Cannabidiol in clinical trials for substance use disorders: outcomes, surrogate endpoints and biomarkers.

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ABSTRACT

Background: Cannabidiol (CBD) is a cannabinoid of potential interest for substance use disorders treatment. Our aim was to review the outcomes, surrogate endpoints and biomarkers in published and ongoing randomized clinical trials assessing the clinical efficacy of CBD in this context.

Methods: We conducted a search in PubMed, "*clinicaltrials.gov*", "*clinicaltrialsregister.eu"* and "*anzctr.org.au*" for published and ongoing studies. Inclusion criteria were randomized clinical trials (RCT) examining the use of CBD alone or in association, in all substance use disorders. Included studies were analyzed in detail and their qualities assessed by the Consolidated Standards of Reporting Trials tool (CONSORT 2010). A short description of excluded studies, when consisting in controlled short term or single administration in non-seeking treatment drug users, is provided.

Findings: The screening retrieved 207 published studies, including only 3 RCT in cannabis use disorder. Furthermore, 12 excluded studies in cannabis, tobacco and opioid use disorders are described.

Interpretation: Primary outcomes were validated withdrawal symptoms scales and drug use reduction in the 3 RCT. In the short-term or cross-over studies, the outcomes measures were visual analogue scales for subjective states, self-rated scales for withdrawal, craving, anxiety or psychomimetic symptoms, as well as laboratory tasks of drug-induced craving, effort expenditure, attentional bias for the substance, impulsivity, or anxiety to serve as surrogate endpoints for treatment efficacy. Of note, ongoing studies are now adding peripheral biomarkers of the endocannabinoid system status to predict treatment response.

Conclusion: The outcomes and biomarkers assessed in the ongoing CBD trials for substance use disorders is improving.

INTRODUCTION

The legalization of "medical marijuana" in several parts of the United States, soon followed by other countries, has produced an exponential increase in research using different active compounds derived from the cannabis sativa plant in various medical conditions including substance use disorders (1).

Among those pharmacological agents, Cannabidiol (CBD) maybe the one provoking the highest expectations. For the general audience, it is an pain-killer and anxiolytic compound consumed either in oil for dermal delivery, oral in oil (2) or herbal tea, or smoked in electronic cigarettes (3,4) for the self-treatment of several conditions associated with chronic pains, insomnia and various psychological suffering. Compared to Tetrahydrocannabinol (THC), CBD is the product of choice for medical cannabis users who do not have an associated recreational use (5).

Pharmacologically speaking, CBD is a CB1-receptor low affinity agonist (5, 6), with inverse-agonist properties in the presence of THC (8). Targeting the specific CB1-receptor could be of interest in the treatment not only of cannabis use disorder. Indeed, it could be relevant also in depression, anxiety or substances-related disorders in general for three reasons. First, this G-coupled protein is abundant and ubiquitous in the Human brain, from the brainstem and cerebellum to the basal ganglia, hippocampus and neo-cortex, thus regulating several important brain functions (9). Second, CB1 antagonists can provoke serious mood disorders (10), thus supporting the reverse hypothesis, that CB1 agonists, including those with low affinity as CBD, might have antidepressant effects. Third, several genetic variants of *CNR1*, the CB1-coding gene, located on chromosome 6q14–15 (NC_000006.12), have been associated with either addictive ((11–15) or mood disorders ((16) in case-control studies, highlighting again the potential therapeutic properties of the pharmacological modulation of this target. The published GWASes of lifetime cannabis use and cannabis use disorders ((17–19) did not confirm the association. But, the genetic risk conferred by minor alleles in *CNR1* are expected to have a small effect size and to interplay with several risk alleles for various

psychiatric disorders. Still, genetic variants of *CNR1*, especially those located in the 3'UTR region, regulating the translation and stability of RNA, are good candidate biomarkers for treatment efficacy of pharmacological agents targeting the CB1-receptor.

Furthermore, CBD has several non-direct CB1-receptor effects, as demonstrated in animal or cellular models. It modulates the conformation of CB1- and CB2-receptors heteromeric complexes(8). It is also a strong agonist of TRPV (vanilloid channel receptors family) located on endothelial cells, including the blood brain barrier (20), mediating its anti-inflammatory effects along with second messengers pathways activation. CBD inhibits the cellular re-uptake of the endocannabinoid anadamide, increasing its activity (21), but also increasing its disposition (22). Lastly, CBD seems to have 5HT1-receptor agonist properties (23) and 5HT3a antagonist properties (24). Those last two properties, like the CB1-receptor agonist activity, are theoretically of interest in managing anxiety and depressive symptoms often at work in substance use disorders relapse.

CBD has demonstrated some anxiolytic properties in preclinical (25) and Human studies (26), but most of this effect was obtained in studies where CBD was compared to THC, the major compound of smoked cannabis. CBD has also anticonvulsant properties (27), now well established in controlled trials as an adjunctive treatment in child refractory conditions (Lennox-Gastaut and Dravet syndromes), and has a Food and Drug Administration (FDA) approval for those indications.

As safety is concerned, in Human studies, CBD has been safely administrated for several weeks to human subjects. Especially CBD does not induce psychodysleptic effects or abuse. Indeed, as an add-on treatment of schizophrenia (28), at a dose of 1000 mg per day during 6 weeks, CBD produced only a slight decrease in positive symptoms compared to placebo, but with acceptable tolerance (the main side effects being nausea in 1/3 of patients in the active group). CBD does not induce withdrawal symptoms as was shown by a specific trial assessing withdrawal symptoms after 4 weeks of CBD 750 mg twice a day and either blind maintenance

or abrupt cessation under placebo (29). In this trial, as in the literature, to the best of our knowledge, no report of CBD use disorder has been published.

As efficacy is concerned, CBD has shown some promising properties in preclinical studies, and some clinical studies in the field of psychiatry and addiction medicine. To help identify the methods currently used to assess the potential therapeutic properties of CBD in substance use disorders and isolate them from the noise of the high expectations, we choose to perform a review of both published and on-going randomized clinical trials in Humans. We present the studies with a specific focus on the outcomes, surrogate endpoints and biomarkers developed by the authors to show clinical efficacy or at least to show that CBD could modify targets associated with efficacy in substance use disorders.

METHODS

Search strategy and selection criteria

First, we conducted a review of the published clinical trials through a PubMED data search. Looking for double-blind randomized trials, published before May 2020, we led 10 separate searches. CBD could be assessed alone or in association, in a) alcohol, b) amphetamine, c) cannabis, d) cocaine, e) hallucinogen, f) inhalant g) opioid, h) phencyclidine, i) sedative, j) tobacco use disorder.

We used the terms : “(cannabidiol OR CBD) AND (randomized trial OR randomized study) AND (substance related disorder OR addiction OR use disorder OR use OR abuse OR excessive use OR dependence OR withdrawal) AND either “(alcohol)”, “(amphetamine OR speed OR stimulant)”, “(cannabis OR marijuana OR THC)”, (cocaine OR crack OR freebase)”, “(hallucinogen)”, “(inhalant)”, “(opioid OR heroin)”, “(PCP OR phencyclidine OR angel dust)”, “(benzodiazepine OR sedative)”, or “(tobacco OR nicotine)”. Inclusion criteria for the articles were: double-blinded, randomized, placebo or adequate control, in subjects with a formal diagnosis of substance use disorder, assessing CBD alone or in association with other

cannabinoids, and reporting at least one primary outcome regarding the substance use disorder.

Exclusion criteria were: studies in healthy volunteers, single administration, preclinical studies, reviews, opinion papers, protocols, open-label studies, case reports, and studies not published in English.

Two authors (AM and PL) independently examined titles and abstracts. Relevant articles were obtained in full-text and assessed for inclusion criteria blindly by the two reviewers. Disagreement was resolved via discussion to reach consensus.

Detailed data on each included randomized controlled trial, including target population, intervention, treatment dose, frequency and route of administration, treatment duration, control group, outcomes, surrogate endpoints and biomarkers, adverse events and study withdrawals are described. The risk of bias was assessed with the Cochrane risk of bias tool, which includes assessment of indicators of selection bias, performance bias, detection bias, attrition bias, and reporting bias. Furthermore, the CONSORT 2010 (Consolidated Standards of Reporting Trials) statement was used to rate the report made in each article of the study design, analysis and interpretation.

For excluded studies consisting in short term or single-administrations, proof of concept studies, conducted mostly in not-seeking-treatment drug users, only a shorter presentation of outcomes, surrogate endpoints and biomarkers is provided.

Lastly, to identify ongoing or unpublished studies, we searched different on-line registries: "*clinicaltrials.gov*", "*clinicaltrialsregister.eu"* and "*anzctr.org.au*" websites, using the terms "substance related disorder OR addiction OR use disorder OR use OR abuse OR excessive use OR dependence OR withdrawal" and "cannabidiol OR CBD OR nabiximols OR (THC + CBD)" .

RESULTS

The PRISMA flowcharts presenting the studies selection are shown in figures 1. The initial screening identified 17 published articles presenting studies assessing CBD for alcohol, 2 for amphetamine, 105 for cannabis, 59 for hallucinogen, 6 for inhalant, 8 for opioid, 3 for sedative, and 7 for tobacco use disorder. All the other researches that we conducted retrieved no results. Of those screened studies, we finally retained only 3 studies meeting the inclusion criteria with a classical design of randomization in parallel groups, versus placebo, for cannabis use disorder, all assessing the efficacy of nabiximol spray (a 1:1 THC/CBD ratio). Their outcomes, surrogate endpoints and biomarkers are detailed in Table 1.

Although not properly speaking randomized controlled trials of efficacy, 12 other controlled studies are presented: 3 studies of THC-CBD combination on various endpoints in cannabis users and 9 studies assessing the efficacy of CBD alone, mostly as oral tablets, on surrogate endpoints of efficacy for cannabis (4), opioid (1), tobacco dependence (3), or multiple substance use (1 study). Main considerations for exclusion are detailed in Figure 1.

Outcomes, surrogate endpoints and biomarkers of the 3 randomized controlled trials assessing THC-CBD in cannabis use disorder

Withdrawal symptoms

Only three trials randomized by group, furthermore placebo-controlled, assessed the pharmaceutical preparation nabiximol (1:1 THC/CBD ratio) for cannabis use disorders (30–32). All three studies took place in subjects with verified cannabis use disorder criteria during a cessation attempt. The studies lasted between 6 days to 12 weeks, giving way to observe both early withdrawal symptoms and later abstinence maintenance or relapse, but also to quantify cannabis use. The first published study (30), conducted in 6 consecutive days in hospitalized patients, chose to assess a the CWS (Cannabis Withdrawal Scale) (33) a self-rated withdrawal scale as the main outcome.

Drug use reduction

~~The two other studies, originating from the same team, could use the previously acquired experience.~~ In the two other RCTs, the investigators assessed 12-weeks cannabis use reduction with self-reports collected with the Time Line Follow-Back as their primary outcome (see Table 1), and relegate withdrawal symptoms questionnaires as secondary outcomes. Of note, in those studies, abstinence, defined as a 4 weeks cannabis cessation, as well as time-to -relapse, were also only secondary outcomes. Furthermore, the three studies added urine or plasma cannabis measurement to characterize drug use reduction and act as surrogate endpoints predictors of abstinence. The three trials included a validated self-rated craving questionnaire, the Marijuana Craving Questionnaire (MCQ) (34), either complete or short form, as surrogate endpoints for abstinence. None of those three studies used biomarkers as potential predictor of abstinence or cannabis use reduction.

Quality of the methodology of the randomized controlled trials

Overall, the quality of those three studies was good. The detailed risk of bias and quality rating regarding those studies are presented in Tables 2 and 3. Analyses were performed in intention-to-treat and missing data were handled by several appropriate methods: multiple imputation(30), maximum likelihood estimation(31), or in intention-to-treat restricted to subjects who had received at least one dose of medication(32).

Outcomes, surrogate endpoints and biomarkers of the 12 excluded studies

We chose to give a short presentation of the methodology of 12 controlled studies not aiming at treating a substance use disorder but performed in the intention to develop future studies.

3 cross-over trials assessing THC-CBD in cannabis use disorders

Consecutive administration

Withdrawal symptoms

The study by Trigo et al. 2016 (35) used a cross-over design in 16 participants with cannabis use disorder to assess withdrawal symptoms during repetitive 5-days cannabis cessation sessions assessing several doses of nabiximol. The primary outcome was two withdrawal scales: the CWS (33) and the Marijuana Withdrawal Scale MWC (36). A validated self-rated craving score, the MCQ (34), was used as a secondary outcome, as were side-effects or the quotation of feeling “high” with the THC-CBD doses.

Single administration

Two cross-over controlled studies assessing the effect of a single administration of THC-CBD or CBD alone used motivation and anxiety measures as primary endpoints.

Motivation and Reward expectation

One study chose to assess the motivation for rewarded tasks as a primary outcome (37). In a double-blinded placebo-controlled experimental study, seventeen subjects realized an effort expenditure for rewarded tasks, under 3 conditions: after THC or THC-CBD (vaporized 8 mg THC + 10 mg CBD) or placebo inhalation. The authors measured the amount of the effort produced but also the amount of expected reward associated with the effort produced. The authors observed that CBD could attenuate the indifference provoked by THC, expressed in the attenuation of expected reward.

Anxiety

Another study (38), reported more classical outcomes in terms of heart rate, blood pressure, several self-rated visual analogue of mood states including good drug effect, high, anxiety, but also repetitive assessment state anxiety part of the Spielberger State–Trait Anxiety Inventory (33). Those assessment were repeated several times over 10 hours after a single intake including 6 different single doses: oral THC 5 mg, oral THC 15 mg, oromucosal spray pharmaceutical THC-CBD low-dose (5.4 mg THC + 5.0 mg CBD) or high-dose (16.2 mg THC + 15.0 mg CBD), oral placebo or oromucosal spray placebo. The subjects were 9 occasional

cannabis users. The adjunction of CBD did not prevent the rise of anxiety associated with THC in the few hours after THC-CBD mixtures.

Outcomes, surrogate endpoints and biomarkers of the 9 excluded studies of CBD alone for substance use disorders

Consecutive administration

Drug use reduction

We identified a pilot study in Tobacco dependence (39)) with only an indirect comparison design that did not qualify for our inclusion criteria. We thus classified it as "miscellaneous" (see Figure 1j). The chosen primary outcome was smoking reduction measured by the declared number of cigarettes smoked in one week. Smokers were randomized to receive either *ad libitum* inhaled CBD (n=12) or placebo (n=12) via an inhaler delivering 400 µg of CBD at each press.

Secondary outcome included tobacco craving, self-rated separate visual analogue scales of the MRS (mood rating scale)(40) including depression, anxiety and sedation. The results are presented like those assessments occurred only once on day 0 and once on day 7. No direct comparison of craving reduction between groups is provided.

Single administration

We present here some data from the 8 other published articles of interest. They were conducted in heroin dependent subjects (1 study), in regular cannabis users (4 studies), in dependent tobacco smokers (2 articles), and in subjects with multiple dependences (1 study). Their primary outcomes were diverse and are listed below.

Cue-induced craving and anxiety

The only published study assessing CBD effects in 42 subjects with heroin use disorder, currently abstinent (41) was a cross-over, placebo-controlled trial examining three consecutive days of oral CBD 400 mg per day or CBD 800 mg per day or placebo. The primary outcomes were measured by repetitive visual analogue scales (VASs) of craving and anxiety during cue-induced laboratory sessions, up to 7 days after the end of CBD administration. Several

secondary outcomes were also assessed, the Positive and negative affects scores (PANAS) (42) and several cognition tests, mostly consisting in sustained attention tasks, such as a Digit Symbol Substitution Task (DSST), a Digit Span Test–Backward (DSTB), and a Continuous Performance Task (CPT). The investigators added physiological measures, including heart rate, blood pressure, and body temperature and salivary cortisol levels, as biomarkers of cue-induced stress during the exposition task. The authors concluded that both CBD doses reduced craving and anxiety during the tasks of salient drug cues presentation compared with neutral cues. In addition, the drug cue-induced physiological measures of heart rate and salivary cortisol levels were also attenuated. No sedation effects were observed, but also no cognitive enhancement.

Psychomimetic subjective effects

A study conducted in occasional and regular cannabis users with a single inhalation of either THC 8 mg, CBD 16 mg, THC 8 mg + CBD 16 mg or placebo (43) chose as primary endpoint a scale designed to assess drug-induced psychomimetic effects, the Psychomimetic States Inventory (PSI) (44) along with the validated Brief Psychiatric Rating scale (BPRS) (45). The co-administration of CBD did not attenuate the psychomimetic effects of THC, and CBD alone reduced PSI scores in light users only. This study included a working memory task using a word list and sustained attention tests as secondary outcomes, showing again that CBD in co-administration did not attenuate the impairing memory and cognitive effect of THC, and that CBD alone had no cognitive enhancement properties.

Attentional Bias and Impulsivity

In order to test what could be surrogate endpoints for CBD efficacy in tobacco use disorder, a British team published in two interesting articles the results of a cross-over trial of one administration of 800 mg CBD versus placebo in non-treatment seekers tobacco smokers who underwent assessments during experimental sessions of 24 hours abstinence, separated by one-week wash-outs (46,47). In the first report (46), the primary outcome was the attentional bias toward tobacco cues (AB) as a slower response time during a visual probe task (VPT)

with both neutral and smoking-related cues. Furthermore, participants had to quote the pleasantness of the task. Secondary outcomes included withdrawal and craving scales, heart rate, blood pressure and side-effects, were also measured by state questionnaires. In the second report (47), the primary outcome was impulsivity, and was measured by two tests. A Delay discounting task, finding no significant difference between CBD and placebo, while ~~and~~ a go/no-go task showed significantly more errors with CBD than placebo. Memory was measured by a prose recall task (PRT), showing no significant difference between CBD and placebo. Furthermore, a N back test (NBT), showed no difference for correct responses, reaction time and maintenance and manipulation. Thus, CBD was not shown to improve cognition in the specific condition of nicotine withdrawal.

Cognitive performance

Several cognitive tests were also assessed in another specific condition, this time the pre-treatment with a single dose of 200, 400 or 800 mg CBD prior to smoked cannabis intake (48), along with several VAS exploring the reinforcing and subjective effect of this interaction, during 8 sessions. Once again, no specific significant differences were found between CBD or placebo, and neither any signal of abuse liability (49).

Abuse liability

Another team performed the same kind of experiment to assess the abuse liability of oral CBD in healthy recreational polydrug users (50). The investigators compared single administrations 750, 1500 and 4500mg oral CBD ~~at~~ to alprazolam 2mg (APZ) or dronabinol (THC) 10 and 30mg. The primary outcome was again the maximum effect (Emax) on a drug-liking VAS scale, with also positive (“feeling high” and “feeling stoned”) and negative effects, and several other subjective effects as secondary outcomes. Cognitive, memory and psychomotor functions were measured by a divided attention test (DAT), the Hopkins verbal learning test-revised (HVLT), and the DSST. Again, this study confirmed that single dose oral CBD does not show any signal of abuse liability as well as no detectable cognitive effect in this condition.

Facial emotion recognition task

Originally, rather than the classical choice of VAS and cognitive tests as primary outcomes for single administration studies, we identify a study conducted by C. Hindocha (51), that examined the acute effects of THC, CBD, and their combination, on facial emotion recognition. This task consists in showing 6 basics emotions (happiness, sadness, anger, disgust, fearful, surprise, and neutrality) and with an intensity degree in 5 levels. It is regarded as impaired in mood and anxiety disorder and is proposed as a surrogate endpoint for treatment efficacy in anxiety disorders when screening new molecules (43). Regular cannabis smokers attended 4 sessions with a one week wash out and were administered by inhalation either THC 8 mg, CBD 16 mg, THC+CBD (8+16 mg) or placebo. The results showed that at 60% intensity, participants were more accurate with CBD alone than placebo. With more ambiguous emotions, at 40% intensity, participants with THC-CBD were more accurate than participants with THC alone. As a secondary outcome, participants also completed subjective effects VASs for “stoned”, “anxiety”, “alert”, and “happy or sad”, among other subjective states. A hypothesis from the investigators that cannabis users would differ according to their score on a Schizotypal Proneness Questionnaire was not supported by the data. ~~The same team published more recently a study assessing the effect of singles doses of either~~

None of those single administration studies correlated their primary or secondary outcome analysis with indirect brain biomarkers of substance use disorders severity or evolution. In the studies presenting time-curve evolution of mood or cognitive effects over some hours, no correlation with plasma CBD level was shown.

On-going studies

Our screening led in the American clinical trial registry (*clinicaltrials.gov*) identified 87 studies. The same screening in the European clinical trial web-base (*clinialtrialsregister.eu*) identified 2 studies, and 7 from the Australian and New-Zealand clinical trial registry (*anzctr.org.au*). We did not retain studies not performed in substance use disorders (mostly performed in epilepsy

or chronic pain), already published studies (previously included in this review) and studies recorded in several registries. This left 13 studies. Of note, and this is an important change from the past few years, all those studies are evaluating CBD alone as treatment of interest. The substance use disorder condition assessed in those studies were: Cannabis UD (5 studies), Opioid UD (4 studies), Alcohol UD (3 studies), and 1 study was also found in ~~in~~ Cocaine UD. Eight studies are led in North America, 2 in Europe, 2 in Oceania, and 1 with unknown location. Protocols, CBD dose and duration vary according to the study. The duration of CBD administration ranges from 4 single administrations to 3 months, with the majority of studies assessing 1-2 months treatment. CBD doses range from 300 to 1400 mg per day. The primary outcomes are withdrawal symptoms or craving in the shortest studies (on opioid UD, alcohol UD) but substance use or relapse, associated with craving in several-weeks duration trials (Cannabis UD, Alcohol UD, Cocaine UD). Most studies have also secondary outcomes with various subjective symptoms scales: anxiety, sleep quality, psychotic symptoms, craving, to serve as surrogate endpoints for efficacy. On top of that, those more recent studies add several biomarkers to be tested as surrogate endpoints for efficacy: cannabidiol plasma levels (Alcohol UD studies, Opioid UD studies, Cocaine UD study), combined with endocannabinoid plasma levels (Cannabis UD studies and Cocaine UD study) composed of both CBD and anandamide plasma levels, sometimes combined with other biomarkers: mono-amines plasma levels or inflammatory biomarkers including plasma cortisol in cocaine UD.

DISCUSSION

Despite the great expectations toward the possible therapeutic effects of CBD in substance use disorders, this review showed that published data are limited. When choosing stringent inclusion criteria, only 3 high quality randomized placebo-controlled trials can be retained. Those three studies tested THC/CBD compounds, and proposed to treat cannabis use disorder. Their primary outcomes were validated scales of withdrawal symptoms or cannabis use reduction. In the context of efficacy trials, validated craving scales, although validated to

be associated with relapse, are only secondary outcomes. Those 3 studies did not report on any biomarker that could be used as a useful predictor of efficacy.

To date, no published study assessing the efficacy of CBD alone in any substance use disorder can qualify as a high quality randomized controlled trial. Published data are limited to very short-term or even single administrations cross-over designs. In such short-term studies, the efficacy assessment can only rely on primary outcomes sensitive to short-term change. In that context, series of visual analogue scales of various subjective effects, describing the drug effects or anxiety or mood states, are useful and allow repetitive assessments and the establishment of time curves. The adjunction of validated withdrawal or craving scales, as well as scales assessing anxiety or psychomimetic effects is an improvement if those scales are validated for such repetitive assessments.

It is remarkable that the investigators identified tasks that could be surrogate endpoints for treatment efficacy in substance use disorders, by mimicking conditions where relapse can occur: drug-induced craving, attentional bias for the substance, impulsivity or by targeting conditions that are known to favor relapse, such as anxiety. The assessment of the cognitive properties of CBD seems not to be part of this picture, and rather a way to rule out cognitive side effects that are known to be induced by THC.

There is a shift in the most recently declared clinical trials toward more prolonged efficacy trials and toward targeting more substance use disorders, including alcohol and cocaine use disorders. This shift is also accompanied by a qualitative improvement of the methodology toward the use of biomarkers that could be predictive of CBD efficacy. Above classical pharmacokinetic parameters such as CBD plasma level, that could help to define a therapeutic range, researchers are now adding new peripheral biomarkers assessing the current state of the endocannabinoid system, the mono-amine system or the immune system. Of note, those biomarkers could be applied to all substance use disorders. Indeed, the repetitive drug intake produces homeostatic changes in the common final pathway of the brain reward circuit. The endocannabinoid system could be a modulator of this circuit. Those therapeutic trials could benefit from a more general enhancement in research for the identification of valid biomarkers

of the reward circuit homeostatic state. They could include peripheral biomarkers, combined with brain imagery or neuropsychological tasks, and eventually drug administration challenges to describe the various stages of substance use disorder. In particular, an entire research era consisting in the design of study protocols able to assess the central nervous system pharmacological target engagement by CBD could emerge in the next years. They could include the association of *CNR1* gene polymorphisms with treatment response, or specific measures of the central nervous system inflammation state through radioactive ligands, or markers of CB1- or 5HT-receptors or TRPV channels activity.

Among the strengths of our review, we would like to point out the stringent definition of included/excluded published studies, the double-selection made independently by 2 reviewers and the separate presentation of declared on-going studies.

Among the limitations, the choice to restrain our searches for published studies in the PubMed database could be discussed.

CONCLUSION

The field of research assessing the efficacy of CBD in substance use disorder is emergent. To date, published randomized controlled trials are limited to THC-CBD compounds. But, pilot studies assessing single administrations or short-term efficacy of CBD alone on surrogate endpoints of efficacy have already been conducted. They targeted cue-induced craving, effort expenditure, attentional bias for the substance, impulsivity or anxiety. The next generation of trials, already ongoing, will include peripheral biomarkers of the endocannabinoid system homeostatic state as well as immunologic biomarkers as potential predictors of efficacy. Our recommendation for future randomized clinical trials testing the efficacy of CBD to treat substance use disorders would be to combine the repetitive assessment of three types of biomarkers of efficacy: peripheral biomarkers of the endocannabinoid system such as cannabinoids plasma level, short term surrogate endpoints (such as craving or attentional bias reduction) and long term validated measures of abstinence, dose reduction or harm reduction.

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TABLES

Table 1 : Characteristics of the three included randomized controlled trials assessing inhaled THC-CBD in Cannabis use disorder.

Author	Allsop, 2014, Australlia	Trigo, 2018, Canada	Lintzeris, 2019, Australia
Number of subjects	P n = 24/ N n = 27	P n = 20 / N n= 20	P n = 73/ N n = 64
Out/in patient	Inpatient	outpatient	outpatient
Withdrawal	during withdrawal	during withdrawal / follow-up	during withdrawal / follow-up
Treatment	self-titrated maximum 86.4 mg THC + 80 mg CBD /day + CBT	self-titrated maximum 113.4 mg THC + 105 mg CBD /day + MET/CBT	self-titrated maximum 86.4 mg THC + 80 mg CBD /day + CBT
Duration	6 days of treatment, 3 days of wash-out, 28 days follow-up	12 weeks	12 weeks
Primary outcome	(intervention) withdrawal score	cannabis use, tolerability	cannabis use
Secondary outcome	(intervention) craving (follow-up) time to relapse use reduction psychosocial outcome tolerability	craving score, withdrawal score	abstinence, use reduction, withdrawal score, craving score tolerability
Instruments	CWS urine and plasma drug test	TLFB (7 days) urine and plasma drug tests MWC MCQ-SF	TLFB (28 days) Urine drug test (placebo group) MWC MCQ
Main results	CWS : N (-66%) > P (+52%) p=0.01 Retention : N>P at day 6	cannabis use : NSD tolerability : NSD	P (53/84d) > N (35/84d) p=0.02
Secondary results	time to relapse : NSD reduction use : NSD psychososcial: NSD tolerability : NSD	withdrawal : NSD craving : NSD	abstinence: NSD withdrawal : NSD craving : NSD
Quality	CONSORT : 31/32 Biases 1/10	CONSORT : 24/32 Biases 2/10	CONSORT : 30/32 Biases 3/10

MET/CBT = Motivational Enhancement Therapy and Cognitive Behaviour Therapy. CBT = Cognitive Behaviour Therapy. TFLB = Timeline Followback. MWC = Marijuana Withdrawal Checklist. MCQ = Marijuana Craving Questionnaire. MCQ-SF = Marijuana Craving Questionnaire Short Form. CWS = Cannabis Withdrawal Scale. NSD= Non Significant Difference. P = Placebo. N = Nabiximol.

Table 2 : Internal and external validity of the three THC-CBD trials in Cannabis use disorder.

	Allsop 2014	Trigo 2018	Lintzeris 2019
Internal validity			
Selection biais			
Random sequence generation	y	y	y
Allocation protected from contamination	y	y	y
Similar baseline characteristics	y	y	y
Detection biais			
PPG calcul	y	y	y
Blinding of outcome assessment	y	y	y
Performant outcome measurement	y	y	y
Equivalent evaluation	y	y	y
Attrition biais			
Incomplete outcome data	y (ITT)	y (ITT)	y (mITT)
Report biais			
No selective reporting	y	y	y
External validity			
Appropriate comparator	y	y	y

PPG = participant per group
y = yes
ITT = Intention to Treat
mITT = modified Intention To Treat

Table 3 : CONSORT quality ratings of the three THC-CBD trials in Cannabis use disorder. (n = no. y = yes. n/a = non applicable)

CONSORT 2010			Allsop 2014	Trigo 2018	Lintzeris 2019
TITLE AND ABSTRACT		1a	y	n	y
		1b	y	y	y
INTRODUCTION		2a	y	y	y
		2b	y	y	y
METHODS	trial design	3a	y	y	y
		3b	n/a	n/a	n/a
	participants	4a	y	y	y
		4b	y	n	y
	interventions	5	y	y	y
	outcomes	6a	y	n	y
		6b	n/a	n/a	n/a
	sample size	7a	y	y	y
		7b	n/a	n/a	n/a
RANDOMISATION	sequence generation	8a	y	y	y
		8b	y	y	y
	allocation concealment mechanism	9	y	n	n
	implementation	10	n	y	y
	blinding	11a	y	y	y
		11b	y	y	y
	statistical methods	12a	y	y	y
		12b	y	y	y
RESULTS	participant flow	13a	y	n	y
		13b	y	y	y
	recruitment	14a	y	n	y

		14b	n/a	n/a	n/a
	baseline data	15	y	y	y
	numbers analysed	16	y	n	y
	outcomes and estimation	17a	y	y	y
		17b	n/a	n/a	n/a
	ancillary analyses	18	y	y	y
	harms	19	y	y	y
DISCUSSION	limitation	20	y	y	y
	generalisability	21	y	y	y
	interpretation	22	y	y	y
OTHER INFORMATION	registration	23	y	y	y
	protocol	24	n	n	y
	funding	25	y	y	y
TOTAL /32			**31**	**24**	**30**

n = no
y = yes
n/a = non applicable

FIGURES

Figure 1: *Flow chart of screened, selected, included and evaluated studies. (SUD = Substance use disorder. RCT = Randomized Controlled Trial)*

Figure 1.a) alcohol use disorder

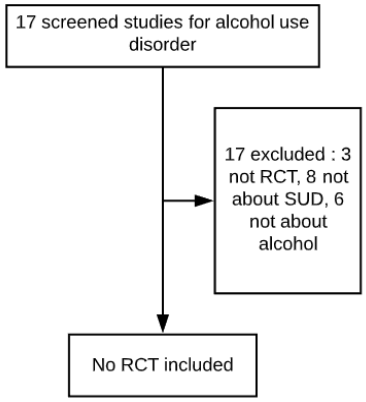

Figure 1.b) amphetamine use disorder

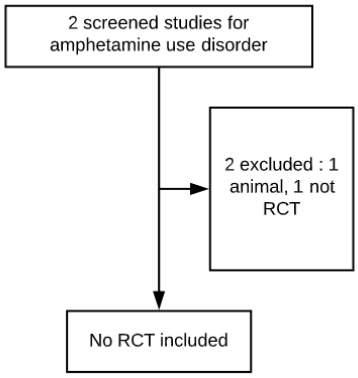

Figure 1.c) cannabis use disorder

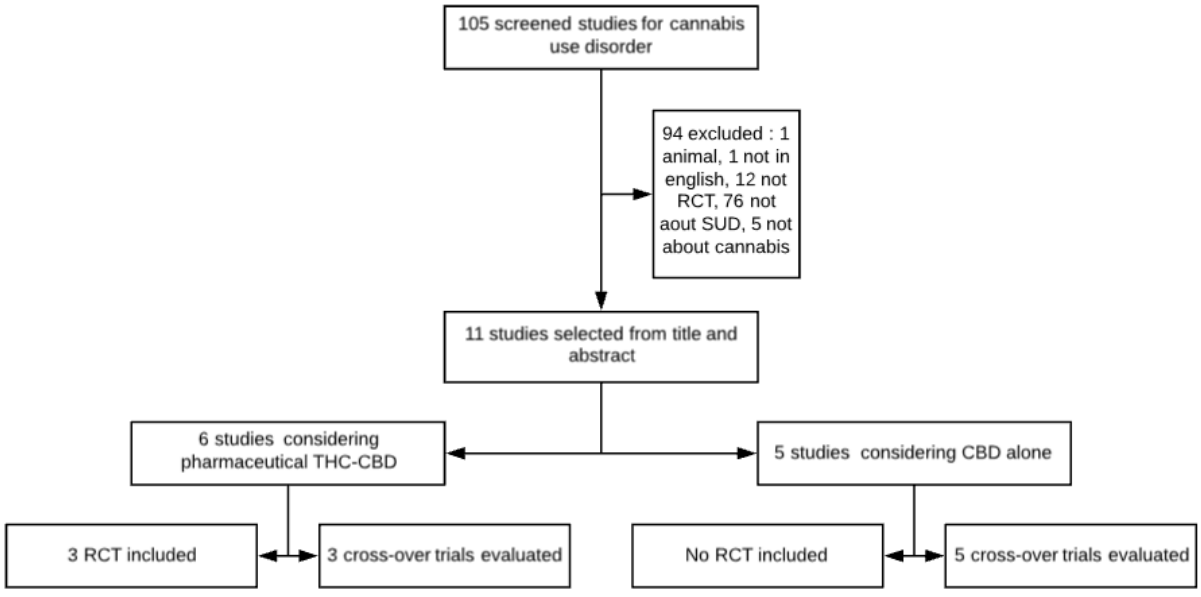

Figure 1.d) cocaine use disorder

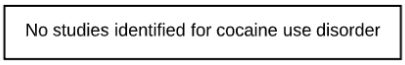

Figure 1.e) hallucinogen use disorder

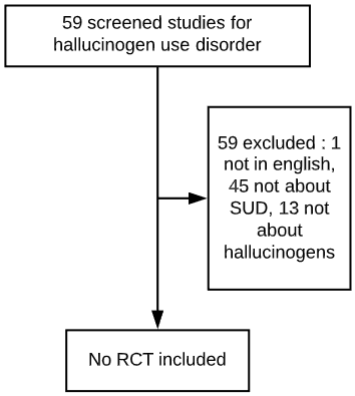

Figure 1.f) inhalant use disorder

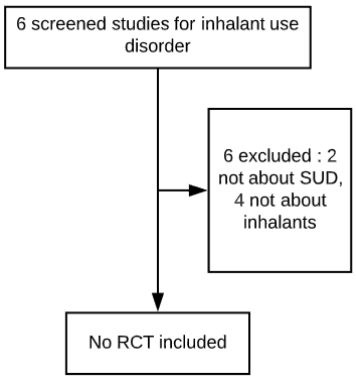

Figure 1.g) opioid use disorder

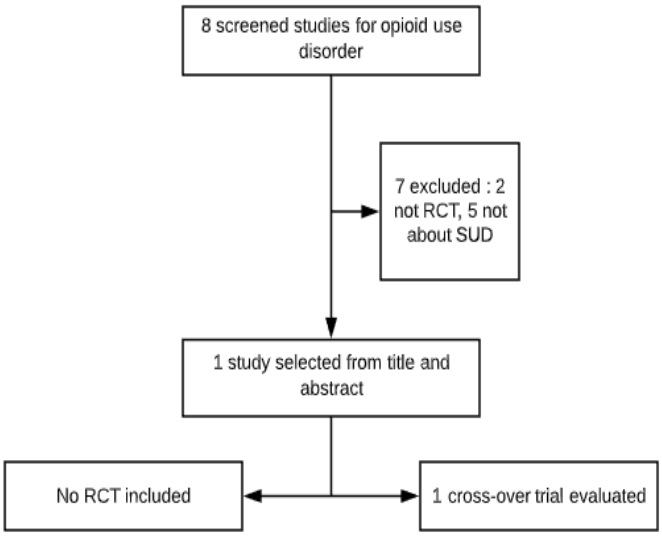

Figure 1.h) phencyclidine use disorder

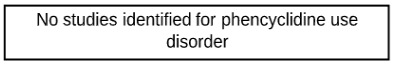

Figure 1.i) sedative use disorder

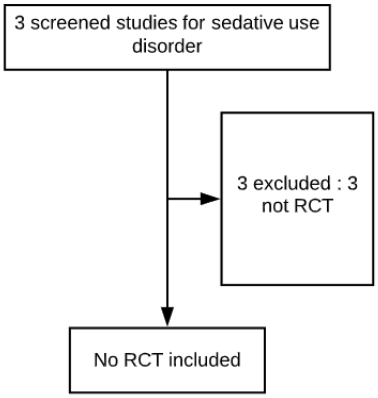

Figure 1.j) tobacco use disorder