

The differential effects of medicinal cannabis on mental health: A systematic review

Nora de Bode^{a,*}, Emese Kroon^a, Sharon R. Sznitman^{b,c}, Janna Cousijn^a

^a Neuroscience of Addiction Lab, Center for Substance Use and Addiction Research, Department of Psychology, Education & Child Studies, Erasmus School of Social and Behavioral Sciences, Erasmus University Rotterdam, the Netherlands

^b School of Public Health, University of Haifa, Israel

^c Institute of Primary Health Care (BIHAM), University of Bern, Switzerland

ARTICLE INFO

Keywords:

Medicinal cannabis
Cannabinoids
Mental health
DSM-5
Controlled studies

ABSTRACT

The use of medicinal cannabis to improve mental health is increasing globally, both in clinical settings and through self-medication. This involves a variety of products containing Δ^9 -tetrahydrocannabinol (THC), cannabidiol (CBD), THC + CBD combinations, or derivatives. This review provides an up-to-date overview of the positive and negative effects of medicinal cannabis on mental health diagnoses and related symptoms of the Diagnostic and Statistical Manual of Mental Disorders 5th Edition. Searches in PubMed, PsycInfo, Embase, and the Cochrane Library (October 2023 and July 2024) identified 18,341 studies, of which 49 controlled studies from 15 different countries were included. All studies focused on treatment-seeking participants using medicinal cannabis for (symptoms of) their mental health diagnosis. Included diagnoses were anxiety disorders, tic disorders, autism spectrum disorder, attention-deficit hyperactivity disorder, obsessive-compulsive disorders, anorexia nervosa, schizophrenia, psychosis, substance use disorders, insomnia, and bipolar disorders. Varying product compositions showed different effects. Most consistently, high doses of CBD were followed by some acute relief in anxiety, while CBD + THC combinations alleviated withdrawal in cannabis use disorder and improved sleep. In clinical trials, THC was associated most with dose-dependent adverse events and, in some cases, deterioration of primary study outcomes, e.g., in psychosis. In naturalistic studies, participants who used THC reported symptom improvement following usage. Risks of bias across studies were prevalent, and no study found long-lasting medicinal effects or improvement. Overall, medicinal cannabis may provide short-term relief for certain symptoms but is not a cure or without mental health risks.

1. Introduction

Cannabis policies are becoming more liberal in various jurisdictions worldwide, partly influenced by the potential medicinal benefits of cannabis (Rafei et al., 2023). This parallels the belief that cannabis use is not as harmful as other drugs (Hill et al., 2022), and an increasing number of individuals report using cannabis for medicinal purposes without the guidance of a healthcare professional (Sexton, Cuttler, Finnell, & Mischley, 2016). Concurrently, a worldwide increase in cannabis related problems, such as cannabis use disorder (CUD) is reported, with people between 15 and 24 years old most affected (Shah et al., 2024).

Improving mental health symptoms is one of the most commonly reported motives for medicinal cannabis use (Lintzeris et al., 2020;

Lucas, Baron, & Jikomes, 2019), and its self-reported positive effects are widely found in the literature (Lyonskey, Athanasiou-Fragkouli, Thurgur, Schlag, & Nutt, 2024; Sexton et al., 2016; Ware, Adams, & Guy, 2005). For instance, in both the United States and Israel, post-traumatic stress disorder (PTSD) ranks as the third most common reason for the acquisition of a medical cannabis license, after pain and cancer related symptoms (Mahabir, Merchant, Smith, & Garibaldi, 2020; Sznitman, 2020; Yakirevich Amir, Treves, Davidson, Bonne, & Matok, 2023). Nonetheless, the evidence for its effectiveness in improving PTSD, or any mental health symptom for that matter, is equivocal. In fact, frequent cannabis use is associated with an increased risk of certain mental disorders. The relationship between heavy cannabis use and schizophrenia and psychosis is well-documented, but prolonged heavy cannabis use is also linked to increases in anxiety, depression, symptoms of bipolar and

* Corresponding author at: Erasmus University Rotterdam, 3000 DR Rotterdam, the Netherlands.

E-mail address: debode@essb.eur.nl (N. de Bode).

<https://doi.org/10.1016/j.cpr.2025.102581>

Received 3 December 2024; Received in revised form 25 February 2025; Accepted 28 March 2025

Available online 29 March 2025

0272-7358/© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

CUD, and other mental health conditions (Campeny et al., 2020; National Academies of Sciences, Engineering, and Medicine, 2017; Richardson, 2010). Although causality is complex, factors such as a young age of initiation (McGee, Williams, Poulton, & Moffitt, 2000), certain genetic predispositions (Verweij et al., 2022), using high potency products (Hines et al., 2020) or large quantities over an extended period of time (Kroon, Kuhns, Hoch, & Cousijn, 2020) may put an individual at risk for developing psychiatric symptoms.

Furthermore, benefits reported by medicinal users are minimally reflected by the findings of clinical trials (Sarris, Sinclair, Karamacosa, Davidson, & Firth, 2020), currently the gold standard for assessing the efficacy and safety of medicines. This discrepancy may be attributable to various factors. First, clinical trials evaluating the efficacy of medicinal cannabis for treating mental disorders are often of suboptimal quality (Black et al., 2019; Whiting et al., 2015). Deficits in study design, small sample sizes and questionable reporting (e.g., reporting improvement of symptoms without reaching actual significance) make it challenging to draw conclusions about the efficacy of medicinal cannabis. Moreover, medicinal users often suffer from a plethora of psychological symptoms (Yau et al., 2019), which may not be captured in studies focusing on a specific diagnosis. It has also been suggested that the perceived effectiveness of medicinal cannabis may be attributable to the use of cannabis to cope with one's symptoms, a relief of its own withdrawal effects, or mere placebo effects (Sexton, Cuttler, & Mischley, 2019; Turna et al., 2020).

Prior systematic reviews and meta-analyses report inconclusive evidence for the effectiveness of medicinal cannabis in relieving mental health symptoms and often report low quality of reviewed studies (Black et al., 2019; Z. Walsh et al., 2017; Whiting et al., 2015). A comprehensive systematic review and meta-analysis on the medicinal use of cannabinoids for depression, anxiety, PTSD, tic disorders, and psychosis found little to no evidence for the effectiveness of cannabidiol (CBD) or plant-based cannabis for mental health symptoms (Black et al., 2019). The review found some evidence for the effectiveness of pharmaceutical Δ^9 -tetrahydrocannabinol (THC) in treating anxiety, but solely in those suffering from other medical conditions, like multiple sclerosis. Another systematic review of cannabinoids in various mental and physical health conditions found evidence for improvement in sleep disorders, Tourette Syndrome (TS) symptoms, and anxiety, although the authors describe the evidence to be of low to very low quality (Whiting et al., 2015). A narrative review reported that THC and CBD were associated with reduced symptoms of anxiety, TS, anorexia nervosa, cannabis use disorder, and opioid use disorder when administered adjunctively with other psychosocial interventions (Hoch et al., 2019). Moreover, in a large ongoing observational study, improvement in mental health symptoms, such as PTSD and depression scores, were found in treatment seeking individuals prescribed medicinal cannabis to improve their symptoms (Lynskey, Athanasiou-Fragkouli, et al., 2024).

The puzzle of the effects of medicinal cannabis is clearly complex and the currently available evidence is ambiguous. Nonetheless, both medical cannabis prescriptions and the prevalence of self-reported current medicinal use are increasing across the world (Leung et al., 2022; Mills et al., 2024; Nationale Drug Monitor, 2024; Rhee & Rosenheck, 2023; Sznitman, 2020). Unlike other pharmacological treatments for mental health, individuals who use medicinal cannabis often obtain their products through unsupervised routes, such as recreational outlets (e.g., Dutch "coffeeshops" that sell cannabis over the counter), or online services with minimal oversight (Bradlow & Armstrong, 2024; Lintzeris, Mills, Surave, et al., 2020). As a result, individuals may acquire medicinal cannabis without necessarily meeting prescription requirements, even in regions where (recreational) cannabis is prohibited (Rehm, Elton-Marshall, Sornpaisarn, & Manthey, 2019; Salazar, Tomko, Akbar, Squeglia, & McClure, 2019). Furthermore, in places where legislation has recently loosened and medicinal cannabis has gained attention (for example through advertisements in the United States, Canada, or Thailand), usage is rising but regulations are falling behind (Kalayasiri &

Boonthae, 2023; Noël, Scharf, Koné, Armiento, & Dylan, 2024; Whitehill, Trangenstein, Jenkins, Jernigan, & Moreno, 2020). While an increase in use is mostly reported among adults (Assanangkornchai, Kalayasiri, Ratta-Apha, & Tanaree, 2023; Hall & Lynskey, 2020), vulnerable groups—such as adolescents and young adults—may face additional risks, including a higher susceptibility to substance use disorders (SUDs) and other psychiatric symptoms (Newton-Howes, 2018). Especially in this group, self-medicating with cannabis may increase mental health problems. Nonetheless, current evidence whether usage in young people has risen due to legislative changes remains mixed (Assanangkornchai et al., 2023; Bailey et al., 2023; Zuckermann et al., 2021). Altogether, this illustrates the need for rigorous yet nuanced research into the medicinal properties of cannabis for mental health, considering the characteristics of medicinal users, type of product, and mental health symptomatology.

For medicinal purposes, plant-based and synthetic cannabinoids are used. In plant products, THC and CBD are the main active components, whereas in pharmaceutical cannabinoids, either THC (dronabinol), its derivative (nabilone), or CBD can be present, as well as a combination of THC and CBD (nabiximols) (Murnion, 2015; see Appendix A of the Supplementary Materials). Throughout this paper, medicinal cannabis will be used as an umbrella term, and when referring to specific products, this will be specified.

Following PRISMA guidelines (Page et al., 2021), this systematic review aims to provide an overview of the current research on individuals of any age or background who report cannabis use to improve mental health symptoms, either in a healthcare setting or by self-medication, compared to a control group or condition. All diagnoses listed under section II of the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5: American Psychiatric Association, 2013) will be considered, with the exception of elimination disorders, somatic symptom and related disorders, neurocognitive disorders, medication induced disorders and symptoms, and diagnoses in the category other mental disorders or conditions. To our knowledge, this is the first review with such a broad inclusion of DSM-5 mental health diagnoses and symptoms, considering both positive and negative effects on mental health symptoms. Given the rapidly evolving nature of this field, it is of ongoing importance to have an up-to-date overview of the current evidence of the mental health effects of medicinal cannabis.

2. Methods

2.1. Inclusion and exclusion criteria

Our inclusion criteria were human studies written in English (full-text available), including treatment-seeking participants with a primary mental health diagnosis or symptoms receiving or self-medicating with cannabis/cannabinoids to improve their diagnosis or symptoms. Validated measurement tools had to be used to measure (changes in) the diagnosis or symptoms, which was checked in the method section of the included studies. Furthermore, studies were only eligible if a control group or condition was present, e.g., non-cannabinoid product (placebo) or no use, and the only treatment difference between the cannabis/cannabinoid condition and control was the cannabis product. The following mental health diagnoses under the headers of section II of the DSM-5 were eligible: neurodevelopmental disorders, schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma- and stressor-related disorders, dissociative disorders, feeding and eating disorders, sleep-wake disorders, sexual dysfunctions, gender dysphoria, disruptive, impulse-control, and conduct disorders, substance-related and addictive disorders, personality disorders, paraphilic disorders. The full inclusion criteria can be found in Appendix B of the Supplementary Materials. The study was preregistered at Prospero (CRD42023436950). Amendments to the preregistration can be found on crd.york.ac.uk and in Appendix C of the

Supplementary Materials.

2.2. Search strategy & screening procedures

A search was conducted in the electronic databases PubMed, PsycInfo, Embase, and the Cochrane Library on 4 October 2023 and updated on 23 July 2024. Search terms were related to the medicinal use of cannabis (and synonyms) and mental health diagnoses and symptoms. The full search syntax can be found in Appendix D of the Supplementary Materials.

After extracting all resulting studies, duplicates were removed before two reviewers (NDB and EK) independently screened all studies for inclusion. First, titles and abstracts were screened using Rayyan review software and studies that did not meet the inclusion criteria upon first review were excluded. Second, full texts of the remaining studies were assessed, excluding studies that did not meet the inclusion criteria. The remaining studies were unblinded and discrepancies between reviewers were resolved through discussion. Citations of the included studies were also searched. For data extraction, all authors agreed on the main categories (see columns of Table 1) and it was carried out by NDB. The PRISMA flow diagrams for study selection can be found in Appendix E of the Supplementary Materials.

2.3. Risk of bias assessment

Risk of bias assessments were conducted for each included study considering all outcome measures. For randomized controlled trials, the Cochrane Risk of Bias tool (ROB-2) (Sterne et al., 2019) was used, evaluating five domains of bias as either low, high, or unclear risk. The risk of bias for non-randomized studies was assessed using the Newcastle Ottawa Scale (Wells et al., 2011). The full risk of bias assessment can be found in Appendix F and G of the Supplementary Materials.

3. Results

Most of the included studies employed a randomized controlled trial (RCT) design, where participants were randomly and (double) blindly assigned to receive either the cannabinoid/cannabis treatment or a control condition, e.g., placebo. Multiple studies utilized a cross-over design, in which participants receive both the active treatment and the placebo in a random sequence, separated by a washout period. If the participants received a titrated dose of cannabis medication, the dosage was gradually increased to find the optimal dosage for the participant. This result section solely focuses on the assessments related to the included mental health diagnoses. For the full overview of all assessments and study designs please see Table 1. For complex designs, descriptions are also provided here. Additionally, Fig 1 provides an overview of whether medicinal cannabis (split per type of cannabinoid) had positive, negative or no effects on at least one of the primary outcome measures of every study, grouped by disorder.

Concerning the risk of bias, 22 out of 49 studies (44.9 %) were rated as having an overall unclear risk of bias. Determining the impact of this on the evidence of these studies is difficult, as many studies did not provide sufficient information to accurately assess the risk of bias in some domains. Consequently, these studies were classified as having a rating of an unclear risk of bias, or if it concerned most risk of bias domains, a high risk of bias. A high risk of bias was found in 15 studies (30.6 %) and a low risk of bias in 12 studies (24.5 %). The most common high risk domains were missing outcome data (9 studies, 18.3 % of total studies, e.g., large unexplained attrition) and deviations from intended interventions (6 studies, 12.2 % of total studies, e.g., a lack of blinding, see Appendix G).

3.1. Neurodevelopmental disorders

3.1.1. Attention deficit hyperactivity disorder (ADHD)

A pilot RCT investigated the behavioral effects of nabiximols (THC and CBD in a 1:1 ratio) or placebo in 30 participants with ADHD for six weeks. Cognitive performance and activity level (head movements) were the primary outcome measures, while ADHD and emotional lability symptoms were monitored as secondary measures. No significant improvement in any of the outcome measures was observed (R. E. Cooper et al., 2017).

3.1.2. Autism spectrum disorder

The first study assessing the effects of cannabinoids on autism spectrum disorder (ASD) used two types of cannabinoid extracts, i.e., purified THC + CBD and whole plant extract (both at a 20:1 CBD and THC ratio) and placebo. These cannabinoid products were compared to determine if the effects of cannabinoids were solely due to CBD and THC, or if other minor cannabinoids present in the whole plant extract also contributed therapeutically. The sample included 150 people between 5 and 21 years with ASD, each receiving two of the three treatment types (both for 12 weeks, separated by a 4-week washout period). The study included two measures of autism-related disruptive behaviors, and parent-rated scales for non-compliant behaviors and autism severity. The purified extract did not lead to any improvements. However, in the whole plant extract group, significantly more people improved in disruptive behavior and social functioning compared to placebo. (Aran, Cassuto, Lubotzky, Wattad, & Hazan, 2019).

Moreover, in another RCT, 60 children with ASD received placebo or a CBD-dominant extract containing CBD and THC in a 9:1 ratio for 12 weeks (Silva Junior et al., 2024). The primary outcome measure was a change in ASD symptoms, including aggressiveness, concentration, psychomotor agitation, social interaction with peers, speech, sleep, anxiety, and meals per day, all evaluated by the caregivers. ASD severity score was also measured. Compared to placebo, children receiving the CBD extract showed a significant improvement in social interactions, anxiety, psychomotor agitation, and accepted more meals a day. No group differences were found on the other measures. Concerning concentration, only those with mild ASD showed improvement after CBD reception.

3.1.3. Gilles de la Tourette and tic disorders

Six RCTs were identified using medicinal cannabinoids for Gilles de la Tourette Syndrome (GTS) and Tic Disorders. Two studies were carried out in the same sample of 12 adults with GTS, who participated in a single-dose crossover trial, with a THC dose of either 5, 7.5, or 10 mg, based on participant characteristics. One study assessed the effects of THC on tic severity (Müller-Vahl et al., 2002), while the other evaluated neuropsychological performance (Müller-Vahl et al., 2001). Tic severity was measured before and 3–4 h after a single dose of THC or placebo using both self-assessment tools and examiner-based ratings. Compared to a placebo, THC was associated with a significant reduction in some of the self-rated subscales, assessing tics and obsessive-compulsive symptoms, as well as a significant reduction in clinician rated complex motor tics. There was also a positive correlation between tic improvement and maximum plasma concentration of THC metabolites (Müller-Vahl et al., 2002). There was no difference between THC and placebo on neuropsychological measures, including short-term memory, verbal memory and learning, verbal intelligence, immediate and visual memory, speed of information processing, motor, reaction and general reaction time, sustained attention, divided attention, depression scores (Müller-Vahl et al., 2001). Obsessive-compulsive behaviors significantly worsened in the THC group. Interestingly, when comparing the two studies, the same sample showed both improvement and deterioration of obsessive-compulsive behaviors after THC administration, depending on the questionnaire used for assessment.

In a 6-week RCT involving 24 adults with GTS, the efficacy and safety

Table 1

Summary of studies

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
Autism								
1*	Aran et al. (2019)	Israel	3 products: whole-plant cannabis extract containing CBD: THC = 20:1, purified cannabinoids CBD:THC = 20:1 or placebo.	<i>N</i> = 150 (<i>n</i> = 50 per group, 5–21 years, age <i>M</i> (<i>SD</i>) = 11.8 (4.1), 80 % male). Autism spectrum disorder (ASD) per DSM-5, confirmed by Autism Diagnostic Observation Schedule (ADOS-2), ≥ moderate behavioral problems on the Clinical Global Impression Severity scale. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial with cross-over.	Placebo or either of the two cannabinoids for 12 weeks, followed by a 4-week washout and 12-week cross-over. Assessments at baseline and after each treatment period.	Primary outcomes: the Home Situation Questionnaire-ASD (HSQ-ASD) and the Clinical Global Impression-Improvement scale measuring (CGI-I). Secondary outcomes: the Social Responsiveness Scale (SRS-2) Total Score and Autism Parenting Stress Index (APSI).	No significant difference in HSQ-ASD and APSI total scores between cannabinoid and placebo groups. Improvement in SRS-2 total score was significantly higher for whole-plant extract versus placebo. Drop out AEs whole plant <i>n</i> = 1, placebo <i>n</i> = 1.
2	Silva Junior et al. (2024)	Brazil	CBD-dominant cannabis extract 0.5 % (5 mg/mL), with CBD: THC = 9:1 or placebo.	<i>N</i> = 60 (5–11 years, 31 CBD: age <i>M</i> (<i>SD</i>) = 7.6 (1.7), 80.1 % male, 29 placebo: age <i>M</i> (<i>SD</i>) = 7.7 (1.8), 93.1 % male). Medical diagnosis of autism spectrum disorder (ASD), a cut-off score of 15 on the Childhood Autism Rating Scale (CARS). Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial.	Stratification based on ASD severity. Caregivers administered CBD or placebo every 12 h, with a starting dose of 3 drops, which could be increased twice a week to max 70 drops per day. Assessments at baseline and at the end of the study.	A semi-structured interview for caregivers about ASD symptoms, the Childhood Autism Rating Scale (CARS) and the Autism Treatment Evaluation Checklist (ATEC).	In CBD versus placebo, psychomotor agitation, social interaction and anxiety improved, and the number of meals increased. Other measures did not differ between groups. Concentration improved in those receiving CBD with mild ASD. AEs CBD <i>n</i> = 4, placebo <i>n</i> = 5.
Attention deficit hyperactivity disorder								
3	Cooper et al. (2017)	The United Kingdom	Nabiximols (2.7 mg THC and 2.5 mg CBD) or placebo.	<i>N</i> = 30 (18–55 years, 15 nabiximols: age <i>M</i> (<i>SD</i>) = 36.8 (11.7), 60 % male, 15 placebo: age <i>M</i> (<i>SD</i>) = 38.9 (11.5), 50 % male). Combined type ADHD per DSM-5, score of ≥24 on the 18-item Conners' Adult ADHD Rating Scale (CAARS). Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	Nabiximols or placebo for a 2-week titration period with daily dosage increase (max 14 sprays per day), followed by 4-weeks of stable dose. Assessments at baseline and 42 days after randomization.	Primary outcomes: Quantitative Behavioral Test (QbTest). Secondary outcomes: ADHD symptoms (rated by the investigators), the Conners Adult ADHD Rating Scale (CAARS), the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADS), the Sustained Attention to Response Task (SART), the Centre for Neurologic Study Liability Scale (CNS-LS) and Affective Liability Scale-Short Form (ALS-SF) and the Weiss Functional Impairment Rating Scale Self Report (WFIRS-S).	No significant group differences on primary or secondary outcome measures after correction for multiple testing. Serious AEs nabiximols <i>n</i> = 1, placebo <i>n</i> = 1. Mild AEs, nabiximols <i>n</i> = 3.

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
Anxiety disorders								
4	Gundugurti et al. (2024)	India	150 ml nano dispersible CBD or placebo.	N = 178 (89 CBD: age M(SD) = 37.2 (10.4), 37.1 % female, 89 placebo: age M(SD) = 37.6 (11.3), 36 % female). Generalized anxiety disorder per the International Classification of Diseases 11th revision (ICD-11), mild to moderate anxiety on the Depression Anxiety Stress Scale-21 (DASS-21) questionnaire. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial.	15-week multicenter study with 15 sessions, 11 on-site (assessments conducted) and 4 via the telephone. After a placebo phase (exclusion if participants already showed significant changes in outcome measures) placebo or CBD twice daily.	Primary outcomes: changes in the Generalized Anxiety Disorder 7 (GAD-7), Hamilton Anxiety Rating Scale (HAM-A). Secondary outcomes: the Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), Patient's Health Questionnaire-9 (PHQ-9), changes in DASS-21 scores, and Pittsburgh Sleep Quality Index (PSQI).	Mean GAD-7 and HAM-A scores significantly decreased in CBD throughout the study until week 13 (visit 11), unlike placebo. Contrary to placebo, all secondary measures significantly improved in CBD at the end of treatment versus baseline. Mild to moderate AEs CBD n = 28, placebo n = 13.
5	Fabre and McLendon (1981)	The United States	2–8 mg nabilone (open study), 1 mg nabilone (RCT) or placebo.	N = 5 (open label, all male, all Caucasian, 22–35 years, age M = 29.4 years), N = 20 (RCT, 19–41 years, 10 nabilone: 10 placebo, age M = 29, 15 males, 5 females, 19 Caucasian, 1 Black). Outpatients with anxiety for a sufficient time to indicate spontaneous remission would not occur. Entire sample cannabis naïve: unknown.	Open label study and double-blind, randomized, placebo-controlled trial.	Open label study and RCT, both started with a 4-day washout period, followed by a 28-day treatment, assessments at baseline and throughout the study.	The Self Rating Symptom Scale, Hamilton Anxiety Rating Scale, and the Patient's Global Impressions and the Physician's Global Impressions.	Open label study: the Hamilton Rating Scale total score and the somatic and psychic anxiety subscale scores significantly reduced compared to before treatment. In the RCT, nabilone showed significant improvement on the Hamilton Rating Scale total score and the somatic and psychic anxiety subscale versus placebo. The efficacy index of the Physician's Global Impressions improved only in the nabilone group. Mild to moderate AEs nabilone = 51, moderate to severe AEs = 16. Drop out placebo n = 5 (due to lack of effects).

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
6	Bergamaschi et al. (2011)	Brazil	600 mg CBD or placebo.	$N = 36$ (12 CBD: age $M(SD) = 24.6$ (3.6), 50 % male, 12 placebo: age $M(SD) = 22.9$ (2.4), 50 % male, 12 HC's: age $M(SD) = 23.3$ (1.7), 50 % male). Treatment naïve, Social Anxiety Disorder, assessed by the Social Phobia Inventory and the social anxiety module of Structural Clinical Interview for the DSM-IV, clinical version (SCID-IV). Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	A public speaking test was administered to healthy controls (no treatment) and SAD participants receiving either 600 mg CBD or placebo 1.5 h prior. Assessments before, during, and after the test.	State-anxiety level during the test measured with the Visual Analogue Mood Scale (VAMS), The Self-Statements during Public Speaking Scale negative evaluation subscale (SSPS-n), The Bodily Symptoms Scale (BSS), and physiological measures.	During the test, placebo had significantly higher levels of anxiety, cognitive impairment, discomfort, and alertness than healthy controls (VAMS scale scores). Compared to placebo, CBD had significantly lower cognitive impairment, anxiety, and discomfort in their speech performance and decreased alert in their anticipatory speech. The scores of the CBD group were similar to the healthy controls during the task. Number of AEs not reported. No significant group differences on any of the outcome measures. Non serious AEs CBD $n = 4$, placebo $n = 6$. In the CBD group, drop out $n = 1$ (suicide ideation).
7	Kwee et al. (2022)	The Netherlands	300 mg CBD or placebo.	$N = 80$ (18–65 years old, 39 CBD: age $M(SD) = 34.9$ (9.3), 60 % male, 41 placebo: age $M(SD) = 38.3$ (11.3), 63.4 % male). Social anxiety disorder or panic disorder with agoraphobia per DSM-IV. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial.	At 3 mental health care centers, 8 weekly therapist-assisted exposure sessions were combined with CBD or placebo. Assessments at baseline, during and after treatment, and at 3- and 6-month follow-up.	Primary outcomes: the Fear Questionnaire (FQ). Secondary outcomes: the Beck Anxiety Inventory (BAI). Other outcomes: Beck Depression Inventory-II (BDI-II), the Social Phobia and Anxiety Inventory-18 (SPAI-18), Body Sensations Questionnaire (BSQ), Clinical Global Impression severity scale (CGI), Subjective Units of Distress (SUDS), Panic Disorder Severity Scale, (PDSS), Mobility Inventory (MI), Agoraphobic Cognitions Questionnaire (ACQ), and Liebowitz Social Anxiety Scale (LSAS). The Fear of Negative Evaluation Questionnaire (FNE), the Liebowitz Social Anxiety Scale (LSAS), and changes in the Structured Clinical Interview for DSM-IV (SCID-I and SCID-II).	Reduction in FNE scores was significant pre versus posttreatment in CBD, but no group difference. In CBD, LSAS scores decreased significantly post treatment, unlike placebo. SCID changes and AEs were not reported.
8	Masataka (2019)	Japan	300 mg CBD or placebo.	$N = 37$ (18–19 years old, 17 CBD: 70.6 % male, 20 placebo: 70 % male). Social anxiety disorder or avoidant personality disorder per DSM-IV, symptoms present ≥ 6 months prior to the study. Entire sample cannabis naïve: yes.	Double-blind, randomized, placebo-controlled trial.	4 weeks of CBD or placebo twice daily. Assessments at baseline and after the treatment.		

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
Anorexia nervosa (AN)								
9	Andries et al. (2014)	Denmark	2.5 mg dronabinol or placebo.	N = 24 (≥ 18 years, 11 dronabinol, 13 placebo, all female). AN per DSM IV - TR for ≥ 5 years. Entire sample cannabis naïve: unknown.	Double blind, randomized, placebo-controlled, cross-over trial.	2 $\times$ 4 weeks of dronabinol or placebo twice daily, separated by a 4-week wash-out period, along with standard psychotherapy and nutritional interventions (cross-over). Primary outcome assessed at each visit, secondary outcome the first and last week of each treatment period.	Primary outcome: mean change in body weight. Secondary outcome: scoring changes on the Eating Disorder Inventory-2 (EDI-2).	There was significant weight gain during dronabinol treatment compared to placebo (+0.73 kg). Regardless of drug sequence, participants gained 0.76 kg more during the first treatment period than the second period. No significant differences in EDI-2 scores during treatment with either treatment. 50 % reported ≥ 1 AE, but none serious.
10	Gross et al. (1983)	Germany	7.5 - 30 mg THC or active placebo (3 - 15 mg diazepam).	N = 11 (all female, all Caucasian, age M (SD) = 23.6 (1.8)). Primary AN per Feighner criteria, all amenorrheic, and lost at least 25 % of their body weight. Entire sample cannabis naïve: unknown.	Double blind, randomized, placebo-controlled, cross-over trial.	4 weeks of titrated THC or diazepam 3 times daily, along with a standardized behavior modification plan. 1 week post-study, a high THC dose was administered to measure physiological effects. Assessments mostly daily, some weekly.	Daily weight, daily caloric intake, the Hopkins Symptoms Checklist-90, the Goldberg Anorectic Attitude Questionnaire and the Goldberg Situational Discomfort Scale (all rated by the participant) and The Psychiatric Rating Scale (PRS) assessed by a physician.	Only significant changes over time were worsening of somatization, interpersonal sensitivity, and sleep disturbance in THC compared to diazepam. Severe AEs THC n = 3.
Obsessive Compulsive Disorders								
11	Kayser et al. (2020)	The United States	3 cannabis variations: placebo = 0 % THC/0 % CBD, high THC = 7 % THC /0.18 %, high CBD = 0.4 % THC/ 10.4 % CBD.	N = 14 (21–55 years old, 5 THC, 5 CBD, 4 placebo, age M(SD) = 26.8 (7.4), 67 % male, 75 % white, 17 % Black, 17 % Hispanic, 8 % Asian). Obsessive-compulsive disorder per DSM-5 (research version), ≥ 1 year with constant symptoms, score of ≥ 16 on the Yale-Brown Obsessive Compulsive Scale. Entire sample cannabis naïve: no.	Double blind, randomized, placebo-controlled, cross-over trial.	In 3 lab sessions, participants smoked different randomized cannabis products. Acute changes in outcome measures were assessed, OCD symptoms also prior to the session.	The Yale-Brown Obsessive-Compulsive Scale (YBOCS) assessed by a clinician and the participants, the Obsessive Compulsive Visual Analogue Scale (OCD-VAS), the Spielberger State-Trait Anxiety Inventory state subscale, Marijuana Rating Form (MRF), and physiological measures.	THC heightened heart rate, blood pressure, and the feeling of being high, in contrast to CBD and placebo. Self-reported OCD symptoms and anxiety decreased over time in all 3 treatments, but administration of placebo was followed by a steeper reduction of state anxiety compared to THC and CBD. Serious AE THC = 1.
12	Grant et al. (2022)	The United States	5 - 15 mg dronabinol or placebo.	N = 50 (18–65 years, 25 dronabinol: age M (SD) = 33 (12.5), 76 % female, 25 placebo: age M(SD)	Double-blind, randomized, placebo-controlled trial.	10 weeks of titrated dronabinol or placebo with assessments at baseline and	Primary outcomes: the National Institute of Mental Health (NIMH) Symptom Severity Scale total score. Secondary outcomes: the self-report Massachusetts	Both dronabinol and placebo were associated with reduced symptoms from baseline to week

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
				= 28.4 (7.3), 84 % female, predominantly Caucasian percentage not specified). Trichotillomania or skin picking disorder per DSM-5. Entire sample cannabis naïve: no.		every 2 weeks (first 4 weeks), then every 3 weeks (remaining 6 weeks).	General Hospital Hair Pulling Scale (MGH-HPS) or the self-report MGH-HPS version for Skin Picking, the Sheehan Disability Scale, and the Clinical Global Impressions (CGI) severity and improvement scales.	10, but without a significant group difference on any measure. Dronabinol had more frequent side effects than placebo. No significant benefit for dronabinol compared to placebo was found. Mild to moderate AEs dronabinol 64 %, placebo 28 %.
Tic Disorders								
13	Müller-Vahl et al. (2001)	Germany	2.5 or 5.0 mg THC or placebo.	N = 12 patients (18–66 years, age M (SD) = 34 (13), 11 men, 1 woman). Tourette Syndrome per DSM – III. Entire sample cannabis naïve: no. Same study sample as Muller-Vahl 2002	Double blind, randomized, placebo-controlled, cross-over trial.	1 single dose THC and placebo on 2 days separated by a 4-week washout (cross-over). Assessments 1 h after administration in the lab.	The Auditory Verbal Learning Test (VLMT), Digit Span (subtest of the Hamburg-Wechsler Intelligence Scale), multiple choice vocabulary test (MWT-B), Benton Visual Retention Test, Signal Detection, Vienna Reaction Time, measures for sustained and divided attention, Hamilton Depression Scale, Symptom Checklist 90-R (SCL-90-R) including the items somatization, obsessive compulsive behaviors (OCB), interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychoticism. This test also yielded a symptomatic index (GSI), a positive symptom total (PST) and a positive symptom distress index (PSDI).	Compared to placebo, no significant differences after THC on any of the measures. Only the OCB item of SCL-90-R demonstrated a significant worsening after THC treatment. Mild AEs, THC <i>n</i> = 5, placebo <i>n</i> = 2.
14	Müller-Vahl et al. (2002)	Germany	2.5 or 5.0 mg THC or placebo.	N = 12 patients (18–66 years, age M (SD) = 34 (13), 11 men, 1 woman). Tourette Syndrome per DSM – III. Entire sample cannabis naïve: no. Same study sample as Muller-Vahl 2001	Double blind, randomized, placebo-controlled, cross-over trial.	1 single dose THC and placebo on 2 days separated by a 4-week washout (cross-over). Assessments 1 h after administration in the lab.	Primary outcomes: the self-rating scale Tourette's syndrome Symptom List (TSSL) and examiner ratings conducted with the Shapiro Tourette's Syndrome Severity Scale (STSS), Yale Global Tic Severity Scale (YGTSS), Tourette's syndrome Global Scale (TSGS) and plasma levels of THC and associated metabolites.	Compared to placebo, THC was associated with a significant improvement on the TSSL and on its subitems obsessive-compulsive behavior (OCB), motor tics, simple motor tics, complex motor tics and complex vocal tics. Examiner ratings demonstrated a significant difference for the TSGS subscore complex motor tics after THC, but not for the other

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
								measures.
15	Müller-Vahl et al. (2023)	Germany	2.5 or 5.0 mg THC or placebo.	N = 24 (18–68 years old, 12 THC, 12 placebo, age M(SD) = 33 (11), 19 men, 5 women). Tourette Syndrome per DSM - III-R. Entire sample cannabis naïve: no	Double-blind, randomized, placebo-controlled trial.	6 weeks of up to 10 mg/day of THC or placebo, assessments at 6 visits.	Primary outcomes: the examiner rating scales Tourette Syndrome Clinical Global Impressions scale (TS-CGI), the Yale Global Tic Severity Scale (YGTSS), the Shapiro Tourette Syndrome Severity Scale (STSS), a video-based rating scale, and self-rating with the Tourette Syndrome Symptom List (TSSL) and the severity of their premonitory urges.	Mild AEs THC n = 5, placebo n = 2. After a Bonferroni correction, the only group difference found was on the TS-CGI at visit 4, with THC being superior to placebo. Mild AEs THC n = 5, placebo n = 3. THC n = 1 drop out due to AEs
16	Müller-Vahl et al. (2023)	Germany	Nabiximols (2.7 mg THC and 2.5 mg CBD) or placebo.	N = 97 ($\geq$ 18 years, 64 nabiximols: age M(SD) = 37.4 (14.3), 33 placebo: age M(SD) = 34.9 (11.2), 75.3 % male). Chronic Tic Disorder per DSM-5, total tic score of the Yale Global Tic Severity Scale of $\geq$ 14 for those with Tourette Syndrome and $\geq$ 10 for those with chronic motor or vocal tic disorders, score of $\geq$ 4 on the Clinical Global Impression scale for severity. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	After a 4-week titration phase a 9-week treatment phase with stable dosage, max 12 sprays per day. 11 study visits took place for assessments.	Primary outcomes: the total Tic Score of the Yale Global Tic Severity Scale (YGTSS-TTS). Efficacy was measured by a reduction of at least 25 % of the total score. Secondary outcomes: the YGTSS, Adult Tic Questionnaire (ATQ), the Modified Rush Video-Based Tic Rating Scale (MRVS), Premonitory Urge for Tics Scale (PUTS), Gilles de la Tourette syndrome-Quality of Life Scale (GTS-QoL) Clinical Global, the Conners' Adult ADHD Rating Scale (CAARS), Impression scale for improvement (CGI-I), 12-item short-form Health Survey (SF-12), the Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory, (BAI), Skala Impulsives-Verhalten-8 (I-8) for impulsivity, Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Rage Attacks Questionnaire for adults with GTS (RAQ-GTS), and Pittsburgh Sleep Quality Index (PSQI).	Nabiximols were not superior compared to placebo for almost all outcome measures. Only the exploratory measure ATQ motoric subscale improved in nabiximols versus placebo. In nabiximols, males and those with more severe tics had better improvement on the YGTSS-TTS than females or those with less severe tics. AEs nabiximols n = 61 (1 severe), placebo n = 26.
17	Abi-Jaoude et al. (2023)	Canada	4 products with 0.25 g vaporized cannabis containing 10 % THC, 9 % THC/9 %CBD, 13 % CBD, placebo THC/CBD <0.3 %.	N = 12 (18–65 years old, 11 males, age M = 38). Tic score of $\geq$ 16 on the Yale Global Tic Severity Scale Total Tic Score, a frequency subscore of 5, intensity subscore of $\geq$ 2, and tic-free intervals of max 2 min. Entire sample cannabis naïve: no.	Double blind, randomized, placebo-controlled, cross-over trial.	Single dose during 4 sessions (all treatments), assessments at 0 h, 0.5 h, 2, 3, and 5 h post administration.	Primary outcomes: the clinician rated Modified Rush Video-Based Tic Rating Scale (MRVTRS). Secondary outcomes: the Premonitory Urge for Tics Scale (PUTS), Subjective Units of Distress Scale (SUDS), Clinical Global Impression-Improvement (CGI-I), and correlations between outcomes and cannabinoid plasma levels.	No differences between treatments were observed on outcome measures for tic reduction. At almost all timepoints, 10 % THC showed significant improvement versus placebo on the PUTS and SUDS, and a significantly higher number of 10 % THC participants improved on the CGI-I versus placebo. THC and its metabolites negatively

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
18	Mosley et al. (2023)	Australia	1 - 4 mL with 5 mg THC and 5 mg CBD and placebo.	$N = 22$ (18–70 years old, 8 women, 90 % white, 10 % Asian, age $M(SD) = 31$ (12.5)). Confirmed diagnosis of Tourette Syndrome by a neurologist or psychiatrist, moderate to severe burden of tics, total tic score of ≥ 20 on the YGTSS. Entire sample cannabis naïve: no.	Double blind, randomized, placebo-controlled, cross-over trial.	After a 4-week titration period, 2×2 weeks of placebo or active treatment, separated by a 4-week washout (cross-over). Assessments at baseline, twice during treatment and at the end of the treatment period.	Primary outcomes: the total tic score on the clinician rated Yale Global Tic Severity Scale (YGTSS). Secondary outcomes: YGTSS global score, the Modified Rush Video-Based Rating Scale (MRVRS), the Montgomery–Åsberg Depression Rating Scale (MADRS), the Hamilton Anxiety Rating Scale (HAM-A) and the Yale–Brown Obsessive-Compulsive Scale (YBOCS). Plasma cannabinoids and the Cambridge Neuropsychological Test Automated Battery were also assessed.	correlated with SUDS and PUTS scores. No significant differences between 13 % CBD and placebo. AEs THC group $n = 24$, 14 THC/CBD $n = 14$, CBD $n = 13$, placebo $n = 4$. There was a greater improvement on the YGTSS total tic score in the active group versus placebo and compared to baseline. The YGTSS global score, the YBOGS, MRVRS, and HAM-A improved in the active treatment versus placebo and compared to baseline. This was not the case for the MADRS scores. Cognitive assessments did not differ between groups. Mild to moderate AEs THC/CBD $n = 8$, placebo $n = 7$.
19	Freeman et al. (2020)	The United Kingdom	CBD (200 mg, 400 mg, 800 mg) or placebo.	$N = 48$ (16–60 years, 12 placebo: age $M = 24.9$, 73.9 % male, 12 CBD 200: age $M = 27.3$, 75 % male, 12 CBD 400: age $M = 26.6$, 70.8 % male, 12 CBD 800: age $M = 27.4$, 69.8 % male). $\geq$ moderate cannabis use disorder per DSM-5, treatment seeking, at least 1 failed quit attempt. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	4 weeks of either 200 mg, 400 mg, 800 mg, or placebo, including a brief psychological intervention with motivational interviewing. An adaptive Bayesian dose-finding design to determine effective and ineffective doses (the main objective of the study).	Primary outcomes: cannabis use measured by the metabolites in urine and days of abstinence. Secondary outcomes: the Cannabis Withdrawal Scale (CWS), tobacco and alcohol use, the Pittsburgh Sleep Quality Index (PSQI), the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI).	200 mg was removed due to ineffectiveness. At the end of the trial, 400 mg and 800 mg had a probability of ≥ 90 % to be more effective than placebo for primary outcomes. At follow-up, only 400 mg was more effective than placebo. Compared to placebo, 400 mg CBD was associated with less cigarettes smoked per week during treatment and until the follow-up, but sleep quality was worse (increased PSQI scores). 800 mg improved

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
								CWS scores and anxiety during treatment and until the final follow up compared to placebo.
								Mild AEs 200 mg $n = 42$, 400 mg $n = 96$, 800 mg $n = 78$, placebo $n = 65$.
20	Hill et al. (2017)	The United States	2 mg nabilone or placebo.	$N = 12$ (18–45 years, 3 female, 9 male, all Caucasian, age $M(SD) = 25.1$ (6.8)). Cannabis dependence per DSM-IV. Entire sample cannabis naïve: no.	Randomized, placebo-controlled trial	10 weeks of titrated nabilone or placebo daily in addition to weekly in-person medication management. Assessments at baseline and throughout the study, urine samples twice a week.	Primary outcomes: cannabis use via self-report of days of use and twice weekly urine cannabinoid tests, safety, and tolerability. Secondary outcomes: the Marijuana Craving Questionnaire (MCQ), the Quick Inventory for Depressive Symptoms (QIDS), the Beck Anxiety Inventory (BAI).	No significant differences in cannabis use between the two treatment groups. Both groups showed a reduction in MCQ total scores without a group effect. No significant difference in QIDS scores.
21	Levin et al. (2011)	The United States	20 mg dronabinol or placebo.	$N = 156$ adults (18–60 years, 77 placebo: age $M(SD) = 38.4$ (9.2), 79.2 % male, 20.8 % Hispanic, 15.6 % Black, 55.8 % white, 7.8 % white, 76 dronabinol: age $M(SD) = 36.9$ (10.8), 84.4 % male, 27.9 % Hispanic, 24.1 % Black, 40.5 % white, 7.6 % other). Cannabis dependence per DSM-IV-TR, all seeking outpatient treatment. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	12 weeks of titrated dronabinol or placebo twice daily, including a 1-week placebo lead-in phase and 2-week placebo lead-out phase. Lab visits were twice per week and motivational enhancement and relapse prevention therapy weekly.	Primary outcomes: 2 consecutive weeks of self-reported abstinence. Other outcomes: urinalysis, treatment retention, average amount of cannabis use, days of usage, marijuana withdrawal measured by Withdrawal Checklist (WC) and a Withdrawal Discomfort score (WDS), the Marijuana Craving Questionnaire (MCQ), and the Modified Systematic Assessment for Treatment and Emergent Events.	Mild to moderate AEs nabilone $n = 2$, placebo $n = 4$. No significant group difference in the proportion of patients achieving abstinence, participants attending treatment sessions, or maximum number of days abstinent. Use days decreased regardless of group. Treatment retention and withdrawal scores significantly improved in dronabinol versus placebo. A significant interaction between treatment, time, and baseline cannabis use, with high baseline users initially using more cannabis in the dronabinol group than in placebo. This difference decreased over time as both groups' use became similar. AEs dronabinol 67 %, placebo 58 %.

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
22	Lintzeris et al. (2019)	Australia	Nabiximols (2.7 mg THC and 2.5 mg CBD) or placebo.	<i>N</i> = 128 (18–64 years old, 61 nabiximols: age <i>M</i> (SD) = 36.2 (11.5), 26.2 % female, 83.6 % born in Australia, 6.6 % Aboriginal or Torres Strait Islander, 67 placebo: age <i>M</i> (SD) = 33.8 (10.3), 20.9 % female, 83.6 % Born in Australia, 7.8 % Aboriginal or Torres Strait Islander). Cannabis dependence per ICD - 10, prior cessation attempts unsuccessful.	Double-blind, randomized, placebo-controlled trial.	Multisite 12-week outpatient study with nabiximols or placebo (maximum of 32 sprays per day) alongside psychosocial interventions. Assessments at baseline, at 4,8,12 weeks, and 3 months after the end of the treatment.	Primary outcomes: self-reported total days cannabis use during weeks 1–12 (validated by urinalysis). Secondary outcomes: the Marijuana Craving Questionnaire, Cannabis Withdrawal Scale, Cannabis Problems Questionnaire, 36-item Short Form Survey measuring general health status and psychosocial function, Alcohol Use Disorders Identification Test, Fagerström Test for Nicotine Dependence, global satisfaction, and the Opioid Treatment Index crime subscale measuring participation in crime.	The nabiximol group reported significantly less cannabis use days in the treatment period than placebo. The MCQ, CWS, CPQ, general health (SFS), and crime rates improved in both groups, without a group difference. Alcohol and nicotine use did not change over time. AEs nabiximols <i>n</i> = 15, placebo <i>n</i> = 17.
23	Lintzeris et al. (2020)	Australia	Nabiximols (2.7 mg THC and 2.5 mg CBD) or placebo.	Entire sample cannabis naïve: no. <i>N</i> = 128 (18–64 years old, 61 nabiximols: age <i>M</i> (SD) = 36.2 (11.5), 26.2 % female, 83.6 % born in Australia, 6.6 % Aboriginal or Torres Strait Islander, 67 placebo: age <i>M</i> (SD) = 33.8 (10.3), 20.9 % female, 83.6 % Born in Australia, 7.8 % Aboriginal or Torres Strait Islander). Cannabis dependence per ICD - 10, prior cessation attempts unsuccessful.	Double-blind, randomized, placebo-controlled trial.	This study examined the follow up data (from week 12) of Lintzeris et al., 2019	Primary outcomes: self-report of days of cannabis use and abstinence, both in the preceding 28 days. Urinalysis validated self-reported cannabis use.	Compared to placebo, the nabiximols group used significantly fewer days measured at week 12 and week 24. At week 24, a bigger proportion of the nabiximols group compared to placebo reported abstinence. High attrition was observed in the follow up (57 %).
24	Allsop et al. (2014)	Australia	Nabiximols (2.7 mg THC and 2.5 mg CBD) or placebo.	Entire sample cannabis naïve: no. <i>N</i> = 51 (18–65 years, 27 nabiximols: age <i>M</i> (SD) = 35 (9.7), 67 % male, 7 % Aboriginal or Torres Strait Islander, 24 placebo: age <i>M</i> (SD) = 35.9 (8.1), 88 % male, 4 % Aboriginal or Torres Strait Islander). Cannabis dependence per DSM-IV-TR. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	6-day inpatient trial with daily nabiximols (2 to 4 times 8 sprays) or placebo in addition to psychotherapy, 3-day washout, and a 28-day follow-up period.	Primary outcome: the Cannabis Withdrawal Scale. Other outcomes: retention in treatment, details of cannabis, alcohol, and tobacco use, Cannabis Problems Questionnaire, Athens Insomnia Scale, Brief Treatment Outcome Measure Social Functioning Scale, Severity of Dependence Scale (SDS), Distress Tolerance Scale, Sheehan Disability Scale, subscales from the Depression, Anxiety, and Stress Scale, self-coping and efficacy for Quitting Cannabis Questionnaire, Anxiety Sensitivity Index Revised, the Barratt Impulsiveness Scale, and cannabinoids in plasma and urine.	During treatment, CWS scores and treatment retention were significantly better in nabiximols versus placebo. Nabiximols reduced cravings, and withdrawal symptoms irritability, anger, and depression significantly more than placebo. At follow-up, cannabis use, severity of cannabis dependence, and number of cannabis related problems was decreased in all

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
								groups. Time until relapse after hospital discharge was similar between groups.
25	Trigo et al. (2018)	Canada	Nabiximols (2.7 mg THC and 2.5 mg CBD) or placebo.	<i>N</i> = 40 (18–65 years; 20 nabiximols: age <i>M</i> (SD) = 30.7 (10.4), 70 % male, 55 % White, non-Hispanic, 15 % mixed, 20 % Asian, 10 % Black, 20 placebo: age <i>M</i> (SD) = 30.7 (10.4), 75 % male, 65 % White, non-Hispanic, 20 % mixed, 10 % Asian, 5 % Latin American). Cannabis dependence per DSM-IV, treatment-seeking, ≥ 5 days per week cannabis use. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	12 weeks of daily titrated nabiximols (up to 42 sprays per day) or placebo, along with Motivational Enhancement Therapy and Cognitive Behavioral Therapy during 2 weekly assessment visits.	Primary outcomes: tolerability of dosage and cannabis abstinence, as measured by self-report and THC metabolites in urine and plasma. Secondary outcomes: the Marijuana Withdrawal Checklist (MWC), the Marijuana Craving Questionnaire–Short Form (MCQ-SF), and days and amount of cannabis use.	AEs did not differ between groups, but there was 1 severe AE in placebo group. Cannabis use decreased in both groups regardless of treatment. Abstinence rates, withdrawal and craving scores improved without a group effect. Urinalysis showed significantly higher concentrations of CBD in nabiximols than in placebo. No changes in body weight, blood pressure, or other physiological measures in either treatment.
26	Mongeau-Pérusse et al. (2021)	Canada	Up to 800 mg CBD or placebo.	<i>N</i> = 78 (18–65 years, 40 CBD: age <i>M</i> (SD) = 46.0 (10.7), 17.5 % female, 85 % white, 15 % other, 38 placebo: age <i>M</i> (SD) = 45.8 (11.8), 18.4 % female, 86.8 % white, 14.1 % white). Cocaine use disorder per DSM-5, cocaine use within 2 weeks prior to admission. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial	After a 10-day inpatient detoxification with group therapy, 12-week outpatient follow-up with daily 800 mg CBD or placebo, including weekly in-person visits and group therapy sessions.	Primary outcomes: drug–cue-induced craving (during detoxification) and time until cocaine relapse (during subsequent the outpatient treatment phase). Secondary outcomes: stress-induced craving and cocaine use (measured by urinalysis). Exploratory outcomes: the Cocaine Craving Questionnaire-Brief (CCQ-Brief) and a craving VAS for daily cocaine craving, the Cocaine Selective Severity Assessment, self-reported days of cocaine use and sustained abstinence (21 days without cocaine use).	No group differences in drug cue induced craving, time until relapse, sustained abstinence, cocaine use at follow-up, cocaine craving, or withdrawal symptoms. All participants (apart from 3) relapsed to cocaine by week 12. CBD AEs = 40, placebo AEs = 14 (1 severe)
27	Meneses-Gaya et al. (2021)	Brazil	300 mg CBD or placebo.	<i>N</i> = 31 (18 years and older, all men, 14 CBD: age <i>M</i> (SD) = 32.5 (6.9), 17 placebo: age <i>M</i> (SD) = 33.2 (6.9)). DSM-IV diagnosis of cocaine crack dependence and abstinent for maximal 30 days. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	10-day inpatient trial testing the effects of daily CBD or placebo on craving induction, i.e., video relating to crack use. Assessments at baseline and at the end of the study.	Primary outcomes: Cocaine craving questionnaire brief version (CCQ - brief) and the Minnesota Cocaine Craving Scale (MCCS). Other outcomes: the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), Beck Depression Inventory, Beck Anxiety Inventory, Visual Analog Sleep Scales (VAS) measuring sleep and wakefulness over the last 24 h, UKU Side Effects Rating Scale (UKU-SERS) measuring psychological,	In both groups, craving, anxiety, and depression scores significantly reduced during the study, with no group differences. Sleep scores did not change. AEs mild to moderate, no group differences.

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
28	Lofwall et al. (2016)	The United States	5, 10, 20 or 30 mg dronabinol, 30 or 60 mg oxycodone or placebo.	$N = 12$ (18–50 years old, 50 % female, age $M(SD) = 31.3$ (1.5)). Opioid dependent, self-reported use of short-acting opioids on ≥ 21 days of the last 30, and urine test positive for opioids. Entire sample cannabis naïve: no.	Randomized, double-blind, placebo-controlled, within subjects design.	After oxycodone stabilization for ≥ 5 days, a placebo training session followed to ensure opioid withdrawal. Then, 7 sessions were completed with ≥ 3 days in between, during which morning and evening oxycodone doses were replaced with placebos, inducing a 21-h withdrawal period before sessions began. During each 6-h session, participants received 1 of the treatments.	neurological and autonomic effects of drugs. Drug effects (VAS items including: “do you feel any drug effect?”, “how high are you?”, “does the drug have any good...bad effects?”, “how much do you like the drug?...desire opiates right now?”, and “how severe is your opioid withdrawal?”), a 16-item opioid agonist, 21-item antagonist adjective scale, a 13 item objective opiate withdrawal scale (OOWS: all 3 conducted by trained research assistants) a 10-item short opiate withdrawal scale (SOWS), a modified drug class identification questionnaire, a street value estimate of the drug received, and cognitive tasks, including a time estimation task, a continuous performance task measuring various aspects of attention.	30 mg dronabinol and oxycodone increased scoring on the VAS items ‘drug effect’ and ‘high’ 75 min after administration. 60 mg oxycodone significantly increased ‘liking’ compared to placebo. This was not the case for dronabinol. 20 mg dronabinol also reduced the desire for opioids, similar to 60 mg oxycodone. All oxycodone doses significantly decreased withdrawal symptoms on all scales. 20 mg and 30 mg dronabinol only showed some improvement on withdrawal sub items (e.g., feeling sick and runny eyes) compared to placebo. On the opioid agonist adjective scale, oxycodone scored significantly higher than placebo. Dronabinol only scored higher on some subitems (e.g., coasting/spaced out, dry mouth). 20 mg and 30 mg of dronabinol were identified as cannabis (and placebo not), with dronabinol’s perceived street value increasing with dose. However, the perceived street value of dronabinol remained lower than that of oxycodone. For the tasks, all doses of dronabinol led participants to underestimate timed intervals. This was most pronounced for 20 mg and 30 mg doses. In the CPT test, dronabinol at 5 mg led to more errors compared

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
								to placebo.
29	Bisaga et al. (2015)	The United States	30 mg dronabinol or placebo.	N = 60 (18–60 years old, 40 dronabinol: age M(SD) = 38.5 (11.6), 87.2 % male, 57.5 % white, 7.5 % Black, 32.5 % Hispanic, 2.5 % other, 20 placebo: age M(SD) = 37.3 (11.1), 80 % male, 60 % white, 10 % Black, 25 % Hispanic, 3.7 % other). Opioid dependence per DSM-IV, treatment seeking, 50 % was injecting heroine and 16 % prescription opioids.	Double-blind, randomized, placebo-controlled trial.	8-day inpatient detoxification and induction on naltrexone and start with daily titrated dronabinol or placebo, followed by an 8-week outpatient treatment including 5 weeks of treatment and weekly therapy sessions. Assessments at clinic visits (3 times per week).	Primary outcomes: the Subjective Opioid Withdrawal Scale and retention in treatment (measured at two timepoints). Other outcomes: the Hamilton Rating Scale for Depression.	AEs generally mild and mostly associated with 30 mg dronabinol. Severity of opioid withdrawal was lower in the dronabinol group versus placebo during the inpatient period. Rates of successful induction onto XR-naltrexone and completion of treatment were not significantly different between groups. Moderate to severe AEs, dronabinol n = 27 (1 drop out due to AEs, placebo, n = 11
30	Hurd et al. (2019)	The United States	CBD (400 or 800 mg), or placebo	Entire sample cannabis naïve: no. N = 42 (21–65 years old, 15 placebo: age M(SD) = 47.3 (8), 20 % white, 60 % black, 13.3 % Hispanic, 6.7 % other, 80 % male, 14 CBD400: age M(SD) = 51.9 (7.9), 7.1 % white, 85.7 % black, 7.1 % Hispanic, 85.7 % male, 13 CBD800: age M(SD) = 50.5 (11.6), 7.7 % white, 61.5 % black, 30.8 % Hispanic, 84.6 % male). Opioid dependence per DSM-IV, all abstinent. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	Placebo or CBD on 3 consecutive days testing the effects on drug cue induced craving and anxiety. Assessments after 1, 2, 24 h, 3 and 7 days.	Primary outcomes: cue induced craving and anxiety, measured before and after exposure to drug cues and neutral cues. Other outcomes: the Positive and Negative Affect Scale (PANAS), cognitive tasks and physiological measures.	Baseline craving was the same across all groups. Drug cues significantly increased craving and anxiety compared to neutral cues and after cue exposure (session 1), craving and anxiety was significantly higher in placebo versus CBD. In the other cue sessions, placebo showed a decrease in craving (versus session 1). Craving remained stably low in CBD groups. In the last cue session, 1 week after the last treatment, craving increased in placebo group versus 800 mg CBD. 400 mg CBD showed a greater increase in positive affect than those on 800 mg (session 1). Drug cues consistently raised negative affect scores across sessions. CBD decreased drug cue induced heart rate and salivary cortisol

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
31	Morgan et al. (2013)	The United Kingdom	Inhaler containing 400 µg CBD or placebo.	N = 24 (18–35 years old, 50 % female, 12 CBD: age M(SD) = 28 (4.3), 12 placebo: age M(SD) = 28.1 (6.2)). Smokers (>10 cigarettes per day) intending to quit smoking. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial.	1-week trial testing the effects of an inhaler with CBD or placebo on the urge to smoke, including daily diary and text messages to indicate craving and cigarette and inhaler usage. Assessments at baseline and 1 week post treatment.	Primary outcomes: number of cigarettes smoked (also assessed with exhaled carbon monoxide levels). Other outcomes: the Tiffany Craving Questionnaire (TCQ), VAS momentary craving, the 16-item Mood Rating Scale (MRS), the 4-item severity of dependence scale (SDS), Spiegelberger Trait Anxiety Inventory (STAI), the Behavior Impulsivity Scale (BIS) and the Beck Depression Inventory (BDI).	levels. No effects on cognitive task performance were observed. Placebo and 400 mg mild AEs = 5, 800 mg mild AEs = 8. CBD reduced the number of smoked cigarettes during the treatment, unlike placebo. Craving and anxiety scores reduced in both groups. Depression and MRS scores did not change over time. AEs not reported.
Schizophrenia Spectrum and Other Psychotic Disorders								
32	Boggs et al. (2018)	The United States	600 mg CBD or placebo.	N = 36 adults (18 CBD: 66.7 % male, age M(SD) = 48.4 (9.3), 55.6 % Caucasian, 38.9 % African American, 5.5 % other, 18 placebo: 72.2 % male, age M(SD) = 46.4 (9.5), 66.7 % African American, 27.8 % Caucasian, 5.5 % other). Schizophrenia per DSM-IV-TR, at least 3 months of stable antipsychotic medication. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial.	6 weeks of daily 600 mg CBD or placebo alongside a stable dose of antipsychotic medication. Cognitive functioning assessed at baseline and the end of the treatment, psychotic symptoms at baseline and twice per week.	MATRICES Consensus Cognitive Battery (MCCB), Positive and Negative Syndrome Scale (PANSS), the Barnes Akathisia Scale (BAS), the Abnormal Involuntary Movements Scale (AIMS), Simpson Angus Scale (SAS), and the UKU-Side Effect Scale.	Only placebo improved on the MCCB total score and on the subscales of reasoning and problem solving. PANSS scores improved over time, regardless of the group. No group differences on the SAS, BAS, or AIMS. On the UKU-Side Effects Scale only sedation was more prevalent in CBD and n = 1 withdrew.
33	D'Souza et al. (2005)	The United States	2.5 or 5 mg intravenous THC or placebo.	N = 35 (13 schizophrenia patients: 10 men, 3 women, age M(SD) = 44.5 (10.4), 6 Caucasian, 5 African American, 1 Native American, 1 Hispanic, 22 HC's: 14 men, 8 women, age M(SD) = 29 (11.6), 15 Caucasian, 6 African American, 1 Indian). Schizophrenia or schizoaffective disorder per DSM-IV and interview by a research psychiatrist, mild to moderate baseline symptoms, stable antipsychotic medication.	Double-blind, randomized, placebo-controlled trial.	During 3 test days (1 week in between), intravenous THC (2.5 or 5 mg) or placebo (ethanol). Assessments before and 10 to 200 min after injection.	Cognitive test battery including the Hopkins Verbal Learning Test (HVLT), a verbal fluency test, and a continuous performance test, behavioral assessments (reported elsewhere), the Positive and Negative Syndrome Scale (PANSS), the Clinician Administered Dissociative Symptom Scale (CADSS), self-reported cannabis intoxication (VAS), a motor test battery, and neurochemical measures.	THC increased learning and recall deficits (HVLT) significantly, which was more pronounced in schizophrenia participants. THC also momentarily increased positive, negative, and general schizophrenia symptoms, perceptual alterations, impaired motor skills, and was associated with increases in cortisol and prolactin. All THC effects were dose dependent.

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
34	Leweke et al. (2012)	Germany	200 - 800 mg CBD or amisulpride.	Entire sample cannabis naïve: no. $N = 39$ (18–50 years, 82 % male, 20 CBD: age $M(SD) = 29.7$ (8.3), 19 amisulpride: age $M(SD) = 30.6$ (9.4)). Hospitalized, schizophrenia or schizophreniform psychosis per DSM-IV (37 had acute paranoid schizophrenia and 5 schizophreniform psychosis) total BPRS score ≥ 36, BPRS Thought Disorders factor score ≥ 12. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial.	4 weeks of daily 200 mg CBD (increased to max 800 mg) or amisulpride, after a 7-day screening and at least 3 antipsychotic free days. Lorazepam co-medication was allowed. Assessments at baseline, and at day 14 and 28.	Primary outcomes: Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS).	Drop out AEs THC $n = 2$, placebo $n = 1$ Both groups showed a significant improvement of the PANSS total score, its subcategories, and BPRS scores. Response to treatment was also similar across groups. Serum anandamide levels were significantly increased after CBD administration, which was associated with improved PANSS scores. CBD was associated with significantly less side effects than amisulpride, e.g., motor impairment, sexual dysfunction, and weight gain.
35	McGuire et al. (2018)	The United Kingdom, Romania, and Poland	1000 mg CBD or placebo.	$N = 88$ (18–65 years, 43 CBD: age $M(SD) = 40.9$ (12.5), 65.1 % male, 93 % white or Caucasian, 4.7 % Black or African, 2.3 % other, 45 placebo: age $M(SD) = 40.8$ (11), 51.1 % male, 93.3 % white or Caucasian, 2.2 % Black or African, 4.4 % other). Schizophrenia or psychotic related disorder per DSM-IV (83 had schizophrenia, 3 schizoaffective disorder, 1 schizophreniform disorder, and 1 delusional disorder), stable dosage of antipsychotic medication ≥ 4 weeks.	Double-blind, randomized, placebo-controlled trial.	6 weeks of 1000 mg CBD or placebo twice daily at 15 sites, alongside their existing medication. Assessments at baseline and throughout the treatment period.	The Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning scale (GAF), the total score of the Brief Assessment of Cognition in Schizophrenia (BACS), the improvement and severity scales of the Clinical Global Impressions Scale (CGI-I and CGI-S), the sleep and functioning scales of the Participant and the Carer Global Impression of Change Scale, extrapyramidal symptoms with the Simpson-Angus Scale and physiological measures.	Number of AEs not reported. The only significant group difference in symptom severity was the positive subscale of the PANSS, with CBD showing more improvement than placebo. A higher proportion of people receiving CBD than placebo was rated as improved by their clinician on the CGI-I scale. The CBD group also showed more improvement on the CGI-S scale than placebo. AEs CBD $n = 15$, placebo $n = 16$.
36	Köck et al. (2021)	Switzerland	Cigarettes containing CBD-rich cannabis (10 % CBD, THC	Entire sample cannabis naïve: no. $N = 31$ (18–65 years, 71 % male, 16 CBD: age $M(SD) = 32.2$ (8.2), 78.9 %	Open label, randomized, placebo-controlled trial	Cigarettes containing CBD-rich cannabis (10 % CBD, THC < 1	Primary outcomes: the Positive and Negative Syndrome Scale (PANSS), Brøset Violence Checklist,	The PANSS, BDI and Brøset decreased during the study (but not

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
			< 1 %) versus standard tobacco cigarettes.	white, 15 placebo, age M(SD) = 38.2 (11.9), 56.3 % white). All acute psychosis; 23 schizophrenia, 4 schizoaffective disorder, 1 an acute polymorphic psychotic disorder with symptoms of schizophrenia, 2 bipolar disorder with psychotic symptoms, and 1 psychotic disorder due to cannabis use. Entire sample cannabis naïve: no.		%), or normal cigarettes adjunctively to standard psychiatric treatment in acutely hospitalized participants. Assessments on days 0, 7, 14, 21, and 28, and follow-up on day 91 and day 175.	Beck's Depression Inventory (BDI), Subjective Well-Being Under Neuroleptics Scale short form (SWN-K), and the amount of antipsychotics used. Secondary outcomes: tobacco and cannabis use, treatment retention, feasibility, enforced medication and isolation events. THC and CBD whole blood levels were correlated with PANSS scores.	at follow-up), regardless of treatment. For the SWN-K no time or group effect was found. During treatment, the amount of antipsychotics increased in the placebo group only. Tobacco and cannabis use was similar across groups. AEs CBD $n = 1$ withdrawal, $n = 1$ death.
Bipolar and Related Disorders								
37	Gruber et al. (2012)	The United States	Personal cannabis use or no use.	$N = 43$ (12 MJBP: age M(SD) = 24.3 (4.3), 20 MJ: age M(SD) = 20.8 (2.7), 11 BP: age M(SD) = 29.5 (7.2)). MJBP: patients with bipolar disorder who smoke cannabis, BP: patients with bipolar disorder who did not smoke, MJ: participants who smoke cannabis (abuse or dependence) but without Axis I pathology. Bipolar I in the BP groups, and cannabis abuse or dependence in the MJ group, all per DSM-IV. Entire sample cannabis naïve: no.	Observational study	4 weeks of daily mood rating on an electronic times (participants chose the time frame, at least 5 h in-between) on an application containing online versions of several clinical rating scales.	The Hamilton Anxiety Rating Scale (HAM-A), Montgomery-Åsberg Depression Rating Scale (MADRS), and Young Mania Rating Scale (YMRS), Profile of Mood States (POMS) including the subscales vigor, anger, confusion, tension, fatigue, depression, and a total score for total mood disturbance (TMD).	MJBP group: before cannabis use, worse mood ratings than BP group ratings, including vigor, anger, confusion, tension, fatigue and depression subscores of the POMS, and higher MADRS and YMRS scores. After cannabis use, improvement on the scores of the HAM-A, the MADRS, and on POMS measures, including higher, vigor and lower tension, depression and TMD. MJ group: cannabis use was followed by a decrease in mood, i.e., lower HAM-A scores, and an increase in confusion, fatigue subscores, and the TMD of the POMS. After cannabis use ratings scales indicate generally better overall mood in the MJBP group relative to the BP group, particularly in confusion, tension, fatigue and TMD subscales of the POMS. MJBP participants also reported generally higher MADRS and YMRS ratings

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
38	Pinto et al. (2024)	Brazil	150 - 300 mg CBD or placebo.	$N = 35$ (19 CBD: age $M(SD) = 42.2$ (13.8), 68.4 % female, 16 placebo: age $M(SD) = 45.9$ (13), 68.8 % female). Bipolar I or II per DSM-5, current major depressive episode per MINI International Neuropsychiatric Interview, stable dosage antipsychotic medication ≥ 4 weeks, Montgomery-Åsberg Depression Rating Scale total score ≥ 12, including the items apparent sadness and reported sadness and a total score of ≤ 11 on Young Mania Rating Scale. Entire sample cannabis naïve: no.	Double-blind, randomized, placebo-controlled trial.	12 weeks of daily CBD or placebo, assessments at 5 clinical visits.	Primary outcome: the Montgomery-Åsberg Depression Rating Scale (MADRS). Secondary outcomes: response rate (50 % or more reduction in MADRS scores) and remission rate (scores of 7 or less on the MADRS and Young Mania Rating Scale). Other outcomes: changes in the Clinical Global Impression-Severity (CGI-S) scale, Patient Health Questionnaire-9 (PHQ-9), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAMA), Brief Psychiatric Rating Scale (BPRS) and Functioning Assessment Short Test (FAST).	compared to the BP group, even after cannabis use. MADRS scores significantly decreased over time but without group difference. Exploratory analysis: in some participants (the non-early responders) CBD was more successful in reducing MADRS scores week 2–8 than placebo. No group differences on other measures. Drop out AEs CBD $n = 1$
Sleep-Wake disorders								
39	Walsh et al. (2021)	Australia	0.5 - 1 mL oil containing 10 mg/mL THC, 15 mg/mL CBD and 2 mg/mL cannabidiol (CBN), or placebo.	$N = 23$ (25–70 years, 12 THC, 12 placebo, age $M(SD) = 52$ (9), 22 Caucasian, 19 female). Clinical insomnia: self-reported difficulty falling asleep (>30 min), and/or staying asleep (>30 min awake, or waking >30 min before desired waking time) on ≥ 3 nights per week, for ≥ 3 months and an Insomnia Severity Index (ISI) score > 10. Entire sample cannabis naïve: unknown.	Double blind, randomized, placebo-controlled, cross-over trial.	After a 2-week baseline with assessments and a 1-week wash out, 2×2 -weeks of either treatment daily, separated by 1 week washout (cross-over). Assessments continuously and at the 14th night of each treatment period.	Primary outcomes: type, frequency, and severity of AEs during treatment, and Insomnia Severity Index. Secondary outcomes: sleep quality and quantity measured by a sleep diary, actigraphy and polysomnography (PSG), including sleep onset latency (SOL), sleep efficiency (SE: proportion of time spent asleep between the period of lights out and out of bedtime), wake after sleep onset (WASO: time spent awake after initially falling asleep), total sleep time, and awakening index (AI: number of awakenings per hour of sleep from lights out to out of bedtime). Perceived sleep quality (sSQ) and feeling rested/refreshed on waking was also measured.	Serious AEs = 0, non-serious AE's = 36 ($n = 17$, likely related to active treatment), non-serious AEs = 4 ($n = 4$, likely placebo), non-serious AE = 1 (during sensitivity testing). ISI scores at the end of the active treatment were significantly lower than placebo. SOL, TST, SQ, and feeling more refreshed when waking up improved in the active group, as well as the actigraphy WASO TST, and SE, compared to placebo. PSG did not differ significantly between placebo and active treatment.
40	Ried et al. (2023)	Australia	0.2–1.5 mL oil containing 10 mg/mL THC and 15 mg/mL CBD.	$N = 31$ (25–75 years, all Caucasian, age $M(SD) = 47$ (14.3), 76 % female).	Double blind, randomized, placebo-	6-week study with 1-week baseline, 2×2 -weeks of either treatment	Primary outcomes: saliva midnight melatonin levels and the Insomnia Severity Index (ISI). Secondary	Melatonin levels increased by 30 % in the active group but

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
				Self-reported clinical insomnia: score of >14 score on the Insomnia Severity Index. Entire sample cannabis naïve: unknown.	controlled, cross-over trial.	daily, separated by 1-week wash out (cross-over). Assessments at the start and end of each treatment.	outcomes: sleep pattern measurements using a Fitbit wrist activity/sleep tracker and The Stanford Sleepiness Scale, Pittsburgh Sleep Quality Index, The Brief Fatigue Inventory, and The Bond-Lader Mood Scale.	decreased by 20 % in placebo during treatment. Clinical insomnia rates reduced overall at the end of the study, but the active group had a greater reduction in total ISI scores than placebo. Total and light sleep improved in the active group versus baseline and placebo. Sleep quality, quantity, and mood improved in both groups, regardless of treatment. Mild AEs THC/CBD $n = 24$, more serious AEs $n = 2$, mild AEs placebo $n = 10$.
41	Narayan et al. (2024)	Australia	150 mg CBD or placebo.	$N = 30$ (18–45 years old, 15 CBD: age $M(SD) = 33.5(7.1)$, 53 % female, 100 % European/European descent, 15 placebo: age $M(SD) = 29.7(6.0)$, 47 % female, 80 % European/European descent, 13.3 % Indian, 6.7 % Chinese). Moderate to severe clinical insomnia: score of >15 on the Insomnia Severity Index. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial.	After a 1-week single-blind placebo lead-in, 2 weeks of daily CBD or placebo. Assessments continuously throughout the study.	Primary outcomes: Insomnia Severity Index and sleep diary data including daily sleep onset latency (SOL), wake after sleep onset sleep (WASO), and the ratio of total reported hours of sleep divided by time spent in bed (SE) Secondary outcomes: sleep diary data including sleep quality, total sleep time, total amount of waking up during the night, and actigraphy measures WASO, SOL, total sleep time, SE, and number of nighttime awakenings. Other outcomes: the World Health Organization Well-being Index 5, the Leeds Sleep Evaluation Questionnaire, the Glasgow Sleep Effort Scale, and the State Trait Anxiety Index.	No group or time effect on ISI scores, sleep diary WASO, SOL and SE. The self-reported number of awakenings after sleep onset, WASO, SE, and LSEQ wakefulness subscale improved during the study in CBD, but not at the end of the study. Other secondary outcomes did not change. Well-being improved in CBD versus placebo up until the end of the study. AEs were mild, but $n = 1$ withdrew due to AEs.
				$N = 45$ (18–60 years, 21 placebo, 24 CBD, age $M(SD) = 45.1(11.7)$, 33.3 % male). Chronic insomnia per DSM-5, moderate-to-severe clinical insomnia: > 15 on the Insomnia Severity Index (ISI) and insomnia >3 times a week for >3 months.				
42	Aiewtrakoon (2024)	Thailand	Soluble CBD 1 mg/kg or placebo.	Entire sample	Double blind, randomized, placebo-controlled, cross-over trial.	Phase 1: 2×1 week of treatment twice daily, separated by a 2-week wash out (cross-over). Phase 2: 12 weeks of CBD. Assessments continuously and during visits.	With actigraphy (ACT) and polysomnography (PSG): total sleep time (TST), daily sleep onset latency (SOL), wake after sleep onset sleep (WASO), the ratio of total reported hours of sleep divided by time spent in bed (SE), number of awakenings, Pittsburgh sleep quality index (PSQI), Epworth Sleepiness Scale (ESS), and quality of life questionnaire (EQ-5D-5L).	Compared to placebo, CBD showed longer sleep duration, fewer awakenings, less WASO, improved quality of life, overall sleep quality, daytime wakefulness, and better SOL. AEs CBD $n = 10$ (2 dropout)

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
43	Gilman et al. (2022)	The United States	Immediate acquisition of medical marijuana or delayed acquisition.	cannabis naïve: unknown. $N = 186$ (18–65 years, 105 card: age $M(SD) = 37.9$ (14.3), 68.6 % female, 83.8 % white, 6.7 % African American or Black, 5.7 % Asian, 3.8 % Hispanic, 2.9 % multiracial, 1 % unknown, 81 waiting list: age $M(SD) = 36.3$ (14.5), 61.7 % female, 79 % white, 8.6 % African American or Black, 4.9 % Asian, 8.6 % Hispanic, 3.7 % multiracial, 3.7 % unknown). All seeking medical cannabis for pain, insomnia, and anxiety or depressive symptoms. Entire sample cannabis naïve: no. Same sample as Tervo-Clemmens 2023	Single-blind, randomized clinical trial.	12 weeks of immediate or delayed acquisition (waiting list; WL) of a medical cannabis card. Assessments at baseline, week 2, 4, and 12.	Primary outcomes: Cannabis Use Disorder Checklist of DSM-5, the Hospital Anxiety and Depression Scale, the severity subscale of the Brief Pain Inventory, and the Athens Insomnia Scale. Secondary outcomes: the SF-12 Physical and Mental scales and the Cambridge Neuropsychological Test Automated Battery (CANTAB). Exploratory outcomes: the Cannabis Use Disorders Identification Test (CUDIT), the Marijuana Craving Questionnaire, Brief Pain Inventory Pain Interference scale, Pain Catastrophizing Scale, Perceived Stress Scale, Concise Health Risk Tracking scale, and the Clinical Global Impressions Severity and Improvement subscale, cannabis use (Likert Scale).	Compared to WL, the immediate card group reported more cannabis use and CUD symptoms, less self-rated insomnia symptoms and perceived stress, greater score improvement in mental well-being on the SF-12, and more likely to develop a DSM-5 CUD. No group effects were observed on scores of depression, anxiety, pain, or cognitive performance. The CGI improvement scale improved in the immediate card group, but severity remained the same between groups. AEs immediate card $n = 85$ (1 severe), WL $n = 60$
44	Tervo-Clemmens et al. (2023)	The United States	Immediate acquisition of medical marijuana or delayed acquisition.	$N = 186$ (18–65 years, 105 card: age $M(SD) = 37.9$ (14.3), 68.6 % female, 83.8 % white, 6.7 % African American or Black, 5.7 % Asian, 3.8 % Hispanic, 2.9 % multiracial, 1 % unknown, 81 waiting list: age $M(SD) = 36.3$ (14.5), 61.7 % female, 79 % white, 8.6 % African American or Black, 4.9 % Asian, 8.6 % Hispanic, 3.7 % multiracial, 3.7 % unknown). All seeking medical cannabis for pain, insomnia, and anxiety or depressive symptoms. Entire sample cannabis naïve: no. Same sample as Gilman 2022	Single-blind, randomized clinical trial.	12 weeks of immediate or delayed acquisition (waiting list; WL) of a medical cannabis card, daily surveys.	Baseline outcomes: Hospital Anxiety and Depression Scale, Athens Insomnia Scale, monthly cannabis use and Brief Pain Inventory. Daily outcomes: cannabis use details (use: yes/no, if yes: how many cannabis use moments), sleep quality, pain, and depression. THC metabolites was measured by urinalysis.	The immediate card group reported more use of cannabis than WL. The card group also reported better sleep quality on the same day compared to days they did not use. This was not the case for mood and pain. AEs immediate card $n = 85$ (1 severe), WL $n = 60$

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
Post traumatic stress disorder								
45	Bonn-Miller et al. (2022)	The United States	Either (1) reported using cannabis at least once per week from a licensed medical or recreational dispensary in Colorado (cannabis group), or (2) reported no cannabis use in the prior 6 months.	$N = 150$ adults (75 cannabis license: age $M(SD) = 57.5$ (15.3), 77 % male, 68 % Caucasian or white, 17 % Black or African American, 8 % Native American or Alaskan Native, 1 % multiracial, 5 % other, 75 controls: age $M(SD) = 44.4$ (12.6), 69 % male, 69 % Caucasian or white, 13 % Black or African American, 3 % Native American or Alaskan Native, 3 % multiracial, 12 % other). PTSD per DSM-5. Entire sample cannabis naïve: no.	Prospective, observational study	1 year study comparing of PTSD symptoms and functioning every 3 months in dispensary cannabis users and non-users.	Primary outcome: changes Clinician Administered PTSD checklist for DSM –5 (CAPS-5) score. Secondary outcomes: the rate of change of PTSD diagnosis (CAPS-5), and changes on the Psychosocial Functioning (IPF) total score, Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI), International Physical Activity Questionnaire (IPAQ), and change in sleep-onset latency (SOL), sleep efficiency (SE), wake after sleep onset (WASO), number of awakenings (NWAK), and total sleep time (TST), all measured by an actigraphy.	CAPS-5 scores reduced in both groups over time, but in a greater rate in cannabis users. Cannabis users were also more likely to no longer meet the PTSD diagnosis than the non-users at each assessment point. The PSQI, IPF, IPAQ and ISI did not differ between groups or over time. For actigraphy measures, only the NWAK differed between groups, with less awakenings in cannabis users. For the CAPS-5 subscales, cannabis users showed a greater decline of hyperarousal symptoms than non-users.
46	Bonn-Miller et al. (2021)	The United States	Different variations of smoked cannabis, high THC: 12 % THC and < 0.05 % CBD, high CBD: 11 % CBD and 0.50 % THC, THC + CBD: approximately 7.9 % THC and 8.1 % CBD, placebo: < 0.03 % THC and < 0.01 % CBD.	$N = 80$ (20 high THC: age $M(SD) = 45.0$ (16.6), 95 % male, 55 % non-Hispanic white, 45 % other, 20 placebo: age $M(SD) = 43.7$ (12.5), 90 % male, 70 % non-Hispanic white, 30 % other, 20 high CBD: age $M(SD) = 40.4$ (11.2), 90 % male, 70 % non-Hispanic white, 30 % other, 20 THC + CBD: age $M(SD) = 50.6$ (13.3), 85 % male, 70 % non-Hispanic white, 30 % other). US military veterans, PTSD per DSM-5 of at least moderate PTSD severity: > 25 score on the Clinician-Administered PTSD Scale for DSM-5 Total Severity Score (CAPS-5). Entire sample cannabis naïve: no.	Double blind, randomized, placebo-controlled, cross-over trial.	Phase 1: 3 weeks of any of the active treatments or placebo, followed by a 2-week wash out period. Phase 2: any of the 3 active treatments. Primary outcome measure assessed after phase 1, other outcomes at several timepoints.	Primary outcome: changes Clinician Administered PTSD checklist for DSM –5 (CAPS-5) score. Secondary outcomes: a modified version of the self-report PTSD Checklist for DSM-5 (PCL-5), general depression and anxiety subscales from the self-report Inventory of Depression and Anxiety Symptoms (IDAS), the Inventory of Psychosocial Functioning (IPF) and the Insomnia Severity Index (ISI).	AEs not reported. Phase 1: no group differences in cannabis use or on any subscale scores of the CAPS-5. Phase 2: participants used more THC + CBD than THC-rich or CBD-rich variants. In all treatments significant reductions in PTSD severity. CAPS-5 avoidance and negative thoughts and emotions subscales were different between CBD and THC + CBD, and the negative thoughts and emotions subscale was also different between THC and THC + CBD. The PCL-5 and IDAS anxiety scale were only a significantly different between group, with THC + CBD being superior to CBD only. IPF and insomnia was not significantly

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
								different between groups.
								AEs (phase 1) active treatment $n = 37$ (1 suicide ideation) AEs (phase 2) active treatment $n = 47$ (1 suicide ideation) Drop out AEs $n = 3$ Compared to placebo, nabilone showed a reduction of CAPS Recurring and Distressing Dream scores (both frequency and intensity, and frequency separately) and improvement on the CGI—C. The GWBQ also improved in the nabilone group. No effect on sleep quality and quantity (as measured by CAPS items) was observed.
47	Jetly et al. (2015)	Canada	0.5–3 mg nabilone or placebo.	$N = 10$ (18–65 years, all male and Caucasian, age M (SD) = 43.6 (8.2)). PTSD per DSM-IV-TR, current distressing nightmares (CAPS recurrent distressing dreams item score of ≥ 5) and difficulty falling or staying asleep (CAPS item score of ≥ 5), despite standard treatment still experiencing trauma-related dreams. Trauma ≥ 2 years before the study. Entire sample cannabis naïve: unknown.	Double blind, randomized, placebo-controlled, cross-over trial.	2×7 weeks of daily titrated nabilone or placebo, separated by a 2 week wash-out (cross-over). Weekly and before and after treatment assessments.	Primary outcome: the CAPS Recurrent, Distressing Dreams Item. Other measures: CAPS Difficulty Falling or Staying Asleep Item, the Clinical Global Impression of Change (CGI—C), the PTSD Dream Rating Scale, and the General, Well Being Questionnaire (WBQ), and a Sleep Diary Log recording total sleep time and numbers of awakenings each night.	
48	Bolsoni, Crippa, Hallak, Guimarães, and Zuardi (2022a) <i>Same study as</i> Bolsoni et al., 2022b	Brazil	300 mg CBD or placebo.	$N = 33$ (18–60 years old, 17 CBD: age M (SD) = 33.9 (11.6), 30.8 % male, 16 placebo: age M (SD) = 32.5 (13), 33.3 % male). PTSD per DSM-5. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial.	3 sessions separated by 1 week. Session 1: participants described the event that triggered their PTSD while being recorded and afterwards imagined the event for 30 s. Session 2: either CBD or placebo before recall of the event with physiological and psychological measures. Session 3: same as session 2 without any treatment.	State-Trait Anxiety Inventory (Portuguese version: IDATE) and the Portuguese version of the Visual and Analogical Mood Scale (VAMS) with four factors relating to anxiety, sedation, cognitive impairment, and discomfort, and physiological measures.	AEs nabilone 50 %, placebo 60 % Both groups showed a significant increase in anxiety (STAI-E and VAMS) after recall. There was significantly less cognitive impairment after recall in the CBD group compared to placebo, lasting until the final session. No group differences on VAMS sedation and discomfort, or the physiological measures.
49	Bolsoni et al. (2022b) <i>Same study as</i> Bolsoni et al., 2022a	Brazil	300 mg CBD or placebo.	$N = 33$ (18–60 years old, 17 CBD: age M (SD) = 33.9 (11.6), 30.8 % male, 16 placebo: age M (SD) = 32.5 (13), 33.3 % male). PTSD per DSM-5. Entire sample cannabis naïve: unknown.	Double-blind, randomized, placebo-controlled trial	Same methodology Bolsoni et al., 2022a . Data was analyzed based on the nature of the trauma, i.e., sexual vs. nonsexual trauma.	Portuguese version of the VAMS and physiological measures.	AEs not reported. After recall, all groups showed a significant increase in VAMS anxiety, discomfort, cognitive impairment, and sedation. Cognitive impairment after recall was greater in placebo than in CBD. In those with nonsexual

(continued on next page)

Table 1 (continued)

No.	Author (year)	Country	Product and control	Sample details	Design	Methodology	Outcome measures	Summary results
								trauma, the change in VAMS anxiety and VAMS cognitive impairment before and after the recall event was significantly lower in the CBD group than the placebo group. No group differences between CBD and placebo in those with sexual trauma. Systolic BP and HR were significantly higher after recall, most so in those with sexual trauma.
								AEs not reported.

AE = adverse event, THC = Δ9-tetrahydrocannabinol, CBD = cannabidiol,
* Number refers to Fig. 1.

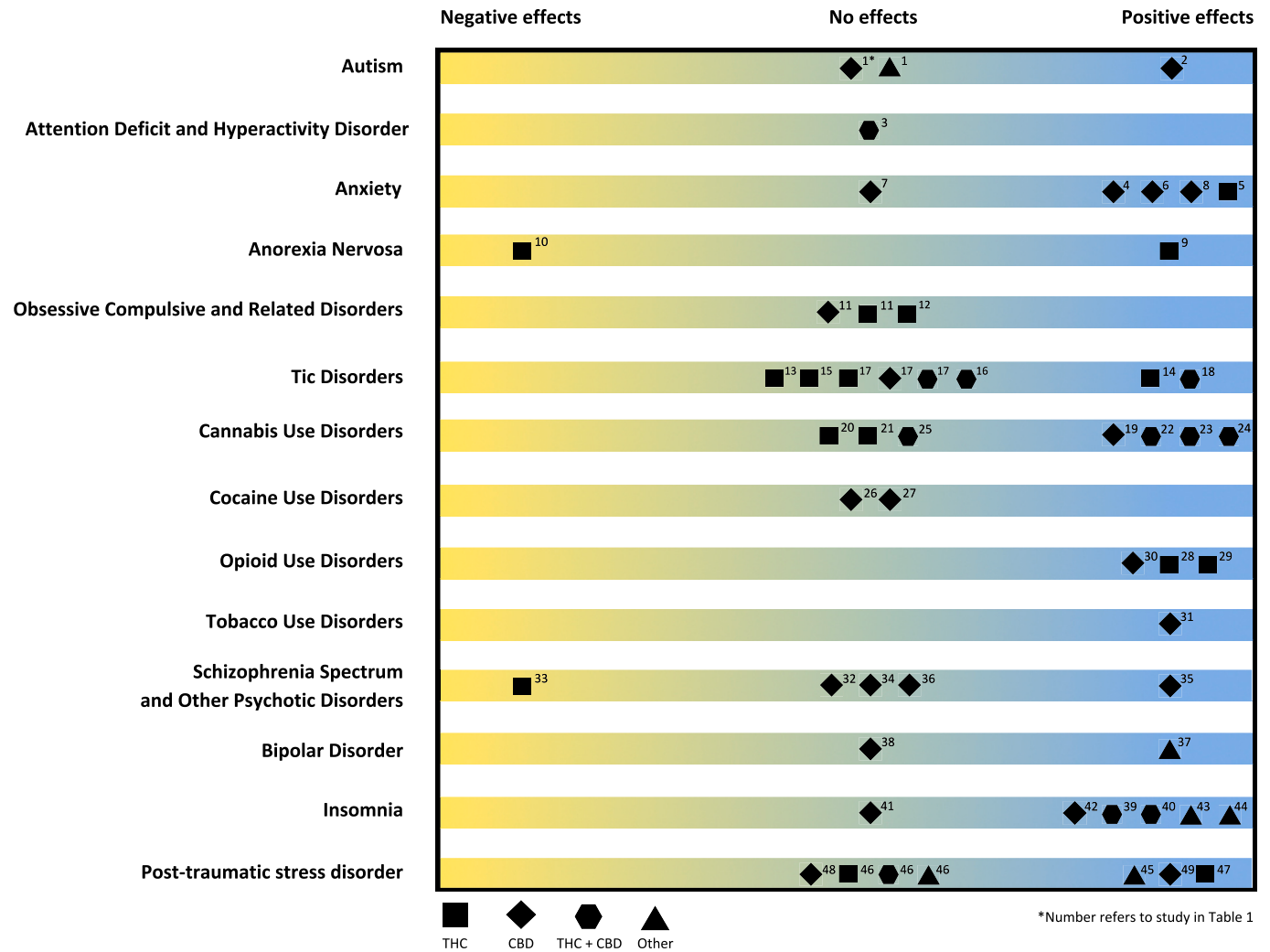


Fig. 1. Effects of medicinal cannabis on the primary outcome measures of all studies.
THC = Δ9-tetrahydrocannabinol, CBD = cannabidiol.

of up to 10 mg/day of THC in reducing tics were investigated (Müller-Vahl et al., 2003). The primary outcome measure was tic severity measured at several timepoints during and after the treatment period, using both a self-rating measure and examiner ratings, including a video-based rating scale. One patient in the THC group dropped out due to adverse side effects. Only at day 20–22 (third visit, during which participants received the maximum dosage) and day 30–31 (fourth visit, last day of maximum dosage, before it was reduced again), the THC group showed improvement on a GTS global impression scale compared to placebo. Some of the examiner rating tools also showed a significant improvement in the THC group at third or fourth visit. This was not the case for placebo.

Recently, findings were published of a larger multicenter RCT testing the effects of nabiximols on tic symptoms in 97 adults with GTS or chronic tic disorder (Müller-Vahl et al., 2023), receiving 1 to 12 puffs per day (1 puff = 100 µl spray with 2.7 mg THC and 2.5 mg CBD). The primary outcome measure was treatment response, defined as a reduction of at least 30 % (later changed to 25 %) in severity of tics. Secondary measures included questionnaires measuring Gilles de La Tourette symptoms, tic severity, quality of life, ADHD, depression, anxiety, obsessive-compulsive symptoms, impulsiveness, and sleep quality. No differences were found between nabiximols and placebo on any of the outcome measures. Moreover, in a crossover RCT 22 adults with TS and at least moderate to severe burden of the tics received an oil containing 5 mg/ml THC and 5 mg/ml CBD or placebo, with up to 4 ml per day. Both treatments lasted for 6 weeks and were separated by a 4-week washout period. The primary outcome measure was a clinician rated scale of the number, frequency, intensity, and complexity and interference from motor and vocal tics, secondary outcome measures included a video-based rating scale of the tics, and a global scale of tic severity and impairment. Cognitive functioning was also assessed. Compared to placebo, there was a greater improvement over time in the clinician rated tic scores in the active group (Mosley et al., 2023). Finally, 12 participants with GTS participated in an RCT and received a single vaporized 0.25 g dose including 10 % THC, 9 % THC and 9 % CBD, 13 % CBD, or placebo (Abi-Jaoude et al., 2023). Participants received all four variations, with a period of two weeks in between. The primary outcome measure was severity, frequency, and body areas of the tics, assessed via a video recording. Secondary outcomes included changes in the premonitory urge for tics, distress, and overall impression of clinical improvement. All these measures were conducted at six timepoints (30 min, 1, 2, 3 and 5 h) after administration. No difference between treatments was found on the primary outcome measure. Regarding the premonitory urge to tic and distress, there was a significant improvement at almost all timepoints in the 10 % THC treatment, compared to placebo. However, the 10 % THC treatment was also associated with the most adverse events, compared to the other active treatments and placebo.

Thus, when considering neurodevelopmental disorders, no strong evidence for the efficacy of CBD was found. Combined THC and CBD seemed to have some efficacy in ASD as a whole plant extract, but not in purified form. One study found efficacy of combined THC and CBD in GTS, but another study failed to do so. THC was associated with both improvement and worsening of GTS symptoms. Four studies had a high risk of bias, two studies had an unclear risk of bias, and three studies had a low risk of bias.

3.2. Substance use disorders (SUDs)

Several studies in this section describe participants with a substance dependence, which is the DSM-IV diagnosis and terminology. In the DSM-5, all symptoms are categorized under the broader diagnosis SUD, which can occur in the mild, moderate and severe category.

3.2.1. Cannabis use disorder (CUD)

Seven RCTs assessing the effects of cannabinoids on several

symptoms of CUD were included. Participants were diagnosed with CUD according to DSM or ICD-10 criteria.

Freeman et al. (2020) examined the effects of 200, 400, and 800 mg CBD and placebo on CUD symptoms in a 4-week RCT involving 48 participants. The 200 mg treatment was discontinued due to the lack of efficacy. Both 400 mg and 800 mg significantly reduced cannabis use compared to placebo, as measured by metabolites in urine and the reported number of days cannabis used (both primary outcome measures), with 400 mg being slightly more effective than 800 mg.

Another 12-week RCT including 156 participants assessed the effects of 20 mg dronabinol or placebo twice daily, combined with psychotherapeutic interventions, on abstinence (the primary outcome measure), cannabis use, and withdrawal symptoms after a 1-week placebo lead-in phase (Levin et al., 2011). Both groups showed a reduction in cannabis use. There was no significant difference between the groups in terms of abstinence or cannabis use at two weeks, although overall cannabis use decreased over the entire treatment period. Withdrawal symptoms were less severe in the dronabinol group than in the placebo group.

Another 10-week RCT compared 2 mg/day nabilone to placebo in 18 participants with CUD (Hill et al., 2017). All participants simultaneously received medication management, a type of treatment that offers guidance for using the medication and decreasing cannabis use. The primary outcome measures were days of cannabis use, measured by self-report and urine samples, safety, and tolerability. Craving and anxiety were also assessed. No difference in cannabis use (both self-report and urinalysis) was found between groups. Craving reduced in both groups, regardless of treatment. Anxiety did not change throughout the treatment period.

In a 9-day inpatient trial, 51 participants received either nabiximols (up to 32 sprays of 86.4 mg THC and 80 mg CBD daily) or placebo for 6 days (Allsop et al., 2014). Effects were assessed during treatment and in another study at 28-day follow-up. During treatment, the primary outcome measure withdrawal symptoms, including craving, irritability, anger, and aggression, was significantly less in the nabiximols group compared to the placebo group. Although cannabis use decreased at follow-up, this was not significantly different between the groups.

Trigo et al. (2018) assessed the effects of daily nabiximols (up to 113.4 mg THC and 105 mg CBD) versus placebo in 40 patients with CUD, along with cognitive behavioral therapy and motivational enhancement therapy for 12 weeks, with as primary outcome measures tolerability and cannabis abstinence. While there were no significant differences in withdrawal scores or abstinence rates, all participants showed a significant reduction in cannabis use and craving across the 12 weeks, regardless of treatment.

A large, multicenter RCT assessed the efficacy of nabiximols (up to 86.4 mg/day THC and 80 mg/day CBD) or placebo along with psychosocial interventions for 12 weeks in 128 participants with CUD who did not respond to prior treatment efforts (Lintzeris et al., 2019). Both groups showed improvement in cannabis-related problems, craving, and withdrawal symptoms. However, the nabiximols group had a significantly lower number of days using cannabis, the primary outcome measure, than the placebo group. A follow up study of this RCT assessed the same outcome measures 3 months after cessation of treatment (Lintzeris et al., 2020). Only 55 of the initial 128 participants participated in the follow-up study. Both the nabiximols and placebo group showed a reduction in the number of days of cannabis use, but the reduction was significantly greater in the nabiximols group. Also, the proportion of participants achieving abstinence increased in both groups but was greater in the nabiximols group.

Taken together, combinations of THC and CBD and high doses of CBD may have some efficacy in reducing CUD symptoms. Solely THC did not have superior effects compared to placebo. Four studies had a low risk of bias, one study had an unclear risk of bias, and two studies had a high risk of bias.

3.2.2. Opioid use disorder (OUD)

A total of 60 patients with opioid dependency (DSM-IV use disorder diagnosis) received either daily 30 mg dronabinol or placebo during inpatient detoxification and naltrexone induction (8 days) (Bisaga et al., 2015). Naltrexone is an opioid antagonist that blocks the effects of opioids and reduces craving. The treatment continued for 5 weeks after being discharged (on day 9). The primary outcome measures were withdrawal symptoms and treatment retention. The severity of opioid withdrawal was lower in the dronabinol group relative to the placebo group, as measured by the Subjective Opiate Withdrawal Scale. However, there were no significant differences between groups in the rates of successful induction onto naltrexone or treatment completion.

In a 5-week inpatient RCT, 12 participants with opioid dependency (DSM-IV use disorder diagnosis) were first stabilized on oxycodone (5 days), followed by a placebo lead-in phase to induce withdrawal (Lofwall, Babalonis, Nuzzo, Elayi, & Walsh, 2016). Subsequently, participants received oxycodone (30 or 60 mg), placebo, or dronabinol (5, 10, 20, or 40 mg) daily. The 40 mg dronabinol was reduced to 30 mg due to the adverse events. The outcome measures were clinician and participant rated opioid antagonist and agonist scales (measuring morphine-like and withdrawal effects), VAS items related to drug effects, a street value estimation, a drug class identification questionnaire, and cognitive tasks. The lower doses of dronabinol (5 or 10 mg) performed similarly to placebo. The high doses of dronabinol (20 and 30 mg) provided some reduction in withdrawal symptoms but were never more effective than oxycodone. These doses were also associated with psychoactive effects and adverse events.

Finally, 42 abstinent participants with heroin use disorder received 400 mg, 800 mg of CBD or placebo on 3 consecutive days and the acute (1, 2 and 24 h post administration), short-term (3 days) and long term (7 days) effects on the primary outcome measures drug cue induced craving and anxiety were assessed (Hurd et al., 2019). The cue sessions were either a neutral video, or a video showing intranasal or intravenous drug use, based on the participant's preferred route of administration. After the videos, the participants were also shown neutral objects or drug related objects. The participants also completed cognitive tasks and questionnaires. The drug cues significantly increased craving in all groups, which was not the case for the neutral cues. Craving was significantly higher in placebo than in the CBD groups, most prominently 1 to 2 h post administration. After 24 h, craving after drug cues remained the same in the CBD groups, but also decreased in the placebo group, indicating a habituation effect. However, 1 week after administration, drug cue induced craving increased again in the placebo group, compared to the 800 mg CBD group. Across all sessions, drug cues were associated with increases in anxiety compared to neutral cues, and this was significantly higher in placebo than in the CBD groups. Two studies had an unclear risk of bias and one study had a low risk of bias.

3.2.3. Cocaine use disorder

An RCT assessed the effects of 800 mg CBD versus placebo in 78 patients with cocaine-use disorder over a 10-day in-patient treatment period (Mongeau-Pérusse et al., 2021). No group differences were observed on the primary outcome measures drug cue induced craving or time until relapse, nor on sustained abstinence, cocaine use at follow-up, cocaine craving, or withdrawal symptoms.

In an exploratory RCT, 31 men with a diagnosis of crack-cocaine dependence received either 300 mg CBD or placebo for 10 days (Meneses-Gaya et al., 2021). Participants were hospitalized for the entire duration of the study. Cocaine craving and problems related to a variety of addictive substances were assessed at baseline and the end of the study. Additionally, the participants had to watch a video about crack usage and craving was assessed before and after the video. Craving decreased over time in the entire sample, regardless of treatment. The other outcome measures, including craving before and after the video, did also not differ between groups. Both studies had an unclear risk of bias.

3.2.4. Tobacco use disorder

A total of 24 tobacco smokers who intended to stop smoking were given an inhaler containing either 0.4 mg CBD or placebo and were instructed to use it whenever they felt the urge to smoke for 1 week (Morgan, Das, Joye, Curran, & Kamboj, 2013). In the CBD group, the primary outcome measure number of cigarettes smoked during treatment significantly decreased, which was not the case in the placebo group. This effect was maintained for 2 weeks following the study. Craving for cigarettes did not change. Anxiety scores decreased in both groups during treatment. The study had an unclear risk of bias.

3.3. Schizophrenia spectrum and other psychotic disorders

3.3.1. Schizophrenia

Four studies were identified that investigated the effects of cannabinoids in patients with schizophrenia. One RCT administered 2.5 mg, 5 mg THC or placebo intravenously to 22 healthy controls and 13 patients with schizophrenia over 3 separate test days, while the acute effects on cognition, schizophrenia symptoms, and motor coordination were monitored. In schizophrenia patients, THC seemed to exacerbate positive and negative schizophrenia symptoms and impaired certain aspects of cognition in a dose-dependent manner. No improvement was observed in any of the assessments (D'Souza et al., 2005). An RCT by Leweke et al. (2012) tested 600–800 mg/day of oral CBD versus the antipsychotic amisulpride over 4 weeks in 42 schizophrenic patients. It was hypothesized that CBD might improve schizophrenia symptoms by inhibiting anandamide reuptake, as the authors found that elevated anandamide levels were associated with lower psychotic symptoms and risk in earlier studies. There was no group difference, but both groups showed improvement compared to baseline in the primary outcome measures, i.e., positive and negative schizophrenia symptoms, as well as on a general psychiatric rating scale. However, the CBD group experienced fewer side effects, such as extrapyramidal symptoms and weight gain. Additionally, a significant association was found between increased anandamide levels and decreased symptoms in the CBD group, which was not observed in the amisulpride group. Boggs et al. (2018) examined the effects of 600 mg/day CBD versus placebo on cognition and positive and negative schizophrenia symptom severity in 41 patients with chronic schizophrenia for 6 weeks. Both groups showed improvement in positive and negative symptoms, with no significant differences between CBD and placebo. Only the placebo group showed improvement over time in cognitive performance.

Conversely, a multi-center exploratory 6-week RCT involving 88 patients with schizophrenia who received either 1000 mg CBD or a placebo daily adjunctively to antipsychotic medication found significant effects of CBD compared to placebo. Compared to the placebo group, participants receiving CBD showed significantly improved positive schizophrenia scores, and a greater proportion of them were rated as improved by their clinicians. However no differences between groups were observed on the other measures, including negative schizophrenia symptoms, aspects of cognition related to schizophrenia, the extent to which overall functioning is impaired due to the mental illness, and clinician-rated severity of the disorder (McGuire et al., 2018).

3.3.2. Psychosis

In an open-label 4-week RCT, 31 patients with acute psychosis were treated with either cigarettes containing hemp (10 % CBD and < 1 % THC) and tobacco, or regular tobacco cigarettes, in addition to psychiatric treatment (Köck et al., 2021). The psychosis-related primary outcome measures were positive and negative schizophrenia symptoms and the amount of necessary antipsychotic medication. Additionally, depression and violent behavior were assessed. In both treatment groups, schizophrenia symptoms decreased during treatment, but this was not persistent as no effects were observed at 91- or 175- day follow-up. The other measures, including the amount of necessary antipsychotic drugs, did not improve during or after treatment.

In sum, THC was found to exacerbate schizophrenia symptoms in a dose-dependent manner, while CBD was associated with improvement in symptoms, albeit not consistently. In acute psychosis, treatment with hemp cigarettes containing CBD and THC showed temporary relief in symptoms. One study had a high risk of bias, two studies had an unclear risk of bias, and two studies had a low risk of bias.

3.4. Bipolar and related disorders

3.4.1. Bipolar disorder

In an ecological momentary assessment study of 4 weeks, 12 participants with bipolar disorder (BP) who used cannabis, 11 BP participants who did not use cannabis, and 20 cannabis users with cannabis dependency (DSM-IV use disorder diagnosis) but without Axis 1 pathology reported their mood and cannabis use throughout the day on an electronic device (Gruber et al., 2012). Although details on cannabis use were not specified, the participants seemed to use predominantly THC-dominant cannabis based on supplementary data. Among cannabis using BP participants, cannabis use was followed by improvements in scores of anxiety, depression, overall mood and the subscales vigor and tension. Conversely, the cannabis users without BP experienced a worsening of anxiety and mood subscales after cannabis use. Compared to the BP group who did not use cannabis, cannabis using BP participants reported generally worse depression, manic symptoms, and mood as measured by various mood subscales. After cannabis use, the cannabis using BP participants had less anxiety and improved on mood subscales compared to the BP group, but depression and manic symptoms remained worse.

Moreover, a 12-week pilot RCT including 35 participants with bipolar disorder I or bipolar disorder II with a current major depressive episode assessed the effects of 150 to 300 mg CBD per day or placebo, along with therapeutic doses of atypical antipsychotics (Pinto et al., 2024). The primary outcome measure was a change in depression scores. The secondary outcome measures were response rate (measured by a minimum of 50 % reduction in depression scores), remission rate (measured with a cut-off score for depression and mania symptoms) and changes in anxiety and psychotic symptoms. Depression scores improved in both groups, regardless of treatment. As this improvement happened in the first 2 weeks (and thus most likely attributable to placebo effects), an additional exploratory analysis investigated the depression scores in the participants that reported changes later than in the first two weeks. This analysis showed that in the late responders, CBD was more effective than placebo in reducing depression scores. The other measures did not significantly change during the study.

In sum, THC does not seem to be associated with improvement of mental health symptoms in bipolar disorder, rather potentially associated with overall worse symptomatology and temporarily relief some anxiety and mood aspects. CBD may be associated with improvement of depression, but only observed on one scale. Both studies had a high risk of bias.

3.5. Anxiety disorders

3.5.1. Anxiety

In 1981 the oldest study included in this review was published, consisting of two parts examining the effects of nabilone on psychoneurotic anxiety (Fabre & McLendon, 1981). The first part was an open-label study including 5 participants who were treated with nabilone (up to 10 mg/day) for 28 days. Assessments were conducted at baseline and every 3 to 4 days until the end of the study at day 32. Total anxiety scores, as well as somatic and psychic anxiety subscales, were significantly reduced in the nabilone group compared to the placebo group. The second part was a 28-day RCT with 20 participants, with weekly assessments. Half of the participants received 2 to 8 mg nabilone per day, with an average of 2.8 mg/day, while the other half received placebo. The nabilone group showed improvement in somatic, psychic, and total anxiety scores, compared to placebo. In a more recent study, 178

participants with generalized anxiety disorder received either a solution of 150 mg/ml nano dispersible CBD or placebo after a placebo lead-in phase for 12 weeks (Gundugurti et al., 2024). The primary outcome measures were changes in generalized anxiety symptoms and overall anxiety symptoms. The secondary outcome measures included overall impression of clinical improvement, severity, sleep, and depression characteristics. Throughout the study, all and secondary outcome measures improved significantly in the CBD group compared to placebo.

3.5.2. Social anxiety

Bergamaschi et al. (2011) examined the acute effects of 600 mg CBD or placebo before a public speaking task in 24 treatment-naïve patients with social anxiety disorder. Additionally, 12 healthy controls performed the same task without any treatment. Assessments included a measure of self-perception during public speaking, an analogue scale measuring various mood states including anxiety, blood pressure, heart rate, and skin conductance, measured prior to the drug intake, just after, and at various time points during the speaking task. At multiple timepoints, the CBD group scored significantly lower on anxiety levels, and the subscales cognitive impairment and discomfort compared to the placebo group. Only at one timepoint, the CBD group and healthy controls differed on anxiety. Moreover, in another study, 37 participants with social anxiety received 300 mg CBD or placebo twice daily for 4 weeks. The primary outcome measure was anxiety and apprehension over anticipated social situations. Additionally, more general fear participants felt over a range of social situations was measured. The study found no overall difference between the CBD and placebo groups. However, anticipation anxiety significantly reduced from pre-intervention to post-intervention within the CBD group only. The fear over social situations scores also significantly decreased within the CBD group, but no main effect of group was found (Masataka, 2019). The final study assessed 80 participants with panic disorder with agoraphobia or social anxiety disorder at three mental health care centers (Kwee et al., 2022). Participants underwent 8 weekly therapist-assisted exposure sessions while simultaneously receiving either 300 mg CBD or a placebo. The primary outcome measure was the level of avoidance because of the anxiety disorder. The overall severity of anxiety was also measured. The results showed no significant differences between the CBD and placebo groups regarding treatment outcomes.

The reviewed studies mostly use CBD to reduce social anxiety symptoms, and the findings suggest some efficacy in doing so. Only one study found no differences between CBD and placebo, while the other studies found improvement in various anxiety symptoms, including on important core symptoms of social anxiety. Interestingly, THC (in the form of nabilone) was also found to improve symptoms of anxiety, which may be counterintuitive given the more arousing effects of THC. One study had a high risk of bias, three studies had an unclear risk of bias, and one study had a low risk of bias.

3.6. Obsessive-compulsive and related disorders

3.6.1. Obsessive-compulsive disorder

An RCT involving 14 adults with obsessive-compulsive disorder compared the acute effects of cigarettes containing approximately 800 mg of cannabis with variable ratios, i.e., CBD-rich: 0.4 % THC/10.4 % CBD, THC-rich: 7.0 % THC, 0.18 % CBD, and placebo: 0 % THC, 0 % CBD (Kayser, Haney, Raskin, Arout, & Simpson, 2020). The outcome measures were OCD symptoms and anxiety, assessed immediately after administration, as well as at several timepoints up to 3 h later. Significant decreases in state anxiety scores were observed across all three conditions. The scores were significantly lower for placebo compared to the active groups 20 min and 40 min after administration, but not anymore at 60 min or later. Other OCD ratings were not significantly affected by either treatment. In the THC group, participants reported feeling 'high', and experienced increased heart rate and blood pressure compared to the other groups.

3.6.2. Skin picking disorder

In another RCT, 50 participants with skin picking disorder received titrated 5–15 mg/day dronabinol or placebo for 10 weeks (Grant, Valle, Chesivoir, & Ehsan, 2022). The primary outcome measure was changes in symptom severity for hair pulling or skin picking disorder. Both dronabinol and placebo significantly reduced symptoms from baseline to the end of the study, with no significant differences between the two groups. Dronabinol was associated with more frequent side effects than placebo. Both studies had an unclear risk of bias.

3.7. Trauma- and stressor-related disorders

3.7.1. Post-traumatic stress disorder

Five papers were included that assessed the effects of cannabinoids in PTSD, with two papers originating from the same study. Jetly, Heber, Fraser, and Boisvert (2015) assessed the effects of titrated nabilone (up to 3 mg/day) versus placebo on nightmares in 9 male military personnel with PTSD who did not respond to prior treatment. Both treatments lasted for 7 weeks and were separated by a 2-week washout period. The primary outcome measure was a reduction in the frequency and intensity of recurring and distressing dreams. Additionally, measurements included overall PTSD severity, difficulty in falling or staying asleep, and well-being. Compared to baseline, there was a group difference in favor of nabilone regarding the overall score of frequency and intensity of nightmares, as well as the subscale frequency, overall impression of PTSD severity, and well-being. However, the difficulty of falling and staying asleep, or hours of sleep, did not differ between the groups.

In two included studies that originated from the RCT of Bolsoni et al. (2022b, 2022a), 33 participants with diagnosed PTSD were administered 300 mg CBD or placebo before describing the event that initiated their symptoms. They were recorded while describing the event and asked to also vividly reimagine it (study 1). Seven days later, they received CBD or placebo again and subsequently had to listen to their recording of the event (study 2). The primary outcome measure was a visual analogue scale assessing factors related to mood, anxiety, and cognition. Physiological measures were also collected. In the first study, no differences were found between the CBD group and placebo on physiological and psychological measures. For the second study, participants were split into groups based on whether their trauma was of sexual nature or not. In the non-sexual trauma group, CBD but not placebo attenuated anxiety and cognitive impairment induced by the recall. This difference was not observed in the sexual trauma group.

Bonn-Miller et al. (2021) investigated the effects of different ratios of cannabinoids on PTSD symptoms in 80 military personnel with diagnosed PTSD. The treatment options were a THC-rich variant (12 % THC and < 0.05 % CBD), a CBD-rich variant (11 % CBD and 0.50 % THC) a THC + CBD variant (7.9 % THC and 8.1 % CBD), and a placebo (< 0.03 % THC and < 0.01 % CBD). The participants randomly received one of the three active treatments or placebo in the first period of 3 weeks, followed by three weeks of one of the active treatments. A 2-week washout period took place in between. The study failed to find any significant effects on the primary outcome measure, a change in PTSD symptomatology, regardless of treatment.

Finally, a longitudinal, prospective study with 150 participants was included (Bonn-Miller et al., 2022). The study compared PTSD symptoms between patients who used medicinal cannabis and those who did not use cannabis over the course of 1 year. Approximately 91 % of the medicinal cannabis group used THC-dominant cannabis, with smoked cannabis flower being the most reported product. The primary outcome measure was a change in PTSD symptom severity. Both groups showed a decrease in PTSD symptoms over time, but this decrease was steeper in the cannabis users. When the subscales were assessed, this only concerned hyperarousal symptoms, while other symptoms did not differ between groups.

Altogether, both CBD and THC show some efficacy in improving sleep and anxiety related symptoms of PTSD. Although overall PTSD

diagnoses did not alter, improved sleep may still have an important (long-term) therapeutic effect, as sleep impairment is pivotal for the development and maintenance of PTSD. Four studies had an unclear risk of bias and one study a high risk of bias.

3.8. Feeding and eating disorders

3.8.1. Anorexia nervosa

Two cross-over studies were identified investigating the effects of cannabinoids on Anorexia Nervosa (AN) symptoms. Gross et al. (1983) administered THC and diazepam as an active placebo to 11 women who got acutely admitted to the psychiatric hospital for primary anorexia nervosa. Both medications were given in increasing doses for 2 weeks, followed by 2 weeks of the other treatment. THC dosage started with three times per day 2.5 mg and increased to three times per day 3 mg. Diazepam dosage started with three times per day 3 mg and increased to 5 mg three times per day.

The effects on daily weight, caloric intake, and psychiatric assessments were assessed, while the participants also received psychotherapy. The only differences between treatment groups were worsening of symptoms in the THC group during administration (i.e., higher somatization, sleep disturbance, and interpersonal sensitivity). Within the group treated with THC, three participants withdrew due to severe adverse reactions.

In a more recent cross-over RCT, 25 women with anorexia nervosa received either first dronabinol (2.5 mg twice daily) or placebo in combination with psychotherapy and a nutritional intervention (Andries, Frystyk, Flyvbjerg, & Støvring, 2014). Both treatments had a duration of 4 weeks, with a 4-week washout period in between. Weight gain and eating disorder symptoms were assessed. No significant changes in eating disorder symptoms were observed, regardless of group. In the first treatment phase, all participants gained a significant amount of weight regardless of condition. However, the weight gain was significantly higher in dronabinol than in placebo. The authors did not mention the values of weight gain in the second period, so it is not clear how placebo or dronabinol were effective in the second round. No severe side effects were reported.

In the treatment of anorexia nervosa, only THC has been examined. It was associated with worsening symptoms and adverse effects, although it was associated with more weight gain during regular treatment than placebo. One study had an unclear risk of bias and one study a low risk of bias.

3.9. Sleep-wake disorders

3.9.1. Insomnia

Four RCTs were identified that looked at the effects of cannabinoids on insomnia. Two separate cross-over RCTs investigated the effects of combined THC and CBD on self-reported clinical insomnia (Ried, Tamanna, Matthews, & Sali, 2023; J. H. Walsh et al., 2021). In Ried et al. (2023) 29 participants received a mixture of 10 mg/ml THC and 15 mg CBD/ml or placebo, both for 2 weeks with a 2-week washout period in between. The primary outcome measure was melatonin levels and secondary measures included physiological effects measured by a Fitbit, and questionnaires on sleep quality. The active group showed a 30 % increase in melatonin levels, while the placebo group showed a 20 % decrease in melatonin levels. In both groups, the number of people classifying for clinical insomnia reduced, but the reduction in clinical insomnia scores was greater in the active group than the placebo group. Light sleep improved in the active group compared to the placebo group, with the active group showing 21 min longer light sleep compared to baseline, but the placebo group only showing 0.2 min longer sleep. In Walsh et al. (J. H. Walsh et al., 2021) 23 participants received a mixture containing 20 mg/ml THC, 1 mg/ml CBD, and 2 mg/ml cannabidiol (CBN) or placebo, both for two weeks, separated by a 1-week washout period. They measured clinical and physiological measures of sleep

quality, while adverse events were also monitored. In the active treatment group, clinical insomnia scores and some of the self-reported measures of sleep quality significantly improved after two weeks of active treatment compared to placebo. However, polysomnography measures did not differ between treatments.

Moreover, two recent RCT's looked at the effects of CBD on moderate to severe insomnia symptoms (Aiewtrakoon, 2024; Narayan, Downey, Rose, Di Natale, & Hayley, 2024). Firstly, Aiewtrakoon (2024) examined how 10 mg CBD in the morning and 1 mg/kg CBD before bedtime versus placebo affected insomnia symptoms in 45 participants. For 4 weeks, the participants first received either CBD treatment followed by 4 weeks of placebo, or the other way around. The two treatments were separated by a 2-week washout period. Subsequently, all participants received the CBD treatment for 12 weeks. Clinical and physiological sleep measures were assessed. Compared to placebo, the CBD group showed improvement in the following sleep parameters: sleep duration, duration until falling asleep, waking times during sleep, duration of time spent awake after initially falling asleep, daytime sleepiness, and overall sleep quality. The other RCT examined the effects of 150 mg CBD or placebo nightly in 30 participants over a period of 2 weeks, after a 2-week placebo lead-in phase. The effects were assessed on insomnia symptoms and severity, the primary outcome measure, while the secondary outcome measures were physiological measures of sleep quality, daily diary sleep data, sleep-related questionnaires, trait anxiety, and overall wellbeing. Regardless of treatment, no consistent changes in the primary outcome measures or sleep related secondary outcome measures, as well as mood, were observed throughout the trial. Overall well-being was significantly and consistently higher in the CBD group compared to placebo (Narayan et al., 2024).

In sum, the combination of THC and CBD is associated with improvement assessed by subjective sleep measures, but not by polysomnography. One study found improvement on all measures after CBD administration, but one study did not observe any differences in sleep compared to placebo.

3.9.2. Sleep quality and mental health

Two other studies looked at sleep quality and various mental health symptoms after the acquisition of a medicinal cannabis card versus waiting list (at least 12 weeks, the duration of the study), both in the same sample of 186 participants. CUD symptoms, sleep quality, anxiety, and depression scores were measured (Gilman et al., 2022), as well as daily diary measures focusing on sleep quality and CUD symptoms (Tervo-Clemmens et al., 2023). The biggest proportion of participants reported using THC-dominant products and administration via vaping. In both studies, immediate acquisition of the card was associated with more CUD symptoms and cannabis use, but also better sleep quality. In one of the studies, mental well-being also improved in the cannabis group compared to the waiting list group, but depression and anxiety did not (Gilman et al., 2022).

In all included studies, cannabinoids were associated with improved sleep, both measured via self-report and physiological measures. However, adverse events were prevalent, and other mental health factors did not improve or worsen. Three studies had a high risk of bias, two studies had an unclear risk of bias, and one study had a low risk of bias.

4. Discussion

This systematic review aimed to give an up-to-date overview of the current application of medicinal cannabis for the reduction of mental health problems, considering the majority of mental health diagnoses of the DSM-5. Our search identified 49 studies from 15 countries, including treatment-seeking individuals who received medicinal cannabis for their mental health diagnosis, using a control group or condition and a wide range of assessment methods to evaluate its efficacy. Overall, the evidence suggests both positive and negative effects on mental health symptoms. More specifically, the most consistent improvements were

observed in anxiety and sleep-related symptoms, as well as less intense withdrawal and craving in SUDs. However, deterioration of symptoms related to anorexia nervosa, psychosis, and schizophrenia was also reported. Nonetheless, the variety of cannabis products and study designs limit our ability to draw final conclusions on the therapeutic properties of medicinal cannabis.

4.1. Effects CBD and THC in mental health symptoms

In four out of nine studies, high doses of CBD (400 mg or more) showed some acute efficacy in relieving anxiety symptoms. This was most consistently observed in a laboratory setting after an experimental procedure inducing stress (e.g., spontaneous public speaking) in participants with (social) anxiety and PTSD (Bergamaschi et al., 2011; Bolsoni et al., 2022b; Gundugurti et al., 2024; Jetly et al., 2015). In comparison, most popular cannabis products produced in the Netherlands contain around 0.1 % CBD (Oomen & Rigter, 2024). Moreover, CBD was associated with less cigarette consumption in smokers, lasting up to 2 weeks after treatment (Morgan et al., 2013), a reduction of positive schizophrenia symptoms in one study (in the other two studies both groups improved regardless of treatment) (McGuire et al., 2018), acute relief in psychosis symptoms in an open-label study, (Köck et al., 2021), and improved ASD symptomatology in all included ASD studies (Aran et al., 2019; Silva Junior et al., 2024).

In two out of four studies assessing clinical insomnia, improvement in self-reported sleep measures was observed after THC + CBD administration and in one study, CBD was associated with improvement on almost all sleep parameters (Aiewtrakoon, 2024; Ried et al., 2023; J. H. Walsh et al., 2021). In participants who sought treatment for CUD, craving and withdrawal were in five out of six studies reduced by CBD or combined THC + CBD (Allsop et al., 2014; Freeman et al., 2020; Levin et al., 2011; Lintzeris et al., 2019; Lintzeris, Mills, Dunlop, et al., 2020). In all CUD studies, participants showed a reduction in cannabis use, regardless of the type of treatment. This indicates that cannabinoids may not have a specific efficacy but could still be useful due to the reduction in withdrawal effects.

THC showed some efficacy in relieving withdrawal symptoms of OUD, although higher doses were also associated with adverse effects (Bisaga et al., 2015; Lofwall et al., 2016). Nonetheless, cannabinoids may be a tool worth considering in addition to existing treatments for OUD. In schizophrenia, psychotic symptoms, and anorexia nervosa, THC administered in a controlled setting was associated with deterioration of symptoms and adverse effects (D'Souza et al., 2005; Gross et al., 1983). In tic disorders, both improvement and worsening of symptoms were reported (Abi-Jaoude et al., 2023; Müller-Vahl et al., 2001, 2002, 2003). In all naturalistic studies, the usage of THC-dominant products for self-medication was associated with improvement of PTSD symptoms (Bonn-Miller et al., 2022), bipolar symptoms (Gruber et al., 2012), and sleep quality (Gilman et al., 2022; Tervo-Clemmens et al., 2023).

4.2. Therapeutic mechanism of cannabinoids

Cannabis has a long history as a medicine in mental health research (Nutt, 2019), albeit sometimes without clear justification why it could be efficacious. Several factors could be considered to determine whether the application of medicinal cannabis holds potential. It may be feasible to examine whether cannabis' mechanism of action could target the mental health symptoms one is aiming to treat. A putative mechanism of therapeutic action is the activation of the body's endocannabinoid system (ECS), through the binding of cannabis to the CB1 receptors (Black et al., 2019), located among others in the hippocampus, amygdala, striatum, and cortex (Volkow, Hampson, & Baler, 2017). The ECS is implicated among others in the modulation of stress, reward processing, and pain perception (Volkow et al., 2017). Preclinical studies indicate that the ECS plays a role in the regulation of stress at baseline, but its activation also decreases the duration and intensity of the stress

response when triggered (Morena, Patel, Bains, & Hill, 2016). This downregulating role of the ECS may be relevant in psychiatric disorders exacerbated by stress (Coelho, Lima-Bastos, Gobira, & Lisboa, 2023), including PTSD, SUDs, and anxiety related disorders. Given their potential association with the ECS, it is notable that in some mental health disorders, medicinal cannabis has *not* been explored. For example, no RCT's were identified focusing on major depressive disorder as a main diagnosis, despite some evidence of the role of the ECS in depressive symptoms (Navarrete et al., 2020). Conversely, in disorders characterized by psychotic or dissociative symptoms, THC may not provide desirable effects. As found by D'Souza et al. (2005), THC exacerbated schizophrenia symptoms in a dose dependent manner, and this was also observed in healthy controls (D'Souza et al., 2004; Englund et al., 2023). Additionally, as antipsychotic medication is effective in reducing symptoms in most people (Huhn et al., 2019), medicinal cannabis may not be an avenue that is very necessary to explore in these individuals. For disorders with limited or no effective medication available, and pathophysiological mechanisms that may be responsive to the therapeutic effects of cannabis, further exploration of medicinal cannabis could be viable. Currently, the most consistent evidence for the therapeutic benefits of cannabis is observed in somatic and neurological disorders, including pain symptoms (National Academies of Sciences, Engineering, and Medicine et al., 2017; Solmi et al., 2023). Often, these treatment effects are small but indirectly also seem to improve individuals self-reported quality-of-life (Lyonskey, Thurgur, Athanasiou-Fragkouli, Schlag, & Nutt, 2024). This review only included studies that used medicinal cannabis for mental disorders or symptoms as a primary target, but the impact of alleviating somatic and neurological symptoms and improving general quality of life may also improve mental health in some individuals. Moreover, the findings of the UK's first medicinal cannabis registry of individuals indicate that especially people with complex comorbidities (Schlag et al., 2022), as well as people above the age of 60 years (Lyonskey, Thurgur, et al., 2024), report positive effects from cannabis while these people are often excluded from RCT's.

Finally, to determine the efficacy of medicinal cannabis, future studies could also focus on directly comparing it to existing treatment options. This review included three studies that compared cannabis to other active treatments (i.e., the antipsychotic amisulpride, oxycodone, and diazepam), showing that oxycodone and diazepam had more efficacy in symptom relief (Gross et al., 1983; Leweke et al., 2012; Lofwall et al., 2016). However, further research comparing cannabis to commonly prescribed pharmacological treatments for mental health or psychotherapy could provide insight into its efficacy relative to more widely available treatments.

4.3. Cautions regarding the use of cannabinoids as medicine

Several important caveats of cannabinoids as medicine must be considered. First, dose dependent adverse events are prevalently reported, especially when using THC (Abi-Jaoude et al., 2023; Grant et al., 2022; Kayser et al., 2020). Thus, finding an optimal individual dosage should be prioritized when using cannabis or cannabinoids in a medicinal context. Second, long term cannabis use is associated with changes in the ECS, potentially increasing susceptibility to drug use or other psychiatric symptoms (Volkow et al., 2017). Third, frequent usage may increase the probability of developing a CUD, although the occurrence and risks of CUD symptoms in the context of medicinal use need more investigation (Feingold et al., 2024; Sznitman & Room, 2018). Long-term regular usage can lead to physical dependence symptoms (tolerance and withdrawal) that fulfill DSM-5 CUD criteria, but to what extent medicinal users are at risk for psychological CUD symptoms and escalation of usage, and how they may be similar or different to recreational users regarding CUD risk is to be determined (Sznitman & Room, 2018). Therefore, CUD criteria may have to be assessed differently in the context of medicinal use. Nonetheless, regular usage still poses a risk, in

part also because physical symptoms of (near) daily use are associated with deterioration of mental health, such as sleep problems or anxiety (Connor, Stjepanovic, Budney, Le Foll, & Hall, 2022). Thus, additional monitoring for CUD development, taking into account vulnerable groups, such as individuals under the age of 25 years old, or those with a history of a SUDs or other mental health vulnerabilities, may be required (Coelho et al., 2023; Volkow et al., 2017). Fourth, individuals who are at risk for psychosis or schizophrenia related symptoms, cannabis usage is still not recommended, as there is some evidence for an increased risk of symptom worsening (National Academies of Sciences, Engineering, and Medicine, 2017). Fifth, self-medication with cannabis for mental health is becoming increasingly popular, especially in regions with more lenient medicinal and recreational cannabis laws (Wallis et al., 2022). These individuals often report long term usage of products high in THC, increasing the risk of cannabis associated problems (Asselin et al., 2022).

4.4. Limitations of cannabis research

Despite the large volume of studies assessing medicinal cannabis, determining its efficacy is not straightforward. Although we only included studies with a control condition or group, resulting in primarily inclusion of RCTs (the golden standard to assess efficacy of medication), the large variety in designs and the use of different cannabinoids challenge the synthesis of results. Furthermore, our risk of bias assessment showed various caveats, including unclear blinding strategies, missing outcome data, and sometimes the report of effect without achieving significance. Moreover, multiple questionnaires and assessments measuring the same symptoms or diagnosis, without justification for why this would be feasible. These biases, although present across all disorders, were most prevalent in older studies, RCTs without any form of (pre)registration, or studies that – perhaps due to their design, i.e., observational studies – either could not perform blinding or failed to do so successfully. More recent trials, particularly those assessing CUD, showed a lower risk of bias, indicating that this issue is improving.

Furthermore, not all studies specified the source of their cannabis products. This is problematic for various reasons, including the uncertainty whether the composition of the cannabis product is trustworthy. For example, dispensaries often do not accurately label the composition of their medicinally sold cannabis products (Geweda et al., 2024). This problem can in part be contributed to the convoluted ways researchers need to obtain medicinal cannabis, an obstacle often faced when researching controlled substances. Currently researchers are required to use cannabis that is manufactured according to specific guidelines, due to the expansion of medicinal cannabis laws. However, finding sources for cannabis that meet these standard is difficult and costly (Z. D. Cooper, Abrams, Gust, Salicrup, & Throckmorton, 2021), which slows down the advancement of the field and hinders the ability to compare it to existing findings.

4.5. Concluding remarks

The lack of consistent proof for the efficacy of medicinal cannabis in RCTs keeps the medical field divided about potential benefits and risks in treating mental disorders, while further advancements face regulatory challenges. Nonetheless, as self-reported positive effects on mental health are ample, research focusing on the usefulness of cannabis and cannabinoids for subjective symptom relief and improved quality of life – rather than as a 'cure' – remains important. Additionally, the potential of medicinal cannabis, both alongside and in comparison with regular treatment, should be considered. Moreover, due to the nature of cannabinoids and their interaction with the ECS, it is crucial to identify individual characteristics of those experiencing positive or negative effects and create more nuanced guidelines on the potential effectiveness of cannabis and cannabinoids as medicine for mental health.

Funding

This research was supported by a Vidi grant (VI.Vidi.211.027) awarded to Janna Cousijn from the Dutch Research Council (NWO).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary material to this article can be found online at <http://doi.org/10.1016/j.cpr.2025.102581>.

Data availability

No data was used for the research described in the article.

References

- Abi-Jaoude, E., Bhikram, T., Parveen, F., Levenbach, J., Lafreniere-Roula, M., & Sandor, P. (2023). A double-blind, randomized, controlled crossover trial of Cannabis in adults with Tourette syndrome. *Cannabis and Cannabinoid Research*, 8(5), 835–845. <https://doi.org/10.1089/can.2022.0091>
- Aiewtrakoon, C. (2024). Efficacy and safety of Cannabidiol oil on chronic insomnia: The first randomized, double-blind, placebo-controlled, crossover, pilot study in Thailand. *Journal of the Medical Association of Thailand*, 107(3), 160–170. <https://doi.org/10.35755/jmedassocthai.2024.3.13952>
- Allsop, D. J., Copeland, J., Lintzeris, N., Dunlop, A. J., Montebello, M., Sadler, C., ... McGregor, I. S. (2014). Nabiximols as an agonist replacement therapy during cannabis withdrawal: A randomized clinical trial. *JAMA Psychiatry*, 71(3), 281–291. <https://doi.org/10.1001/jamapsychiatry.2013.3947>
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association. <https://doi.org/10.1176/appi.books.9780890425596>
- Andries, A., Frystyk, J., Flyvbjerg, A., & Støvring, R. K. (2014). Dronabinol in severe, enduring anorexia nervosa: A randomized controlled trial. *The International Journal of Eating Disorders*, 47(1), 18–23. <https://doi.org/10.1002/eat.22173>
- Aran, A., Cassuto, H., Lubotzky, A., Wattad, N., & Hazan, E. (2019). Brief report: Cannabidiol-rich Cannabis in children with autism Spectrum disorder and severe behavioral problems-A retrospective feasibility study. *Journal of Autism and Developmental Disorders*, 49(3), 1284–1288. <https://doi.org/10.1007/s10803-018-3808-2>
- Assanangkornchai, S., Kalayasi, R., Ratta-Apha, W., & Tanaree, A. (2023). Effects of cannabis legalization on the use of cannabis and other substances. *Current Opinion in Psychiatry*, 36(4), 283–289. <https://doi.org/10.1097/YCO.0000000000000868>
- Asselin, A., Lamarre, O. B., Chamberland, R., McNeil, S.-J., Demers, E., & Zongo, A. (2022). A description of self-medication with cannabis among adults with legal access to cannabis in Quebec, Canada. *Journal of Cannabis Research*, 4(1). <https://doi.org/10.1186/s42238-022-00135-y>
- Bailey, J. A., Tiberio, S. S., Kerr, D. C. R., Epstein, M., Henry, K. L., & Capaldi, D. M. (2023). Effects of Cannabis legalization on adolescent Cannabis use across 3 studies. *American Journal of Preventive Medicine*, 64(3), 361–367. <https://doi.org/10.1016/j.amepre.2022.09.019>
- Bergamaschi, M. M., Queiroz, R. H. C., Chagas, M. H. N., de Oliveira, D. C. G., De Martinis, B. S., Kapczinski, F., ... Crippa, J. A. S. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 36(6), 1219–1226. <https://doi.org/10.1038/npp.2011.6>
- Bisaga, A., Sullivan, M. A., Glass, A., Mishlen, K., Pavlicova, M., Haney, M., ... Nunes, E. V. (2015). The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone. *Drug and Alcohol Dependence*, 154, 38–45. <https://doi.org/10.1016/j.drugalcdep.2015.05.013>
- Black, N., Stockings, E., Campbell, G., Tran, L. T., Zagic, D., Hall, W. D., ... Degenhardt, L. (2019). Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: A systematic review and meta-analysis. *The Lancet Psychiatry*, 6(12), 995–1010. [https://doi.org/10.1016/S2215-0366\(19\)30401-8](https://doi.org/10.1016/S2215-0366(19)30401-8)
- Boggs, D. L., Surti, T., Gupta, A., Gupta, S., Nicu, M., Pittman, B., ... Ranganathan, M. (2018). The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. *Psychopharmacology*, 235(7), 1923–1932. <https://doi.org/10.1007/s00213-018-4885-9>
- Bolsoni, L. M., Crippa, J. A. S., Hallak, J. E. C., Guimarães, F. S., & Zuardi, A. W. (2022a). Effects of cannabidiol on symptoms induced by the recall of traumatic events in patients with posttraumatic stress disorder. *Psychopharmacology*, 239(5), 1499–1507. <https://doi.org/10.1007/s00213-021-06043-y>
- Bolsoni, L. M., Crippa, J. A. S., Hallak, J. E. C., Guimarães, F. S., & Zuardi, A. W. (2022b). The anxiolytic effect of cannabidiol depends on the nature of the trauma when patients with post-traumatic stress disorder recall their trigger event. *Revista Brasileira de Psiquiatria (Sao Paulo, Brazil: 1999)*, 44(3), 298–307. <https://doi.org/10.1590/1516-4446-2021-2317>
- Bonn-Miller, M. O., Brunstetter, M., Simonian, A., Loflin, M. J., Vandrey, R., Babson, K. A., & Wortzel, H. (2022). The long-term, prospective, therapeutic impact of Cannabis on post-traumatic stress disorder. *Cannabis and Cannabinoid Research*, 7(2), 214–223. <https://doi.org/10.1089/can.2020.0056>
- Bonn-Miller, M. O., Sisley, S., Riggs, P., Yazar-Klosinski, B., Wang, J. B., Loflin, M. J. E., ... Doblin, R. (2021). The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial. *PLoS One*, 16(3), Article e0246990. <https://doi.org/10.1371/journal.pone.0246990>
- Bradlow, R. C., & Armstrong, F. (2024). Is the current commercial model of medicinal cannabis in the best interest of patients? *Medical Journal of Australia*, 220(11), 592. <https://doi.org/10.5694/mja2.52313>
- Campany, E., López-Pelayo, H., Nutt, D., Blithikioti, C., Oliveras, C., Nuño, L., ... Gual, A. (2020). The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, 33, 1–35. <https://doi.org/10.1016/j.euroneuro.2020.02.003>
- Coelho, A. A., Lima-Bastos, S., Gobira, P. H., & Lisboa, S. F. (2023). Endocannabinoid signaling and epigenetics modifications in the neurobiology of stress-related disorders. *Neuronal Signaling*, 7(2), Article NS20220034. <https://doi.org/10.1042/NS20220034>
- Connor, J. P., Stjepanovic, D., Budney, A. J., Le Foll, B., & Hall, W. D. (2022). Clinical management of cannabis withdrawal. *Addiction*, 117(7), 2075–2095. <https://doi.org/10.1111/add.15743>
- Cooper, R. E., Williams, E., Seegobin, S., Tye, C., Kuntsi, J., & Asherson, P. (2017). Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial. *European Neuropsychopharmacology*, 27(8), 795–808. <https://doi.org/10.1016/j.euroneuro.2017.05.005>
- Cooper, Z. D., Abrams, D. I., Gust, S., Salicrup, A., & Throckmorton, D. C. (2021). Challenges for clinical Cannabis and cannabinoid research in the United States. *Journal of the National Cancer Institute. Monographs*, 2021(58), 114–122. <https://doi.org/10.1093/jncimonographs/igab009>
- D'Souza, D. C., Abi-Saab, W. M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., ... Krystal, J. H. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. *Biological Psychiatry*, 57(6), 594–608. <https://doi.org/10.1016/j.biopsych.2004.12.006>
- D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y.-T., ... Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 29(8), 1558–1572. <https://doi.org/10.1038/sj.npp.1300496>
- Englund, A., Oliver, D., Chesney, E., Chester, L., Wilson, J., Sovi, S., ... McGuire, P. (2023). Does cannabidiol make cannabis safer? A randomised, double-blind, cross-over trial of cannabis with four different CBD:THC ratios. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 48(6), 869–876. <https://doi.org/10.1038/s41386-022-01478-z>
- Fabre, L. F., & McLendon, D. (1981). The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. *Journal of Clinical Pharmacology*, 21(S1), 377S–382S. <https://doi.org/10.1002/j.1552-4604.1981.tb02617.x>
- Feingold, D., Glikberg, O., Brill, S., Amit, B. H., Lev-Ran, S., Kushnir, T., & Sznitman, S. R. (2024). Conceptualizing problematic use of medicinal Cannabis: Development and preliminary validation of a brief screening questionnaire. *Addictive Behaviors*, 158, Article 108122. <https://doi.org/10.1016/j.addbeh.2024.108122>
- Freeman, T. P., Hindocha, C., Baio, G., Shaban, N. D. C., Thomas, E. M., Astbury, D., ... Curran, H. V. (2020). Cannabidiol for the treatment of cannabis use disorder: A phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *The Lancet. Psychiatry*, 7(10), 865–874. [https://doi.org/10.1016/S2215-0366\(20\)30290-X](https://doi.org/10.1016/S2215-0366(20)30290-X)
- Geweda, M. M., Majumdar, C. G., Moore, M. N., Elhendawy, M. A., Radwan, M. M., Chandra, S., & ElSohly, M. A. (2024). Evaluation of dispensaries' cannabis flowers for accuracy of labeling of cannabinoids content. *Journal of Cannabis Research*, 6(1). <https://doi.org/10.1186/s42238-024-00220-4>
- Gilman, J. M., Schuster, R. M., Potter, K. W., Schmitt, W., Wheeler, G., Pachas, G. N., ... Evins, A. E. (2022). Effect of medical marijuana card ownership on pain, insomnia, and affective disorder symptoms in adults: A randomized clinical trial. *JAMA Network Open*, 5(3), Article e222106. <https://doi.org/10.1001/jamanetworkopen.2022.2106>
- Grant, J. E., Valle, S., Chesivoir, E., & Ehsan, D. (2022). Tetrahydrocannabinol fails to reduce hair pulling or skin picking: Results of a double-blind, placebo-controlled study of dronabinol. *International Clinical Psychopharmacology*, 37(1), 14–20. <https://doi.org/10.1097/YIC.0000000000000382>
- Gross, H., Ebert, M. H., Faden, V. B., Goldberg, S. C., Kaye, W. H., Caine, E. D., ... Zinberg, N. (1983). A double-blind trial of delta 9-tetrahydrocannabinol in primary anorexia nervosa. *Journal of Clinical Psychopharmacology*, 3(3), 165–171.
- Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Olson, D. P., Centorrino, F., & Lukas, S. E. (2012). Marijuana impacts mood in bipolar disorder: A pilot study. *Mental Health and Substance Use: Dual Diagnosis*, 5(3), 228–239. <https://doi.org/10.1080/17523281.2012.659751>
- Gundugurti, P. R., Banda, N., Yadlapalli, S. S. R., Narala, A., Thatikonda, R., Kocherlakota, C., & Kothapalli, K. S. (2024). Evaluation of the efficacy, safety, and pharmacokinetics of nanodispersible cannabidiol oral solution (150 mg/mL) versus

- placebo in mild to moderate anxiety subjects: A double blind multicenter randomized clinical trial. *Asian Journal of Psychiatry*, 97, Article 104073. <https://doi.org/10.1016/j.ajp.2024.104073>
- Hall, W., & Lynskey, M. (2020). Assessing the public health impacts of legalizing recreational cannabis use: The US experience. *World Psychiatry*, 19(2), 179–186. <https://doi.org/10.1002/wps.20735>
- Hill, K. P., Gold, M. S., Nemeroff, C. B., McDonald, W., Grzenda, A., Widge, A. S., ... Carpenter, L. L. (2022). Risks and benefits of Cannabis and cannabinoids in psychiatry. *The American Journal of Psychiatry*, 179(2), 98–109. <https://doi.org/10.1176/appi.ajp.2021.21030320>
- Hill, K. P., Palastro, M. D., Gruber, S. A., Fitzmaurice, G. M., Greenfield, S. F., Lukas, S. E., & Weiss, R. D. (2017). Nabilone pharmacotherapy for cannabis dependence: A randomized, controlled pilot study. *The American Journal on Addictions*, 26(8), 795–801. <https://doi.org/10.1111/ajad.12622>
- Hines, L. A., Freeman, T. P., Gage, S. H., Zammit, S., Hickman, M., Cannon, M., ... Heron, J. (2020). Association of high-potency cannabis use with mental health and substance use in adolescence. *JAMA Psychiatry*, 77(10), 1044–1051. <https://doi.org/10.1001/jamapsychiatry.2020.1035>
- Hoch, E., Niemann, D., von Keller, R., Schneider, M., Friemel, C. M., Preuss, U. W., ... Pogarell, O. (2019). How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. *European Archives of Psychiatry and Clinical Neuroscience*, 269(1), 87–105. <https://doi.org/10.1007/s00406-019-00984-4>
- Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., & Leucht, S. (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *Lancet (London, England)*, 394(10202), 939–951. [https://doi.org/10.1016/S0140-6736\(19\)31135-3](https://doi.org/10.1016/S0140-6736(19)31135-3)
- Hurd, Y. L., Spriggs, S., Alishayev, J., Winkel, G., Gurgov, K., Kudrich, C., ... Salsitz, E. (2019). Cannabidiol for the reduction of Cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: A double-blind randomized placebo-controlled trial. *The American Journal of Psychiatry*, 176(11), 911–922. <https://doi.org/10.1176/appi.ajp.2019.18101191>
- Jetly, R., Heber, A., Fraser, G., & Boisvert, D. (2015). The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology*, 51, 585–588. <https://doi.org/10.1016/j.psyneuen.2014.11.002>
- Kalayasiri, R., & Boonthae, S. (2023). Trends of cannabis use and related harms before and after legalization for recreational purpose in a developing country in Asia. *BMC Public Health*, 23(1), 911. <https://doi.org/10.1186/s12889-023-15883-6>
- Kayser, R. R., Haney, M., Raskin, M., Arout, C., & Simpson, H. B. (2020). Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study. *Depression and Anxiety*, 37(8), 801–811. <https://doi.org/10.1002/da.23032>
- Köck, P., Lang, E., Trulley, V.-N., Dechent, F., Mercer-Chalmers-Bender, K., Frei, P., ... Borgwardt, S. (2021). Cannabidiol cigarettes as adjunctive treatment for psychotic disorders – A randomized, Open-Label Pilot-Study. *Frontiers in Psychiatry*, 12. <https://doi.org/10.3389/fpsy.2021.736822>
- Kroon, E., Kuhns, L., Hoch, E., & Cousijn, J. (2020). Heavy cannabis use, dependence and the brain: A clinical perspective. *Addiction (Abingdon, England)*, 115(3), 559–572. <https://doi.org/10.1111/add.14776>
- Kwee, C. M., Baas, J. M., van der Flier, F. E., Groenink, L., Duits, P., Eikelenboom, M., ... Cath, D. C. (2022). Cannabidiol enhancement of exposure therapy in treatment refractory patients with social anxiety disorder and panic disorder with agoraphobia: A randomised controlled trial. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, 59, 58–67. <https://doi.org/10.1016/j.euroneuro.2022.04.003>
- Leung, J., Chan, G., Stjepanović, D., Chung, J. Y. C., Hall, W., & Hammond, D. (2022). Prevalence and self-reported reasons of cannabis use for medical purposes in USA and Canada. *Psychopharmacology*, 239(5), 1509–1519. <https://doi.org/10.1007/s00213-021-06047-8>
- Levin, F. R., Mariani, J. J., Brooks, D. J., Pavlicova, M., Cheng, W., & Nunes, E. V. (2011). Dronabinol for the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial. *Drug and Alcohol Dependence*, 116(1–3), 142–150. <https://doi.org/10.1016/j.drugalcdep.2010.12.010>
- Lewke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C., ... Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry*, 2(3), Article e94. <https://doi.org/10.1038/tp.2012.15>
- Lintzeris, N., Bhardwaj, A., Mills, L., Dunlop, A., Copeland, J., McGregor, I., ... Agonist Replacement for Cannabis Dependence (ARCD) study group. (2019). Nabiximols for the treatment of Cannabis dependence: A randomized clinical trial. *JAMA Internal Medicine*, 179(9), 1242. <https://doi.org/10.1001/jamainternmed.2019.1993>
- Lintzeris, N., Mills, L., Dunlop, A., Copeland, J., McGregor, I., Bruno, R., Kirby, A., Montebello, M., Hall, M., Jefferies, M., Kevin, R., & Bhardwaj, A. (2020). Cannabis use in patients 3 months after ceasing nabiximols for the treatment of cannabis dependence: Results from a placebo-controlled randomised trial. *Drug and Alcohol Dependence*, 215. <https://doi.org/10.1016/j.drugalcdep.2020.108220>
- Lintzeris, N., Mills, L., Suraev, A., Bravo, M., Arkell, T., Arnold, J. C., ... McGregor, I. S. (2020). Medical cannabis use in the Australian community following introduction of legal access: The 2018–2019 online cross-sectional Cannabis as medicine survey (CAMS-18). *Harm Reduction Journal*, 17(1), 37. <https://doi.org/10.1186/s12954-020-00377-0>
- Lofwall, M. R., Babalonis, S., Nuzzo, P. A., Elayi, S. C., & Walsh, S. L. (2016). Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. *Drug and Alcohol Dependence*, 164, 143–150. <https://doi.org/10.1016/j.drugalcdep.2016.05.002>
- Lucas, P., Baron, E. P., & Jikomes, N. (2019). Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduction Journal*, 16(1), 9. <https://doi.org/10.1186/s12954-019-0278-6>
- Lynskey, M. T., Athanasiou-Fragkouli, A., Thurgur, H., Schlag, A. K., & Nutt, D. J. (2024). Medicinal cannabis for treating post-traumatic stress disorder and comorbid depression: Real-world evidence. *BJPsych Open*, 10(2), Article e62. <https://doi.org/10.1192/bjo.2024.13>
- Lynskey, M. T., Thurgur, H., Athanasiou-Fragkouli, A., Schlag, A. K., & Nutt, D. J. (2024). Prescribed medical Cannabis use among older individuals: Patient characteristics and improvements in well-being: Findings from T21. *Drugs & Aging*, 41(6), 521–530. <https://doi.org/10.1007/s40266-024-01123-y>
- Mahabir, V. K., Merchant, J. J., Smith, C., & Garibaldi, A. (2020). Medical cannabis use in the United States: A retrospective database study. *Journal of Cannabis Research*, 2(1), 32. <https://doi.org/10.1186/s42238-020-00038-w>
- Masataka, N. (2019). Anxiolytic effects of repeated Cannabidiol treatment in teenagers with social anxiety disorders. *Frontiers in Psychology*, 10, 2466. <https://doi.org/10.3389/fpsyg.2019.02466>
- McGee, R., Williams, S., Poulton, R., & Moffitt, T. (2000). A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction (Abingdon, England)*, 95(4), 491–503. <https://doi.org/10.1046/j.1360-0443.2000.9544912.x>
- McGuire, P., Robson, P., Cubala, W. J., Vasile, D., Morrison, P. D., Barron, R., ... Wright, S. (2018). Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *The American Journal of Psychiatry*, 175(3), 225–231. <https://doi.org/10.1176/appi.ajp.2017.17030325>
- Meneses-Gaya, C. D., Crippa, J. A., Hallak, J. E., Miguel, A. Q., Laranjeira, R., Bressan, R. A., ... Lacerda, A. L. (2021). Cannabidiol for the treatment of crack-cocaine craving: An exploratory double-blind study. *Brazilian Journal of Psychiatry*, 43(5), 467–476. <https://doi.org/10.1590/1516-4446-2020-1416>
- Mills, L., Arnold, J. C., Suraev, A., Abelev, S. V., Zhou, C., Arkell, T. R., ... Lintzeris, N. (2024). Medical cannabis use in Australia seven years after legalisation: Findings from the online Cannabis as medicine survey 2022–2023 (CAMS-22). *Harm Reduction Journal*, 21(1), 104. <https://doi.org/10.1186/s12954-024-00992-1>
- Mongeau-Pérusse, V., Brissette, S., Bruneau, J., Conrod, P., Dubreucq, S., Gazil, G., Stip, E., & Jutras-Aswad, D. (2021). Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: A randomized placebo-controlled trial. *Addiction (Abingdon, England)*, 116(9), 2431–2442. <https://doi.org/10.1111/add.15417>
- Morena, M., Patel, S., Bains, J. S., & Hill, M. N. (2016). Neurobiological interactions between stress and the endocannabinoid system. *Neuropsychopharmacology*, 41(1), 80–102. <https://doi.org/10.1038/npp.2015.166>
- Morgan, C. J. A., Das, R. K., Joye, A., Curran, H. V., & Kamboj, S. K. (2013). Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. *Addictive Behaviors*, 38(9), 2433–2436. <https://doi.org/10.1016/j.addbeh.2013.03.011>
- Mosley, P. E., Webb, L., Suraev, A., Hingston, L., Turnbull, T., Foster, K., ... McGregor, I. S. (2023). Tetrahydrocannabinol and Cannabidiol in Tourette syndrome. *NEJM Evidence*, 2(9). <https://doi.org/10.1056/EVIDoa2300012>
- Müller-Vahl, K. R., Koblenz, A., Jöbges, M., Kolbe, H., Emrich, H. M., & Schneider, U. (2001). Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. *Pharmacopsychiatry*, 34(1), 19–24. <https://doi.org/10.1055/s-2001-15191>
- Müller-Vahl, K. R., Pisarenko, A., Szejko, N., Haas, M., Fremer, C., Jakubovskij, E., ... Großhennig, A. (2023). CANNA-TICS: Efficacy and safety of oral treatment with nabiximols in adults with chronic tic disorders—Results of a prospective, multicenter, randomized, double-blind, placebo controlled, phase IIb superiority study. *Psychiatry Research*, 323, Article 115135. <https://doi.org/10.1016/j.psychres.2023.115135>
- Müller-Vahl, K. R., Schneider, U., Koblenz, A., Jöbges, M., Kolbe, H., Daldrup, T., & Emrich, H. M. (2002). Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): A randomized crossover trial. *Pharmacopsychiatry*, 35(2), 57–61. <https://doi.org/10.1055/s-2002-25028>
- Müller-Vahl, K. R., Schneider, U., Prevedel, H., Theloe, K., Kolbe, H., Daldrup, T., & Emrich, H. M. (2003). Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial. *The Journal of Clinical Psychiatry*, 64(4), 459–465. <https://doi.org/10.4088/jcp.v64n0417>
- Murnion, B. (2015). Medicinal cannabis. *Australian Prescriber*, 38(6), 212–215. <https://doi.org/10.18773/austprescr.2015.072>
- Narayan, A. J., Downey, L. A., Rose, S., Di Natale, L., & Hayley, A. C. (2024). Cannabidiol for moderate-severe insomnia: A randomized controlled pilot trial of 150 mg of nightly dosing. *Journal of Clinical Sleep Medicine*, 20(5), 753–763. <https://doi.org/10.5664/jcs.m.10998>
- National Academies of Sciences, Engineering, and Medicine. (2017). *The health effects of Cannabis and cannabinoids: The current state of evidence and recommendations for research*. The National Academies Press. <https://doi.org/10.17226/24625>
- Nationale Drug Monitor. (2024). *Nationale drug monitor editie 2024 (Cannabis 3.2.4 Medicinaal Gebruik - Nationale drug monitor)*. Den Haag: Trimbos-instituut, Utrecht & WODC. <https://www.nationaledrugmonitor.nl/cannabis-medicinaal-gebruik/>
- Navarrete, F., García-Gutiérrez, M. S., Jurado-Barba, R., Rubio, G., Gasparyan, A., Austrich-Olivares, A., & Manzanares, J. (2020). Endocannabinoid system components as potential biomarkers in psychiatry. *Frontiers in Psychiatry*, 11, 315. <https://doi.org/10.3389/fpsy.2020.00315>

- Newton-Howes, G. (2018). The challenges of “medical cannabis” and mental health: A clinical perspective. *British Journal of Clinical Pharmacology*, 84(11), 2499–2501. <https://doi.org/10.1111/bcp.13687>
- Noël, C., Scharf, D., Koné, A., Armiento, C., & Dylan, D. (2024). Cannabis advertising impacts on youth cannabis use intentions following recreational legalization in Canada: An ecological momentary assessment (EMA) study. *Addictive Behaviors*, 153, Article 107981. <https://doi.org/10.1016/j.addbeh.2024.107981>
- Nutt, D. (2019). Why medical cannabis is still out of patients' reach—an essay by David Nutt. *BMJ (Online)*, 365. <https://doi.org/10.1136/bmj.l1903>
- Oomen, P., & Rigter, S. (2024). *THC-concentraties in wiet, nederwiet en hasj in Nederlandse coffeeshops 2022–2023 (drugs Informatie En monitoring Systeem (DIMS) Programma drug monitoring & policy)*. Trimbos Instituut. <https://www.trimbos.nl/wp-content/uploads/2024/09/THC-monitor-2022-2023.pdf>
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*, 372, Article n71. <https://doi.org/10.1136/bmj.n71>
- Pinto, J. V., Crippa, J. A. S., Ceresér, K. M., Vianna-Sulzbach, M. F., Silveira Júnior, E. D. M., Santana Da Rosa, G., ... Kauer-Sant'Anna, M. (2024). Cannabidiol as an Adjunctive Treatment for Acute Bipolar Depression: A Pilot Study: Le cannabidiol comme traitement d'appoint de la dépression bipolaire aiguë: une étude pilote. *The Canadian Journal of Psychiatry*, 69(4), 242–251. <https://doi.org/10.1177/07067437231209650>
- Rafei, P., Englund, A., Lorenzetti, V., Elkholly, H., Potenza, M. N., & Baldacchino, A. M. (2023). Transcultural aspects of Cannabis use: A descriptive overview of Cannabis use across cultures. *Current Addiction Reports*, 10(3), 458–471. <https://doi.org/10.1007/s40429-023-00500-8>
- Rehm, J., Elton-Marshall, T., Sornpaisarn, B., & Manthey, J. (2019). Medical marijuana. What can we learn from the experiences in Canada, Germany and Thailand? *The International Journal on Drug Policy*, 74, 47–51. <https://doi.org/10.1016/j.drugpo.2019.09.001>
- Rhee, T. G., & Rosenheck, R. A. (2023). Increasing use of cannabis for medical purposes among U.S. residents, 2013–2020. *American Journal of Preventive Medicine*, 65(3), 528–533. <https://doi.org/10.1016/j.amepre.2023.03.005>
- Richardson, T. H. (2010). Cannabis use and mental health: A review of recent epidemiological research. *International Journal of Pharmacology*, 6(6), 796–807. <https://doi.org/10.3923/ijp.2010.796.807>
- Ried, K., Tamanna, T., Matthews, S., & Sali, A. (2023). Medicinal cannabis improves sleep in adults with insomnia: A randomised double-blind placebo-controlled crossover study. *Journal of Sleep Research*, 32(3), Article e13793. <https://doi.org/10.1111/jsr.13793>
- Salazar, C. A., Tomko, R. L., Akbar, S. A., Squeglia, L. M., & McClure, E. A. (2019). Medical Cannabis use among adults in the southeastern United States. *Cannabis (Albuquerque, N.M.)*, 2(1), 53–65.
- Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., & Firth, J. (2020). Medicinal cannabis for psychiatric disorders: A clinically-focused systematic review. *BMC Psychiatry*, 20(1), 24. <https://doi.org/10.1186/s12888-019-2409-8>
- Schlag, A. K., Zafar, R. R., Lynskey, M. T., Athanasios-Fragkouli, A., Phillips, L. D., & Nutt, D. J. (2022). The value of real world evidence: The case of medical cannabis. *Frontiers in Psychiatry*, 13, Article 1027159. <https://doi.org/10.3389/fpsy.2022.1027159>
- Sexton, M., Cuttler, C., Finnell, J. S., & Mischley, L. K. (2016). A cross-sectional survey of medical Cannabis users: Patterns of use and perceived efficacy. *Cannabis and Cannabinoid Research*, 1(1), 131–138. <https://doi.org/10.1089/can.2016.0007>
- Sexton, M., Cuttler, C., & Mischley, L. K. (2019). A survey of Cannabis acute effects and withdrawal symptoms: Differential responses across user types and age. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 25(3), 326–335. <https://doi.org/10.1089/acm.2018.0319>
- Shah, K., Farwa, U. E., Vanaparti, A., Patel, S., Kanumuri, M., Vashishth, O., ... Tripathi, S. (2024). Global epidemiology of cannabis use disorders and its trend from 1990 to 2019: Benchmarking analysis of the global burden of disease study. *Journal of Family Medicine and Primary Care*, 13(3), 881–889. <https://doi.org/10.4103/jfmpc.jfmpc.824.23>
- Silva Junior, E. A. D., Medeiros, W. M. B., Santos, J. P. M. D., Sousa, J. M. M. D., Costa, F. B. D., Pontes, K. M., ... Albuquerque, K. L. G. D. D. (2024). Evaluation of the efficacy and safety of cannabidiol-rich cannabis extract in children with autism spectrum disorder: Randomized, double-blind, and placebo-controlled clinical trial. *Trends in Psychiatry and Psychotherapy*. <https://doi.org/10.47626/2237-6089-2021-0396>
- Solmi, M., De Toffol, M., Kim, J. Y., Choi, M. J., Stubbs, B., Thompson, T., ... Dragioti, E. (2023). Balancing risks and benefits of cannabis use: Umbrella review of meta-analyses of randomised controlled trials and observational studies. *BMJ*, Article e072348. <https://doi.org/10.1136/bmj-2022-072348>
- Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.)*, 366, Article 14898. <https://doi.org/10.1136/bmj.14898>
- Sznitman, S. R. (2020). Trends in medical cannabis licensure, Israel, 2013–2018. *Drug and Alcohol Review*, 39(6), 763–767. <https://doi.org/10.1111/dar.13116>
- Sznitman, S. R., & Room, R. (2018). Rethinking indicators of problematic cannabis use in the era of medical cannabis legalization. *Addictive Behaviors*, 77, 100–101. <https://doi.org/10.1016/j.addbeh.2017.09.026>
- Tervo-Clemmens, B., Schmitt, W., Wheeler, G., Cooke, M. E., Schuster, R. M., Hickey, S., ... Gilman, J. M. (2023). Cannabis use and sleep quality in daily life: An electronic daily diary study of adults starting cannabis for health concerns. *Drug and Alcohol Dependence*, 243, Article 109760. <https://doi.org/10.1016/j.drugalcdep.2022.109760>
- Trigo, J. M., Soliman, A., Quilty, L. C., Fischer, B., Rehm, J., Selby, P., ... Le Foll, B. (2018). Nabiximols combined with motivational enhancement/cognitive behavioral therapy for the treatment of cannabis dependence: A pilot randomized clinical trial. *PLoS One*, 13(1), Article e0190768. <https://doi.org/10.1371/journal.pone.0190768>
- Turna, J., Balodis, I., Munn, C., Van Ameringen, M., Busse, J., & MacKillop, J. (2020). Overlapping patterns of recreational and medical cannabis use in a large community sample of cannabis users. *Comprehensive Psychiatry*, 102, Article 152188. <https://doi.org/10.1016/j.comppsy.2020.152188>
- Verweij, K. J. H., Vink, J. M., Abdellaoui, A., Gillespie, N. A., Derks, E. M., & Treur, J. L. (2022). The genetic aetiology of cannabis use: From twin models to genome-wide association studies and beyond. *Translational Psychiatry*, 12(1), 489. <https://doi.org/10.1038/s41398-022-02215-2>
- Volkow, N. D., Hampson, A. J., & Baler, R. D. (2017). Don't worry, be happy: Endocannabinoids and Cannabis at the intersection of stress and reward. *Annual Review of Pharmacology and Toxicology*, 57, 285–308. <https://doi.org/10.1146/annurev-pharmtox-010716-104615>
- Wallis, D., Coatsworth, J. D., Mennis, J., Riggs, N. R., Zaharakis, N., Russell, M. A., ... Mason, M. J. (2022). Predicting self-medication with Cannabis in young adults with hazardous Cannabis use. *International Journal of Environmental Research and Public Health*, 19(3), 1850. <https://doi.org/10.3390/ijerph19031850>
- Walsh, J. H., Maddison, K. J., Rankin, T., Murray, K., McArdle, N., Ree, M. J., ... Eastwood, P. R. (2021). Treating insomnia symptoms with medicinal cannabis: A randomized, crossover trial of the efficacy of a cannabinoid medicine compared with placebo. *Sleep*, 44(11). <https://doi.org/10.1093/sleep/zsab149>
- Walsh, Z., Gonzalez, R., Crosby, K., S Thiesen, M., Carroll, C., & Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review. *Clinical Psychology Review*, 51, 15–29. <https://doi.org/10.1016/j.cpr.2016.10.002>
- Ware, M. A., Adams, H., & Guy, G. W. (2005). The medicinal use of cannabis in the UK: Results of a nationwide survey. *International Journal of Clinical Practice*, 59(3), 291–295. <https://doi.org/10.1111/j.1742-1241.2004.00271.x>
- Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2011). The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
- Whitehill, J. M., Trangenstein, P. J., Jenkins, M. C., Jernigan, D. H., & Moreno, M. A. (2020). Exposure to Cannabis Marketing in Social and Traditional Media and past-year use among adolescents in states with legal retail Cannabis. *Journal of Adolescent Health*, 66(2), 247–254. <https://doi.org/10.1016/j.jadohealth.2019.08.024>
- Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., ... Kleijnen, J. (2015). Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA*, 313(24), 2456–2473. <https://doi.org/10.1001/jama.2015.6358>
- Yakirevich Amir, N., Treves, N., Davidson, E., Bonne, O., & Matok, I. (2023). Medical cannabis use among patients with post-traumatic stress disorder (PTSD): A nationwide database study. *European Psychiatry*, 66(S1), S111–S112. <https://doi.org/10.1192/j.eurpsy.2023.306>
- Yau, J. C., Yu, S. M., Panenka, W. J., Pearce, H., Gicas, K. M., Procyshyn, R. M., ... Barr, A. M. (2019). Characterization of mental health in cannabis dispensary users, using structured clinical interviews and standardized assessment instruments. *BMC Psychiatry*, 19(1), 335. <https://doi.org/10.1186/s12888-019-2324-z>
- Zuckermann, A. M. E., Battista, K. V., Bélanger, R. E., Haddad, S., Butler, A., Costello, M. J., & Leatherdale, S. T. (2021). Trends in youth cannabis use across cannabis legalization: Data from the COMPASS prospective cohort study. *Preventive Medicine Reports*, 22, Article 101351. <https://doi.org/10.1016/j.pmedr.2021.101351>