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REVIEW

ADDICTION SSA

Efficacy of cannabidiol alone or in combination with Δ-9-tetrahydrocannabinol for the management of substance use disorders: An umbrella review of the evidence

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Abstract

Background and Aims: Substance use disorders (SUD) lead to a high burden of disease, yet treatment options are limited. Cannabidiol (CBD) is being investigated as a potential therapeutic target due to its pharmacological properties and mode of action in the endocannabinoid system. Recent systematic reviews (SR) on CBD and SUDs have shown inconsistent results. The objective of this umbrella review was to determine whether CBD alone or in combination with Δ-9-tetrahydrocannabinol (THC) is effective for managing and treating SUDs.

Methods: Following a registered protocol, we searched PubMed, Web of Science and Epistemonikos databases for SRs, with or without a meta-analysis, of randomized controlled trials focusing on interventions dispensing CBD, alone or in combination with THC, to treat SUDs, published from 1 January 2000 to 15 October 2024. Screening, data extraction and quality assessment with the AMSTAR 2 tool were performed by two researchers in parallel and duplicated.

Results: 22 SRs were included, 5 of which performed a meta-analysis. We found mixed evidence regarding the efficacy of CBD to manage and treat SUDs. Findings were interpreted in light of the quality of the SRs. Nabiximols, which contains CBD and THC, demonstrated positive effects on cannabis withdrawal and craving symptoms. Evidence supporting the efficacy of CBD is limited and inconclusive for abstinence, reduction or cessation of use of cannabis, tobacco, alcohol, opiates and other psychoactive substances.

Conclusion: Cannabidiol (CBD) monotherapy does not appear to be efficacious for treatment of substance use disorders. CBD primarily exhibits effects on cannabis withdrawal and craving when combined with Δ-9-tetrahydrocannabinol (THC). Existing data on the efficacy of CBD alone with regard to other outcomes related to substance use disorders are limited.

KEYWORDS
cannabidiol, CBD, randomized controlled trials, substance use disorders, substance use treatment, umbrella review

INTRODUCTION

The misuse of psychoactive substances, including alcohol, tobacco and illicit drugs, can have a broad range of consequences that affect an individual's physical health, mental well-being, as well as societal functioning [1–4]. The 2022 European Union Drugs Agency (EUDA) report estimated that nearly 83.4 million Europeans reported having used an illicit drug at least once in their lifetime, and 22.2 million reported having used cannabis in the last year [5]. In 2018, the Global Burden Study (GBD) estimated that 1.5% of the overall global burden of disease was attributable to substance use disorders (SUD) [6, 7]. Furthermore, in 2019, the GBD highlighted a significant rise in deaths because of SUDs over the past decade [8]. According to the World Health Organization, approximately 35 million people suffer from SUDs [9]. Alcohol use disorders (AUDs) were the most prevalent of all SUDs in 2016 with an estimated 100.4 million cases. The most common SUDs were cannabis dependence (22.1 million cases) and opioid dependence (26.8 million cases) [6]. For illicit drugs, the estimated number of users increased by 23% from 2011 to 2021, partly because of population growth [10].

Affecting individuals' brain and behavior, SUDs are chronic and relapsing conditions characterized by an uncontrollable use of psychoactive substances [11] classified into 10 distinct classes, among which alcohol, tobacco, cannabis and opioids are predominant [12]. SUDs may co-occur with physical and mental health conditions, leading to negative health and social outcomes [13, 14]. Consequently, various pharmacotherapies have been developed and are sought after to manage SUDs [15], including methadone and buprenorphine for opioid use disorder [16], nicotine replacement therapy for smoking cessation [17] and 'anti-craving' medications for alcohol use disorder [18], alongside psychosocial interventions [19]. Despite these interventions, relapse rates remain high [20] because available drugs may be ineffective for reducing or ceasing substance use and specific treatments are lacking for substances such as cannabis, cocaine or amphetamine-type stimulants [21]. There remains an ongoing need for pharmacological tools to alleviate symptoms of substance-related disorders and prevent drug relapse [22].

Cannabidiol (CBD) has garnered significant interest for the treatment of SUDs and is being investigated as a potential therapeutic agent. Among the major phytochemicals identified from the cannabis plant, Δ-9-tetrahydrocannabinol (THC) and CBD are the main cannabinoids [23–25], each possessing distinct pharmacological properties. Unlike THC, CBD lacks addictive potential and several studies in animals and humans have demonstrated its absence of rewarding properties [26]. Additionally, CBD may potentially exhibit sedative, anti-craving, antidepressant, mood-stabilizing and anxiolytic properties [27–30], along with antioxidant, anti-inflammatory and neuroprotective effects [31], as well as anticonvulsant properties [32], anti-emetic effects [33] and analgesic properties. Although CBD and THC share certain therapeutic effects, such as anti-inflammatory and antiemetic properties, CBD may also modulate the effects of THC [34].

Several distinct mechanisms explaining the action for CBD, and its efficacy in treating SUD, have been hypothesized including the modulation of the endocannabinoid, serotoninergic and glutamatergic systems [34]. Specifically, the endocannabinoid system (ECS), which is part of a broader neurobiological signaling pathway, plays a functional role in regulating mood, stress, memory and reward in the brain and is implicated in the development of SUDs [35, 36]. CBD is believed to regulate neuronal circuits involved in addiction, including emotion, cognition and reward [26]. Cannabinoid compounds such as CBD interact with CB1 and CB2 receptors in a 'key and lock' manner, modulating the ECS [37]. Specifically, CBD has shown effectiveness in inhibiting the reinforcing and rewarding properties of drugs in both human and animal studies [38]. In the last 20 years, CBD research [39] and specific interest in CBD as a promising agent for addiction treatment have increased. However, evidence regarding the effectiveness of CBD use, particularly in the treatment of SUDs, has been inconsistent. This led us to conduct an umbrella review to synthesize findings from previous systematic reviews (SRs) evaluating whether CBD has beneficial effects on the management and treatment of SUDs. Because CBD has been used alone or in combination with THC, we considered SRs of RCT testing both CBD formulations.

METHODS

Umbrella review design

We followed methodological guidelines regarding the conduct of umbrella reviews [40, 41], to summarize and evaluate evidence from multiple SRs and meta-analyses on the effectiveness of CBD for treating SUDs, using a uniform approach to facilitate comparison [41]. We registered our protocol with the International Prospective Register of Systematic Review hosted by the Centre for Reviews and Dissemination (PROSPERO, registration number CRD42023447217).

Literature search strategy and study selection

Two independent reviewers (B.R. and F.E.) conducted a systematic search in the PubMed and Web of Science databases (which offer thorough coverage of health-related research) and the Epistemonikos database, which aims to identify all of SRs relevant for health decision-making and includes multiple databases such as PsycINFO, CINAHL and EMBASE. We used a combination of keywords related to SUDs, CBD and SRs. We applied restrictions based on language (English) and publication date (1 January 2000–15 October 2024). Search equations were tailored to each database and are detailed in Table 1. We deduplicated search results using ASysd [42], Zotero and Rayyan to ensure no duplicates remained. Both reviewers (B.R. and F.E.) independently screened the results based on abstracts and titles while maintaining blinding. Disagreements were resolved through discussion or with the intervention of a third reviewer

TABLE 1 Search strategies for each database included in our umbrella review, from January 1, 2020, to on October 15, 2024.

	MESH term searches	No. of selected articles in results
PubMed		
No. 1	"CBD" OR cannabidiol OR cannabinoids OR cannab*	65 323
No. 2	"Substance-Related Disorders"[Mesh] OR substance[tiab] OR drug[tiab] OR "use disorder"[tiab] OR depend* [tiab] OR abuse[tiab] OR addict*[tiab]	4 222 489
No. 3	therap*[TIAB] OR effect*[TIAB] OR treatment [TIAB] OR medic*[TIAB] OR effic*[TIAB]	14 861 219
No. 4	1 AND 2 AND 3	20 540
No. 5	Limit 4 to [language="English","French"; year="2000-Current"]	18 094
No. 6	"systematic review" [tiab] OR "meta-analysis"[tiab] OR "meta analysis"[tiab]	382 721
No. 7	5 AND 6	585
Final equation	["CBD" OR cannabidiol OR cannabinoids OR cannab*] AND ["Substance-Related Disorders"[Mesh] OR substance[tiab] OR drug[tiab] OR "use disorder"[tiab] OR depend*[tiab] OR abuse[tiab] OR addict*[tiab]] AND [therap*[TIAB] OR effect*[TIAB] OR treatment[TIAB] OR medic*[TIAB] OR effic*[TIAB]] AND ["systematic review" [tiab] OR "meta-analysis"[tiab] OR "meta analysis"[tiab]]	585
Web of Science		
No. 1	ALL=["CBD" OR cannabidiol OR cannabinoids OR cannab*]	81 815
No. 2	TS=[[substance OR drug OR use] NEAR [disorder OR use OR abuse OR depend*] OR addict*]	24 727 402
No. 3	TS=[therap* OR effect* OR treatment OR medic* OR effic*]	25 023 945
No. 4	1 AND 2 AND 3	31 391
No. 5	Limit 4 to [language="English","French"; year="2000-Current"	29 765
No. 6	TS=["systematic review" OR "meta-analysis" OR "meta analysis"]	453 841
No. 7	5 AND 6	1049
Final equation	[[[ALL=["CBD" OR cannabidiol OR cannabinoids OR cannab*]] AND TS=[[substance OR drug OR use] NEAR [disorder OR use OR abuse OR depend*] OR addict*]] AND TS=[therap* OR effect* OR treatment OR medic* OR effic*]] AND TS=["systematic review "OR "meta-analysis" OR meta analysis"]	1049
Epistemonikos		
No. 1	[title:[[title:["CBD" OR cannabidiol OR cannabinoids OR cannab*] OR abstract:["CBD" OR cannabidiol OR cannabinoids OR cannab*]]] OR abstract:[[title:["CBD" OR cannabidiol OR cannabinoids OR cannab*] OR abstract:["CBD" OR cannabidiol OR cannabinoids OR cannab*]]]]	15 881
No. 2	[title:[[substance OR drug] OR "use disorder" OR depend* OR abuse OR addict*] OR abstract:[[substance OR drug] OR "use disorder" OR depend* OR abuse OR addict*]]	300 211
No. 3	[title:[therap* OR effect* OR treatment OR medic* OR effic*] OR abstract:[therap* OR effect* OR treatment OR medic* OR effic*]]	1 952767
No. 4	1 AND 2 AND 3	5496
No. 5	Limit 4 to [year="2000-2024"]	5242
No. 6	[title:["systematic review" OR "meta-analysis" OR "meta analysis"] OR abstract:["systematic review" OR "meta-analysis" OR "meta analysis"]]	392 167
No. 7	5 AND 6	258
Final equation	[title:[[title:[[title:["CBD" OR cannabidiol OR cannabinoids OR cannab*] OR abstract:["CBD" OR cannabidiol OR cannabinoids OR cannab*]]] OR abstract:[[title:["CBD" OR cannabidiol OR cannabinoids OR cannab*] OR abstract:["CBD" OR cannabidiol OR cannabinoids OR cannab*]]]] AND [title:[[substance OR drug] OR "use disorder" OR depend* OR abuse OR addict*] OR abstract:[[substance OR drug] OR "use disorder" OR depend* OR abuse OR addict*]] AND [title:["systematic review" OR "meta-analysis" OR "meta analysis"] OR abstract:["systematic review" OR "meta-analysis" OR "meta analysis"]]] OR abstract:[[title:[[title:["CBD" OR cannabidiol OR cannabinoids OR cannab*] OR abstract:["CBD" OR cannabidiol OR cannabinoids OR cannab*]]] OR abstract:[[title:["CBD" OR cannabidiol OR cannabinoids OR cannab*] OR abstract:["CBD" OR cannabidiol OR cannabinoids OR cannab*]]]] AND [title:[[substance OR drug] OR "use disorder" OR depend* OR abuse OR addict*] OR abstract:[[substance OR drug] OR "use disorder" OR depend* OR abuse OR addict*]] AND [title:["systematic review" OR "meta-analysis" OR "meta analysis"] OR abstract:["systematic review" OR "meta-analysis" OR "meta analysis"]]]]	258

(M.M.K.). Full-text screening of the remaining articles against the inclusion/exclusion criteria was independently conducted by the two reviewers using Rayyan while maintaining blinding. Additionally, we checked the scientific literature to include any new SRs if they were available.

Quality assessment

Two reviewers (B.R. and F.E.) independently assessed the quality of the SRs and meta-analyses included using the Assessment of Multiple Systematic Review (AMSTAR-2) instrument [43]. To rate the overall methodological quality of the SRs included, we used a scale indicating high, moderate, low or critically low confidence levels, based on critical item scores* evaluating 16 domains [43].

Eligibility criteria and data extraction

Articles were included in our umbrella review based on the following criteria: SRs with or without meta-analysis of RCTs that focused on CBD interventions to treat SUDs, published between 1 January 1 2000 and 15 October 2024. Other publications, such as scoping reviews, were excluded. Additionally, we searched for and included any RCTs published after the most recent review, if available.

Population, intervention, comparison and outcomes (PICO) elements were determined as follows:

- Population: Adult humans with SUDs, whether current users or abstinent from one or more psychoactive substances (e.g. tobacco, alcohol, cannabis, heroin, opiates, cocaine and stimulants). Articles reporting solely on animal studies were excluded.
- Intervention: Interventions involving CBD administered either alone or in combination with THC or another cannabinoid were included, namely interventions with nabiximols,† which contains CBD and THC at a 1:1 ratio. Interventions that involved only THC or another cannabinoid without CBD were excluded.
- Comparison: Groups included a placebo group (no intervention) or another pharmacological treatment/intervention group. Studies focusing solely on psychosocial interventions were excluded.
- Outcome: The main outcome is SUDs related to any substance. Outcome measures of SUDs could include withdrawal symptoms, craving, reductions in use or dependency and abstinence from one or more substances. Additionally, other outcomes such as efficacy, benefits and adverse effects were considered.

Data extraction was carried out independently twice by two reviewers (B.R. and F.E.), using a data extraction form developed by the Joanna Briggs Institute for umbrella reviews [40] and adapted for this study. This Excel-based form included the first author, year of publication, objectives, inclusion criteria, PICO information, number of RCTs relevant to CBD-containing products and SUDs, results of meta-analysis, quality assessment of included SRs, synthesis of findings, quality of evidence, our AMSTAR-2 rating and funding details. In our study, a meta-analysis could not be performed because of heterogeneity of the SRs included, which presented a variety of study designs, outcomes and statistical approaches. Therefore, the results were synthesized in a narrative way.

RESULTS

Selection and inclusion of SRs

The initial systematic search yielded 1892 record entries, reduced to 1182 after deduplication. Following the screening of titles and abstracts, and identification of additional articles through references and other searches, 22 SRs were included in our umbrella review. The study selection process is outlined in Figure 1.

Characteristics of SRs included

Of the 22 SRs included, 17 conducted a narrative synthesis of the literature [26, 44–59], whereas the remaining five SRs performed a meta-analysis [60–64]. Characteristics of the SRs included are summarized in Table 2 and RCTs cited in these SRs are summarized in Table S1.

The SRs included varied in terms of interventions and outcomes of interest. Regarding interventions, six reviews focused on cannabinoids and medical cannabis [44, 49, 58–60], 13 focused primarily on CBD, including CBD interventions alone and in combination with THC [26, 45, 46, 48, 50–57, 63], and three explored broader pharmacotherapy as the primary intervention [47, 62, 64]. More precisely, nine reviews examined the effects of CBD and nabiximols (CBD:THC 1:1), four focused solely on nabiximols, four on CBD alone, two on CBD and its effects on THC induced symptoms and THC acute effects, two considered all cannabinoids, and one review examined the effects of CBD and rimonabant.‡

The outcomes considered in our study varied and were, therefore, categorized into the following groups: all medical conditions, including SUDs [52, 60]; all psychiatric disorders, including SUDs [45, 46, 49–51, 55, 63]; only SUDs [53, 54, 56, 64]; only cannabis use disorders (CUD) [44, 58, 61, 62, 64]; only cannabis withdrawal symptoms (CWS) [59]; only on THC induced symptoms and THC acute effects [47, 48]; and AUD only [57].

*Critical items were: protocol registered before commencement of the review, adequacy of the literature search, justification for excluding individual studies, risk of bias from individual studies being included in the review, appropriateness of meta-analytical methods, consideration of risk of bias when interpreting the results of the review, assessment of presence and likely impact of publication bias.

†United States Adopted Name: nabiximols, trade name: Sativex

‡Rimonabant is a synthetic form of CBD, also known for its anorectic properties and suggested for addiction treatment; however, it was discontinued due to adverse effects.

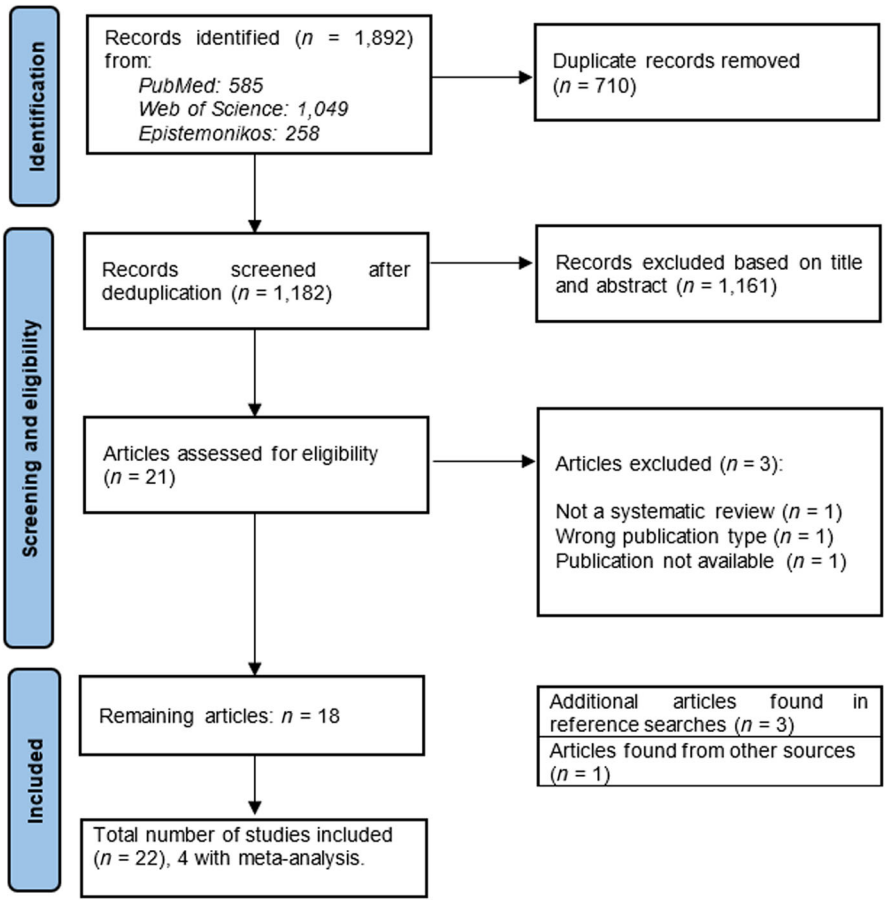

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart depicting the study selection process.

Quality of included reviews

The AMSTAR-2 ratings of the quality of the included studies were as follows: 'critically low' for seven SRs [26, 44–47, 54, 55], 'low' for five SRs [52, 53, 59, 60, 63], 'moderate' for six SRs [50, 51, 56–58, 62] and 'high' for four SRs [48, 49, 61, 64]. Of the 22 SRs, only 13 assessed the quality of the included RCTs using various tools, indicating that quality assessment is not consistently performed across the literature. The effects of CBD described by SRs, according to the quality of the study are presented in Figure 2.

CBD effects on SUDs

CUD

A combination of CBD and THC in a 1:1 ratio (nabiximols) demonstrated more positive effects in the treatment of CUDs than CBD alone [58]. Several SRs [26, 44, 45, 51, 59] suggested that nabiximols administration leads to a short-term reduction in cannabis withdrawal and craving symptoms, although these effects are limited to the acute phase [46, 48]. CBD also demonstrated efficacy in increasing treatment retention measured at 4 weeks, a relatively short time period [44, 53]. However, CBD did not show sustained efficacy in reducing use or promoting abstinence from cannabis [46, 63]. Other SRs reported no effect of CBD on CUD [52, 55], insufficient evidence on CWS and low evidence of a reduction in cannabis use and retention in CUD treatment [62]. One review identified moderate evidence of decreased cannabis use, but found no evidence of reductions in craving or withdrawal symptoms [26]. CBD may moderate some of the effects of THC, leading to a reduction in acute effects; however, this observation was inconsistently noted across the trials included in SRs [48, 61].

Tobacco use disorders

Some studies reported a positive effect of CBD [52], indicating a decrease in the number of cigarettes smoked [26, 54, 55]. However, findings regarding withdrawal symptoms or craving have been limited and mixed [45] with some studies suggesting no effect on cigarette cravings [55] or cessation rates [56, 63].

AUD

CBD was found to have no impact during the alcohol intoxication phase [56], and it did not alter the acute cognitive effects of alcohol [57].

TABLE 2 Characteristics of SRs included with the AMSTAR-2 quality assessment.

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
Bahji et al., 2016 [44]	Assess the efficacy of synthetic cannabinoid preparations for the treatment of cannabis dependence in clinical settings	RCTs Inclusion of synthetic THC/treatment/ intervention with synthetic cannabinoids Diagnosis of cannabis dependence/ CUD/ mental and behavioral disorder due to use of cannabinoids using valid diagnostic criteria	P = human adults diagnosed with cannabis/dependence/ CUD/mental and behavioral disorder using valid diagnostic criteria I = synthetic cannabinoids C = placebo O = withdrawal, reduction and retention	1 RCT (3 total) Allsop 2014	No—narrative synthesis only	No quality assessment	No reduction in cannabis use. Some reduction in cannabis withdrawal. Some treatment retention Limited evidence for efficacy of synthetic cannabinoids for the treatment of cannabis dependence		None declared
Batalla et al., 2019 [45]	Investigate efficacy of CBD treatment for schizophrenia/ SUD and/or comorbidities and if there are specific subgroups that may benefit most from CBD	Clinical trials case reports which described the effects of CBD on the symptomatology of psychotic disorders (schizophrenia and related disorders), SUD or both	P = human adults with symptoms of psychotic disorders [i.e., schizophrenia and related disorders], SUD, or both I = CBD-containing compounds C = placebo O = withdrawal, craving, use, substance related problems, severity, abstinence, relapse	6 (16 total) Allsop 2014 Hindocha 2018 Morgan 2013 Solowij 2018 Trigo 2016 Trigo 2018	No—narrative synthesis only	No quality assessment	Positive effects in reducing short-term withdrawal and craving in CUD Limited and mixed results in tobacco craving and withdrawal		Netherlands Organization for Scientific Research
Bilbao & Spanagel, 2022 [60] (PROSPERO: CRD4202122993)	Compare pharmacology-based systematic results for medical cannabinoids for all relevant medical conditions including SUD	RCTs single or double blinded Humans with a medical condition and using medical cannabinoids except natural cannabis-based formulations (i.e., smoked marijuana).	P = humans of any age or sex, with a medical condition or health problem of any type I = cannabinoids: dronabinol, nabilone, CBD, and nabiximols C = placebo O = patient-important and disease-specific	11 (152 total) Allsop 2014 Freeman 2020 Haney 2016 Hindocha 2018 Hurd 2019 Lintzeris 2019 Meneses-Gaya 2020	Yes CBD vs. placebo SMD = −0.2 (95% CI = −0.63, 0.24) low evidence on the effect estimate for CBD	Cochrane's Collaboration tool (Higgins, 2011 The RoB within studies was typically low	Limited or low evidence for CBD (GRADE 1/4), moderate evidence for nabiximols (GRADE 3/4) for having significant therapeutic effects on SUDs		

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
			outcomes, retention and adverse events	Mongeau-Perusse 2021 Morgan 2013 Trigo 2016 Trigo 2018	Moderate evidence on the effect estimate for nabiximols (SMD −0.48, 95% CI −0.92 to −0.04; p =0.03)				
Bonaccorso et al., 2019 [46]	Assess efficacy and safety of CBD use in patients with psychiatric disorders	RCTs with patients presenting SUD, psychosis, anxiety and other psychiatric disorders, and ongoing RCTs	P = adults with psychiatric disorders, including SUD I = CBDC = placebo 0 = reduction in SUD use or symptoms (withdrawal, craving, abstinence)	6 (27 total) Allsop 2014 Bhardwaj 2018 Hindocha 2018 Hurd 2015 Trigo 2016 Trigo 2018	No—narrative synthesis only	No quality assessment	Potential therapeutic effects of CBD for SUD, with some efficacy in the treatment of cannabis withdrawal symptoms, although its effect seems limited to the acute phase		None declared
Crippa et al., 2012 [47]	Review pharmacological interventions for the treatment of the acute effects of cannabis	Articles (case reports, controlled clinical trials, clinical trials of psychiatric and non-psychiatric medications, trials that promoted symptom reduction and investigations related to the period of cannabis intoxication]; studies involving human samples	P = humans I = CBD and rimonabant C = placebo 0 = physiological and psychological effects of cannabis	3 (10 total) Huestis 2001 Huestis 2007 Zuardi 1982	No—narrative synthesis only	No quality assessment	CBD and rimonabant found to counteract (…) anxious and psychotic states, but evidence lacks strength. Rimonabant and its important side effect of inducing depressive episodes limit its employment in this context		FAEPA, Brazil, and SGR2009/1435, Generalitat de Catalunya, Spain
Freeman et al., 2019 [48] (PROSPERO: CRD42019126994)	Review how CBD influences the acute effects of THC	1. Group in which THC is acutely administered, participants with previous	P = humans I = THC with or without CBD	16 (16 total in 23 articles) Arkell 2019 Bhattacharrya 2010 Bird 1980	No—narrative synthesis only	RoB within studies: Cochrane's Collaboration tool (Higgins,	CBD may moderate some of the effects of THC, commonly resulting in a reduction of its		None declared

(Continues)

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
		experience of cannabis 2. A matched group where the same dose of THC is acutely administered together with CBD, under experimental conditions 3. THC must be delivered via the same route of administration in both conditions 4. The studies must include either a placebo condition or a control condition without drug administration (necessary to evaluate the acute effects of THC) 5. Included must be peer-reviewed	C = placebo or control condition with no drug administered O = change in THC-induced effects when THC is administered with CBD	Dalton 1976a Dalton 1976b Englund 2013 Freeman 2018 Guy 2003 Haney 2016 Hindocha 2015 Hollister 1975 Hunt 1981 Juckel 2007 Karniol 1974 Lawn 2016 Morgan 2018 Nadulski 2005 Nicholson 2004 Roser 2009 Stadelmann 2011 Wall 2019 Zuardi 1982		2011), RoB across studies: ROB2ROB2 The RoB within and across studies was typically low. Potential conflicts of interest	acute effects, but this was not observed across all studies		
Hindley et al., 2020 [61] (PROSPERO: CRD42019136674)	Investigate the psychotomimetic and psychiatric effects of THC and CBD, the moderating effects of CBD on THC-induced symptoms	1. Double-blind studies that included healthy participants 2. Reported symptom changes in response to acute administration of	P = healthy participants I = acute administration of cannabinoids (THC, CBD or other) either delivered orally, through inhalation or intravenously C = placebo	4 (19 total) Bhattacharyya 2010 Englund 2013 Morgan 2018 Mueller 2016	Narrative synthesis only for CBD's moderating effects as an outcome, due to limited number of studies	Newcastle–Ottawa Scale One study had a score 6 = moderate RoB (Morgan et al., 2018), and 3 studies had scores of 7 or	No consistent evidence that CBD induces symptoms or moderates the effects of THC. Concurrent CBD administration did not significantly reduce the		UK Medical Research Council (no. MCA6565QD30), Maudsley Charity (no. 666), Brain and Behavior Research Foundation, and

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
		intravenous, oral, or inhaled THC 3. Contained either a placebo condition [for the effects of THC or CBD alone] or concurrent administration of THC + CBD or placebo CBD 4. Used a within-person, crossover design; reported total, positive or negative symptoms using BPRS or PANSS 5. Presented data allowing the calculation of the standardized mean difference and deviation between the THC and placebo condition	O = positive, negative, general and total symptom change in response to cannabinoid administration when compared to placebo Measures of effect: PANSS; BPRS			more = low RoB (Englund et al., 2013; Mueller et al., 2016, Bhattacharyya et al., 2010)	induction of symptoms in three of four studies identified		Wellcome Trust (no. 094849/Z/10/Z) grants to ODH, and the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London (London, UK). KB from Rosetrees Trust and the Stoneygate Trust
Hoch et al., 2019 [49] (PROSPERO: CRD42016053592)	Systematically screen the RCTs to assess the efficacy and safety of cannabis-based medicines as a treatment of mental disorders	1. SRs and RCTs 2. Testing the efficacy and safety of medical cannabis [with or without additional medication and psychotherapy] for the treatment of mental disorders 3. Published between 2006 and 2018	P = humans only I = medical cannabis C = placebo or any other active medication O = efficacy, tolerability and safety of medical cannabinoids	3 (25 total) Allsop 2014 Trigo 2016 Trigo 2018	No—narrative synthesis only	SIGN Checklist for methodological quality and 2011 OCEBM. Levels of evidence based on study type and quality (1 = *highest* to 5 = *lowest*) 2 studies (Allsop, 2014, and Trigo,	Some evidence available for THC-based medicine (nabiximols) as an add-on to other interventions in the treatment of substance use disorders (CBT) Reduction of cannabis withdrawal symptoms and also		The German Ministry of Health

(Continues)

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
						2018) had a level of evidence of 2 and a + SIGN (acceptable) One study had a level of evidence of 3 and a − SIGN (low quality)	craving was found in some studies but not consistently		
Khan et al., 2020 [50]	Review the use but also the efficacy, safety, and psychiatric benefits of CBD and CBD-containing compounds to treat psychiatric disorders	All studies including CBD and CBD-containing compounds use for psychiatric disorders	P = humans with psychiatric disorders including SUDs I = CBD and nabiximols C = placebo O = change in global psychiatric disorders outcomes or symptoms	5 (23 in total) Allsop 2014 Pokorski 2017 Solowij 2018 Trigo 2016 Trigo 2018	No—narrative synthesis only	2019 OCEBM levels of evidence to grade the quality of evidence per study 3 studies had a level of evidence of 2 (Allsop 2014, Trigo 2016, Trigo 2018) 2 studies (Pokorski 2017 and Solowij 2018) had a level of evidence of 3	Beneficial effects of nabiximols and CBD on cannabis-related disorders with grade B recommendation Decreased risk of withdrawal symptoms, dependence and craving among participants, with an additive benefit from the use of psychotherapeutic options such as MET or CBT		No funding
Khoury et al., 2017 [51]	Assess the benefits and AEs of CBD in the treatment of psychiatric disorders	1. Studies assessing the outcomes of CBD in the treatment of anxiety, psychosis, schizophrenia, depressive disorder, bipolar disorder, or substance use disorders	P = humans with psychiatry disorders I = CBD C = placebo O = schizophrenia, psychotic disorders, anxiety disorders, depression, bipolar disorder, and substance use disorders	3 (13 studies + 21 additional RCTs with no published results total) Allsop 2014 Morgan 2013 Trigo 2016	No—narrative synthesis only	No individual RoB/or quality assessment of papers	Global grade of evidence for effect of CBD done using WFSBP task forces standards Use of Sativex in the treatment of withdrawal in cannabis dependent patients is B (limited positive evidence		Supported by FAPEMIG under grant APQ-01714-13 and National Council for Scientific and Technological Development, CNPq (Conselho Nacional de Desenvolvimento

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
		2. All types of study designs: clinical trials (randomized or not), observational, retrospective and prospective studies, and case reports					from controlled studies) and recommendation grade 3 Use of CBD in the treatment of tobacco addiction is C1 (uncontrolled studies) and recommendation grade 4 Use of oral CBD for the treatment of cannabis dependence has grade C2 (evidence from uncontrolled studies or case reports/expert opinion) and recommendation grade 4		Tecnológico, Brazil) under grant 486221/2013-0
Kondo et al., 2020 [62] (PROSPERO: CRD42018108064)	Examine the benefits and harms of pharmacotherapies to treat CUD	Studies: 1. Which were RCTs 2. Involving adults or adolescents who had diagnosed CUD or reported heavy cannabis use 3. Which directly compared any pharmacologic interventions or compared pharmacotherapy with placebo, usual care, or psychotherapy	P = non-pregnant adults and adolescents with known or suspected cannabis use disorder I = pharmacotherapies treatment for cannabis use disorder (including nabiximol) with or without adjunctive treatment C = usual care, placebo, or other interventions O = abstinence, reduction of use, severity of withdrawal	3 (26 in total) Allsop 2014 Lintzeris 2019 Trigo 2018	Yes Meta-analysis only on treatment completion outcome and nabiximols as intervention Allsop 2014: RR 1.22 [0.59, 2.53] Lintzeris 2019: N/A Trigo 2018: RR 0.93 [0.60, 1.43]	Cochrane's Collaboration tool Low RoB: Allsop 2014 Unclear RoB: Trigo 2018 Unknown RoB: Lintzeris 2019	Global SoE given for each outcome Low SoE for cannabis use reduction, retention Moderate SoE for abstinence Insufficient SoE for withdrawal symptoms		US Department of Veterans Affairs

(Continues)

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
		4. Assessed 1 or more of cannabis-related outcomes of interest (abstinence, cannabis use, treatment retention, and withdrawal symptoms Limited inclusion to studies of 4 weeks or longer for all outcomes except withdrawal symptoms	symptoms, retention in treatment of cannabis use disorder						
Larsen and Shahinas, 2020 [52]	To collect dose[s], dosage schemes, efficacy and safety reports of CBD use in adults from clinical studies	Studies including human and more than 10 adult patients, with single treatment of CBD	P = humans I = CBD single treatment C = placebo or active control group 0 = disorder specific outcome measures	3 (25 in total) Haney 2016 Hindocha 2018 Morgan 2013	No—narrative synthesis only	Cochrane's Collaboration tool Two studies were judged at uncertain risk of bias and one at high risk (name of studies not available)	No effect on primary outcome measures for cannabis use disorder Positive effect reported on tobacco addiction GRADE not available for SUD outcome		Nordic Cannabis Research Institute
McKee et al., 2021 [63]	To examine the potential therapeutic benefits clinical indications of cannabinoid products in psychiatric disorders	All RCTs examining the effectiveness of cannabinoids and CBPs as a treatment for mental health-related symptoms. Subjects had to have a primary diagnosis of a psychiatric disorder Treatment was defined as single or repeated administration of a	P = adults with psychiatric disorders I = single or repeated administration of a cannabinoid or CBP C = placebo or an active comparator condition 0 = reduction in symptom frequency or severity	8 (31 total) Allsop 2014 Freeman 2020 Hurd 2019 Lintzeris 2019 Morgan 2013 Robinson 2018 Trigo 2016 Trigo 2018	Yes No pooling of studies trialing dissimilar cannabinoids for meta-analyses SMD for the effectiveness of improved withdrawal discomfort	RoB2 Low RoB: Allsop 2014 Unclear RoB: Morgan 2013, Robinson 2018, Trigo 2018, Trigo 2016 High RoB: Freeman 2020, Lintzeris 2019, Hurd 2019	Mixed effectiveness with some reports of reductions in withdrawal and cravings, with increased treatment retention, but limited evidence for sustained reductions in cannabis use or abstinence rates		Sanofi, Janssen, Allergan, Asia-Pacific Economic Cooperation, BC Leading Edge Foundation, Canadian Network for Mood and Anxiety Treatments, Healthy Minds Canada, Janssen,

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
		cannabinoid or CBP. All routes of cannabinoid administration			score of nabiximol: −0.21 [−0.52, 0.11] No statistical difference in WDS in treatment and control groups (Allsop 2014, Lintzeris 2019, Trigo, 2016, 2018)				Lundbeck, Lundbeck Institute, Michael Smith Foundation for Health Research, MITACS, Myriad Neuroscience, Ontario Brain Institute, Otsuka, Pfizer, Unity Health, and VGH Foundation
Morel et al., 2021 [53]	To review the outcome measures, surrogate endpoints, and biomarkers in published and ongoing randomized clinical trials	Double-blinded, randomized, placebo or adequate control in subjects with a formal diagnosis of SUD, assessing CBD alone or in association with other cannabinoids and reporting at least one primary outcome regarding SUD	P = adults with formal diagnosis. I = CBD alone or in association with other cannabinoids C = placebo or adequate control 0 = substance use, abuse addiction, dependence	3 (3 total) Allsop 2014 Lintzeris 2019 Trigo 2018	No—narrative synthesis only	Cochrane's Collaboration tool and CONSORT 2010 Allsop 2014: Consort: 31/32 Biases: 1/10 Trigo 2018: Consort = 24/32 Biases = 2/10 Lintzeris 2019: CONSORT = 30/32 Biases: 3/10 →good overall quality	No published study demonstrating the efficacy of CBD alone to treat any SUD Nabiximols showed effects for withdrawal symptoms and retention, no significant findings on other outcomes		DRCI, Assistance Publique–Hôpitaux de Paris
Navarrete et al., 2021 [26]	To review preclinical and clinical reports regarding the effects of CBD on the regulation of the reinforcing, motivational and	All original articles, SRs or meta-analyses focusing on the effects of CBD on drug addiction in humans and animals	P = humans and animals I = CBD C = placebo O = effects on the regulation of the reinforcing, motivational and	14 (total not indicated) Allsop 2014 Beale 2018 Bhardwaj 2018 Freeman 2020 Haney 2016 Hindocha 2018a	No—narrative synthesis only	No quality assessment	Moderate evidence for decreased cannabis use; none for craving and withdrawal Reported short-term decrease in opioid craving, decrease in		Instituto de Salud Carlos III, Fondos FEDER, RTA (RD16/0017/0014), Ministerio de Sanidad, Delegación del

(Continues)

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
	withdrawal-related effects of different drugs of abuse		withdrawal-related effects of different drugs of abuse: alcohol, opioids (morphine, heroin), cannabinoids, nicotine, and psychostimulants (cocaine, amphetamine)	Hindocha 2018b Hurd 2019 Lintzeris 2019 Morgan 2013 Solowij 2018 Trigo 2016a Trigo 2016b Trigo 2018			number of cigarettes smoked No results in human trials for alcohol and psychostimulants		Gobierno para el PNSD (2019I012)
Nielsen et al., 2021 [64]	To assess the effectiveness and safety of medicines for the treatment of cannabis dependence	RCTs and quasi-RCTS involving the use of medications to treat cannabis withdrawal, to promote cessation or reduction of cannabis use or both	P = patients diagnosed as or likely to be cannabis dependent I = any drug therapy to treat cannabis dependence C = placebo or no medication (supportive counseling) O = reduction of withdrawal symptoms, cessation or reduction of use, adverse effects, patient compliance	2 (21 total) Allsop 2014 Trigo 2018	Yes Meta-analysis does not concern studies with only CBD Allsop 2014 and Trigo 2018 included only in THC-containing products vs. placebo analyses Abstinence: Trigo 2018 RR 0.77 (0.32, 1.83) Adverse effects: Trigo 2018 RR 0.89 (0.68, 1.16) Withdrawn due to adverse effects: Trigo 2018 not estimable Completion of treatment:	Cochrane's Collaboration tool Low RoB: Allsop 2014, Trigo 2018	GRADE quality of evidence for effect of CBD Reported only for THC-containing products Moderate certainty of evidence for abstinence, adverse effects (Trigo 2018 + 2 THC only RCTs) Low certainty of evidence for withdrawal due to adverse effect (Trigo 2018 + 2 THC only RCTs), completion (Allsop 2014, Trigo 2018 + 2 THC only RCTs) THC and CBD products may be of potential value based on qualitative data from individual studies; no significant effect on outcomes in meta-analyses		DASSA-WHO Collaborating Centre in the Treatment of Drug and Alcohol Problems, Australia

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
					Trigo 2018 RR 0.93 (0.6, 1.43) and Allsop 2014, RR 1.36 (0.93, 1.93)				
Paulus et al., 2022 [54]	To provide a comprehensive summary of evidence of the effect of CBD in the context of substance use and addictive disorders	Articles that evaluated the effects of CBD on SUD All types of animal and human studies, including case reports Studies not included if CBD was only in combination with THC	P = humans and animals I = CBD C = placebo 0 = SUD outcomes for tobacco, cannabis, alcohol, opioids, cocaine, methamphetamine	12 (40 total) Consroe 1979 Freeman 2020 Hindocha 2018a Hindocha 2018b Hurd 2015 Hurd 2019 Manini 2015 Meneses-Gaya 2020 Mongeau-Pérusse 2021 Morgan 2010a Morgan 2010b Morgan 2013	No—narrative synthesis only	No quality assessment	Human studies showed a positive effect of CBD in the context of tobacco (decrease of number of cigarettes, decrease of pleasure associated to smoking, no difference in craving or withdrawal), cannabis [decrease of frequency of use], and opioid use (decrease of craving scores, no effect on relapse) No effect in human studies on cocaine or alcohol use No human study identified on methamphetamine use		No funding
Pavel et al., 2021 [55]	To assess the effect of CBD as a pharmacological intervention in psychiatric disorders and its impact on disease severity	Studies assessing the effect of CBD as monotherapy or add-on therapy on disease severity as primary outcome in psychiatric disorders	P = humans with psychiatric disorders I = CBD as add-on or mono therapy C = placebo O = disease severity in psychiatric disorders	3 (9 total) Hill 2016 Hurd 2019 Morgan 2013	No—narrative synthesis only	RoB2 High RoB for all 3 studies	Evidence regarding its effect on disease severity is contradictory CBD significantly reduced the number of cigarettes smoked but had no		No funding

(Continues)

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
							impact on cigarette craving. CBD reduced heroin craving compared to placebo. No effect on cannabis use disorder		
Prud'Homme et al., 2015 [56]	To systematically examine the existing preclinical and clinical evidence on the effects of CBD on addictive behaviors	Studies of all designs that evaluated the outcomes of CBD on addictive behaviors	P = human and animals I = CBD C = placebo O = for major types of substances of abuse (opioids, psychostimulants, cannabis, hallucinogens, sedatives, alcohol, tobacco, etc.) in three phases in intoxication, withdrawal, and craving/relapse	4 (14 total) Consroe 1979 Morgan 2010a Morgan 2010b Morgan 2013	No—narrative synthesis only	No quality assessment	CBD may be beneficial in cannabis and tobacco addiction No impact on the alcohol addiction intoxication phase in humans; no data on other phases No human study was found for opioid-, psychostimulant-, hallucinogen-, or sedative-addictive behaviors		Canadian Institute on Health Research (MOP125864), the CHUM Department of Psychiatry, Université de Montréal. Department of Psychiatry and the CHUM Research Center.
Turna et al., 2019 [57] (PROSPERO : CRD42018109578)	To characterize the existing literature on this topic and to evaluate the credibility of CBD as a candidate pharmacotherapy for AUD	Original article; CBD as an experimental intervention or in an observational design; study outcomes must examine some aspect of alcohol-related harm	P = humans and animals I = CBD C = placebo O = AUD Protection of cognition and prevention of neurodegeneration, motivation and relapse, hepatoxicity	3 (12 total) Belgrave 1979 Bird 1980 Consroe 1979	No—narrative synthesis only	No quality assessment	In three studies, CBD does not alter the acute cognitive effects of alcohol Protection of cognition and prevention of neurodegeneration is the only outcome domain where human studies were identified		Michael G. DeGroote Centre for Medicinal Cannabis Research, the Peter Boris Chair in Addictions Research, and NIH grants AA025849 and AA025911
Vuilleumier et al., 2022 [58]	To summarize and discuss the main findings of RCTs	All placebo-controlled trials including adults with diagnosed CUD	P = adults with a diagnosis of CUD according to a valid	5 (9 total) Allsop 2014 Freeman 2020	No—narrative synthesis only	Cochrane's Collaboration tool	Only modulators of endocannabinoid activity (nabiximols,		Open Access Publication Fund

TABLE 2 (Continued)

First author, year (Protocol)	Objectives	Inclusion criteria	Patients / Interventions / Comparator / Outcomes	No. of included RCTs for CBD containing products and SUD (total number of studies included in SR)	Meta-analysis (yes/no)	RoB/or quality assessment of individual studies within included SRs	Synthesis of findings and quality of evidence	AMSTAR-2 (quality assessment)[a]	Funding/conflict of interest
	[RCTs] evaluating the efficacy, safety and tolerability of different medical cannabinoids in the treatment of CUD	examining any pharmacotherapy with medical cannabinoids, for reduction CUD outcomes [use, abstinence, withdrawal, craving symptoms, treatment retention, safety, and tolerability	diagnostic classification system I = medical cannabinoids (i.e., dronabinol, nabilone, nabiximols, CBD, or endocannabinoid modulators) as add-on or mono-therapy C = placebo O = reduction of cannabis use, maintenance of abstinence, reduction of withdrawal symptoms, reduction of craving, retention in treatment, safety, and tolerability	Lintzeris 2019 Lintzeris 2020 Trigo 2018		High RoB: Allsop Low RoB: Trigo 2018, Lintzeris 2019, 2020, Freeman 2020	CBD), demonstrated broader efficacy for CUD (withdrawal, use, abstinence)		of the University of Duisburg-Essen
Werneck et al., 2018 [59] (PROSPERO: CRD42014014118)	To summarize trials with cannabinoid agonist replacement therapy for cannabis withdrawal symptoms with the aim of evaluating the efficacy of this pharmacological intervention	Original trials on humans and dealing with cannabis users who were treated for cannabis withdrawal symptoms using synthetic cannabinoids	P = humans, cannabis users I = synthetic cannabinoids C = placebo O = cannabis withdrawal symptoms	2 (10 total) Allsop 2014 Trigo 2016	No—narrative synthesis only	Cochrane's Collaboration tool Low RoB: Allsop 2014 (6/6), Trigo 2016 (5/6)	Some evidence for CBD in treatment of cannabis withdrawal symptoms and short-term decrease in relapse rates		No funding

Abbreviations: AEs, adverse events; AMSTAR-2, Assessment of Multiple Systematic Review; AUD, alcohol use disorder; BPRS, Brief Psychiatric Rating Scale; CBD, cannabidiol; CBT, cognitive behavioral therapy; CUD, cannabis use disorder; DASSO-WHO, Drug and Alcohol Services South Australia-World Health Organization; DRCI, Direction de la Recherche Clinique et de l'Innovation; FAPEMIG, Fundação de Amparo à Pesquisa do Estado de Minas Gerais, Brazil; MET, Motivational Enhancement Therapy; NHS, National Health Service; NIH, National Institutes of Health; NIHR, National Institute for Health Research; PANSS, Positive and Negative Syndrome Scale; PNSD, Plan Nacional Sobre Drogas; RoB, risk of bias; RTA, Red de Trastornos Adictivos; SMD, standard mean difference; SoE, strength of evidence; SRs, systematic reviews; SUD, substance use disorder; THC, Δ-9-tetrahydrocannabinol; UK, United Kingdom; USA, United States; WFSBP, World Federation of Societies of Biological Psychiatry.

[a]High quality in green, moderate quality in yellow, low quality in orange, and critically low quality in red.

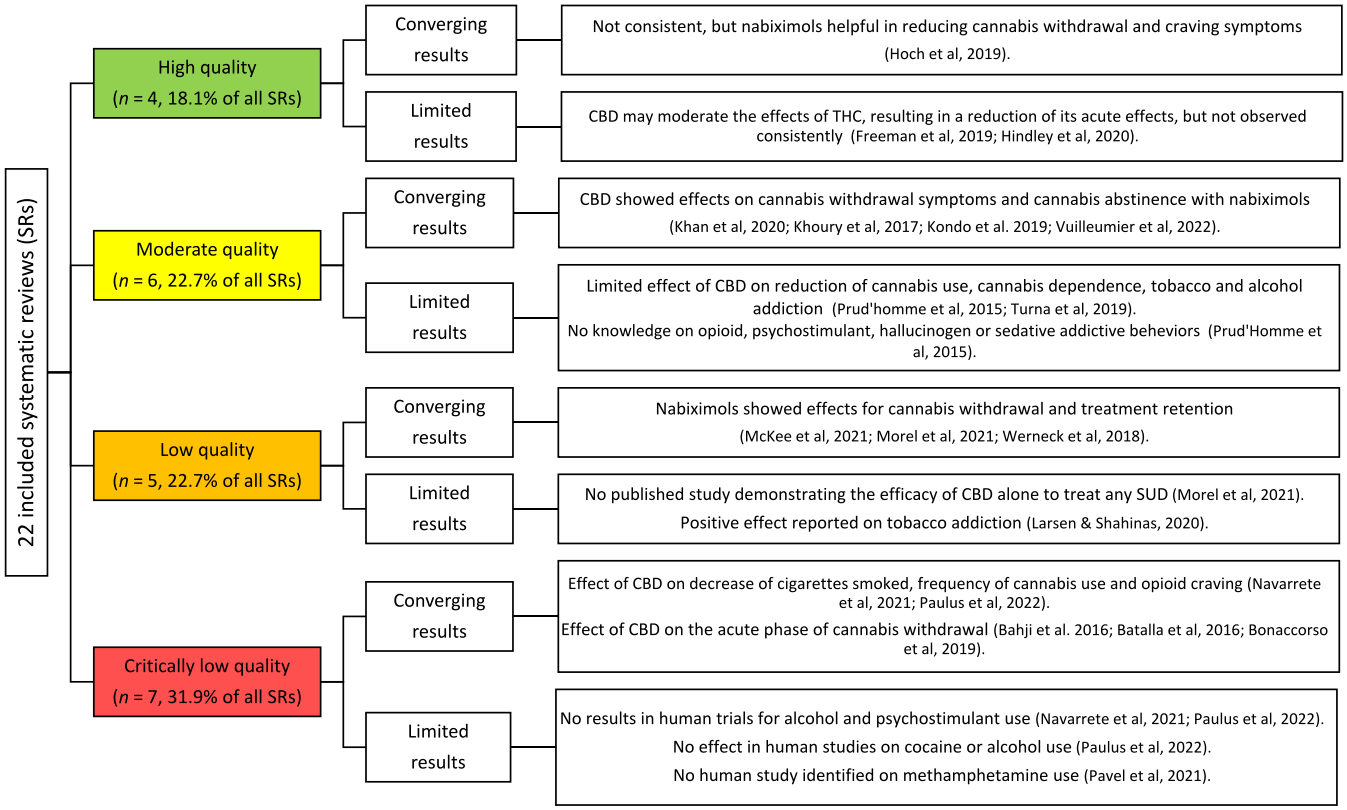

FIGURE 2 Evidence regarding the quality of the included systematic reviews (SRs).

Other SUD

CBD demonstrated some efficacy in the short-term reduction of heroin craving symptoms, measured 7 days after a 3-day CBD exposure at 800 mg/day [26, 54, 55]. No effects of CBD on cocaine and other stimulants use were observed, and no studies were identified regarding methamphetamine use.

Serious adverse events

Overall, CBD and CBD with THC medications were well tolerated and did not cause serious adverse events.

DISCUSSION

Framing the evidence on CBD for SUDs

This study offers a comprehensive overview of the therapeutic effects of CBD, alone or in combination with THC, on all SUDs. In contrast, existing systematic or umbrella reviews primarily focus on various medical conditions or mental disorders as main outcomes, often relegating or excluding SUDs. The only review specifically centered on SUDs as the main outcome was a scoping review by Fernandes *et al.* [65], which indicated that both CBD and THC have potential for treating certain SUDs such as cannabis use disorders, though the evidence is limited. Therefore, this umbrella review consolidates currently available evidence on the possible beneficial effects of CBD as a management strategy for SUDs.

Efficacy of CBD for SUD treatment

Consistent with previous studies, we found mixed evidence regarding the potential of CBD to help manage and treat SUDs [65, 66]. The most common observation from the SRs included, especially those characterized by a high methodological quality, indicated that nabiximols (CBD:THC 1:1) may be beneficial in treating withdrawal and craving symptoms associated with cannabis cessation. Some studies hypothesized that CBD might modulate certain acute effects of THC, such as anxiety or psychosis-like symptoms [48]. However, this observation was not consistently supported across studies, and there is no conclusive evidence that CBD either induces or moderates THC effects [61]. A recent study found that CBD does not mitigate the acute effects caused by THC [67]. Moreover, a recent RCT found no evidence that CBD, at any dose, protects against the acute effects of THC [68].

Moreover, interventions using THC and CBD-containing medications (nabiximols in the case of our included reviews) for SUDs may also benefit from psychotherapeutic interventions commonly used in SUD treatment, such as Motivational Enhancement Therapy (MET) or

Cognitive Behavioral Therapy (CBT) [49, 50], as complementary approaches. For CUD in particular, such interventions, namely CBT, are currently the first-line treatments in the absence of established medication strategies [69]. Nabiximols may reinforce the impact of psychotherapeutic interventions given its effect on cannabis craving and use [70].

When considering abstinence, reduction, or cessation of use of cannabis, tobacco, alcohol, heroin or other psychoactive substances, evidence supporting the efficacy of CBD is limited and inconclusive. In particular, the effects of nabiximols on withdrawal and craving symptoms associated with cessation have not translated into reductions in use or improvements in abstinence. Moreover, findings should be interpreted in the context of the methodological quality of existing SRs, which is unequal. We consistently observed positive effects of nabiximols on cannabis withdrawal and cravings across most SRs and particularly in those of high quality. This underscores the potential therapeutic benefits of the CBD: THC combination for treating cannabis use disorder. However, it is important to note that we could not conclude to these effects with regard to tobacco use, heroin cravings because of the low methodological quality of studies in these areas, pointing to the need for additional high-quality research.

Potential for CBD in harm reduction

The findings across SRs indicate a role for CBD in managing withdrawal and craving symptoms in the use of cannabis, tobacco and opiates, rather than contributing to reduction or cessation of use. In the perspective of established and long-term use where individuals wish to limit their consumption and associated risks at a given point, CBD may be helpful to improve well-being as part of a harm reduction strategy for people who use drugs [71].

Limited quantitative results on CBD for SUD

Out of the 22 SRs, only 5 performed meta-analyses. Three of these reviews [61, 63, 64] could not conduct meta-analyses on CBD-only interventions because of a limited number of studies. One review [62] solely conducted a meta-analysis on the effectiveness of a nabiximols intervention. In another meta-analysis [60], some methodological limitations were identified: subtotal standard mean difference (SMD) scores were assigned by cannabinoid type, but these were applied to different SUDs with distinct symptoms. Then a total SMD score was derived from these subtotal scores, but for compounds with varying cannabinoid compositions. Consequently, there is a paucity of quantitative results regarding the effects of CBD-only interventions on specific SUD outcomes. One systematic review highlighted that no published study demonstrated the efficacy of CBD alone in treating any SUD [53]. This underlines the necessity for additional high-quality, large-sample RCTs to explore the effects of CBD, either alone or in combination with other cannabinoids, on SUDs.

Scarcity of RCTs on CBD for SUD and future challenges

In recent years, the volume of publications on CBD and SUDs has increased; however, the number of clinical trials retained because of satisfactory quality remains limited. Among the 22 SRs, 43 RCTs were reviewed. Interestingly, a few RCTs are frequently cited, including, in decreasing order: Allsop *et al.* [72], Hindocha *et al.* [73], Lintzeris *et al.* [74], Morgan *et al.* [75] and Trigo *et al.* [76], with three of these on CUD and two on tobacco use outcomes. This raises questions about the limited number of RCTs focused on CBD and SUD. At the time of this umbrella review, registered and ongoing trials of CBD on SUD remained scarce. This scarcity may be attributed to challenges inherent to the conduct of large, high-quality RCTs using approved cannabis-based products, especially if such trials do not lead to patent-protected prescription medications within a pharmaceutical framework. Limitations of research on CBD and SUD might stem from licensing and regulatory requirements, such as working with botanical extracts or controlled medications and substances. Additionally, methodological challenges arise when attempting to investigate and isolate the effects of various cannabinoids present in the cannabis plant and available as medication [77].

Limitations and strengths

The findings of our umbrella review must be considered within the context of some limitations. First, we could not conduct a meta-analysis because of heterogeneity of SUD outcomes considered, in cannabinoids studied, methods of administration, CBD dosages (ranging from a maximum of 80 mg CBD/86.4 mg THC to 105 mg CBD/113.4 mg THC in the case of nabiximols, titrated or self-titrated) and small sample sizes. Second, we did not examine the possible effects of CBD dosage and formulation for oral administration on specific SUD outcomes, which should be addressed in future specialized studies (self-titration may lead to different results than titration or a fixed dose and new formulations of oral CBD may become available). Despite these limitations, our study also has strengths. First, we consolidated currently available evidence on the effect of CBD across a broad spectrum of SUDs, including cannabis, alcohol, tobacco and heroin use. Second, we included studies from 2000 to 2024 to capture all recently published SRs on the topic.

CONCLUSION

This umbrella review does not suggest any efficacy of CBD monotherapy as a therapeutic agent in SUDs. CBD primarily exhibits effects on cannabis withdrawal and craving symptoms when combined with THC in nabiximols. The CBD:THC 1:1 effects suggest that the potential benefits observed in cannabis withdrawal and craving may be because of THC, with CBD providing no additional benefit. We found

no evidence for CBD alone, in the absence of THC, in managing cannabis and other SUDs. Notably, few SRs on this topic were of high methodological quality. Additional research is essential, incorporating data from robust RCTs, using comparable CBD interventions and standardized outcome measures.

AUTHOR CONTRIBUTIONS

Bertrand Redonnet: Data curation; formal analysis, investigation, methodology, writing—original draft preparation. **Filiz Eren**: Data curation; formal analysis; investigation; methodology writing—original draft preparation. **Guillaume Avenin**: Writing—review and editing. **Maria Melchior**: Validation; writing—review and editing. **Murielle Mary-Krause**: Conceptualization; methodology; supervision; validation; writing—review and editing.

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DECLARATION OF INTERESTS

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

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