 to 8 weeks (weighted mean difference on a 0-10 pain visual analogue scale -0.68, 95% CI, -0.96 to -0.40, I-2 = 8%, $p < .00001$: n = 16 trials). When stratified by route of administration, pain condition, and type of cannabinoids, oral cannabinoids had a larger reduction in pain compared with placebo relative to oromucosal and smoked formulations but the difference was not significant (*p*[interaction] > .05 in all the 3 durations of treatment); cannabinoids had a smaller reduction in pain due to multiple sclerosis compared with placebo relative to other neuropathic pain (P[interaction] = .05) within 2 weeks and the difference was not significant relative to pain due to rheumatic arthritis; nabilone had a greater reduction in pain compared with placebo relative to other types of cannabinoids longer than 2 weeks of treatment but the difference was not significant (*p*[interaction] > .05). Serious AEs were rare, and similar across the cannabinoid (74 out of 2176, 3.4%) and placebo groups (53 out of 1640, 3.2%). There was an increased risk of non-serious AEs with cannabinoids compared with placebo. Conclusions. There was moderate evidence to support cannabinoids in treating chronic, non-cancer pain at 2 weeks. Similar results were observed at later time points, but the confidence in effect is low. There is little evidence that cannabinoids increase the risk of experiencing serious AEs, although non-serious AEs may be common in the short-term period following use[114].
- Information included in observational studies should be regarded with caution. Within the context of observational studies. Cannabis based medicines had positive effects on multiple symptoms for some CNCP patients and were generally well tolerated and safe. Significance There is very low-quality evidence for the long-term effectiveness (pain, sleep, mood, health-related quality of life), tolerability and safety of medical cannabis for chronic non-cancer pain (CNCP) according to reports of prospective observational studies. Predefined criteria of a large magnitude of effect size in these types of studies

[113] McDonagh, M. S., et al. (2022). Cannabis-based products for chronic pain: A systematic review. *Annals of Internal Medicine, 175(8),* 1143.
[114] Johal, H. (2020). Cannabinoids in chronic non-cancer pain: A systematic review and meta-analysis. *Clinical Medicine Insights – Arthritis and Musculoskeletal Disorders, 13*.

were not met. Nevertheless, long-term medical cannabis therapy can be considered in some carefully selected and monitored patients with CNCP.[115]

Overall considerations.

This is a very diverse literature in terms of the types of studies reported on, the types of health outcomes investigated, and the variety of forms of cannabis or cannabinoids reported on. It makes drawing definitive conclusions extremely difficult.

It is noteworthy that almost every review, even those of a high standard and published in high quality journals, call for better quality future research in order to better inform the debate. Obviously, while a lot has been reported about the health benefits/deficits of cannabis and cannabinoids, a range of issues have compromised this work a plethora of small and under-powered studies, and RCTs with relatively short follow-up periods. It is probably safe to conclude that there is sufficient (low-quality) evidence available to support a variety of positions on this debate. However, a definitive, and objective overall position regarding the benefits or deficits associated with cannabis/cannabinoid use is not currently possible.

Search Strategy[116]

(Cannabis or Cannabi or Hemp Plant or Hemp Plants or Plant Hemp or Plants Hemp or Marihuana or Marijuana or Cannabis indica or Cannabis sativa or Hemp or Hemps or Hashish or Hashishs or Bhang or Bhangs or Ganja or Ganjas)

AND (("systematic review"))

AND ((health) or ("mental health") or ("physical health") or (pain) or (seizure*))

[115] Bialas, P., et al. (2022). Long-term observational studies with cannabis-based medicines for chronic non-cancer pain: A systematic review and meta-analysis of effectiveness and safety. *European Journal of Pain, 26(6)*, 1221-1233.
[116] Searches conducted by Helen McAneney (NIPHRN) in December 2022