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Review article

Cannabinoid treatments for anxiety: A systematic review and consideration of the impact of sleep disturbance

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ABSTRACT

Cannabidiol's (CBD) safety profile and broad action has made it a popular treatment option for anxiety and co-occurring sleep disturbance. However, its efficacy in healthy and clinical populations, treatment duration, formulation and doses for optimal therapeutic benefits remains unclear. Selected databases were examined from inception to October 2022. Study selection, data extraction and Cochrane Risk of Bias assessments were conducted according to PRISMA guidelines and registered on the PROSPERO database (CRD42021247476) with 58 full-text studies meeting the eligibility criteria and administered CBD only or with Δ-9-tetrahydrocannabinol (THC) across healthy and clinical populations. In healthy populations and certain non-cannabis using clinical populations, CBD had greater anxiolytic effects without prominent effects on sleep. An inverted U-shaped dose relationship, and CBD ratio to THC in combined treatments likely moderated these effects. Mechanistically, observed CBD effects occurred via primary modulation of the endocannabinoid system and secondary regulation of neuroendocrine function. Additional research is needed to understand CBD mechanisms of action across diverse groups.

1. Introduction

Cannabis has an extensive history as a broad-spectrum therapeutic in traditional medicine (Pertwee and Aguilar-Turton, 2014). Increasingly, it has shown efficacy in modern psychiatry for treatment of both sleep and affective disorders; each which incur significant health, economic and social burden (Pertwee and Aguilar-Turton, 2014; World Health Organization, 2017; Zuardi et al., 2017). Of the more than 500 compounds within the cannabis plant, Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most extensively described (Pertwee and Aguilar-Turton, 2014). Relative to THC, CBD exhibits a generally high tolerability and safety profile as an anxiolytic and sleep aid (Newton and Newton, 2020). Thus, the growing availability and application of CBD presents as a potentially viable therapeutic option for the treatment of anxiety and disordered sleep-related symptoms over current pharmacological interventions (Schier et al., 2012).

Anxiety and sleep disruption frequently co-occur (Staner, 2003), and presentation of one core symptom of either can precede the development of the other (American Psychiatric Association, 2013). The complex bi-directional relationship between anxiety and sleep disruption is likely modulated through shared, reciprocal pathways of neuroendocrine regulation. Facilitated via negative feedback loop, either anxiety or sleep disruption can equally and cyclically exacerbate one another (Hirotsu et al., 2015; Kalmbach et al., 2018). The efficacy of CBD in the context of this relationship between anxiety and disordered sleep has not been widely studied. Preclinical studies have explored anxiety-induced sleep disruption in rats using a single administration of 1 μg/μl CBD (Hsiao et al., 2012). Microinjection of CBD blocked anxiety-induced rapid eye movement (REM) sleep suppression through its anxiolytic effect rather than through alterations in core sleep regulation, suggesting a direct mechanism of action. Other studies employed similar treatment administration routes and models of anxiety in rodents; however, these have generally lacked sleep measures as primary outcomes, or have inconsistently explored single and/or repeated administrations and varied CBD doses. An inverted u-shaped dose relationship of CBD efficacy is observed with respect to anxiety – low and intermediate doses produced anxiolytic effects, whereas high doses did not (Guimarães et al., 1990). Given these pre-clinical (Fogaça et al., 2014) and clinical findings (Zuardi et al., 2017), there is an urgent need to determine both the efficacy and effective cannabinoid dosages for

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therapeutic application.

Emergent research supports CBD as producing both anxiolytic and sleep enhancing effects in clinical groups (Shannon et al., 2019). Neuroimaging studies have further shown that the limbic and prelimbic cortical regions associated with anxiety may be modulated by a single administration of 400 mg of CBD, leading to reduced anxiety and increased mental sedation (Crippa et al., 2004). Conclusive evidence on effective or optimal CBD doses and treatment periods for clinical populations is, however, lacking. In part, this is due to fluctuating duration of treatment, restrictive study populations, small cohort size and limited research dedicated to simultaneously exploring the effect of CBD on anxiety and sleep outcomes. Anxiety and disordered sleep incur significant personal, economic and health burdens. Given CBD's growing availability despite inconclusive empirical evidence on its clinical efficacy in treating human anxiety and disordered sleep, this systematic review aimed to collate evidence of cannabinoid treatments, dosage and treatment periods, and clinical outcomes in both healthy and clinical populations. Further to this, it aims to supplement discussion on the bi-directional relationship of anxiety and sleep disruption in terms of the effect CBD may have on the shared neuroendocrine pathways that regulate anxiety and sleep.

2. Method

2.1. Protocol and registration

This review was prospectively registered [PROSPERO, registration number CRD42021247476]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to guide reporting standards.

2.2. Eligibility criteria

Articles were included if they measured change in anxiety or change in anxiety and sleep/sedation concurrently and reported the use of CBD treatments with clear dose information in healthy or clinical human adult-only populations. Articles were excluded if treatments consisted of THC or synthetic cannabinoids only, or if anxiety was not measured. Articles with full access, either in the English language or translated to English were included. Study designs were limited to clinical trials and observational, cohort and/or case studies. Articles dated up to June 2021 were eligible for screening.

2.3. Data sources and search strategy

Articles for this review were retrieved through database searches of Scopus, Web of Science, PubMed and PsycNet. In consultation with a university librarian informed by the Peer Review of Electronic Search Strategies (PRESS) checklist and guidelines (McGowan et al., 2016), the refined search string "(anxi* OR sleep) AND (cbd OR cannabidiol OR thc OR tetrahydrocannabinol)" was used to identify articles. To improve database search results, filters including "Article" (Web of Science and Scopus) and "Species – Humans" (PubMed), topic refinements including "human* " (Web of Science) and keywords limited to "article, Human, humans, controlled study, anxiety, cannabidiol, anxiety disorder, sleep, CBD" and excluding "Dronabinol, non-human, depression, animal experiments, animals, adolescent, Animal, Rats, mouse, animal model, nabilone, mice, behavior animal, child, animal behavior" (Scopus) were used. The full search strategy is made available on request.

Two authors (AN, BM) independently used the search string and filters/refinements to extract database citations to Endnote. Duplicate citations were identified and automatically or manually removed. Full text articles were accessed manually to obtain abstracts when missing from Endnote. In case of the unavailability of full-text articles on databases, a Google Scholar search was initiated resulting in six articles. Authors were not contacted directly. Discrepancies throughout the article screening process were settled through discussion between the two reviewers, with a third reviewer (AH) available when necessary.

2.4. Risk of bias and quality assessment

Risk of bias assessment of the included studies were conducted in duplicate by two independent reviewers (AN and BM) using the Cochrane Risk of Bias Tool (RoB2) (Sterne et al., 2019). Scores of low, some concerns, or high risk of bias were assigned to assessment domains for randomized between-groups and randomized crossover studies. Scores of low, moderate, serious or critical risk of bias or no information were assigned to assessment domains for non-randomized studies. Domains for randomized studies included biases 1) Arising from randomization process. 2) Due to deviations from intended intervention. 3) Due to missing outcome data. 4) In measurement of the outcome. 5) In selection of the reported result. Crossover studies included an extra domain assessing bias arising from period and carryover effects. Domains for non-randomized study domains included bias: 1) Due to confounding. 2) Due to selection of participants. 3) In classification of interventions. 4) Due to deviations from intended interventions. 5) Due to missing data. 6) In measurement of outcomes. 7). In selection of reported result.

2.5. Data synthesis

For each study, key demographic characteristics including sample size, age/age range, mean age and standard deviation (or median where mean age was not stated) and gender were extracted and tabulated using Microsoft Word. Studies were then divided into four categories according to cannabinoid treatment and outcome measures: (i) CBD only treatments with anxiety outcomes, (ii) CBD only treatments with anxiety and sleep outcomes, (iii) CBD and THC treatments with anxiety outcomes, and (iv) CBD and THC treatments with anxiety and sleep outcomes. Within these categories, articles were further identified by sample as either healthy or clinical population. In each category, studies were also grouped as clinical trials or observational/cohort/case studies and details including treatment route, dosage, treatment period/dosing sessions, anxiety/sleep measures used, outcomes were extracted and tabulated.

3. Results

3.1. Identification and study selection

The database search yielded a total of 1607 articles, with six records found through other sources (Fig. 1). Of this, 439 duplicate articles were found and removed from the database results. Title and/or abstracts were screened for the remaining 1136 articles. In total, 1089 articles failed to meet the eligibility criteria and were therefore excluded. Full-text assessments resulted in three conflicts with consensus reached after the first round between reviewers and nine articles being excluded. A reference list screening did not produce additional studies that were not already included. A total of 37 studies were included in this review.

A forward search was conducted using the same search strategies except for dates being set to 2021–2022 (except PubMed July 2021–2022) (Fig. 1). This yielded a total of 443 articles. Following the removal of duplicates and title/abstract screening, 51 full texts were screened for eligibility resulting in an additional 21 studies determined as eligible for inclusion. Amongst included studies, two articles by the same authors had used the same sample population with results relevant to this review repeated in both (Bolsoni et al., 2022a, 2022b). This review therefore included one of these articles to avoid repeated results (Bolsoni et al., 2022a). In total, there were $N = 58$ studies deemed eligible and included in this review.

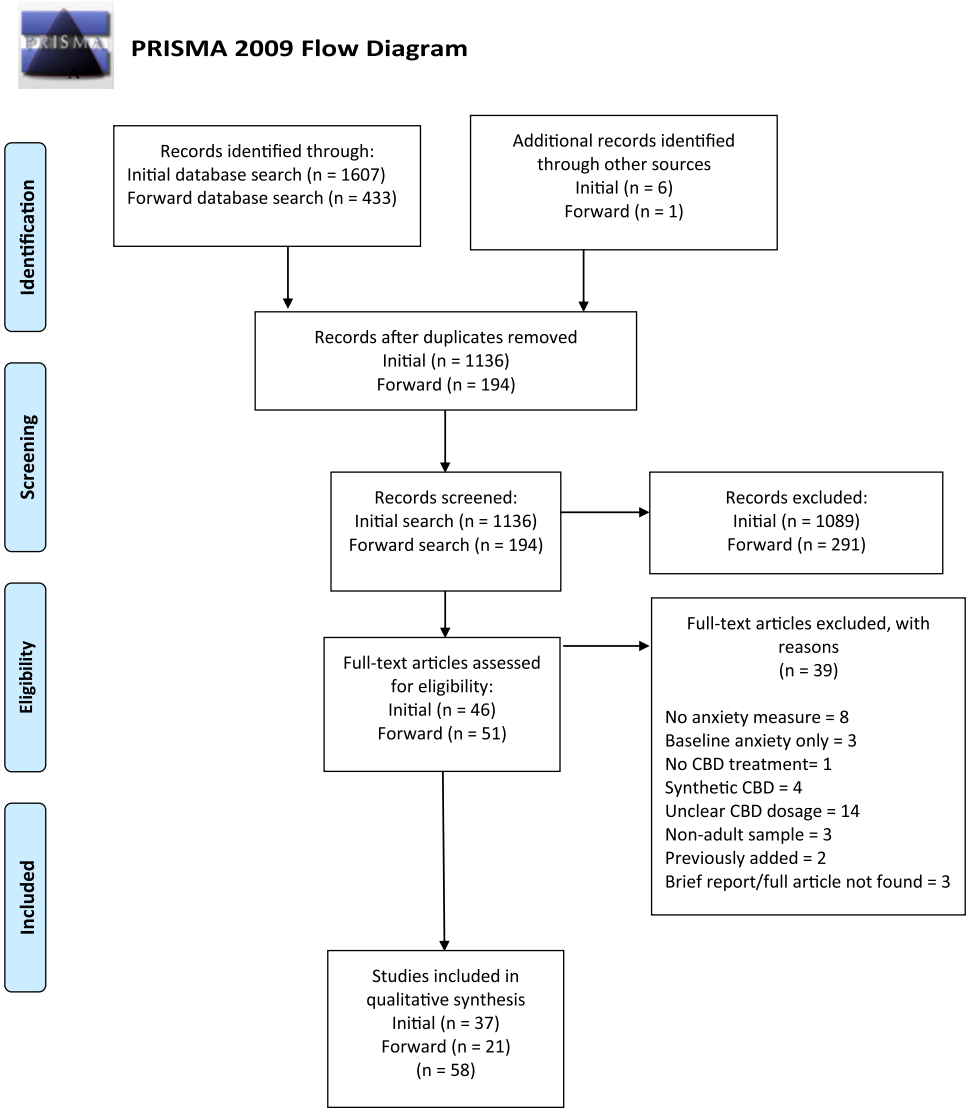

Fig. 1. PRISMA 2009 Flow Diagram. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

3.2. Participant characteristics

Table 1 shows demographic characteristics of included studies. There was a total of 5397 participants, ranging from a minimum of one to maximum 2431 participants for individual samples across studies. Participant ages ranged from 18 to 82 years old. An all-male sample was utilized in 14 studies (Berger et al., 2020; Bhattacharyya et al., 2009; Bindler et al., 2022; Borgwardt et al., 2008; Crippa et al., 2011, 2004, 2022; de de de Meneses-Gaya et al., 2021; Fusar-Poli et al., 2009; Grimm et al., 2018; Linares et al., 2019; Martin-Santos et al., 2012; Shannon and Opila-Lehman, 2015; Winton-Brown et al., 2011) and 15 more studies had a higher proportion of males than females (Allsop et al., 2014; Bonomo et al., 2022; Das et al., 2013; Davies et al., 2022; de Faria et al., 2020; Ergisi et al., 2022; Gibson et al., 2022; Hindocha et al., 2015; Karschner et al., 2011; Kayser et al., 2020; Masataka, 2019; Montebello et al., 2022; O'Neill et al., 2021; Solowij et al., 2018; Zuardi et al., 1982). Only 11 studies had an all-female sample (Crippa et al., 2013) or a higher percentage of female participants, respectively (Aungsumart et al., 2021; Aviram et al., 2020; Bolsoni et al., 2022a; Gambino et al., 2021; Giorgi et al., 2020; Gruber et al., 2021; Harris et al., 2022; Mauzay et al., 2021; Sagar et al., 2021; Stanley et al., 2022). A single study reported a participant with undisclosed gender (Mauzay et al., 2021) and two studies did not state genders (Crippa et al., 2021; de Almeida et al., 2021). The remaining studies had close to equal numbers of male and female participants (Alessandria et al., 2020; Appiah-Kusi et al., 2020; Bergamaschi et al., 2011; Casarett et al., 2019; Cuttler et al., 2018; Drennan et al., 2021a; Ilan et al., 2005; Linares et al., 2018; Morgan et al., 2013; Nimalan et al., 2022; Pacheco et al., 2021; Shannon et al., 2019; Spindle et al., 2020; Zuardi et al., 1993, 2017).

There were 55 single-site studies and four multi-site studies (Alessandria et al., 2020; Allsop et al., 2014; Bonomo et al., 2022; Giorgi et al., 2020) with the majority originating from England/UK (Appiah-Kusi et al., 2020; Bhattacharyya et al., 2009; Borgwardt et al., 2008; Das et al., 2013; Davies et al., 2022; Ergisi et al., 2022; Fusar-Poli et al., 2009; Harris et al., 2022; Hindocha et al., 2015; Martin-Santos et al., 2012; Morgan et al., 2013; Nimalan et al., 2022; O'Neill et al., 2021; Winton-Brown et al., 2011) Brazil (Bergamaschi et al., 2011; Bolsoni et al., 2022a; Crippa et al., 2011, 2013, 2004, 2022, 2021; de Almeida et al., 2021; de Faria et al., 2020; de de de Meneses-Gaya et al., 2021; Linares et al., 2018, 2019; Pacheco et al., 2021) and the United States of America (Bindler et al., 2022; Cuttler et al., 2018; Drennan et al., 2021a; Gibson et al., 2022; Gruber et al., 2021; Hurd et al., 2019; Ilan et al., 2005; Karschner et al., 2011; Kayser et al., 2020; Mauzay et al., 2021; Sagar et al., 2021; Shannon et al., 2019; Shannon and Opila-Lehman,

Table 1
Study Characteristics.

Author	*N*	Age or age range; *Mean* (std dev)	Gender (%)
Included Studies - Initial Search			
1.Alessandria et al. (2020)	N = 20 MS patients	23–67; *50.2* (11.4)	55 F
2. Allsop et al. (2014)	N = 51 cannabis dependence PLA *n* = 24 Nabiximols n = 27	18–65; *35.39* (8.9)	74.5 M
3.Appiah-Kusi et al. (2020)na	N = 58 CHR *n* = 32 (CBD = 16, PLA = 16) HC *n* = 2 6	CHR-CBD *22.33* (5.1) CHR-PLA *25.12* (5.4) HC *23.91* (3.9)	CHR-CBD = 37.5 F CHR-PLA = 58.8 F HC = 52 F
4.Aviram et al. (2020)	N = 108 oncology patients	52–72 *Median (IQR): 64* (52–72)	57 F
5.Bergamaschi et al. (2011)	SAD (treatment naïve) N = 24 HC n = 12	SAD-PLA *22.9* (2.4) SAD-CBD *24.6* (3.6) HC *23.3* (1.7)	SAD-PLA= 25 M, 25 F SAD-CBD= 25 M, 25 F HC= 50 M, 50 F
6.Berger et al. (2020)	N = 1 SAD, attenuated psychosis	20	100 M
7.Bhattacharyya et al. (2009)	N = 15 healthy participants	*26.7* (n)	100 M
8.Borgwardt et al. (2008)	N = 15 healthy participants	20–42; *26.7* (5.7)	100 M
9.Casarett et al. (2019)	N = 2431 (INS *n* = 869 ANX *n* = 1086)	INS= 18–76; *34* (n) ANX= 18–82; *33* (n)	INS= 43.2 M ANX= 43 M
10.Crippa et al. (2004)	N = 10 healthy participants	25–42; *29.8* (5.1)	100 M
11.Crippa et al. (2011)	N = 10 SAD (treatment naïve)	20–33; *24.2* (3.7)	100 M
12.Crippa et al. (2013)	N = 1 cannabis withdrawal syndrome	19	100 F
13.Cuttler et al. (2018)	N = 770 ANX	*33* (10)	52.9 F
14.Das et al. (2013)	N = 48 healthy participants	18–35; (n)	Pre-experiment= 16.7 M, 16.7 F Post-experiment= 20.8 M, 12.4 F PLA= 25 M, 8.3 F
15.de Faria et al. (2020)	N = 24 PD	*64.13* (9.7)	91.7 M
16.Fusar-Poli et al. (2009)	N = 15 healthy participants	18–35; *26.67* (5.7)	100 M
17.Giorgi et al. (2020)	N = 102 FM	*51.9* (11.3)	91 F
18.Grimm et al. (2018)	N = 16 healthy participants	(n)	100 M
19.Hindocha et al. (2015)	N = 48 SCH	Light cannabis use: Low SCH= *21.0* (2.13) High SCH= *22.9* (2.02) Heavy cannabis use: Low SCH= *21.42* (1.62) Heavy SCH= *21.50* (1.38)	Light cannabis use: Low SCH= 18.8 M, 6.25 F High SCH= 14.5 M, 10.4 F Heavy cannabis use: Low SCH = 22.9 M, 2.1 F Heavy SCH = 14.5 M, 10.4 F
20.Hurd et al. (2019)	*N* = 42 Heroin Use Disorder	21–65; *49.8* (9.2)	83.3 M 16.7 F
21.Ilan et al. (2005)	*N* = 23 healthy participants	21–45 High THC group *26.4* (4.8) Low THC group *25.7* (3.1)	52.2 M 47.8 F
22.Karschner et al. (2011)	N = 9 cannabis smokers	18–45 (n)	66.6 M
23.Kayser et al. (2020)	N = 12 OCD	21–55; *26.8* (7.4)	67 M
24.Linares et al. (2018)	N = 26 healthy participants	*29.3* (8.5)	53.8 F
25.Linares et al. (2019)	N = 57 healthy participants	PLA *24.5* 4.04 CBD 150 mg *24.2 (*3.08) CBD 300 mg *24.6* (2.93) CBD 600 mg *22.6* (3.4)	100 M
26.Martin-Santos et al. (2012)	*N* = 16 healthy participants	20–42; *26.4* (5.3)	100 M
27.Mauzay et al. (2021)	N = 87 (ANX *n* = 77)	18–56; *32* (8.8)	37.9 M 60.9 F 1.1 undisclosed (ANX = 40.3 M, 58.4 F, 1.3 undisclosed)
28.Morgan et al. (2013)	N = 24 tobacco smokers	18–35; CBD *28.0* (4.29) PLA *28.08* (6.17)	CBD = 50 M PLA= 50 M
29.O'Neill et al. (2021)	PSY *n* = 15 HC *n* = 9	PSY *27.73* (4.61) HC *23.89* (4.15)	PSY= 66 M HC= 57.9 M
30.Shannon et al. (2019)	N = 103; (ANX *n* = 47; SLEEP *n* = 25)	ANX 18–70; *34* (n) SLEEP 18–72; *36.5* (n)	ANX= 59.6 M SLEEP= 64 F
	N = 1 bipolar disorder, cannabis addiction	27	100 M

(*continued on next page*)

Table 1 (*continued*)

Author	*N*	Age or age range; *Mean* (std dev)	Gender (%)
31.Shannon and Opila-Lehman (2015)			
32.Solowij et al. (2018)	N = 20 cannabis users	20.6–46.8; *25.1* (n)	80 M
33.Spindle et al. (2020)	N = 18 healthy participants	18–45; *31* (6)	50 M
34.Winton-Brown et al. (2011)	*N* = 14 healthy participants	20–42; *26.7* (5.7)	100 M
35.Zuardi et al. (1982)	N = 8 healthy participants	20–38; *27* (n)	75 M
36.Zuardi et al. (1993)	N = 40 healthy participants	20–30; *22.8* (n)	55 F
37.Zuardi et al. (2017)	N = 60 healthy participants	18–35; PLA- *22.0* (2.1) CBD 100 mg - *22.5* (2.9) CBD 300 mg - *22.6* (2.9) CBD 900 mg - *23.3* (2.8) Clonazepam – *22.1* (2.4)	PLA= 10 M, 10 F CBD= 100 mg 10 M, 10 F CBD= 300 mg 8.3 M, 10 F CBD= 900 mg 10 M, 10 F Clonazepam= 10 M, 10 F
Included Studies - Forward Search			
38.Aungsumart et al. (2021)	N = 5 MS	39–60	57.1 F
39.Bindler et al. (2022)	N = 1 chronic pain, history of depression & anxiety	52 years	100 M
40. Bolsoni et al. (2022)	N = 33 PTSD	18–60; CBD *33.94* (11.55) PLA *32.50* (13.01)	CBD= 30.77 M PLA= 33.33 M
41.Bonomo et al. (2022)	N = 9 chronic non-cancer pain	*58.1* (6.2)	77.7 M
42.Crippa et al. (2021)	N = 118 healthy participants (COVID frontline healthcare professionals) CBD *n* = 59 Control *n* = 59	24–60	NA
43.Crippa et al. (2022)	N = 45	18–35	100 M
44.Davies et al. (2022)	CBD CHR n = 14 PLA CHR n = 15 HC CHR n = 16	CBD=*22.7* (5.08) PLA=*24.1* (4.48) HC=*24.3* (4.73)	CBD= 62.5 M PLA= 41.2 M HC= 52.6 M
45.de Almeida et al. (2021)	N = 33 REM sleep behaviour disorder in PD	*57*	NA
46.de Meneses-Gaya et al. (2021)	N = 31 crack cocaine dependence	CBD= *32.5* (6.9) CONTROL=*33.2* (6.9)32.9 (6.8)	100 M
47. Drennan et al. (2021a, 2021b)	N = 54 recreational cannabis users	21–60 both groups; THC dominant=*29.86* (8.7) CBD dominant=*29.88* (10.5)	THC dominant= 42.9 F CBD dominant= 53.8 F
48.Ergisi et al. (2022)	N = 67 GAD	37.42 ± 13.01	67.2 M
49.Gambino et al. (2021)	N = 17 BMS	*71.00* [62.00, 72.00]	82.4 F
50.Gibson et al. (2022)	Healthy participants THC *n* = 57 THC:CBD *n* = 51 CBD *n* = 52	THC = *36.19* (15.27) THC:CBD = *35.80* (16.47) CBD =*36.19* (15.95)	THC= 38.60 F THC:CBD= 43.14 F CBD= 41.18 F
51.Gruber et al. (2021)	n = 37 patients with chronic pain n = 9 control	MC= *54.87* (14.00) CONTROL= *44.00* (17.77)	58.33 F
52.Harris et al. (2022)	N = 190 chronic pain	47.50 ± 14.88	54.7 F
53.Masataka (2019)	N = 37 SAD CBD *n* = 17 PLA *n* = 20	18–19	70.27 M
54.Montebello et al. (2022)	N = 28 cannabis-dependent participants	18–65; *35.0* (10.9)	23 F
55.Nimalan et al. (2022)	N = 16 palliative care patients (cancer)	63.25 ± 12.27	50 F
56.Pacheco et al. (2021)	N = 13 healthy (second-line health care workers during COVID-19)	*32.5* (6.9)	53.8 F
57.Sagar et al. (2021)	N = 54 MC patients	23–78; *49.17* (16.45)	37.04 M
58.Stanley et al. (2022)	N = 32 healthy participants	*20.48* (1.74)	PLA = 83.33 CBD 150 = 64.7 F CBD 300 = 62.5 F CBD 600 = 85.71 F

Notes. This table summarizes demographic details of individual studies, presented in order of initial and forward search inclusions in alphabetical order according to author's name

ANX = Anxiety; *BMS* = Burning Mouth Syndrome; *CBD* = Cannabidiol; *CHR* = Clinically high risk for psychosis; *CHR-CBD* = Clinically high risk for psychosis - CBD group; *CHR-PLA* = Clinically high risk for psychosis - placebo group; *F* = Female; *FM* = Fibromyalgia patients; *GAD* = Generalized Anxiety Disorder; *HC* = Healthy Controls; *INS* = Insomnia; *M* = Male; *MC* = Medicinal cannabis; *MS* = Multiple Sclerosis; OCD = Obsessive Compulsive Disorder; *PD* = Parkinson's Disease; *PLA* = Placebo; *PTSD* = Post-Traumatic Stress Disorder; *PSY* = Psychosis; *SAD-CBD* = Social Anxiety Disorder – CBD group; *SAD-PLA* = Social Anxiety Disorder – placebo group; *SAD* = Social Anxiety Disorder; *SCH* = Schizotypy; *THC* = Delta-9 Tetrahydrocannabinol.

2015; Spindle et al., 2020; Stanley et al., 2022). The remaining studies were conducted in Australia (Allsop et al., 2014; Berger et al., 2020; Bonomo et al., 2022; Montebello et al., 2022; Solowij et al., 2018), Italy (Alessandria et al., 2020; Gambino et al., 2021; Giorgi et al., 2020), Israel (Aviram et al., 2020), Canada (Casarett et al., 2019), Germany (Grimm et al., 2018), Thailand (Aungsumart et al., 2021) and Japan (Masataka, 2019).

3.3. Measures

Most studies used subjective anxiety and sleep/sedation inventories, scales and questionnaires with the exception of a mobile application (Strainprint Cannabis Journal) to track self-reported anxiety and/or insomnia used by medicinal cannabis users in three studies (Casarett et al., 2019; Cuttler et al., 2018; Mauzay et al., 2021). Common measures of anxiety included the State-Trait Anxiety Inventory (STAI), with two studies using assessing state and trait anxiety (Gruber et al., 2021; Sagar et al., 2021), seven studies specifically assessing state anxiety (STAI-S) (Appiah-Kusi et al., 2020; Davies et al., 2022; Grimm et al., 2018; Kayser et al., 2020; Martin-Santos et al., 2012; O'Neill et al., 2021; Stanley et al., 2022) with trait anxiety (STAI-T) measured in addition to STAI-S in eight studies based on a 4-point Likert scale (Bhattacharyya et al., 2009; Borgwardt et al., 2008; Fusar-Poli et al., 2009; Karschner et al., 2011; Linares et al., 2018; Solowij et al., 2018; Zuardi et al., 1993, 1982).

Visual Analogue Mood Scale-Anxiety (VAMS-A) (Bergamaschi et al., 2011; Bolsoni et al., 2022a; Crippa et al., 2011, 2004, 2022; de Faria et al., 2020; Linares et al., 2018, 2019; Martin-Santos et al., 2012; Stanley et al., 2022; Zuardi et al., 1993, 2017) required participants to mark a point on 100 mm straight lines with opposite moods at each end for four different factors. This was similar to the Visual Analogue Scale-Anxiety (VAS-A) used in five studies (Hindocha et al., 2015; Hurd et al., 2019; Ilan et al., 2005; Karschner et al., 2011; Stanley et al., 2022). The Hamilton Anxiety Rating Scale (HAM-A) was also used and to rate the severity of anxiety symptoms (Alessandria et al., 2020; Berger et al., 2020; Shannon et al., 2019; Shannon and Opila-Lehman, 2015).

Other measures included the Generalized Anxiety Disorder Assessment (GAD-7) (Aviram et al., 2020; Crippa et al., 2021; Ergisi et al., 2022; Harris et al., 2022; Nimalan et al., 2022; Pacheco et al., 2021), the Beck Anxiety Inventory (BAI) (Crippa et al., 2013; de Meneses-Gaya et al., 2021; Drennan et al., 2021a; Gruber et al., 2021; Sagar et al., 2021), the Numerical Rating Scale-Anxiety (NRS-A) (Aungsumart et al., 2021; Bindler et al., 2022), the Depression Anxiety and Stress Scale (DASS-A) (Bonomo et al., 2022; Montebello et al., 2022), Parkinson Anxiety Scale (PAS) (de Almeida et al., 2021), Profile of Moods Scale–Anxiety (POMS-A) (Gibson et al., 2022), Liebowitz Social Anxiety Scale (LSAS) (Masataka, 2019), the Hospital Anxiety and Depression Scale (HADS) (Gambino et al., 2021), the Zung Self Rating Anxiety Scale (ZSR-A) (Giorgi et al., 2020) and the Overall Anxiety Severity and Impairment Scale (OASIS) (Berger et al., 2020). Simulation public speaking tests (SPST) (de Faria et al., 2020; Linares et al., 2019; Zuardi et al., 1993), test of public speaking in a real situation (Zuardi et al., 2017), Trier Social Stress Test (TSST) (Davies et al., 2022) and traumatic recall (Bolsoni et al., 2022a) were utilized in six studies to induce anxiety that was then measured by either VAMS-A and/or STAI, with VAMS-S measuring sedation in one study (Zuardi et al., 2017). Objective measures included single-photon computed tomography (SPECT) (Crippa et al., 2004), magnetic resonance imaging (MRI) (Davies et al., 2022) and functional magnetic resonance imaging (fMRI) (Bhattacharyya et al., 2009; Borgwardt et al., 2008; Fusar-Poli et al., 2009; Grimm et al., 2018; Winton-Brown et al., 2011) in addition to subjective measures including VAMS-A, STAI-S and STAI.

Sleep/sedation were most commonly measured by the Visual Analogue Mood Scale-Sedation (VAMS-S) (Bhattacharyya et al., 2009; Bolsoni et al., 2022a; Borgwardt et al., 2008; Crippa et al., 2022; Fusar-Poli et al., 2009; Linares et al., 2019; Martin-Santos et al., 2012; Stanley et al., 2022; Zuardi et al., 1993, 2017) and sleep patterns and quality were measured by the Pittsburgh Sleep Quality Index in seven studies (PSQI) (Aviram et al., 2020; de Almeida et al., 2021; Giorgi et al., 2020; Gruber et al., 2021; Sagar et al., 2021; Shannon et al., 2019; Shannon and Opila-Lehman, 2015). Other measures included the Karolinska Sleep Scale (KISS) (Ilan et al., 2005), Visual Analogue Scale-Sedation (VAS-S) (Drennan et al., 2021a; Winton-Brown et al., 2011), Fibromyalgia Sleep Scale (FAS-S) (Giorgi et al., 2020), Insomnia Severity Index (ISI) (Bonomo et al., 2022; Montebello et al., 2022; Pacheco et al., 2021), Numerical Rating Scale-Insomnia (NRS-INS) (Aungsumart et al., 2021), Epworth Sleep Scale (ESS) and Parkinson Disease Sleep Scale (PDSS) (de Almeida et al., 2021), Single-Item Sleep Quality Scale (SQS) (Ergisi et al., 2022; Harris et al., 2022; Nimalan et al., 2022) as well as self-reporting (Berger et al., 2020) and sleep diaries (Bonomo et al., 2022). Three studies utilised objective sleep measures via overnight polysomnography (PSG) (de Almeida et al., 2021; Linares et al., 2018) and actigraphy (Bindler et al., 2022). Simultaneous assessments of anxiety and sleep were performed using the Mood Rating Scale (MRS) (Das et al., 2013; Morgan et al., 2013), Cannabis Withdrawal Scale (CWS) (Allsop et al., 2014) and the Drug Evaluation Questionnaire (DEQ) (Spindle et al., 2020).

3.4. Interventional drug characteristics

3.4.1. Doses and treatment period

CBD and THC treatments were administered either sequentially or concomitantly in 22 studies, with the remaining 18 studies administering CBD treatments only. Overall, CBD standard dosages within a dosing session ranged from 400 μg (Morgan et al., 2013) to 900 mg (Zuardi et al., 2017). Studies which administered THC used standard doses ranging from 3.7 mg (Spindle et al., 2020) to 86.4 mg (Allsop et al., 2014) within a session. Weighted doses of CBD (1 mg/kg), THC (0.5 mg/kg) and combined CBD (1 mg/kg) and THC (0.5 mg/kg) were utilized in one study (Zuardi et al., 1982). Treatment periods lasted up to a maximum of 12 months of regular daily intake (Giorgi et al., 2020), with dosing sessions ranging between a minimum of one session (Bergamaschi et al., 2011) and a maximum of 9340 sessions (Casarett et al., 2019).

3.4.2. Administration route

Most studies administered cannabinoid treatments via oral capsules. Other oral routes included ethanol and/or oil solutions (Aungsumart et al., 2021; Aviram et al., 2020; Bonomo et al., 2022; Crippa et al., 2021; Ergisi et al., 2022; Gambino et al., 2021; Giorgi et al., 2020; Gruber et al., 2021; Harris et al., 2022; Hurd et al., 2019; Masataka, 2019; Pacheco et al., 2021; Sagar et al., 2021; Stanley et al., 2022; Zuardi et al., 1982) and sprays (Alessandria et al., 2020; Allsop et al., 2014; Karschner et al., 2011; Montebello et al., 2022). Inhalation methods included mixed methods (Drennan et al., 2021a; Gibson et al., 2022; Gruber et al., 2021; Sagar et al., 2021) of vaporized cannabinoids (Das et al., 2013; Ergisi et al., 2022; Harris et al., 2022; Spindle et al., 2020), cigarettes (Bindler et al., 2022; Casarett et al., 2019; Cuttler et al., 2018; Ilan et al., 2005; Kayser et al., 2020; Mauzay et al., 2021) and metered dose inhalers (Aviram et al., 2020; Hindocha et al., 2015; Morgan et al., 2013). Only one study assessed edibles amongst other routes mentioned above (Gruber et al., 2021).

3.5. Effect of cannabinoids on anxiety and sleep

3.5.1. CBD and anxiety

In total, 11 studies measured the effect of CBD only treatments on anxiety reporting varied treatment doses, treatment periods and outcomes (Table 2). CBD doses of 600 mg (Appiah-Kusi et al., 2020; Bergamaschi et al., 2011; Davies et al., 2022; O'Neill et al., 2021), 400 mg (Crippa et al., 2011), 300 mg (de Faria et al., 2020; Masataka, 2019) and 150 mg (taken twice daily) were compared to standard care (Crippa et al., 2021) or placebo. Treatment periods for these doses ranged from a minimum of one dosing session to a maximum of regular daily intake for up to 4 weeks (Appiah-Kusi et al., 2020; Crippa et al., 2021; Masataka, 2019). Results suggested CBD decreased VAMS-A and LSAS scores in doses of 600 mg (Bergamaschi et al., 2011), 400 mg (Crippa et al., 2011) and 300 mg (de Faria et al., 2020; Masataka, 2019) compared to placebo in addition to 150 mg taken twice daily as measured by GAD-7 after 4 weeks (Crippa et al., 2021). However, 600 mg of CBD did not show

Table 2
CBD Only Treatments and Anxiety Outcomes.

Author	Treatment Route	Dosage	Treatment Period/Dosing Sessions	*Anxiety Measure* & Outcomes	
Clinical Trials					
1.Appiah-Kusi et al. (2020)	Capsule	600 mg; PLA	Daily; 1 week	*STAI-S:* ↑ PLA vs HC* ; ↔ CHR-CBD vs CHR-PLA* ; ↔HC vs CHR-CBD (ns)	Increasing anxiety from HC (lowest) to CHR-PLA (highest). Linear relationship across 3 groups driven by significant difference between HC and CHR-PLA. Suggested that abnormal neuroendocrine and psychological responses in CHR-PLA could possibly be attenuated with CBD in CHR patients
2.Bergamaschi et al. (2011)	Capsule	600 mg; PLA (corn oil)	1 session	*SPST; VAMS-A:* ↑SAD PLA vs HC * During speech: ↓ SAD-CBD vs SAD-PLA* ↓ SAD-CBD & HC	Pre-treatment CBD ↓ ANX in SAD. SAD-CBD and HC had similar responses to SPST induced ANX.
3.Crippa et al. (2011)	Capsule	400 mg; PLA (corn oil)	2 sessions; 1 week apart	*SPECT: VAMS-A:* ↓ SAD-CBD vs SAD-PLA*	Single dose CBD showed ↓ state ANX before and after SPECT scan. SPECT showed functional activity changes in limbic and paralimbic cortical areas.
4.Crippa et al. (2021)	Oil	150 mg; Standard care	Twice a day; 4 weeks	*GAD-7:* ↓ CBD vs Standard care* Time, group and time-group interactions*	Compared to BL, CBD GAD-7 decreased significantly by day 28.
5.Davies et al. (2022)	Capsule	600 mg	Daily; 7 days	*TSST; STAI-S:* ↔ CBD vs PLA vs HC	TSST-induced cortisol and fear-related parahippocampal activation differed significantly between the HC and PLA but not between PLA and CBD
6.de Faria et al. (2020)	Capsule	300 mg; PLA (corn oil)	2 sessions, 15 days apart	*SPST; VAMS-A:* ↓ CBD vs PLA*	CBD ↓ SPST induced anxiety and tremor amplitude in Parkinson's
7.Hurd et al. (2019)	Oral solution	400 mg; 800 mg; PLA (ethanol, sucralose, strawberry flavour, refined sesame oil)	Once daily; 3 days	*VAS-A:* ↓ CBD 400 mg & 800 mg vs PLA* Differences between CBD groups (ns)	CBD treatments ↓ ANX in heroin abstinent subjects. Strongest CBD effects observed during first acute session. Protracted effects also noted 7 days after last exposure.
8.Masataka (2019)	Oil	300 mg; PLA	Daily; 4 weeks	*LSAS:* ↓CBD post-intervention vs pre-intervention*	Improvements in anxiety not found in PLA
9.O'Neill et al. (2021)	Capsule	600 mg; PLA (flour)	2 sessions; 1 week apart	*fMRI STAI-S:* CBD vs PLA vs HC (ns)	No significant differences between CBD, PLA & HC in ANX changes. Suggests "that normalization of mediotemporal and prefrontal dysfunction and mediotemporal-striatal functional connectivity may underlie the antipsychotic effects of CBD."
10.Solowij et al. (2018)	Capsule	200 mg	Daily; 10 weeks	Baseline to post-treatment *STAI-S:* ↑ CBD* *STAI-T:* ↔ CBD (ns)	Only dependent cannabis users showed ↑ in state ANX post-treatment vs baseline. However, other benefits were seen in dependent users vs nondependent users (perhaps due to greater therapeutic effects in diseased/compromised brain)
Observational/Cohort/Case Studies					
11.Crippa et al. (2013)	Capsule	300–600 mg	Daily, 10 days	*BAI:* ↓ ANX Baseline Day 0 = 6 Day 1–5 = 1 Day 6–11 = 0	"Absence of cannabis withdrawal symptoms, ANX and dissociative symptoms during treatment. CBD may have therapeutic properties in cannabis withdrawal syndrome, at least in patients with no psychiatric comorbidities."

Notes. This table presents details on studies measuring the effect CBD treatments on anxiety measures and their outcomes.
↓ = decrease; ↑ = increase; ↔ = no difference; (ns) = not significant; * = significant ($p < 0.05$, $p < 0.01$ or $p < 0.001$); ANX = anxiety; *CBD* = Cannabidiol; *CHR* = Clinically high risk for psychosis; *CHR-CBD* = Clinically high risk for psychosis - CBD group; *CHR-PLA* = Clinically high risk for psychosis – placebo group; fMRI = Functional Magnetic Resonance Imaging; *BAI* = Beck's Anxiety Inventory; *HC* = Healthy Controls; *GAD-7* = General Anxiety Disorder-7; *LSAS* = Liebowitz Social Anxiety Scale; PLA = placebo; SAD = Social Anxiety Disorder; SPECT = Single-Photon Emission Computerized Tomography; SPST = Simulated Public Speaking Test; *STAI-S* = State-Trait Anxiety Inventory – State Anxiety; *STAI-T*=State-Trait Anxiety Inventory – Trait Anxiety; *TSST* = Trier Social Stress Test; *VAMS-A* = Visual Analog Mood Scale-Anxiety; *VAS-A* = Visual Analog Scale-Anxiety.

significant ($p > 0.05$) changes in STAI-S in three studies (Appiah-Kusi et al., 2020; Davies et al., 2022; O'Neill et al., 2021), even after 7 days of daily administration (Davies et al., 2022). A study explored 400 mg and 800 mg of CBD and reported a decreased VAS-A score compared to placebo with no significant differences between CBD doses (Hurd et al., 2019). Two studies explored 200 mg (Solowij et al., 2018) and 300–600 mg doses (Crippa et al., 2013) with opposing results. Baseline and post-treatment comparison after daily intake over 10 days with doses ranging from 300 mg to 600 mg produced a reduction in BAI scores from 6 to 0 (Crippa et al., 2013), whereas daily intake of 200 mg for 10 weeks had significantly increased STAI-S scores (reflecting greater anxiety) compared to baseline ($p < 0.05$) only (Solowij et al.,

2018).

3.5.2. CBD, anxiety, and sleep

CBD treatments for anxiety and sleep were assessed in 15 studies (Table 3). Results suggested CBD decreased anxiety scores more commonly than improving sleep. Relative to placebo, doses of 400 mg (Crippa et al., 2004) 300 mg (Bolsoni et al., 2022a; Linares et al., 2018) 32 mg (Das et al., 2013) 400 ug (Morgan et al., 2013), only 400 mg had shown improvements in both VAMS-A and VAMS-S scores (Crippa et al., 2004). In contrast, 300 mg reduced VAMS-A scores after one dose (Bolsoni et al., 2022a) as well as BAI scores after 10 days of daily intake (de Meneses-Gaya et al., 2021) without significantly affecting VAS-S and VAMS-S scores.

Outcomes of remaining doses either only significantly decreased anxiety measured compared to placebo (Das et al., 2013) or implied improved sleep at the trend level ($p = 0.084$) as measured by MRS-Anxiety and MRS-Sedation, respectively (Morgan et al., 2013), with 300 mg showing no significant changes for either STAI, VAMS-A scores or any alterations in sleep structure as measured by PSG (Linares et al., 2018). One study suggested 300 mg of CBD only significantly decreased VAMS-A ($p = 0.017$), but not VAMS-S scores post-SPST relative to placebo and anxiolytics including 10 mg diazepam and 5 mg ipsapirone (Zuardi et al., 1993). A single 150 mg dose (Crippa et al., 2022) and daily intake of 75 mg and 150 mg for 1 week each (de Almeida et al., 2021) did not significantly affect VAMS-A, VAMS-S (Crippa et al., 2022) or BAI and PAS (de Almeida et al., 2021). PSQI scores significantly increased after 300 mg doses were taken daily (de Almeida et al., 2021).

Similarly, 300 mg of CBD resulted in an inverted U-shaped dose response curve, with decreased VAMS-A ($p < 0.05$) scores during the SPST and no significant effect on VAMS-S scores when compared to higher (600 mg and 900 mg) and lower (100 mg and 150 mg) CBD doses, placebo (Linares et al., 2019) and clonazepam (Zuardi et al., 2017). In contrast, 150 mg 300 mg, 600 mg and placebo conditions significantly increased VAS-TA scores without affecting VAMS-A, STAI-S and VAMS-S (Stanley et al., 2022).

Observational and case studies had daily doses ranging from 18 mg to 800 mg, for a minimum of 1–6 months. In one case study, HAM-A mean scores had decreased from 16 to 4 over 4 months and was credited for self-reported regular sleep schedule without any change in PSQI scores over the same period (Shannon and Opila-Lehman, 2015). Another case study reported decreased in HAM-A and OASIS scores over the period of 6 months, with minimal improvement at week 4 (HAM-A = 27; OASIS = 15) with 400 mg CBD with enhance improvements after an escalation in dose to 800 mg CBD at week 8, resulting in decreased HAM-A and OASIS scores compared to baseline (HAM-A = 29; OASIS = 15) at the end of 6 months (HAM-A = 15; OASIS = 7). Self-reported sleep had also improved over the treatment period (Berger et al., 2020). The observational study assessed both HAM-A and PSQI in a sample with anxiety and a sample with disrupted sleep over a 3-month period (Shannon et al., 2019). HAM-A mean scores in the anxiety sample decreased from 23.87 (SD 9.87) at baseline to 16.36 (SD 9.80) at 3 months (Shannon et al., 2019). The sleep sample's scores decreased from 22.18 (SD 7.55) at baseline to 13.78, (SD 7.86) at 3 months. PSQI mean scores did not prominently change for both the anxiety sample (baseline 10.98, [SD 3.43] to 3 months 9.25, [SD 2.46]) and sleep sample (baseline 13.08, [SD 3.03] to 3 months 9.33, [SD 4.63]) (Shannon et al., 2019). A series of prospective case studies reported two daily doses of 165 mg decreased GAD-7 and ISI scores that were sustained after 4 weeks of treatments (Pacheco et al., 2021).

3.5.3. CBD/THC and anxiety

Included clinical trials evaluated either combined CBD and THC treatments relative to placebo (Karschner et al., 2011; Kayser et al., 2020; Montebello et al., 2022) or compared CBD to THC as independent treatments (Grimm et al., 2018; Hindocha et al., 2015). Both categories of treatments had varied dose sizes, CBD:THC ratios treatment periods and outcomes (Table 4). Combined active treatments conditions reported significantly increased VAS-A scores compared to placebo ($p < 0.001$) (Karschner et al., 2011). High Sativex (16.2 mg THC, 15.0 mg CBD), 15 mg THC and 5 mg THC increased STAI outcomes compared to placebo only, and high Sativex showed significant increases in STAI and VAS-A compared to low Sativex (5.4 mg THC, 5.0 mg CBD) ($p < 0.004$) (Karschner et al., 2011). THC and Sativex treatments produced similar increases in anxiety but were not statistically significant (Karschner et al., 2011). Another trial comparing CBD-dominant (0.4% THC/10.4% CBD) and THC-dominant (7.0% THC, 0.18% CBD) to placebo produced significant decreased STAI-S scores across all three conditions (Kayser et al., 2020). Significant decreases in STAI-S scores occurred 20 min after the placebo treatment compared to the active treatments and remained low for placebo at 40 min but trended towards significance for CBD ($p = 0.075$) (Kayser et al., 2020). No group differences occurred at 60 min (Kayser et al., 2020). A significant reduction in mean scores for DASS-A and ISI were reported for doses up to 86.4 mg THC, 80 mg CBD and placebo from baseline to 12 weeks (Montebello et al., 2022).

At a dose of 10 mg, THC significantly increased STAI-S only compared to placebo 3 h after intake ($p = 0.03$) (Grimm et al., 2018). A dose of 600 mg CBD did not show significant changes in STAI (Grimm et al., 2018). One study reported no significant changes in VAS-A for either CBD (16 mg) or THC (8 mg) treatments relative to placebo (Hindocha et al., 2015).

Observational studies reported either no significant changes in HAM-A over 12 months of daily use of Sativex (27 mg/ml THC, 25 mg/ml CBD; ≤ 12 sprays daily) (Alessandria et al., 2020) or decreased self-reported anxiety tracked through the Strainprint Medical Cannabis Journaling application in two other studies. Over 5085 treatment sessions were tracked for repeated combined treatments with a mean dose of 15.26% THC and 3.69% CBD and resulted in 93% decrease in anxiety (Cuttler et al., 2018). A mean dose of 13.62% THC and 3.41% CBD (mean number of puffs 8.50 [SD 6.09], range 1–30 puffs) reduced 52% of anxiety assessed over 1810 sessions in 31 months (Mauzay et al., 2021). Comparisons of THC-dominant treatments (4.99% THC + THCa and < 1% CBD) and CBD-dominant treatments (74.7% CBD, 4.1% CBDa and 4.5% THC + THCa) ssignificantly decreased BAI scores for the CBD-dominant treatment immediately after post-treament and 1-hour post-treatment for the THC-dominant treatment (Drennan et al., 2021a). Significant increased POMS-ANX scores were observed after acute post-use and 1 h post-use in the THC dominant treatment (24% THC+1% CBD) compared to CBD-dominant (1% THC+ 23% CBD) and 1:1 combined treatments (9% THC+10% CBD) (Gibson et al., 2022) whereas Bediol drops (63 mg/g THC, CBD 80 mg/g) showed no significant changes between baseline and at the end of the treatment period (Gambino et al., 2021).

3.5.4. CBD/THC on anxiety and sleep

The effects of 600 mg CBD and 10 mg THC on anxiety and sleep outcomes were compared across five studies. THC significantly increased STAI (Borgwardt et al., 2008; Fusar-Poli et al., 2009; Winton-Brown et al., 2011), STAI-S (Bhattacharyya et al., 2009; Martin-Santos et al., 2012), VAMS-S (Bhattacharyya et al., 2009; Borgwardt et al., 2008; Fusar-Poli et al., 2009),VAS-S (Winton-Brown et al., 2011) relative to either CBD and/or placebo ($p < 0.05$ for all) (Table. 5). CBD doses showed either trend-level decreases in STAI ($p = 0.06$) (Borgwardt et al., 2008; Fusar-Poli et al., 2009) or no significant change from baseline (Winton-Brown et al., 2011) or compared to placebo (Bhattacharyya et al., 2009). A statistically significant difference in VAMS-A scores between THC and CBD was reported 2 h after ingestion in one study (Martin-Santos et al., 2012). This was also reflected in a significant increased STAI-S scores for THC at 2 h compared to CBD and placebo ($p < 0.001$ for VAMS-A and STAI-S). Compared to either THC alone or placebo, CBD showed no significant improvement in VAMS-S

Table 3
CBD Only Treatments and Anxiety/Sleep Outcomes.

Author	Treatment Route	Dosage	Treatment Period/ Dosing Sessions	*Anxiety/Sleep Measure* & Outcome	
Clinical Trials					
1. Bolsoni et al. (2022a, 2022b)	Capsule	300 mg; PLA	1 dosing session	*Traumatic recall; VAMS ANX:* Nonsexual trauma: ↓CBD vs PLA before and after recall* Sexual trauma: CBD vs PLA NS *VAMS SED:* CBD vs PLA NS	Non-sexual trauma anx improvements could be due to symptom severity
2.Crippa et al. (2022)	Capsule (corn oil)	150 mg; PLA	1 dosing session	*VAMS ANX:* ↔NS *VAMS SED:* ↔NS	
3.Crippa et al. (2004)	Capsule	400 mg; PLA (corn oil)	2 sessions; 1 week apart	*SPECT; VAMS-A:* ↓ CBD* , PLA (ns) *VAMS-S:* ↑ CBD* , PLA (ns)	↓ in ANX, ↑ in mental sedation compared to PLA. CBD may affect anticipatory ANX (before SPECT). CBD modulated regions implicated in ANX (predominantly limbic and paralimbic cortical areas)
4.Das et al. (2013)	Vaporized	32 mg; PLA (0.08 mg ethanol)	1 session	*MRS – ANX & SED:* No effect of group at any time for ANX and SED (ns) Main effect of measurement time: ↓ ANX in CBD & PLA groups*	
5.de Almeida et al. (2021)	Capsule	Week 1 – 75 mg Week 2 – 150 mg Week 3–12 – 300 mg; PLA	Daily; 12 weeks	*ANX; BAI, PAS:* ↔ CBD vs PLA ns *SLEEP: PSQI, ESS, PDSS* Week 4 and 8: ↑Sleep satisfaction only CBD vs PLA*	Could be related to CBD direct action in the CNS or indirect anxiolytic/antidepressant effects
6.de Meneses-Gaya et al. (2021)	Capsule	300 mg; PLA	10 days	*BAI:* ↓CBD & PLA* *VAS-S:* ↔ ns	Adverse event sleepiness & increased sleep duration, BAI ↓ might be related to PLA effect
7.Linares et al. (2018)	Capsule	300 mg; PLA (corn oil)	2 sessions; 1 week apart	*PSG; STAI; VAMS-A:* ↔ CBD vs PLA (ns)	No difference in PSG and subjective measures for CBD and placebo in healthy subjects. CBD doesn't appear to interfere with sleep cycle of healthy volunteers.
8.Linares et al. (2019)	Capsule	150 mg; 300 mg; 600 mg; PLA (corn oil)	1 session	*SPST; VAMS-A:* ↓ CBD 300 mg (during speech) vs PLA * ↔ CBD 150 mg & 600 mg, PLA (ns) *VAMS-S:* Phase, group or group-phase interaction effects (ns)	Inverted U-shaped dose-response for CBD on ANX.
9.Morgan et al. (2013)	Inhaler	400 micrograms; PLA (ethanol)	1 week	*MRS-ANX:* Main effect of time ↓ CBD& PLA, Time 2 * *MRS-SED:* Main effect for time: ↑ CBD & PLA (trend). Main effect of treatment/ interaction (ns)	No changes in self-rated ANX or increase in sedation. Reduced cigarettes smoked without increased craving for nicotine.
10.Stanley et al. (2022)	Oil	150 mg; 300 mg; 600 mg; PLA	1 session	*VAS Test Anx* ↑ All conditions mid-test vs BL &pre-test* *VAMS ANX* Main effect of time* *STAI-S* *Main effect of time** *VAMS-SED* Main effect of time*	Higher anxiety regardless of group
11.Zuardi et al. (1993)	Capsule	CBD 300 mg; Diazepam 10 mg;	1 session	*SPST: VAMS-A:* ↓ Diazepam vs PLA (whole	Anxiety differences only detected by VAMS-A and not STAI. Single administration of ipsapirone showed anxiolytic

(*continued on next page*)

Table 3 (*continued*)

Author	Treatment Route	Dosage	Treatment Period/ Dosing Sessions	*Anxiety/Sleep Measure* & Outcome	
		Ipsapirone 5 mg; PLA (corn oil/starch)		trial, pre-stress & post-stress)* ↓ Ipsapirone* ↓ CBD (post-test) ↓ Ipsapirone (test induced)* *STAI:* Drug ANX, drug x time interaction (ns) *VAMS-S:* *MENTAL* ↑ Diazepam (during trial) (trend) *PHYSICAL* ↑ Diazepam vs PLA pre-stress & anticipatory ANX &	effects during anxiogenic situation and not after in contrast to diazepam (before and after speech test).
12.Zuardi et al. (2017)	Capsule	i) 100 mg, ii) 300 mg, iii) 900 mg; Clonazepam 1 mg; PLA	1 session	*TPSRS;* *VAMS-A:* ↓ Clonazepam vs PLA, CBD 900 mg * (speech phase) ↓ CBD 300 mg vs Clonazepam (post stress) ↓ CBD 300 mg vs PLA & CBD 100 mg (post-stress) *VAMS-S:* ↑ Clonazepam vs other treatments *	CBD produced an inverted U-shaped dose-response curve. CBD 300 mg did not reduce systolic & diastolic blood pressure as clonazepam, highlighting its general safety.
Case Studies					
13.Berger et al. (2020)	X	200–800 mg; Mirtazapine 30 mg	Daily, 6 months	*OASIS;* *HAM-A:* 600 mg, week 4 ↓ ANX 800 mg, week 8 ↓ ANX 6 months ↓ ANX 6 months, ↑ sleep (self-reported)	Minimal improvements in first 4 weeks, more improvements occurred with an escalated dose. Continual and sustained improvement after 6 months of treatment. Confirms CBD safety for in treatment of young people with treatment refractory ANX and for attenuated psychotic symptoms.
14.Pacheco et al. (2021)	Oil	330 mg (divided into 165 mg)	4 weeks	*GAD-7:*↓ *ISI:*↓	Quick onset, sustained 4 weeks after discontinuation
15.Shannon and Opila-Lehman (2015)	Oil	CBD 24 mg decreased to 18 mg	4 months; Month 1: 6 sprays (day)/2 sprays (before bed) Month 2: 3–4 sprays (day)/6 sprays (before bed) Month 3:2 sprays (day)/6 sprays (before bed) Month 4: 6 sprays (before bed)	*HAM-A:* ↓ monthly scores (16, 8, 6, 5, 4) *PSQI:* ↔ monthly scores (7, 8, 7, 7, 8)	Maintenance of non-use of cannabis. Regular sleep schedule was credited to patient's ↓ in ANX
16.Shannon et al. (2019)	Capsule	CBD 25 mg/day OR 50 mg/day OR 75 mg/day 1 participant gradually ↑ to 175 mg/day	At least 1 month. ANX– every morning after breakfast Sleep – every evening after dinner	*HAM-A, mean (SD):* ANX sample Baseline 23.87 (9.87) 1 month 18.02 (7.56) 2 months 16.35 (8.80) 3 months 16.36 (9.80) Sleep sample, mean (SD): Baseline 22.18 (7.55) 1 month 17.82 (9.72) 2 months 17.36 (10.91) 3 months 13.78 (7.86) *PSQI, mean (SD):* ANX sample Baseline 10.98 (3.43) 1 month 8.88 (3.68) 2 months 8.59 (2.91) 3 months 9.25 (2.46) Sleep sample Baseline 13.08 (3.03) 1 month 10.64 (3.89)	79.2% ↓ in ANX within the first month and was maintained. 66.7% ↑ in sleep within the first month and fluctuated over time. CBD was well tolerated (except for 3 participants)

(*continued on next page*)

Table 3 (*continued*)

Author	Treatment Route	Dosage	Treatment Period/ Dosing Sessions	*Anxiety/Sleep Measure* & Outcome
				2 months 9.39 (3.81) 3 months 9.33 (4.63)

Notes. This table presents details on studies measuring the effect CBD treatments on anxiety and sleep measures and their outcomes.
↓ = decrease; ↑ = increase; ↔ = no difference/change/effect; (ns) = not significant; * = significant ($p < 0.05$, $p < 0.01$ or $p < 0.001$); *ANX* = Anxiety; *BAI* = Beck Anxiety Inventory; *CBD* = Cannabidiol; *ESS* = Epworth Sleepiness Scale; GAD-7 = Generalized Anxiety Disorder Assess ment; *HAM-A* = Hamilton Anxiety Rating Scale; *ISI* = Insomnia Severity Scale; *MRS*= Mood Rating Scale; *OASIS*= Overall Anxiety Severity and Impairment Scale; *PAS* = Parkinson Anxiety Scale; *PDSS* = Parkinson Disease Sleep Scale; *PLA*= Placebo; *PSQI* = Pittsburgh Sleep Quality Index; *SD*= Standard Deviation; *SED* = Sedation; *SPECT* = Single-photon emission computed tomography; *SPST* = Simulate Public Speaking Test; *STAI* = State-Trait Anxiety Inventory; *STAI-S* = State-Trait Anxiety Inventory-State Anxiety *TPSRS* = Test of Public Speaking in a Real Situation; *VAMS-A* = Visual Analog Mood Scale-Anxiety; *VAMS-S* = Visual Analog Mood Scale-Sedation, *VAS* = *Visual Analog Scale*

and ARCI; however, THC alone significantly increased scores for these same measures (Martin-Santos et al., 2012).

When combined, vaporized CBD-dominant (low THC) treatments increased sleepiness as measured by the DEQ ($p < 0.05$) compared to both capsule and vaporized CBD-only treatments (100 mg) and placebo (Spindle et al., 2020). Compared to placebo, a near 1:1 ratio of CBD to THC of Nabiximols (maximum daily dose 80 mg CBD, 84.6 mg THC) produced statistically significant, albeit limited, improvements in sleep and anxiety as measured by Cannabis Withdrawal Scale ($p < 0.001$) (Allsop et al., 2014). However, one study reported a 2:1 ratio of CBD (1 mg/kg) to THC (0.5 mg/kg) significantly decreased STAI from baseline when compared to THC alone (Zuardi et al., 1982) ($p < 0.05$). Furthermore, studies reported neither CBD alone (Zuardi et al., 1982), CBD-dominant nor placebo treatments showed significant differences from baseline (Spindle et al., 2020) for STAI and DEQ anxiety outcomes respectively ($p > 0.05$). Additionally, high and low concentrations of CBD, THC and cannabichromene (CBC) treatments in combined treatments significantly increased VAS-A outcomes compared to placebo ($p < 0.05$). A converse significant increase in sleepiness scores (KSS scale) was noted following placebo, but not cannabinoid treatment ($p < 0.01$) (Ilan et al., 2005).

Improved GAD-7 scores were reported across THC-dominant (low CBD), CBD-dominant and mixed treatments (near 1:1 ratio of CBD to THC) compared to baseline but were not statistically significant ($p = 0.28$) (Aviram et al., 2020). PSQI sleep quality scores reported increases for all 3 treatments compared to baseline ($p < 0.01$) (Aviram et al., 2020). However, self-reported sleep duration was significantly superior for the THC-dominant treatment compared to CBD-dominant and mixed treatments ($p < 0.05$) (Aviram et al., 2020). Self-reported sleep latency reported trending decreases for treatments but was not significant ($p = 0.10$) (Aviram et al., 2020). In another study, increased subjective sleepiness obtained through interviews in 8 participants for placebo and THC (5 participants), diazepam (6 participants) and combined THC and CBD (7 participants) at 60 – 120 min after ingestion and at 120 – 180 min for diazepam (5 participants) and combined THC and CBD (5 participants) (Zuardi et al., 1982).

Observational studies reported an increased THC:CBD ratio resulted in significant decreased insomnia ($p < 0.05$) but did not result in anxiety changes according to data collected through the Strainprint Medical Cannabis Journal application (Casarett et al., 2019). ZSR-A scores had shown a decreased anxiety in 50% of participants ($p < 0.05$) with baseline mean scores decreased from 64.75 to 61.92 at 6 months with CBD-dominant morning treatments and THC-dominant nightly treatments (Giorgi et al., 2020). PSQI measured increased sleep in 44% of participants, with baseline mean scores decreased from 10.55 to 9.00 at 6 months for the same treatment and treatment period (Giorgi et al., 2020). FAS-S reported slight fluctuations despite overall decreased mean score compared to baseline (8.29), with a small increase in mean score at 6 months (7.47) compared to 3 months (7.02) (Giorgi et al., 2020). No significant changes were reported for NRS-ANX and NRS-INS over 12 weeks for 1:1 combined treatments up to a maximum dose of 27 mg THC and 25 mg CBD (Aungsumart et al., 2021). However, a case study reported NRS-ANX mean had decreased with 1 dose (22.17% THC, 0.12% CBD) over 2 days (Day 1 mean=2.875 [0.64] vs Day 2 mean=2.375 [0.52]) and actigraphy measured sleep duration reducing from a mean of 6.19–3.93 h pre-post treatment (Bindler et al., 2022). 1:1 combined treatment increased in stages (maximum dose 12.5 mg THC/12.5 mg CBD) resulted in significant decreases in DASS-A scores and significantly reduced ISI means compared to baseline, increased sleep quality and perceived sleep onset latency over 23 dosing sessions ($p \leq 0.05$ for all) (Bonomo et al., 2022). Changes in total sleep scores and sleep quality were not significant (Bonomo et al., 2022). In another study, PSQI scores significantly decreased at 3 (THC mg/week = 93.29 ± 228.12, CBD mg/week = 202.18 ± 345.23) and 6 months (THC mg/week = 52.29 ± 92.53, CBD mg/week = 229.93 ± 378.17) post-treatment ($p \leq 0.05$) with decreased STAI and BAI scores not reaching significance (Gruber et al., 2021). Similarly, PSQI scores significantly decreased in a longitudinal study after starting treatment (at 3 months mean = CBD 153.90 [287.79], THC 63.97 [184.18]), however, STAI-S scores significantly decreased when compared to 6 months (mean=CBD 201.64 (321.38), THC 41.89 (78.78)) from baseline only and not at 12 months ($p \leq 0.05$). STAI-T was significantly correlated with CBD use and treatment uses per week ($p \leq 0.05$). Lastly, GAD-7, the anxiety domain for EQ-5D-5 L and SQS scores improved with combined treatments over 6 months (Ergisi et al., 2022) whereas improvements were only noted for GAD-7 and SQS for one study for the same time period, with the exception of a significant improvement in EQ-5D-5 L at 1 month (Harris et al., 2022) ($p < 0.05$). Conversely, SQS and ED-5D-5 L improvements were observed but failed to reach significance in another study (Nimalan et al., 2022).

3.5.5. Clinical/Sub-clinical population outcomes

Clinical or sub-clinical populations were utilized in 38 studies and included cohorts of chronic-disease patients. Diagnoses included multiple sclerosis, cancer, Parkinson's disease (PD), fibromyalgia, chronic pain and burning mouth syndrome (BMS). A general trend of decreased anxiety symptoms as measured by GAD-7, VAMS-A and ZSR-A (Aviram et al., 2020; de Faria et al., 2020; Giorgi et al., 2020; Harris et al., 2022) but not BAI and PAS scores in PD (de Almeida et al., 2021). Increased sleep and sleep satisfaction as measured by PSQI was found across studies (Aviram et al., 2020; de Almeida et al., 2021; Giorgi et al., 2020), apart from two studies in multiple sclerosis patients showing no change in HAM-A scores (Alessandria et al., 2020) and NRS-A and NRS-INS scores (Aungsumart et al., 2021). NRS-A scores slightly decreased in a chronic pain case study with actigraphy measured sleep duration mean also decreasing post-treatment only (Bindler et al., 2022). Longitudinal chronic pain reported significantly decreased DASS-A scores (Bonomo et al., 2022) and STAI and BAI scores despite not reaching significance (Gruber et al., 2021). Improvements in sleep as measured by ISI (Bonomo et al., 2022), PSQI (Bonomo et al., 2022; Gruber et al., 2021) were also reported in addition to perceived sleep onset latency improvements as measured by sleep diaries (Bonomo et al., 2022). No changes in HADS scores were noted for BMS at the end of 4 weeks (Gambino et al., 2021). SQS and EQ-5D-5 L scores were observed to

Table 4
CBD and THC Treatments and Anxiety Outcomes.

Author	Treatment Route	Dosage	Treatment Period/ Dosing Sessions	*Anxiety Measure*, Outcome	
Clinical Trials					
1.Grimm et al. (2018)	Capsule	CBD 600 mg; THC 10 mg; PLA (saline)	3 sessions; ≤ 8 weeks apart	*fMRI;* *STAI:* Effect for THC vs PLA or; CBD vs PLA (ns) ↑ THC vs PLA (state ANX, 3 h after intake)*	CBD ↑ fronto-striatal connectivity compared to placebo - speculates there might be a neural correlate of its anti-psychotic effect in patients. THC didn't show significant opposing effects during fMRI.
2.Hindocha et al. (2015)	Inhaled	CBD 16 mg; THC 8 mg; PLA (ethanol)	4 session; 1 week apart	*VAS-A:* Interaction of drug conditions, drug & time, between subjects main effects or interaction with drug/time (ns)	THC ↓ facial emotion identification in cannabis users. CBD subtly ↑ facial affect recognition & protect against THC impairments.
3.Karschner et al. (2011)	Capsules & Oromucosal spray	*Synthetic THC:* 15 mg & 5 mg *Sativex:* *Low*-5.4 mg THC, 5.0 mg CBD *High*-16.2 mg THC, 15.0 mg CBD PLA (lactose capsule/ spray)	5 sessions; 5 days apart	*STAI:* ↑ High Sativex; THC 15 mg; 5 mg vs PLA * *VAS-A:* ↑Active treatments vs PLA* *STAI & VAS-A:* ↑ High Sativex vs Low Sativex*	"No CBD-induced modulation of THC effects observed. Oral THC produced and Sativex produced similar clinically insignificant increase in ANX"
4.Kayser et al. (2020)	Cigarettes	*THC* (7.0% THC/0.18% CBD); *CBD* (0.4% THC/10.4% CBD); PLA	3 sessions; ≥ 5 days apart	*STAI-S:* Interaction effect cannabis varietal & time (ns) Main effect time (all 3 conditions)* Main effect varietal on STAI-S* ↓ all 3 conditions * ↓ immediately after PLA vs other conditions*	ANX ↓ over time compared to baseline across all 3 conditions (could be effect of time within sessions or may reflect expectancy effects in OCD). PLA group experienced higher state ANX ↓ in first 40 mins after dose compared to either cannabis treatment. CBD produced less reductions in ANX than placebo (could be result of administration). CBD may not be purely anxiolytic, have complex interactions with ANX.
5.Montebello et al. (2022)	Spray	0.1 ml= 2.7 mg THC+ 2.5 mg CBD Max 32 sprays (86.4 mg THC and 80 mg CBD) in 4 divided doses; PLA	12 weeks	*DASS-ANX* ↓* BL= 14.7 (12.1, 17.4) Week 4 = −4.5 (−6.4, −2.6) Week 8 = −5.5 (−7.6, −3.3) Week 12 = −5.9 (−8.2, −3.7) Week 24 = −6.9 (−9.4, −4.5) *ISI* ↓* BL= 17.3 (15.3, 19.3) Week 4 = −3.7 (−5.4, −2.0) Week 8 = −4.5 (−6.4, −2.5) Week 12 = −5.6 (−7.5, −3.5) Week 24 = −6.2 (−8.3, −4.0)	Reduction in illicit cannabis use was the key driver of improvements
Observational/Cohort Studies					
6.Alessandria et al. (2020)	Oromucosal spray	Sativex THC 27 mg/ml; CBD 25 mg/ml ≤ 12 sprays /day	Daily, 12 months	*HAM-A:* ↔ (ns)	ANX and mood did not show significant variation. There is potential for long-term benefits for cognition for MS patients.
7.Cuttler et al. (2018)	Inhalation	(%mean concentration) THC 15.26% CBD 3.69%	5085 sessions	Strainprint® medical cannabis journaling: ↓ 93% sessions, ↑ 2.1% sessions, ↔ 4.4% sessions. CBD/THC not predictors of change in ANX ratings (ns) Perceived efficacy ↔ (ns) Changes in baseline ratings across sessions ↔ (ns)	Cannabis works effectively in the short-term. Women perceived greater ANX reduction than men. Suggested evidence for micro-dosing for ANX (2 puffs perceived to be as effective as 10 + puffs) Repeated use may not lead to long-term reductions in ANX.
8. Drennan et al. (2021a, 2021b)	Inhalation (dab, vape)	THC-dominant: 4.99% THC + THCA and < 1% CBD CBD-dominant: 74.7% CBD, 4.1% CBDa and 4.5% THC + THCa	Overall days used mean (SD): 3.61 (1.12) Over 5 days	*BAI:* ↓ CBD* immediately post treatment ↓ THC* 1 h post-treatment	THC had more robust anx effects
9.Gambino et al. (2021)	Oil	Bediol: 6.3% THC (63 mg/g) + 8% CBD (80 mg/g)	4 weeks: 5 drops twice daily for 5 days; 10 drops twice daily for 5 days; 15 drops twice daily for 5 days; 20 drops twice daily for 13 days	*HADS* ↓ BL median [IQR] = 20.00 [8.00, 25.00] 24 weeks follow-up=median [IQR]= 9.00 [8.00, 15.00]	No changes between BL and end of 4 weeks.

(*continued on next page*)

Table 4 (*continued*)

Author	Treatment Route	Dosage	Treatment Period/ Dosing Sessions	*Anxiety Measure*, Outcome	
10.Gibson et al. (2022)	Inhalation	THC-dominant: 24% THC+ 1% CBD; 1:1 THC+CBD: 9% THC+ 10% CBD; CBD-dominant: 1% THC+ 23% CBD	Days used mean = 3.20 days (1.12) over 5days	*POMS-ANX:* Acute post-use and 1-hour post-use assessments: ↑ THC dominant vs CBD dominant & THC:CBD*	THC had more paranoia and anx than other conditions Possible CBD enhancing positive mood resulting in less thc consumption - enhancing subjective THC high
11.Mauzay et al. (2021)	Inhaled	Mean % THC 13.62 CBD 3.41; Mean #puff (SD) 8.50 (6.09) Range 1–30 puffs	31 months 1810 sessions (ANX=1154)	Strainprint® medical cannabis journaling 52% ↓ ANX *	Reduction in ANX from before to after inhaling cannabis. ANX baseline severity ↓ over time Cannabis has short term benefits on OCD symptoms.

Notes. This table presents details on studies measuring the effect CBD and THC treatments on anxiety measures and their outcomes.
on anxiety measures and their outcomes.
↓ = decrease; ↑ = increase; ↔ = no difference/change/effect; (ns) = not significant, * = significant ($p < 0.05$, $p < 0.01$ or $p < 0.001$); *ANX* = anxiety; *BAI* = Beck Anxiety Inventory; *BL* = Baseline; CBD= Cannabidiol; *DASS-A* = Depression Anxiety and Stress Scale-*Anxiety; fMRI*= Functional Magnetic Resonance Imaging; *HADS* = Hospital Anxiety and Depression Scale; *HAM-A* = Hamilton Anxiety Rating Scale; *ISI* = Insomnia Severity Scale; *MS* = Multiple Sclerosis; *OCD* = Obsessive Compulsive Disorder; *PLA* = Placebo; *POMS-ANX* = Profile of Mood States-Anxiety; *STAI-S* = State-Trait Anxiety Inventory – State Anxiety; *STAI* = State-Trait Anxiety Inventory; *THC* = Delta-9 Tetrahydrocannabinol; *THCA* = tetrahydrocannabinolic acid; *VAS-A*= Visual Analog Scale-Anxiety.

improve or show a trend towards improvement in two studies (Harris et al., 2022; Nimalan et al., 2022).

Populations with affective disorders showed similar trends as cannabinoids decreased anxiety symptoms measured by LSAS (Masataka, 2019) and VAMS-A in social anxiety disorder (Bergamaschi et al., 2011; Crippa et al., 2011), anxiety symptoms reported through the Strainprint Medical Cannabis Journaling application (Cuttler et al., 2018) and obsessive compulsive disorder, with the latter reporting some inconsistency between studies that utilized STAI-S (Kayser et al., 2020) and the Strainprint Medical Cannabis Journaling application (Mauzay et al., 2021). A study identifying its sample as having both social anxiety disorder (SAD) and psychosis reported decreased OASIS and HAM-A scores and increased subjective sleep assessed through verbal participant reports (Berger et al., 2020). However, populations with clinically high risk of psychosis/psychosis did not see improvement in STAI-S outcomes following the administration of 600 mg cannabinoid treatments either once (Appiah-Kusi et al., 2020; Davies et al., 2022; O'Neill et al., 2021) or with 7 days of daily intake (Davies et al., 2022). Traumatic recall of non-sexual trauma in PTSD reported significant decreased VAMS-A scores before and after recall compared to placebo. Sexual trauma recall VAMS-A scores and VAMS-S scores for both sexual and non-sexual trauma groups remained unchanged (Bolsoni et al., 2022a). Lastly, GAD-7, EQ-5D-5 L and SQS scores showed improvements over 6 months in populations with Generalized Anxiety Disorder (Ergisi et al., 2022).

Populations with substance use, dependence or withdrawal showed no overall trends. Studies with cannabis users showed either decreased CWS, DASS-A and BAI anxiety outcomes (Allsop et al., 2014; Crippa et al., 2013; Drennan et al., 2021a; Montebello et al., 2022) or increased STAI, VAS-A (Karschner et al., 2011) and STAI-S anxiety outcomes (Solowij et al., 2018) with only a slight increase in CWS sleep (Allsop et al., 2014) and decreased ISI reported (Montebello et al., 2022). Cannabinoid treatments further decreased VAS-A scores among people who use heroin (Hurd et al., 2019) and BAI scores in crack cocaine dependence without significant changes to VAS-S (de Meneses-Gaya et al., 2021). No change was reported for MRS anxiety scores in those who use tobacco (Morgan et al., 2013). Patients starting medicinal cannabis use reported decreased BAI, STAI and PSQI scored in a longitudinal study (Sagar et al., 2021).

Clinical populations with overlapping conditions included anxiety and sleep symptoms stemming from chronic illness (Casarett et al., 2019) or other psychiatric conditions (Shannon et al., 2019). Both studies suggested cannabinoid treatments decreased anxiety and increased sleep as reported by the Strainprint Medical Cannabis Journaling application (Casarett et al., 2019) and HAM-A and PSQI outcomes (Shannon et al., 2019). Additionally, overlapping between cannabis use and affective disorders such as bipolar and schizotypy samples showed a decrease in HAM-A with no change in PSQI for the cannabis/bipolar sample (Shannon and Opila-Lehman, 2015) and no significant changes for VAS-A in the cannabis/schizotypy sample (Hindocha et al., 2015).

3.5.6. *Healthy population outcomes*

Overall, healthy populations were utilized in 20 studies. Cannabinoid treatments either increased or decreased anxiety as measured in most studies. Trends indicated THC treatments increased anxiety as measured by STAI-S (Bhattacharyya et al., 2009; Martin-Santos et al., 2012), STAI (Borgwardt et al., 2008; Fusar-Poli et al., 2009; Grimm et al., 2018; Winton-Brown et al., 2011) and POMS-A (Gibson et al., 2022) and CBD decreased anxiety as measured by the VAMS-A (Crippa et al., 2004; Linares et al., 2019; Zuardi et al., 1993, 2017), GAD-7 (Crippa et al., 2021; Pacheco et al., 2021) and MRS-anxiety (Das et al., 2013). The remaining studies reported no changes for CBD in STAI (Zuardi et al., 1982) VAMS-A (Crippa et al., 2022; Zuardi et al., 2017) or both measures simultaneously (Linares et al., 2018), as well as the DEQ for both CBD and CBD-dominant treatments (Spindle et al., 2020). One study reported increased VAS-A, VAMS-A and STAI-S for both CBD and placebo groups (Stanley et al., 2022) Combined treatments increased VAS-A scores despite CBD and THC concentrations (Ilan et al., 2005). Additionally, combined CBD and THC (2:1 ratio) decreased STAI scores (Zuardi et al., 1982).

Sleep/sedation was measured in 16 studies. Out of those studies, seven measured sleep/sedation outcomes suggested increased scores, five of which were THC treatments with outcomes measured by VAMS-S (Bhattacharyya et al., 2009; Borgwardt et al., 2008; Fusar-Poli et al., 2009; Martin-Santos et al., 2012), ARCI (Martin-Santos et al., 2012) and VAS-S (Winton-Brown et al., 2011). The remaining administered CBD (Crippa et al., 2004, 2022, 2021; Das et al., 2013; Linares et al., 2018; Pacheco et al., 2021; Stanley et al., 2022; Zuardi et al., 1993, 2017) or CBD and CBD-dominant treatments (Gibson et al., 2022; Ilan et al., 2005; Spindle et al., 2020) in addition to THC (Zuardi et al., 1982). Decreased sleep measured by the KSS was reported for all combined high/low CBD and THC treatments compared to placebo condition in one study (Ilan et al., 2005). Furthermore, no changes in VAMS-S (Crippa et al., 2022; Zuardi et al., 1993, 2017), MRS-sedation (Das et al., 2013) and PSG were reported (Linares et al., 2018) in five studies. Increased VAMS-S (Crippa et al., 2004) and decreased ISI (Pacheco et al., 2021) were reported for CBD in two studies.

Table 5
CBD/THC Treatments and Anxiety/Sleep Outcomes.

Author	Treatment Route	Dosage	Treatment Period/ Dosing Sessions	*Anxiety/Sleep Measure*, Outcome	
Clinical Trials					
1. Allsop et al. (2014)	Spray	Nabiximols: THC 21.6 mg, CBD 20 mg - THC 86.4 mg, CBD 80 mg PLA	6 days Days 2–3 Max. 8 sprays, 4 times daily. Day 4 6 sprays, 4 times daily Day 5 4 sprays, 4 times daily Day 6 2 sprays, 2 times daily	*Cannabis Withdrawal Scale:* *Sleep,* *ANX* ANX & Sleep, treatment x time (ns) Main effect for time: ↓ ANX* ; Slight ↑ Sleep *	Limited positive therapeutic benefit for sleep & ANX. ANX ↓ below baseline levels in both groups during treatment (possibly from high baseline ANX & lack of cannabis-related cues in the inpatient environment). Small ↓ compared to baseline for Nabiximols vs PLA.
2.Aviram et al. (2020)	Type 1 – Inflorescence inhaling Type 2–3 - Oil	*Type I* THC dominant – THC 2000–3600 mg/month+ CBD 400–725 mg/month *Type II* Mixed CBD 1500–2000 mg/month THC 1400–2000 mg/month *Type III* CBD dominant CBD 2000–3000 mg/month+ THC 600–1000 mg/month	1 month	*GAD:* ↓ All treatments (trend) *PSQI:* Difference from baseline ↑ Type I, II & III * Sleep duration (hours) ↑ Type I vs II & III * Sleep latency (min) ↓ (trend)	Improvement in assessed parameters, ↓ in analgesics consumption (rapid and apparent improvement from baseline at one month) No significant short-term improvement for ANX (although a trend was observed) Type I for short sleep duration is preferred. Type II,III for high burden of physical cancer symptoms.
3.Bhattacharyya et al. (2009)	Capsule	THC 10 mg; CBD 600 mg; PLA (flour)	3 sessions	*fMRI;* *STAI-S:* ↑ THC* ↔ CBD vs PLA (ns) *VAMS-S:* ↑ THC* ↔ CBD vs PLA (ns)	THC ↑ ANX and sedation, no significant effect for CBD THC modulated mediotemporal & ventrostriatal function (may be part of the cause of its effects).
4.Borgwardt et al. (2008)	Capsule	THC 10 mg; CBD 600 mg; PLA (flour)	3 sessions, 1 month apart	*fMRI;* *STAI:* ↑ THC vs PLA* ↓ CBD vs PLA (trend) *VAMS-S:* ↑ THC vs PLA* Baseline differences drug vs variable, effects of order (ns)	CBD deactivated left temporal cortex & insula THC attenuated activation in right inferior frontal+anterior cingulate gyrus Effects were not related to changes in ANX/ SED
5.Fusar-Poli et al. (2009)	Capsule	THC 10 mg; CBD 600 mg; PLA (flour)	3 sessions, 1 month apart	*fMRI;* *STAI:* ↑ THC vs PLA* ↓ CBD vs PLA (trend) *VAMS-S:* ↑ THC vs PLA* Baseline differences drug vs variable, effects of order (ns)	CBD ↓ ANX (possibly due to activation in limbic and paralimbic regions) CBD & THC had distinct effects on neural, electrodermal and symptomatic response to fearful faces
6.Ilan et al. (2005)	Cigarette	(% concentration) i) Low CBD (0.27) + THC (1.91) & high CBC (0.60); ii)High CBD (1.06)+THC (2.86) & low CBC (0.15); iii)High CBD (1.52) & low THC (1.88)+ CBC (0.12); iii)Low CBD (0.08) & high THC (3.09) + CBC (0.57) PLA	4 sessions, 1 week apart	*EEG, ERP*; *VAS-A:* ↑ Cannabis vs PLA* ↔ High & Low THC groups (ns) Interaction CBD condition x THC group x recording interval (ns) *KSS:* ↑ PLA * ↓ Cannabis *	20 mins after smoking showed most ↑ ANX. CBD on ANX may be dependent on THC dose – lower dose of THC in high CBD condition reported more ANX vs low CBD conditions. Higher THC in both low CBD conditions reported ANX with less ANX when CBD was high. Effect of CBD on ANX may depend on THC dose. -Low dose THC ↑ ANX in high CBD vs lower CBD conditions. -Higher THC dose = anx in both low CBD conditions. BUT Less anx vs High CBD.
7.Martin-Santos et al. (2012)	Capsule	THC 10 mg; CBD 600 mg; PLA (flour)	3 sessions, 1 month apart	*STAI-S:* ↑ THC vs CBD & PLA (at 2 h)* *VAMS-A:* Difference between THC & CBD (at 2 h) * *VAMS-S, ARCI:* ↑ THC vs CBD & PLA (at 2 h) *	THC ↑ ANX & SED Few differences between CBD and placebo (present dose higher than studies before it, so it may have exceeded dose associated with a clear anxiolytic effect). Suggests CBD alone has few symptomatic effects in healthy non-anxious subjects. THC acute behavioural/physiological effects, CBD well tolerated.

(*continued on next page*)

Table 5 (*continued*)

Author	Treatment Route	Dosage	Treatment Period/ Dosing Sessions	*Anxiety/Sleep Measure*, Outcome	
8.Spindle et al. (2020)	Vaporised, Capsule	CBD 100 mg (cap); CBD 100 mg (vaped); CBD dominant 100 mg THC 3.7 mg (vaped); PLA (cellulose, cherry flavoured syrup)	4 sessions, ≥ 1 week apart	*DEQ:* ANX ↔ All treatments (ns) Sleep ↑ CBD dominant vs CBD vaped*	CBD dominant-cannabis produced the strongest outcomes compared to CBD and PLA. Low amounts of THC can be physiologically/subjectively active. Women may be more sensitive to acute effects of inhaled CBD. Possibility of higher bioavailability of inhaled CBD as opposed to ingested (shown by blood concentration) or with respect to pharmacokinetic time course.
9.Winton-Brown et al. (2011)	Capsule	THC 10 mg; CBD 600 mg; PLA	3 sessions, 1 month apart	*fMRI;* *STAI:* ↑ THC vs PLA* ↔ CBD (ns) *VAS-S:* ↑ THC vs PLA* ↔ CBD (ns)	CBD associated with right temporal cortex during auditory processing, had opposite effects in right posterior superior temporal gyrus (right sided Wernicke's area). THC attenuation of activation here during auditory processing correlated with its acute effect on psychotic symptoms – Single dose CBD and THC therefore modulate brain functions in areas that process auditory and visual stimuli and relate to induced psychosis symptoms.
10.Zuardi et al. (1982)	Oral tincture (alcohol, artificial lemon juice) capsule (lactose)	THC 0.5 mg/kg; CBD 1 mg/kg; THC 0.5 mg/kg + CBD 1 mg/kg; Diazepam 10 mg; PLA	5 sessions; 1 week apart	*STAI:* Difference from baseline ↑ THC* ; ↑ Diazepam * ; ↔ CBD, PLA (ns). ↓ THC+CBD vs THC*	Most ANX ↑ in THC, followed by THC+CBD and then diazepam. CBD "blocked" ANX provoked by THC, this effect also extended to other subjective THC alterations but not tachycardia. Interviews showed sleepiness across all treatments
Observational/Cohort Studies					
11.Aungsumart et al. (2021)		Min THC:CBD 1:1 (2.7 mg: 2.5 mg: 0.1 ml; Max 27 mg THC and 25 mg of CBD	12 Weeks: Week 1 =0.1 ml, Week 2 = 0.1 ml x 2 a day x 3 days Dose inc after 2nd week but not more than 1.5 times with time between doses not in <4hrs	*NRS: ANX, INS* ANX Before treatment median (IQR); After treatment median (IQR): 1(0–3); 0(0–0) ns INS Before treatment median (IQR); After treatment median (IQR): 7(0–8); 0(0–0) ns	Different MS phenotypes and disease durations may have contributed to outcomes
12.Bindler et al. (2022)	Inhalation	0.5 g cigarette= 22.17% THC+ 0.12% CBD	1 dose over 2 days	*NRS-ANX* Day 1 2.875 (0.64) vs Day 2 2.375 (0.52) Actigraphy: 3 nights before treatment mean= 6.19 h; 2 nights after treatment mean= 3.93 h	
13.Bonomo et al. (2022)	Oral solution	THC:CBD 1:1 Stage 1 = Single dose 2.5 mg THC+ 2.5 mg CBD Stage 2 = Single dose 2.5 mg THC+ 2.5 mg CBD followed by high fat meal, then a total daily dose of 5 mg THC/5 mg CBD for 1 week Stage 3 = Single dose 5 mg THC/5 mg CBD; and a total daily dose of 10 mg THC/10 mg CBD for 1 week Stage 4 = single dose of 7.5 mg THC/ 7.5 mg CBD and then receive a total daily dose of 15 mg THC/ 15 mg CBD for 1 week Stage 5 = single dose of 12.5 mg THC/ 12.5 mg CBD on 1 day followed by a 7-day washout	23 dosing sessions over 5 stages.	*DASS-A:* ↓ Mean scores BL 8.22 (6.61) – Day 36 4.71 (6.07)* *ISI*↓ BL Mean = 17.44, SD = 5.75 to Day 22 Mean = 8.93, SD = 4.05 * Sleep quality: ↑ BL Mean = 3.22, SD = 0.83) to Day 22 (Mean = 2.00, SD = 1.07 * Total sleep: ↑ BL 39.11 (SD = 9.28) to day 29 52.78 (SD = 13.65) ns ↓ day 36 Mean = 46.75, SD = 9.91 ns Sleep diary Sleep onset latency: ↑ week 1 (Mean = 2.41, SD = 0.59) to week 2 week 2 (Mean = 1.87, SD = 0.52 *	

(*continued on next page*)

Table 5 (*continued*)

Author	Treatment Route	Dosage	Treatment Period/ Dosing Sessions	*Anxiety/Sleep Measure*, Outcome	
				ns total sleep time Sleep quality ↔	
14.Casarett et al. (2019)	Inhalation	INS: 95% THC, 5%CBD ANX: 84% THC, 16% CBD	13 months (# uses: Insomnia = 4613; Anxiety = 9340)	Strainprint® medical cannabis journaling ↑ THC:CBD = ↓ INS* ; ↔ ANX (ns)	THC:CBD ratios above 1:1 reduced effectiveness for anxiety symptoms (inverted U relationship). Improvement in insomnia observed in higher THC:CBD ratios.
15.Ergisi et al. (2022)	Flower Oil	BL: CBD 16.30 [1.00–20.00], THC 13.00 [1.00–23.75]; 1 month: CBD 20.00 [2.00–40.00], THC 32.00 [10.00–176.00] 3 months: CBD 15.00 [4.75–50.00], THC 20.50 [10.00–189.50]; 6 months: CBD 4.50 [0.00–20.00], THC 28.00 [13.75–50.00]	6 months, frequency NA	*GAD-7 & EQ-5D-5 L:* ↓* 1,3 & 6 months vs BL SQS ↓* 1,3 & 6 months vs BL	
16.Giorgi et al. (2020)	Oil	Night: Bedrocan (22% THC 220 mg/g , <1% CBD), Morning: Bediol (6.3% 63 mg/g THC, 8% CBD 80 mg/g)	6 months, 10–30 drops daily No more than 120 drops in some cases.	BL/3 months/6 months (mean score) *ZSR-A:* ↓ 50% (moderate) * 64.754/61.288/ 61.924 PSQI: 10.554/9.061/ 9.001 Sleep ↑ 44% * *FAS-S:* Slight fluctuations-8.288/7.015/ 7.470	Suggests a clinical advantage and improvement in life quality for fibromyalgia patients. An inverse relationship between body mass index and clinical improvement was noted.
17.Gruber et al. (2021)	Inhalation; Sublingual oil/ solution/tincture; Edible; Capsule; Topical	3months THC mg/week= 93.29 ± 228.12 CBD mg/week= 202.18 ± 345.23; 6 months: THC mg/week= 52.29 ± 92.53 CBD mg/week= 229.93 ± 378.17	3months: 10.15 ± 6.62; 6 months; 9.69 ± 6.24	*STAI* ↓ *BAI* ↓ *PSQI* ↓* at 3 & 6 month post-treatment	"pain-related distress (PDS) were significantly associated with decreases in state anxiety on the STAI [r(28) = 0.36, p = 0.055] PDI scores were also associated with improved trait anxiety [r(28) 0.466, p = 0.01] on the STAI and a trend for improved state anxiety [r(28) = .35, p = 0.06].
18.Harris et al. (2022)	Inhalation; Oil	Daily THC median: 2.0 mg (0.0–442.0 mg); Daily CBD median: 20.0 mg (range: 0.0–188.0 mg)	6 months	*GAD-7* and *EQ-5D-5 L*: ↓* 1,3 & 6 months vs BL SQS ↓* 1,3 & 6 months vs BL	
19.Nimalan et al. (2022)	Oil	CBD median 32.0 mg (Range: 20.0–384.0 mg); THC median 1.3 mg (Range: 1.0–16.0 mg	6 months	*EQ-5D-5 L:* ↓ ns SQS: ↓ ns	
20.Sagar et al. (2021)	Inhalation, Oromucosal, Cutaneous	mg/week at: 3 months= CBD 153.90 (287.79) THC 63.97 (184.18) 6 months= CBD 201.64 (321.38) THC 41.89 (78.78) 12 months= CBD 113.50 (251.47) THC 35.99 (48.86)	12 months Mean use/week 3 months: 9.29 (6.28); 6 months: 10.20 (8.25); 12 months: 11.19 (7.86)	*BAI* ↓* at 6 and 12 months *STAI-S* ↓* BL to 6 month comparison only *STAI-T* ↓* Correlated with CBD use and MC uses per week *PSQI* ↓* after starting treatment	

Notes. This table presents details on studies measuring the effect CBD/THC treatments on anxiety and sleep measures and their outcomes.
↓ = decrease; ↑ = increase; ↔ = no difference/change/effect; (ns) = not significant;* = significant ($p < 0.05$, $p < 0.01$ or $p < 0.001$); *ANX* = anxiety; *ARCI* = Addiction Research Centre Inventor; *BAI* = Beck Anxiety Inventory; *CBD* = Cannabidiol; *DASS-A* = Depression, Anxiety, and Stress Scale; *DEQ* = Drug Evaluation Questionnaire; *EEG* = Electroencephalogram; *ERP* = Event-related potential; *FAS-S* = Fibromyalgia Assessment Score-Sleep; *fMRI* = Functional Magnetic Resonance Imaging; *GAD* = General Anxiety Disorder; GAD-7 = Generalized Anxiety Disorder-7; *INS* = Insomnia; *KSS* = Karolinska Sleep Scale; *MC* = Medicinal cannabis; *NRS* = Numerical Rating Scale; *PLA* = Placebo; *PSQI* = Pittsburgh Sleep Quality Index; *SED* = sedation; *STAI-S* = State-Trait Anxiety Inventory – State Anxiety; *STAI* = State-Trait Anxiety Inventory; *SQS* = Single Item Sleep Quality Scale; *THC* = Delta-9 Tetrahydrocannabinol; *VAMS-A* = Visual Analog Mood Scale-Anxiety; *VAMS-S* = Visual Analog Mood Scale-Sedation; *VAS-A* = Visual Analog Scale-Anxiety; *VAS-S* = Visual Analog Scale-Sedation; *ZSR-A* = Zung Self-Rating Scale-Anxiety.

3.6. Risk of bias assessment

Figs. 2–7 display summaries of the risk of bias assessments categorized by types of study design. Assessments were performed in duplicate using the Cochrane risk of bias tool and consensus was reached within the first round of comparison between reviewers (AN and BM).

Risk-of-bias plots were created using robvis (McGuinness and Higgins, 2020) and Microsoft Excel (Fig. 5 only). Of the included studies, 54 were assessed for risk of bias with the remaining four studies being excluded for assessment due to their single-subject case design (Berger et al., 2020; Bindler et al., 2022; Crippa et al., 2013; Shannon and Opila-Lehman, 2015). Amongst the 54 studies included for risk of bias assessment one study was assessed twice due to its use of both between-groups and crossover designs (Ilan et al., 2005). Therefore, a total of 55 risk of bias assessments were completed of which 21 were assessed as randomized between-groups studies, 17 were assessed as randomized crossover studies and 17 were assessed as non-randomized studies. Overall, all assessed studies ranged from moderate to high risk of bias.

3.6.1. Risk of bias results for randomized between-group studies (Figs. 2 and 3)

All studies in this domain had some concern for bias in the selection of the reported result due to the unavailability of a specified analysis plan that was finalized before the unblinded outcome data was available for analysis. This resulted in most studies having some concerns overall. In addition to this, three studies had some concerns due to a lack of information on randomization (Zuardi et al., 1993), lack of blinding (Crippa et al., 2021), participant and trial personnel awareness of treatment received (Crippa et al., 2021; Drennan et al., 2021a; Gibson et al., 2022) and differences at baseline suggesting problems with randomization (Das et al., 2013) leading to an overall high risk of bias for these studies.

3.6.2. Risk of bias results for crossover studies (Figs. 4 and 5)

The unavailability of a specified analysis plan resulted in some concerns for the overall outcome for all but one study. In addition to this, no information on sufficient time given for carryover effects (Bhattacharyya et al., 2009) and slight imbalances in number of participants allocated to treatment groups due to dropouts (Kayser et al., 2020) resulted in some concerns for bias arising from period and carryover

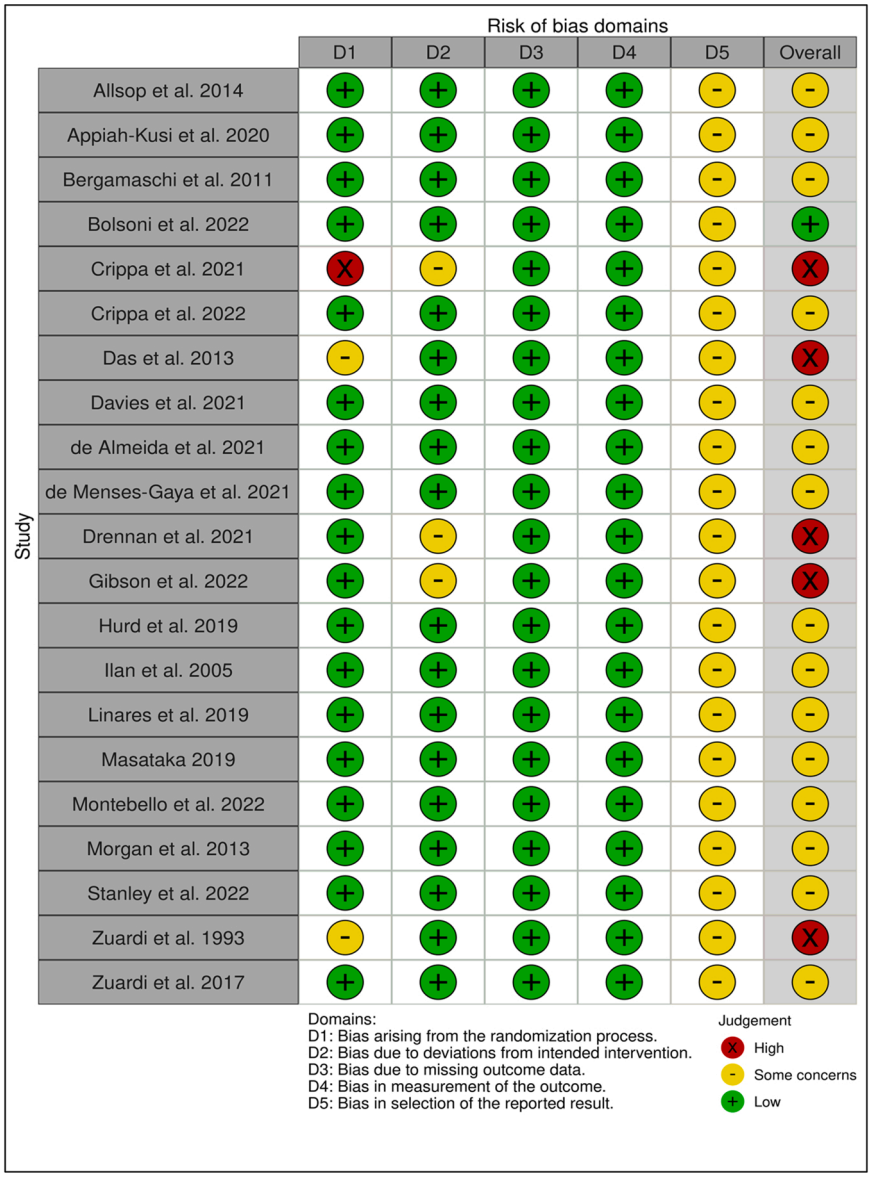

Fig. 2. Individual and overall risk of bias judgement for included randomized between-group studies.

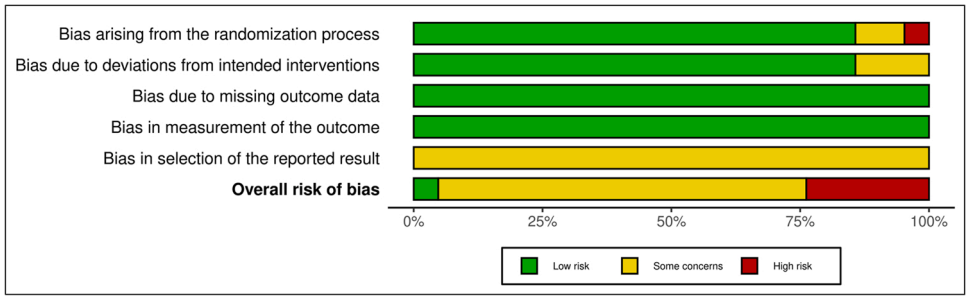

Fig. 3. Summary plot of each domain outcome for included randomized between-groups studies.

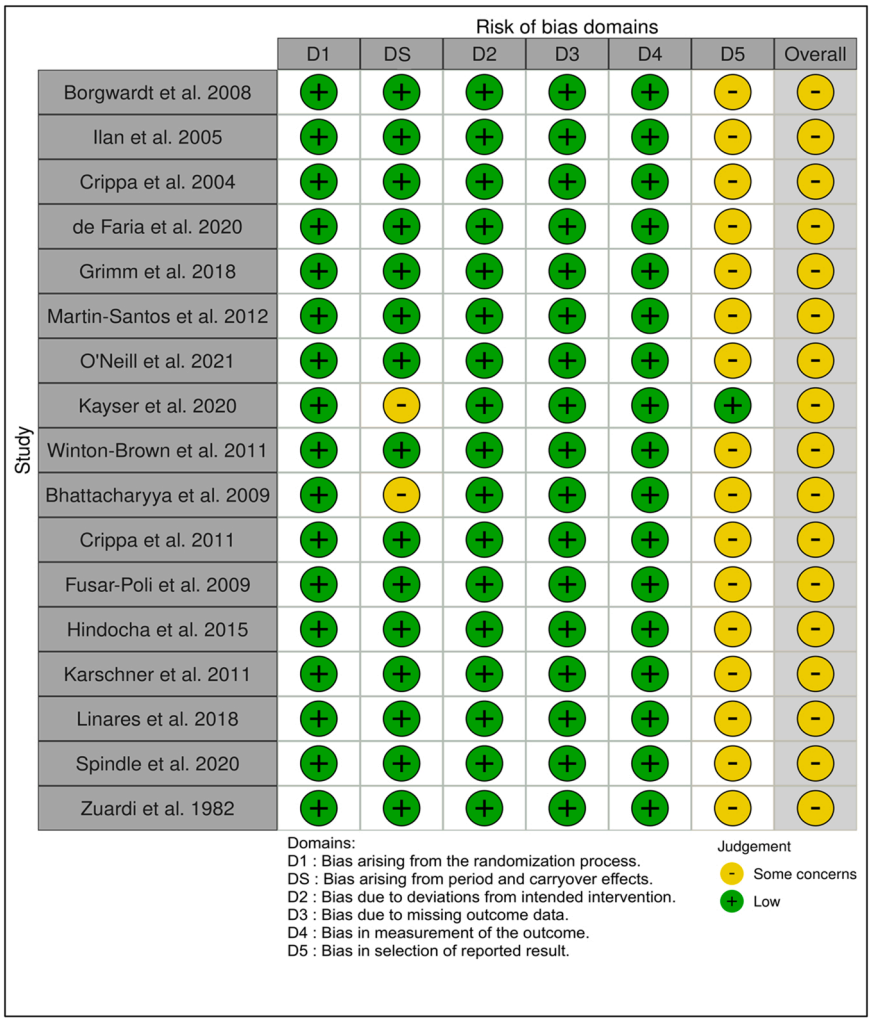

Fig. 4. Individual and overall risk of bias judgement for included randomized crossover studies.

effects but was concluded to not result in an overall high risk of bias for the studies.

3.6.3. Risk of bias results for non-randomized studies (Figs. 6 and 7)

Non-randomized studies had moderate to high risk of bias due to confounding of the effect of intervention. in addition to serious and moderate risk of bias due to deviations from intended interventions in 29% and 47% of studies respectively with serious risk in 24% of studies for bias in the measurement of outcomes. Despite most studies at low risk of bias due to selection of participants, 11% of studies were concluded to be at high risk and 6% at moderate risk. This resulted in overall serious risk of bias for 71% of studies with the remaining being of moderate risk.

4. Discussion

Overall, results for CBD-only treatments suggested more consistent anxiolytic benefits than sedative effects when compared to THC, showing therapeutic efficacy in healthy groups, non-cannabis using populations with certain anxiety or anxiety related disorders, chronic illnesses, and certain psychiatric conditions. An inverted U-shaped beneficial dose relationship was also found for CBD; however, optimal treatment dose and period varied across studies. THC-only treatments produced greater anxiogenic and sleep-inducing effects compared to

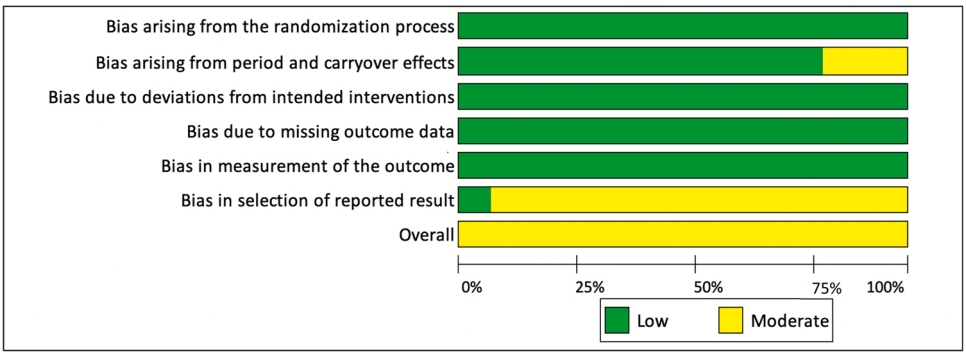

Fig. 5. Summary plot of each domain outcome for included randomized crossover studies.

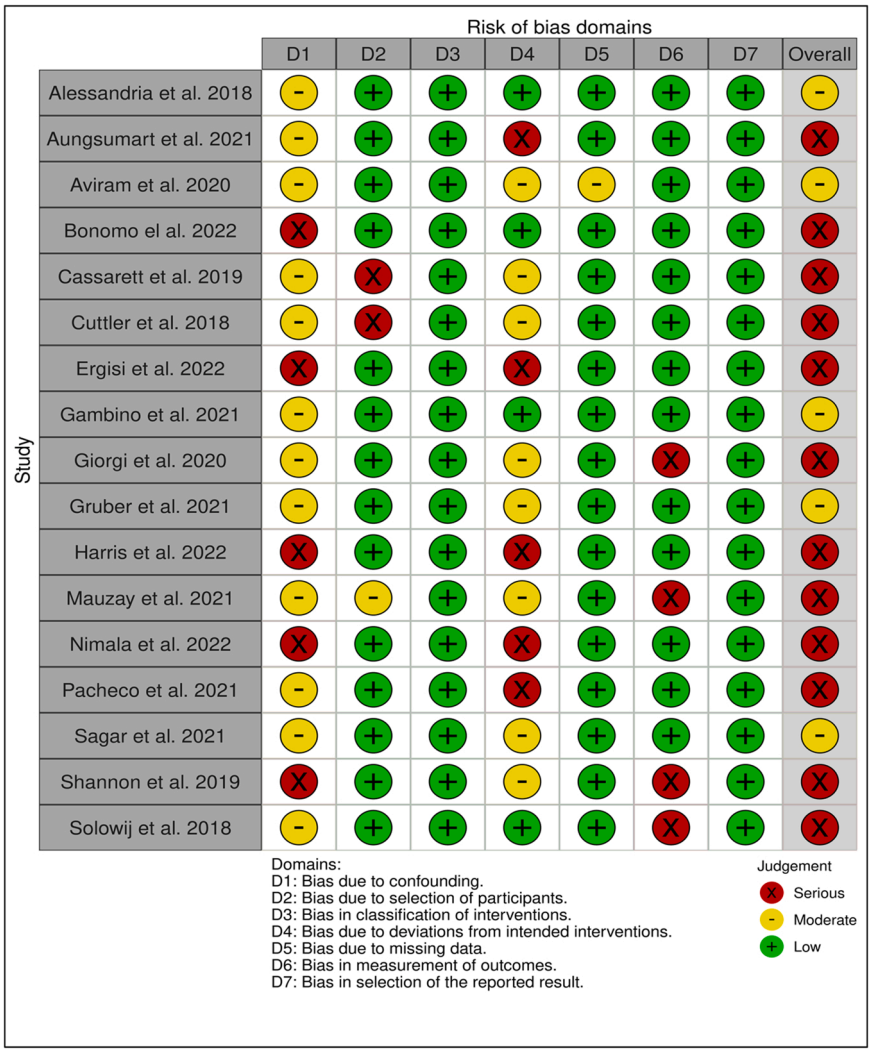

Fig. 6. Individual and overall risk of bias judgement for included non-randomized studies.

CBD. Moreover, combined treatment efficacy appeared contingent on the ratio of CBD:THC and types of symptoms being treated, with greater benefit observed in non-pathological versus clinical groups. Outcomes for cannabinoid treatments therefore suggested varied degrees of anxiolytic and sleep-inducing potential for distinctive populations, highlighting the need for future studies to confirm the optimal treatment dose and period for specific populations.

The reviewed results for CBD treatments support an inverted U-shaped dose-efficacy relationship in healthy adults, with a likely minimum beneficial therapeutic threshold of 300 mg (Linares et al., 2019; Zuardi et al., 2017). Findings from studies assessing single treatments of 300 mg or 400 mg similarly reported decreased anxiety in healthy (Crippa et al., 2004; Linares et al., 2019; Zuardi et al., 1993, 2017) and some clinical populations (Bolsoni et al., 2022a; Crippa et al., 2011; de Faria et al., 2020; Hurd et al., 2019; Masataka, 2019). This supported an effective acute anxiolytic dose range but failed to confirm an inverted-U dose relationship due to single dose treatments being assessed within studies in mainly healthy populations. At doses of

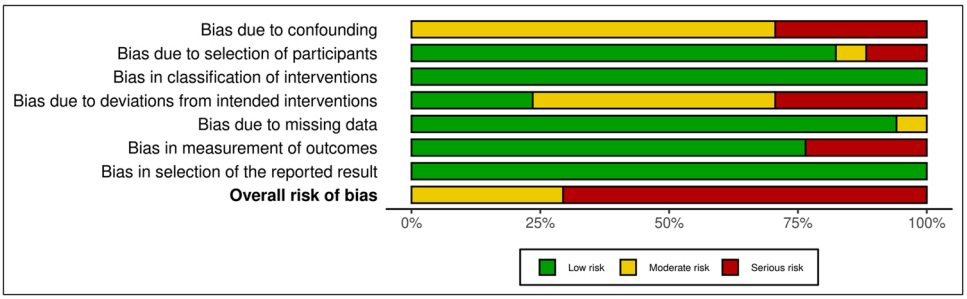

Fig. 7. Summary plot of each domain outcome for included non-randomized studies.

300–400 mg, CBD did not affect sleep or sedation to the same degree as anxiety in healthy populations, but weak evidence was reported for increased sedation effects after acute CBD dosing (Crippa et al., 2004). Therefore, it is difficult to determine if beneficial thresholds of CBD's inverted U-dose relationship may differ for anxiolytic and sleep effects in healthy and clinical populations or if an anxiolytic CBD dose may similarly affect sleep outcomes. For robust discussions on biochemical pathways implicated in the bi-directional sleep-anxiety relationship, see Fogaça et al. (2018), Russo et al. (2005) and Hsiao et al. (2012). Future research studies should consider using different dose sizes and administration routes, as studies typically used capsules which has recently been reported to be limited by irregular absorption and first-pass hepatic metabolism resulting in poor bioavailability compared to routes such as inhalation (Devinsky et al., 2021). In contrast, oil vehicles may reach peak plasma levels quicker and have a fourfold bioavailability in comparison to the same dose in its powder form (delivered via capsule) (Crippa et al., 2022). Significantly heightened bioavailability through oil vehicles may be further enhanced by the avoidance of fasting conditions prior to dosing, to ensure the highly lipophilic nature of CBD leads to potential improved systemic absorption (Crippa et al., 2022). The role of treatment route factors could therefore account, at least in part, for inconsistencies in past study outcomes, and are thus important considerations when interpreting results. Future studies should also determine if there is a consistent beneficial threshold for CBD's anxiolytic effect in healthy populations through independent trial replications, using objective measures to determine changes in sleep architecture.

The inverted U-shaped dose-efficacy relationship was not supported in most clinical populations administered CBD-only treatments in this review. Results indicated both low and high doses (18–800 mg) produced similar anxiolytic effects, particularly when taken daily over a longer treatment period (Berger et al., 2020; Bonomo et al., 2022; Crippa et al., 2013; Shannon et al., 2019; Shannon and Opila-Lehman, 2015). Decreased anxiety compared to baseline was observed after a period of minimal benefits, indicating a latency period before the onset of therapeutic effects (Berger et al., 2020). A similar finding was recently reported for CBD-dominant treatments in medicinal cannabis users when comparing cross-sectional and longitudinal anxiety results, as well as similar evidence for improved anxiety and sleep in recreation users and medicinal cannabis patients beginning treatment measured over 12 months (Drennan et al., 2021a; Montebello et al., 2022; Sagar et al., 2021). This may be extended to CBD alone but this assertion currently lacks supporting evidence from RCTs and CBD-only treatments (Martin et al., 2021).

Ongoing revisions to CBD dosage appear to either maintain or increase and again maintain the anxiolytic effects after baseline and any periods of minimal benefits (Berger et al., 2020; Crippa et al., 2013; Shannon et al., 2019; Shannon and Opila-Lehman, 2015). To a lesser extent, subjective sleep showed small improvements compared to baseline. Taken together, this suggested that some clinical populations with anxiety symptoms may benefit from longer treatment periods. Clinical evidence supported benefits of prolonged CBD treatments in cannabis users, reporting plasma CBD concentration being correlated with hippocampal neurogenesis (Beale et al., 2018). As measured by PSQI and self-reports, limited and fluctuating sleep improvements following decreased anxiety may again indicate anxiolytic effects directly affecting sleep. however, this requires additional confirmation over a longer treatment duration.

This review added recent evidence of subjective anxiolytic effects of chronic CBD treatment for severe SAD that was previously lacking, suggesting efficacy for acute anxiolytic effects in disorders of cyclical mood/sleep disruption (Bergamaschi et al., 2011; Berger et al., 2020; Crippa et al., 2011; Masataka, 2019). CBD in conjunction with cognitive behavioral therapy and antidepressant medication (mirtazapine) provided some interesting results including a period of minimal benefits and ongoing revision to doses (200–800 mg) for therapeutic benefits, including decreased subjective insomnia over 6-months (Berger et al., 2020). This provided a foundation for the potential of CBD as a longitudinal treatment in conjunction with other treatments for SAD; however, limited evidence, issues of high subjectivity and the lack of control measures within this case study will need further exploration in future studies to be generalized. It is likely that with anxiety disorders typically leading to sleep disruption, the anxiolytic effects of cannabinoid treatments over long-term treatment would also positively affect sleep.

The inconsistencies in treatment efficacy from psychosis populations are likely to stem from modest sample sizes (Appiah-Kusi et al., 2020) and research focused on the mechanisms related to the subcortical dopaminergic drive likely to lead to psychotic symptoms instead of mechanisms of anxiety (O'Neill et al., 2021); with the latter often being the emphasis of psychosis and cannabinoid research. It is proposed that CBD attenuates abnormal neuroendocrine and psychological responses (Appiah-Kusi et al., 2020) and potentially normalizes mediotemporal and prefrontal activity, as well as mediotemporal-striatal connectivity (O'Neill et al., 2021). However, no differences in anxiety as measured by STAI-S in populations with psychosis (Appiah-Kusi et al., 2020) or those clinically at risk of psychosis (O'Neill et al., 2021) have been reported after acute treatment. Neuroimaging studies further strengthened possible targets of CBD anxiolytic effects in the brain's fear circuit consisting of the amygdala, limbic forebrain (prefrontal cortex and cingulate gyrus) and bed nucleus of stria terminalis, in addition to other related neurobiological targets (Blessing et al., 2015; Borgwardt et al., 2008; Crippa et al., 2011, 2004; Fusar-Poli et al., 2009; Grimm et al., 2018; Kim and Gorman, 2005). These sites are typically implicated in anxiety disorders and is suggested to result in HPA-axis hyperactivation in chronic anxiety. Key mechanisms such as circadian misalignment, heightened cortisol, increased amygdala response and diminished 5HT1-aR are also suggested to exacerbate anxiety and disrupt sleep (Faravelli et al., 2012; Kim and Gorman, 2005). The observed inconsistencies in CBD treatment efficacy for different clinical samples including psychosis may therefore be the result of different mechanisms that are not impacted by CBD consumption, in addition to specific study characteristics and limitations.

This review further highlighted differences in dosing regimens and CBD:THC ratio in combined cannabinoid treatments that could affect

anxiolytic and sleep outcomes. Key distinctions in CBD and THC binding effects at CB1 receptors (CB1R) found in higher densities in the brain and additional synergetic and entourage effects were likely to improve THC tolerability and safety to a degree through antagonism of psychoactive and other effects (Russo, 2011; Vučković et al., 2018). Studies in this review agreed with past observations of THC's anxiogenic and sedative effects and noted these effects to be more prominent in healthy populations. However, THC's biphasic dose relationship was not observed in studies reviewed despite evidence from past research and was likely due to specific focus on CBD treatments (Viveros et al., 2005). CBD-dominant treatments were observed to provide anxiolytic benefits (Spindle et al., 2020), whereas THC-dominant treatments resulted in improved sleep duration only in addition to decreased sleep latency (Aviram et al., 2020). The latter may only be beneficial in the short-term as THC alone was suggested to decrease sleep latency but could impair long term sleep quality (Babson et al., 2017; Nicholson et al., 2004). Alternatively, higher reported CBD concentration (Winiger et al., 2021) and acute low-dose THC may potentially have therapeutic sleep effects (Babson et al., 2017). Residual sedative effects of THC are suggested to be offset by CBD when administered in higher, 1:1 ratio doses (Nicholson et al., 2004). On the other hand, recent evidence suggested subjective anxiety may show delayed decreases in THC-dominant concentrations (THC 84.99%, <1% CBD) and immediate decreases for CBD-dominant concentrations (CBD 78.8%, THC 4.5%) (Drennan et al., 2021b). Due to the individual differences in depth and duration of inhalation, inhaled THC doses reported as static quantities as opposed to maximum possible dose further highlights the need for a standardized THC unit for effective, accurate and safe dosing and reporting (Arkell et al., 2021). Thus, individual CBD/THC dose relationships, mechanisms of actions and utilization of combined treatment effects are expected to produce both sleep and anxiolytic benefits once in-depth research is conducted on therapeutically beneficial ratios and dosages.

A main finding in clinical populations included suggested blunted or reduced therapeutic effects of combined treatments, specifically in frequent and problematic cannabis users. Observations in cannabis users with co-occurring affective disorders (e.g. schizotypy) also suggested similar blunted therapeutic effects, likely due to pharmacodynamic tolerance to THC through downregulated CB1R (Ramaekers et al., 2020) and hypothalamic-pituitary axis (HPA) dysregulation caused by cannabis use. THC tolerance and HPA dysregulation from problematic cannabis use has been suggested to contribute to combined treatments being anxiogenic than providing relief in these populations (Cornelius et al., 2010; Ranganathan et al., 2008; Somaini et al., 2012). Recent evidence had suggested ongoing, controlled, and revised CBD or CBD dominant treatments may maintain therapeutic effects and improve neuroprotection without causing dysregulation (Martin et al., 2021; Ramaekers et al., 2020; Winiger et al., 2021) and adding to reduced illicit cannabis use in cannabis dependence which is considered a key driver of improved anxiety and sleep outcomes whilst being prescribed a combined cannabinoid treatment over longer period of time (Montebello et al., 2022); however, further research is necessary to strengthen these observations.

Another potential shared mechanism in preclinical and clinical research is CBD suppression of fatty acid amide hydrolase (FAAH) through the prevention of anandamide (AEA) metabolism enabling the increased longevity of AEA leading to greater CB1R signaling (Gray et al., 2015; Russo, 2016). CB1R activation suppressed CRH induced stress responses, with FAAH in the amygdala promoting anxiolytic effects (Gray et al., 2015). Dysregulation of these ECB mechanisms including failure to produce and metabolize ECBs efficiently resulted in failure to regulate cortical excitation and inhibition may result in dysfunctional mood and related disorders, including anxiety and disordered sleep (Ashton and Moore, 2011). Dysregulation in HPA-axis and the ECB system in these conditions may account for mixed results reported in overall clinical populations including OCD, as well as some suggested anxiolytic and sleep benefits in chronic diseases such as cancer (Aviram et al., 2020), Parkinson's disease (de Almeida et al., 2021; de Faria et al., 2020), chronic pain (Bindler et al., 2022; Bonomo et al., 2022; Gruber et al., 2021; Harris et al., 2022) and fibromyalgia (Giorgi et al., 2020). Despite, the small change in PSQI scores for fibromyalgia, the number of participants that reported decreases deemed the result clinically significant (Giorgi et al., 2020). ECB system and 5HT1a-r mechanisms are likely to be affected by CBD and CBD-dominant treatments, with longer treatment periods allowing improvement in ECB system tone and regulation and theorized to act on sleep through the suggested direct mechanism for anxiety (Hsiao et al., 2012). Furthermore, co-morbid anxiety and sleep disruption often occur in these conditions and can be prolonged by symptoms including pain and side effects from medical treatments. Cannabinoid treatments' broad pharmacological action may have therapeutic benefits beyond anxiety and sleep. Thus, it is important for studies to assess if cannabinoid treatments are directly impacting anxiety/sleep directly or relieving other symptoms that may indirectly influence these outcomes (Russo et al., 2005). High rates of sedating-type medication use (such as benzodiazepines) may that may mean that the true efficacy of cannabinoids on anxiety and/or sleep outcomes are underreported (Alessandria et al., 2020; Aviram et al., 2020; Berger et al., 2020; Bindler et al., 2022; Bonomo et al., 2022; de Almeida et al., 2021; de Faria et al., 2020; de Meneses-Gaya et al., 2021; Ergisi et al., 2022; Giorgi et al., 2020; Gruber et al., 2021; Harris et al., 2022; Nimalan et al., 2022; Shannon et al., 2019; Shannon and Opila-Lehman, 2015). As such, additional, high-quality work is needed to clarify the beneficial role of on cannabinoid treatments alone and/or as part of established treatment regimens.

Amongst agonism at 5HT1aR, CBD's action as a low-potency, full agonist at transient receptor potential vanilloid 1 receptors (TRPV1-r) may also play a role in anxiety. Preclinical evidence suggests that high dose CBD agonism at TRPV1-r may lead to its rapid desensitization and the facilitation of glutamate and GABA neurotransmission across the brain (Costa et al., 2007), and high-dose CBD can produce a paradoxical anxiogenic effect due to TRPV1 expression in brain regions associated with anxiety (e.g., medial prefrontal cortex, hippocampus) (Campos and Guimarães, 2009). This activation is suggested to be responsible for CBD's potential to reduce oxidative stress (Atalay et al., 2019); of which is closely related to inflammation, pain, anxiety, and depression (Atalay et al., 2019; Bouayed et al., 2009). Therapeutic application of CBD should therefore consider relevant molecular and neural mechanisms in addition to the effects of varying dose sizes in humans with anxiety, sleep disruption as well as co-morbid conditions such as depression. Increased risk of relapse due to frequent use and/or consumption of high-potency THC will likely limit the efficacy some cannabinoid therapeutics for complex psychiatric cases (Di Forti et al., 2019; Schoeler et al., 2016a,b); particularly considering additional sociodemographic vulnerabilities, such as comorbid psychiatric conditions, substance use and genetics (Colizzi and Bhattacharyya, 2020). The high co-morbidity and bi-directional relationship between anxiety and mood disorders such as depression (Kessler et al., 2015) may further complicate effective treatment with THC or THC-dominant treatments. Cannabis may decrease short-term depressive symptoms but increase baseline depression over time with more use (Cuttler et al., 2018), and depression may conversely increase later cannabis use (Feingold and Weinstein, 2021). Considering that cannabinoid treatments are being prescribed specifically for depression where legally available (Sexton et al., 2016), there is an urgent need for additional, well-controlled RCTs to understand the actions of THC alone and in combination with CBD, their effects on the ECB system and how cannabinoid treatments may be used to correct potential ECB imbalances within both psychiatric and co-morbid conditions prior to its addition to treatment regimens.

Increased access to cannabinoids for therapeutic purposes raises several peripheral safety concerns which are worth mentioning. Drivers with THC in their blood are, on average, more likely to be involved in a crash compared to those who did not, with higher blood THC levels

increasing their culpability (Ramaekers, 2018; Rogeberg, 2019). In the context of medical cannabis, the impact of THC consumption in specific products needs to considered by patients and prescribers. Even though the THC dose is likely to be lower than those consumed recreationally, emerging evidence suggests THC-induced driving impairment is apparent at commonly prescribed levels (e.g.Bhaskar et al., 2021) and this impairment is not attenuated in combined (1:1 CBD/THC) formulations (Arkell et al., 2019). Peak plasma and oral fluid concentrations of THC is highly dependent on administration route, which likely governs degree of associated psychomotor and/or behavioural effects (Sharma et al., 2012). The highly lipophilic nature of THC aids in its absorption into fatty tissue leading to its slow re-entry back into the bloodstream from days to weeks following administration depending on dose size and frequency of use (Arkell et al., 2021). Therefore, blood THC concentrations may not be indicative of cannabis consumption nor predict impairment, particularly over 5 h post-treatment (Arkell et al., 2020) underlining the urgent need for further exploration into its potential for carry-over impacts on cognition as well as its possible therapeutic benefits (Bonn-Miller et al., 2021). Indeed, lengthened detection and uncertain carry-over effects of THC further implicate careers of athletes due to THC prohibition in professional sports despite its long known ergolytic nature, resulting in much controversy (Campos et al., 2003; Eichner, 1993; Huestis et al., 2011).

We acknowledge that the highly heterogenous cannabinoid treatment dosages, treatment periods and administration routes examined likely contributed to inconsistencies in our results. Furthermore, limited sample sizes- particularly in RCTs, high subjectivity and variety of instruments used to measure sleep and anxiety outcomes created difficulty in the equal assessment and quality of results. Moderate to high risk of bias in studies also highlight important quality issues pertaining to study designs, result analysis and reporting in current cannabinoid, anxiety, and sleep literature. Future studies are further recommended to employ and report transparent randomization, treatment, and data analysis processes to limit risk of bias and ensure high quality studies. Future studies assessing objective markers of sleep (such as Actigraphy) are recommended in addition to subjective sleep/sedation measures when assessing the efficacy of cannabinoid treatments. Despite these limitations, purposefully including studies which employ a range of approaches and methodologies enables us to explore the differing therapeutic benefits of individual and combined treatments of cannabinoids more clearly and clarify potential therapeutic effects within clinical vs healthy populations, contextualized within the known bidirectional parameters of anxiety and disordered sleep. Furthermore, this review added to the larger body of research that was focused either solely on the safety and efficacy of cannabinoids in anxiety, anxiety related disorders and anxiety as a symptom of other conditions (Blessing et al., 2015; Skelley et al., 2020; Stanciu et al., 2021) or where cannabinoid therapies have been assessed as a treatment for disordered sleep only (Babson et al., 2017; Gates et al., 2014; Suraev et al., 2020). This distinction strengthens past observations in addition to establishing foundational knowledge for the understudied relationship between anxiety and disrupted sleep and the potential therapeutic role of cannabinoid treatments in next generation treatments.

5. Conclusion

This review provides evidence for an inverted U-shaped dose-efficacy relationship for CBD as a sleep aid and anxiolytic, with a likely minimum therapeutic beneficial threshold of 300 mg for a single treatment. Additional research examining varying ratios and under combined cannabinoid treatments regimens are still required to draw a better understanding of dose/effect relationships and beneficial administration routes in this therapeutic context. Some anxiolytic effects of CBD alone or in combination with THC that may in turn positively affect sleep in certain clinical populations. Despite this, further research is urgently warranted to assessing anxiety and sleep symptomology both concurrently and longitudinally.

Declarations of interest

AH is supported by a Rebecca L Cooper Al and Val Rosenstrauss Fellowship (GNT: F2021894). AN, BM and LD have no conflicts of interests to declare.

Data Availability

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104941.

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