



## The Effect of Medical Cannabis on Anxiety and Depression

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In December 2020, the United Nations removed medical cannabis (MC) from Schedule 4 of the 1961 UN Convention on Narcotic Drugs following a recommendation by the World Health Organization (WHO) on its medical potential to pave the way for the reduction of regulatory barriers for research (United Nations, 2020). Some of the medical indications for MC include but are not limited to rare seizure disorders, symptomatic treatment of nausea and vomiting, insomnia, pain, loss of appetite, anxiety, and post-traumatic stress disorder (PTSD), as well as glaucoma, Huntington's Disease, dystonia, and Parkinson's Disease (Klumpers & Thacker, 2019). In countries like the United States, MC prescriptions are on the rise for various medical indications, especially in symptomatic treatment of nausea and vomiting, loss of appetite, and pain among oncology patients (Corroon et al., 2019; Vinette et al., 2022).

An online survey conducted in North America (United States and Canada) in 2018 utilizing a sample of more than 27,000 participants also found that about 27% of them had used MC at least once in their lifetime (Leung et al., 2022). The findings are consistent with another cross-sectional study that utilized a sample of more than 1600 primary health care patients in Washington state in the United States, whereby it was revealed that the prevalence of MC use was 26.5% (Lapham et al., 2022). The prevalence seems to be particularly high in North American and European countries, which may not be the case in other countries like Israel. For example, a single-centre survey of more than 17,000 cancer patients in Israel revealed a prevalence of CM use of only 1.7% (Waissengrin et al., 2015). This low prevalence could be attributed to the fact that in Israel, MC is

strictly used in the treatment of cancer-related symptoms, and no other medical indications like anxiety and depression, as it is seen in the case of North America (Bar-Lev Schleider et al., 2022). However, it is worth noting that Waissengrin et al. (2015) focused on a sample of licenced MC users, but another study found that the proportion of unlicensed MC users could be larger than that of licenced ones (Sznitman, 2017). For example, in their convenience sample of more than 1400 cannabis users, 38% were self-prescribed MC (unlicensed users), 42% were recreational users, and only 5.6% were licensed users (Sznitman, 2017). Although their study did not reflect the prevalence of MC use in the general population in Israel, it is evident that unlicensed users, if taken to account in a survey, can significantly raise the prevalence far beyond the 1.7% reported by Waissengrin et al. (2015). Currently, no study has estimated the nationwide prevalence of both licenced and unlicensed MC use in Israel. This significant literature gap should be addressed to advance policy in this area of interest.

Furthermore, anxiety and depression remain some of the main reasons people use MC. In a survey of more than 1400 MC users from 18 countries, including the United States, Canada, and the United Kingdom, it was found that 58.1% and 50.3% of them used MC to treat anxiety and depression, respectively (Sexton et al., 2016). The findings are consistent with another online survey conducted in North America that anxiety (52%) and depression (40%) were among the main reasons for using MC among users (Leung et al., 2022). This information is probably not available in Israel due to the strict regulatory environment, whereby MC is commonly prescribed for cancer patients only (Waissengrin et al., 2015). However, because a sizeable proportion of unlicensed MC users in Israel self-prescribe, there are high chance they do so for anxiety and depression, which are some of the reasons (Sznitman, 2017). Therefore, it is important to evaluate the evidence base to determine the effectiveness of MC in treating anxiety and depression. The findings can inform policy regarding the medical indications of MC in

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Israel and other parts of the world. PubMed, Web of Science, ScienceDirect, Cochrane Library, and Google Scholar were searched to identify studies examining the effectiveness of MC in treating anxiety and depression. The findings of the studies were synthesized narratively, and the findings are reported below.

### **The Effectiveness of MC in Treating Anxiety**

A search on each of the databases mentioned above did not yield even a single clinical trial or robustly designed experimental study evaluating the effectiveness of MC in treating generalized anxiety disorders. Studies often focus on two main derivatives of cannabis, namely  $\Delta^9$ -tetrahydrocannabinol (THC) or cannabidiol (CBD) when investigating the effect of MC on anxiety (Berger et al., 2022).

#### **CBD**

Although there is insufficient evidence, various case reports and case series studies have suggested that CBD-dominant MC has demonstrated effectiveness in reducing the severity of anxiety disorders and social anxiety disorders, such as in the case of public speaking (Berger et al., 2020; Klier et al., 2020; Shannon et al., 2019; Shannon & Opila-Lehman, 2016). Unlike generalized anxiety disorders where no fully experimental clinical trial has been conducted so far, a search on the databases yielded two trials evaluating the effect of CBD-based MC on social anxiety disorder (Bergamaschi et al., 2011; Crippa et al., 2011). In their study, Crippa et al. (2011) administered 400 mg of CBD or a placebo to 10 treatment-naïve patients with social anxiety disorder (SAD) in two double-blind sessions, measuring regional cerebral blood flow (rCBF) via neuroimaging. They found that CBD significantly reduced anxiety in SAD patients and altered activity in specific limbic and paralimbic brain areas. Similarly, Bergamaschi et al. (2011) conducted a double-blind, randomized study where 24 SAD patients received either CBD or placebo before a public speaking test, measuring anxiety and physiological responses. They found that CBD significantly reduced anxiety, cognitive impairment, and discomfort during public speaking in SAD patients, like healthy controls. Their findings are endorsed by a recent clinical trial (quasi-experimental), which demonstrated that CBD-dominant MC treatment might be effective in reducing anxiety symptoms both in the short- and long term (Bidwell et al., 2024). Therefore, both studies provide strong evidence that CBD effectively reduces anxiety in patients with SAD.

#### **THC**

On the other hand, there are mixed findings regarding the effectiveness of THC-dominant MC in treating anxiety disorders. Particularly, studies have focused on synthetic derivatives like nabilone that only mimic the effects of THC but are chemically distinct. Four randomized

controlled trials investigating the effectiveness of nabilone on reducing anxiety (a secondary outcome measured in studies whose primary outcome was pain) found mixed findings, with three supporting the effectiveness of the compound (Pini et al., 2012; Skrabek et al., 2008; Toth et al., 2012) and one finding no effectiveness (Frank et al., 2008). Another synthetic THC, dronabinol has shown no effectiveness in reducing anxiety as a secondary outcome in clinical trials investigating its effect on pain as the primary outcome (Malik et al., 2016; Narang et al., 2008). Although none of the six clinical trials/RCTs has focused on patients with a primary anxiety disorder (their participants' anxiety was secondary to a chronic illness), the inconsistent findings between studies further support the ambiguity surrounding the effectiveness of THC and its derivatives in reducing anxiety. This ambiguity was addressed in a meta-analysis of seven clinical trials, whereby the authors concluded that THC with or without CBD improved anxiety secondary to various chronic illnesses with a small effect size, but the quality of the evidence was very low, casting uncertainty on this evidence (Black et al., 2019). Their findings were disputed by a recent meta-analysis of intervention studies that found that THC-dominant MC worsened anxiety symptoms rather than improving them (Crichton et al., 2024). Thus, the mixed findings regarding the effect of THC on anxiety cast uncertainty regarding the clinical application of THC and its derivatives for the treatment of anxiety.

### **The Effectiveness of MC in Treating Depression**

There are mixed findings in the literature regarding the effectiveness of MC, whether CBD or THC, in the treatment of depression (including postpartum depression), according to recent reviews of the literature on this subject (Ayisire et al., 2022; Stanciu et al., 2021). Some studies report significant improvements, while others report the worsening of depression symptoms. For example, a retrospective study demonstrated that MC may be effective in improving both anxiety and depression at 12 months and 18 months follow-up, respectively (Sachedina et al., 2022). Their findings are consistent with that of a clinical trial (non-randomized, single arm) that treated 338 chronic pain patients with a 19% Cannabis Flos decoction for 12 months alongside standard therapy (Poli et al., 2018). Although pain was the primary outcome, and depression was secondary to chronic pain, they found that MC reduced depression significantly over twelve months. The findings of the two studies above contradict an earlier clinical trial that randomized 360 patients with advanced cancer testing nabiximols (contains both THC and CBD at an equal ratio) at varying doses against placebo over five weeks (Portenoy et al., 2012). They showed that nabiximols did not significantly improve depression outcomes compared to placebo in opioid-treated cancer patients (Portenoy et al., 2012). Their findings are consistent with another clinical trial, which demonstrated that using MC among patients diagnosed with depression was associated

with worse mental and physical health functioning (Bahorik et al., 2018). A recent meta-analysis of intervention studies found no significant improvements in depression by both CBD- and THC-dominant MC treatment (Crichton et al., 2024). Such mixed findings in previous studies also demonstrate low uncertainty in the clinical use of MC in treating depression. Therefore, at this stage, MC should not be indicated for the treatment of depression until further research is conducted to clarify inconsistencies in the findings of the current literature.

## CONCLUSION

Treatment of anxiety and depression are some of the main reasons people self-prescribe or seek MC treatment. However, a review of the literature reveals insufficient evidence to support the effectiveness of MC (both THC and CBD) in reducing generalized anxiety disorders and depression. Although CBD has shown potential in reducing anxiety symptoms, especially in the case of SAD, robust clinical trials are lacking for generalized anxiety disorder. There are mixed findings regarding the effectiveness of THC-dominant MC, where some studies suggest worsening anxiety symptoms, which underscores the need for cautious clinical application. Therefore, there is a need for more rigorous, well-designed clinical trials to clarify the effectiveness of MC in treating anxiety and depression, as current literature presents low certainty. Therefore, based on the current evidence, MC should not be broadly indicated for anxiety and depression treatment until more conclusive research is available.

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