How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review.

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Abstract

The recent liberalisation of cannabis regulation has increased public and scientific debate about its potential benefits and risks. A key focus has been the extent to which cannabidiol (CBD) might influence the acute effects of delta-9-tetrahydrocannabinol (THC), but this has never been reviewed systematically. In this systematic review of how CBD influences the acute effects of THC we identified 16 studies involving 466 participants. Ten studies were judged at low risk of bias. The findings were mixed, although CBD was found to reduce the effects of THC in several studies. Some studies found that CBD reduced intense experiences of anxiety or psychosis-like effects of THC and blunted some of the impairments on emotion and reward processing. However, CBD did not consistently influence the effects of THC across all studies and outcomes. There was considerable heterogeneity in dose, route of administration and THC:CBD ratio across studies and no clear dose-response profile emerged. Although findings were mixed, this review suggests that CBD may interact with some acute effects of THC.

1. Introduction

In the last decade, there have been substantial changes to cannabis regulation, with many countries adopting a more permissive stance towards medical and recreational use (Kilmer, 2017). The World Health Organisation recently proposed the rescheduling of cannabis and its removal from the schedule IV category in light of the drug's medicinal properties (Mayor, 2019). Cannabis and cannabinoids have the potential to treat several medical conditions including chronic pain, treatment-resistant epilepsy, and nausea and vomiting due to chemotherapy (T. P. Freeman, Hindocha, Green, & Bloomfield, 2019). However, over 60 years of prohibition and associated regulatory barriers to researching this field (Nutt, 2015) means there are significant gaps in our knowledge about the clinical benefits and potential harms (Hall, Hoch, & Lorenzetti, 2019). Recently, there has been renewed interest in whether the composition of the different cannabinoids within cannabis may improve its safety profile while enhancing medicinal efficacy (McPartland & Russo, 2014).

The cannabis plant (*Cannabis Sativa* L.) produces over 140 different compounds known as phytocannabinoids and terpenoids (Hanuš, Meyer, Muñoz, Taglialatela-Scafati, & Appendino, 2016), many of which directly modulate the endogenous cannabinoid system in humans (Lu & Mackie, 2016). The endocannabinoid system consists of at least two types of cannabinoid receptors (CB_1 and CB_2) and endogenous ligands (endocannabinoids such as anandamide and 2-arachidonoylglycerol) that bind to these receptors and ligand metabolic enzymes. Cannabinoid receptors are as abundant as glutamate, gamma-aminobutyric acid (GABA), or dopamine receptors in the brain (Katona & Freund, 2012), and consequently are involved in a wide range of functions including regulation of mood, memory and reward processing (Bossong, Jansma, Bhattacharyya, & Ramsey, 2014;

Curran et al., 2016). CB_1 receptors are primarily located in central and peripheral neurons and mediate the release of transmitters at the synaptic terminal, including acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine (5-HT), GABA, glutamate, D-aspartate and cholecystokinin. Inside and outside of the central nervous system, CB_2 receptors are predominant in the immune system and have a role in altering the release of chemical messengers, cytokines, and the modulation of immune cell migration (Pertwee, 2008).

Two of the most widely researched cannabinoids are delta-9-tetrahydrocannabinol (THC), and cannabidiol (CBD), which have contrasting mechanisms of action and effect profiles. THC and CBD concentrations vary across different types of cannabis products used for recreational (T. P. Freeman et al., 2014) and medicinal purposes (T. P. Freeman et al., 2019). Although some strains of cannabis contain both THC and CBD in similar quantities, concentrations of THC in cannabis doubled over the past ten years (T. P. Freeman, Groshkova, et al., 2018). CBD content, which may attenuate the effects of THC, has become nearly obsolete in illicit samples of the drug across Europe and the USA (Chandra et al., 2019; Potter, Hammond, Tuffnell, Walker, & Di Forti, 2018).

1.1. **Pharmacology of THC and CBD**

The pharmacology of THC, although reasonably well understood, is complex. THC interacts with several pharmacological targets (see Pertwee and Cascio (2014) for a review). THC is a partial cannabinoid receptor agonist acting on both CB_1 and CB_2 and can behave as both an agonist and antagonist at the CB_1 receptor. Although THC acts primarily through the neuronal presynaptic CB_1 receptors to inhibit ongoing

neurotransmitter release. Repeated administration of THC may give rise to tolerance to its effects and the action of endocannabinoids (Colizzi & Bhattacharyya, 2018; Pertwee, 2008).

CBD differs from THC in several important ways. CBD has no intoxicating properties at typical doses (Pertwee, 2008). CBD has minimal direct activity at CB_1 and CB_2 receptors, having low affinity for both receptor subtypes (Thomas et al., 2007). Unlike THC, which acts at the orthosteric site of CB_1 receptors, CBD is a negative allosteric modulator that can alter the potency and efficacy of the orthosteric ligand without activating the receptor (Hayakawa et al., 2008; Laprairie, Bagher, Kelly, & Denovan-Wright, 2015). This may explain preclinical findings which suggest that, when administered together, CBD may counteract some of the actions of THC, while also potentiating other actions of THC (McPartland & Russo, 2014). CBD has also been shown to modulate $5HT_{1A}$ (Ross, 2007; Russo, Burnett, Hall, & Parker, 2005) and PPARγ (Campos, Moreira, Gomes, Del Bel, & Guimaraes, 2012) as an agonist, GPR55 as an antagonist (Ryberg et al., 2007), and to inhibit the hydrolysis and reuptake of the Fatty Acid Amide Hydrolase enzyme (Bisogno et al., 2001).

1.2. **Acute effects of THC**

When acutely administered, THC induces a broad range of transient and dose-dependent effects. THC causes psychotropic effects of cannabis, inducing the “high” or “stoned” effect associated with its ingestion (Gaoni & Mechoulam, 1964). THC is associated with a dose-dependent increase in heart rate (Karniol & Carlini, 1973; Zuurman et al., 2008). Although many studies have investigated the subjective effects of THC, there has been considerable variation in doses, routes of administration and

outcomes used. THC induces appetitive effects including wanting more of the drug and liking the drug's effects (Curran, Brignell, Fletcher, Middleton, & Henry, 2002). It reduces anxiety at low doses, but increases anxiety at higher doses (Hunault et al., 2009) and has been shown to robustly reduce alertness (Zuurman et al., 2008). However, these effects can vary between individuals and within individuals on different occasions of use (Green, Kavanagh, & Young, 2003). THC produces transient psychosis-like effects (D'Souza et al., 2004; Morrison & Stone, 2011; Morrison et al., 2009), which may be enhanced in individuals prone to psychosis (Mason et al., 2009). THC also interferes with several behavioural and cognitive processes impairing episodic memory, attention and working memory (Ranganathan & D'Souza, 2006; Volkow et al., 2016). Functional imaging studies have shown that THC disrupts the neural correlates of emotional processes, executive function and reward function (Bloomfield et al., 2018).

1.3. **Acute effects of CBD**

Originally believed to have a minimal effect due to its lack of subjective effects, CBD has recently received renewed interest for its potential therapeutic properties (Khoury et al., 2019; Zuardi, 2008). Few studies have investigated the acute effects of CBD, and the results of these studies have been mixed. Some studies report that low doses of CBD (30mg oral; 25mg IV respectively) has no intoxicating effects (Hollister, 1973; Perez-Reyes, Timmons, Davis, & Wall, 1973). However, in a small double-blind crossover study (n=7), Zuardi, Guimaraes, and Moreira (1993) found that CBD (300mg oral) acutely increased somnolence and reduced anxiety and two studies found that CBD (200mg oral; 400mg vaporised respectively) produced mood altering and subjective intoxicating effects (Leweke, Schneider, Radwan, Schmidt, & Emrich,

2000; Solowij et al., 2019). CBD (400-600mg oral) administered alone is also associated with anxiolytic effects (Crippa et al., 2011; Hundal et al., 2018; Zuardi et al., 1993), however, in a recent study of emotional processing tasks, CBD (300-900mg oral) induced minimal behavioural and subjective effects (Arndt & De Wit, 2017). CBD (32mg vaporised) has been shown to enhance consolidation of fear extinction learning in humans (Das et al., 2013), which suggests its effects on emotional processing may be nuanced and related to other cognitive processes. Several studies have investigated chronic administration of CBD for a range of therapeutic indications including as an antiepileptic, anxiolytic, antipsychotic and neuroprotective drug (for a review see White, 2019; and Whiting et al., 2015).

1.4. **The interaction between THC and CBD**

A much debated question is whether, when administered together, CBD interacts with THC's effects. Some researchers have suggested that CBD can influence the effects of THC, increasing its clinical efficacy and reducing harmful effects (Ben-Shabat et al., 1998; Bonn-Miller, ElSohly, Loflin, Chandra, & Vandrey, 2018; Russo & McPartland, 2003). Some studies have demonstrated this effect, for example: evidence from survey data (Schubart et al., 2011), and naturalistic hair analysis studies suggests that increased CBD content in cannabis may be protective against various memory-impairing effects and psychosis-like experiences associated with cannabis use (Demirakca et al., 2011; Morgan & Curran, 2008; Morgan et al., 2011). Another naturalistic study, where cannabis users smoked their own cannabis which was later analysed for THC and CBD content, found that high CBD content was associated with reduced impairment of verbal memory and a reversal of attentional bias towards

cannabis and food cues (Morgan, Freeman, Schafer, & Curran, 2010; Morgan, Schafer, Freeman, & Curran, 2010).

Evidence from repeated dosing studies is more mixed. One parallel group, randomised controlled trial (n=177) study in patients with intractable cancer-related pain showed that a combination of THC (2.7 mg) and CBD (2.5mg) in an oromucosal spray produced a significant improvement on a pain rating scale compared to placebo, whereas the THC (2.7mg) group showed no significant change. Twice as many patients (43% of patients) taking THC and CBD showed a 30% pain reduction (on a 0-10 Numerical Rating Scale) from baseline compared to placebo (21% of patients) (Johnson et al., 2010). Others, however, have found THC alone to be more clinically effective than a combination of the two in chronic pain, fibromyalgia and neuropathic pain (Notcutt et al., 2004; van de Donk et al., 2019; Wade, Robson, House, Makela, & Aram, 2003).

Much uncertainty also exists around whether CBD alters the pharmacokinetic profile of THC (Lucas, Galettis, & Schneider, 2018). For example, while Agurell et al. (1981) found that co-administration of CBD with THC did not alter the pharmacokinetics of THC, van de Donk et al. (2019) showed that plasma concentrations of THC were higher than expected when a treatment containing both THC (13.4mg) and CBD (17.8mg) was administered compared to a treatment containing THC (22.4mg) and CBD (1mg).

Previous non-systematic reviews have suggested that CBD may attenuate the acute harmful effects of THC (Colizzi & Bhattacharyya, 2017; Englund, Freeman, Murray, & McGuire, 2017; Niesink & van Laar, 2013) while potentiating its positive

effects (Russo, 2019; Russo & Guy, 2006). One systematic review investigating whether CBD has antipsychotic effects found that CBD may offset the psychosis-like effects of THC (Iseger & Bossong, 2015). Although several narrative reviews have discussed the question of whether CBD interacts with THC when administered together acutely, this question has never been reviewed systematically. This systematic review aimed to establish how CBD influences the acute effects of THC in humans.

2. Methods

2.1. **Protocol and registration**

This review was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) and a checklist is provided in Appendix A. The protocol (Appendix B) and registration for the current systematic review was prospectively registered (PROSPERO: CRD42019126994) on 28th February 2019 (A. M. Freeman et al., 2019).

2.2. **Eligibility criteria**

2.2.1.1. Inclusion criteria

a) A condition or group in which THC is acutely administered.
b) A matched condition or group where the same dose of THC is acutely administered together with cannabidiol (CBD), under experimental conditions.
c) THC must be delivered via the same route of administration in both conditions, as different routes (e.g., oral THC alone versus intravenous THC combined with CBD) may lead to a different profile of effects related to different pharmacokinetics and metabolism of the drug, as well as the interaction between the compounds.

d) The studies must include either a placebo condition or a control condition where there is no drug administered, for example, a pre-drug measurement or baseline measurement. This is necessary to evaluate the acute effects of THC.
e) The included papers must be peer-reviewed.
f) Articles must be published in English.

2.2.2. Exclusion criteria

a) Conference extracts or abstracts, theses, reviews, supplements, editorial reports, correspondence, non-peer reviewed material, e.g. books extracts, notes, and letters.
b) Studies where there was no matched dose and route of administration for THC, with and without CBD.
c) Repeated dosing studies.
d) Studies where the statistical analysis did not directly compare either 1) THC alone to a matched dose of THC with CBD, or 2) THC to placebo, and a matched dose of THC with CBD and placebo.
e) Studies not including humans.

2.3. **Information sources**

A systematic search was conducted on 28th February 2019 using the following electronic bibliographic databases: MEDLINE, EMBASE, PsycINFO, and CINAHL Plus. The search strategy included only terms relating to or describing the intervention (THC and CBD). The terms were combined with the Ovid filter for human studies and studies published in English. The search terms were adapted for use for each bibliographic database and run in combination with database-specific filters for human

trials and peer-reviewed articles, where these were available. The search terms and results are provided in Appendix C.

2.4. **Study selection**

The titles and abstracts of studies retrieved using the search strategy, and those from additional sources, were screened independently by two reviewers (AF and RL) to identify studies that potentially met the inclusion criteria outlined above. The full text of these potentially eligible studies was retrieved and independently assessed for eligibility by two review team members (AF and KP). Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third reviewer (TF).

2.5. **Data collection process and data items**

A standardised, pre-piloted form (in Microsoft Excel) was used to extract data from the included studies for assessment of study quality and evidence synthesis (Appendix D). This form was adapted from the Cochrane Collaboration's Data collection form for intervention review – randomised controlled trials (RCT). Through the development process, some irrelevant sections were removed from the original form and new sections added. The extracted information included: study setting; study population and details of the dose and route of administration for THC and CBD; THC:CBD ratio; study methodology; recruitment and study completion rates; outcomes and times of measurement; information for the assessment of the risk of bias. Two reviewers (AF and KP) extracted the data, and discrepancies were resolved through discussion with a third reviewer (CH) where necessary. A subset of the extracted data was randomly checked by another reviewer (CH).

2.6. **Risk of bias in individual studies**

Two reviewers (AF and KP) independently assessed the risk of bias in included studies by considering the criteria set out by the Cochrane's Risk of Bias (RoB2) assessment tools as appropriate for the study design (Higgins et al., 2011). Disagreements between the reviewers over the risk of bias in particular studies were resolved by discussion, with the involvement of a third review author (CH) where necessary.

2.7. **Risk of bias across studies**

This review assessed the risk of publication bias by considering the different types of bias laid out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2008; Higgins et al., 2016).

2.8. **Summary measures**

It was acknowledged that the included studies would have investigated a variety of outcome measures and therefore this review planned to take an inclusive approach and report all outcomes where the effects of THC alone were compared to the effects of the same dose of THC combined with CBD.

3. Results

The initial search on 28th February 2019 identified 1808 records, of which 601 were duplicates and excluded. Four additional articles were identified as they were published after the initial search. The abstract and title of 1211 articles were reviewed, and 47 articles were considered potentially relevant and subject to full-text searching. Study selection procedures yielded 23 published articles reporting on 16 studies which met the inclusion criteria. A table summarising the excluded studies is provided in

Appendix E. Figure 2 displays a flow diagram of the reasons for exclusion at each stage (Appendix F).

3.1. **Study characteristics**

Altogether, 16 studies reported in 23 articles were included in this review (Arkell et al., 2019; Bhattacharyya et al., 2010; Bird et al., 1980; Dalton, Martz, Lemberger, Rodda, & Forney, 1976; Englund et al., 2013; T. P. Freeman, Pope, et al., 2018; Guy & Robson, 2003; Haney et al., 2016; Hindocha et al., 2015; Hollister & Gillespie, 1975; Hunt, Jones, Herning, & Bachman, 1981; Juckel, Roser, Nadulski, Stadelmann, & Gallinat, 2007; Karniol, Shirakawa, Kasinski, Pfeferman, & Carlini, 1974; Lawn et al., 2016; Morgan et al., 2018; Nadulski et al., 2005; Nicholson, Turner, Stone, & Robson, 2004; Roser et al., 2009; Roser et al., 2008; Stadelmann et al., 2011; Zuardi, Shirakawa, Finkelfarb, & Karniol, 1982). Table 1 provides details of each study's aims, the participants and their cannabis use history, the intervention groups, and outcome measures.

All studies were experimental human laboratory studies. Only three studies (Bird et al., 1980; Englund et al., 2013; Karniol & Carlini, 1974) used parallel group designs, and the rest used a crossover design. Study sample sizes varied between 4 and 155 participants, with a total of 466 participants. Some studies were explicitly designed to evaluate drug safety and pharmacokinetics, and were therefore not powered to detect treatment effects (Guy & Robson, 2003; Hunt et al., 1981). One parallel group study (Karniol et al., 1974) and five crossover-design studies (Bhattacharyya et al., 2010; Dalton et al., 1976; Hunt et al., 1981; Nicholson et al., 2004; Zuardi et al., 1982) had

less than 10 participants (4-8) per treatment cell and therefore may not be powered to detect smaller effect sizes (Simmons, Nelson, & Simonsohn, 2011).

Table 1 Summary of Study Characteristics and Findings

Study and location	Aim	Participants	Design	*Intervention	Outcomes	Main findings	Risk of Bias
Arkell et al. (2019), Australia	To compare the subjective, cognitive, and driving-related effects of vaporized THC, and THC and CBD combined.	14 healthy volunteers (three women; 11 men) 21-38 years with self-reported cannabis use ≤ 2 times a week for three months and lifetime use ≥ 10 times Three participants did not complete, one withdrew, one did not comply with the protocol and another was discharged due to elevated blood pressure and heart rate. No illicit drugs for duration of the study. Breathalyser and oral fluid screening for recent alcohol and drug use on each day.	Placebo-controlled, double-blind, crossover study across three treatment conditions. Randomized and counterbalanced order.	Vaporised THC 3.75 mg + CBD 13.75 mg; vaporised THC 13.75 mg + CBD < 1.25 mg; vaporised Placebo < 1.25 mg THC/CBD	DAT driving simulation task, DSST, PASAT, pharmacokinetics, self-rating of subjective intoxicating effects.	Peak plasma concentrations of THC higher in THC+CBD ↑ No difference in self-rated subjective intoxication or confidence to drive for THC and THC+CBD = STAI and anxious self-rating was increased in both THC and THC+CBD at 15 mins but not THC+CBD at 1 hour =/↓ Car following task both THC and THC+CBD impaired SDLP = THC with CBD impaired performance on the DAT compared to THC or placebo ↑	Low
Bhattachary ya et al. (2010), United Kingdom	To investigate whether pre-treatment with CBD can prevent THC from provoking psychotic symptoms.	Six healthy volunteers (three women; three men) 21-42 years, with mean lifetime self-reported cannabis use 150 times; minimal exposure to other illicit drugs. Negative urinary drug screen before each testing session.	Placebo-controlled, double-blind, crossover study, across two treatment conditions. Pseudo-randomisation.	Pre-treatment (T-5mins) intravenous CBD 5 mg followed by intravenous THC 1.25 mg; pre-treatment (T-5mins) intravenous Placebo	PANSS, pharmacokinetics.	No significant difference in blood levels of THC with or without pre-treatment with CBD = THC increases psychotic symptoms on PANSS in three participants; pre-treatment (T-210 mins) with CBD but not placebo CBD blocks the emergence of these in all three volunteers ↓	Low

Bird et al. (1980)[a], Australia	To examine the effect of all of the possible combinations between ethanol and the major constituents of cannabis, in one experimental design.	161 recruited (39 women; 122 men, six excluded following breathalyser); 18-36 years, whom 50% self-reported cannabis use at least once a week; experience varied from 1-13years, with a median of 3.8 years. Breathalyser to confirm no presence of alcohol on test day.	Placebo-controlled, double-blind, parallel study across 16 treatment conditions. Randomly assigned to treatment group.	Oral THC 0.215 mg/kg + CBD 0.320 mg/kg; oral THC 0.215 mg; oral Placebo	Auditory and complex reaction times, conjunctival hyperaemia, pulse rates, the pursuit-rotor (errors and time off target), self-rating of subjective intoxicating effects, standing steadiness (eyes open and closed), visual, VDA.	When co-administered CBD did not modify the effects of THC, where THC reduced performance on perceptual, cognitive and motor function tests and increased pulse rate, conjunctival hyperaemia and subjective intoxication =	Some concerns
Dalton et al. (1976), United States	To evaluate the interaction between THC and CBD in typical doses used by cannabis smokers.	16 healthy volunteers (men) 21-24 years, with self-reported cannabis use at least once, but never regular use. Abstinence not reported.	Placebo-controlled, double-blind, crossover study with four treatment conditions. Randomised treatment order using Latin Squares. One participant withdrew.	Smoked THC 0.025mg + CBD 0.150 mg/kg; smoked THC 0.025mg; smoked Placebo	Blood pressure, CMI, DAF, heart rate mental coordination (peg-board), modified pursuit meter, wobble board.	Combined CBD + THC reduced the subjective feeling 'high' associated with THC alone ↓ CBD did not alter the effects of THC standing steadiness, hand-eye coordination, manual coordination, heart rate, and performance on a delayed auditory feedback task =	Low
Dalton et al. (1976), United States	To evaluate the interaction between THC and CBD in doses typical of doses being used by cannabis smokers.	Eight healthy volunteers (men) 21-24 years, with self-reported cannabis use at least once, but never regular use. Abstinence not reported.	Placebo-controlled, double-blind, crossover study with two treatment conditions. Randomised using Latin Squares design.	Pre-treatment (T-30mins) oral CBD 0.150mg/kg followed by smoked THC 0.025 mg/kg; smoked THC 0.025 mg/kg;	CMI, blood pressure, heart rate.	Pre-treatment with CBD did not alter the effects of THC on any measure =	Low

				smoked Placebo			
Englund et al. (2013)[b], United Kingdom	To investigate whether pre-treatment with CBD would attenuate positive psychotic symptoms and cognitive impairment following THC.	48 healthy volunteers (21 women; 27 men) 21-50 years, with self-reported cannabis use at least once; mean lifetime cannabis use: 119-137 times. Failure of cannulation prevented the administration of THC in three participants. A urine drug screen was carried out. No alcohol 24hrs or drugs one week before testing.	Placebo-controlled, double-blind, parallel study across two treatment conditions. 26 received placebo and 22 CBD. Randomly allocated, counterbalanced.	Pre-treatment (T-210 mins) oral CBD 600 mg followed by intravenous THC 1.5 mg; pre-treatment (T-210 mins) oral Placebo followed by intravenous THC 1.5 mg	Digit span forward and backward, HVLT-R, MCCB, NAB mazes PANSS, plasma blood concentration, SSPS, symbol coding, UMACL.	Clinically significant increase in positive symptoms following THC were more common in the group pre-treated with placebo compared with the group pre-treated with CBD ↓ Post-THC paranoia was lower in the CBD group ↓ CBD inhibited the effects of THC on episodic memory ↓ No difference in plasma concentrations between groups =	Low
Guy and Robson (2003), United Kingdom	To assess the pharmacokinetic profile, safety and tolerability of the test treatments.	24 healthy volunteers (men) 18-50 years, with self-reported cannabis use at least once. A urine drug screen was carried out pre-dose, follow-up drug screens. No cannabis 30 days before testing; no alcohol or caffeine 48hr before testing.	Placebo-controlled, double-blind, crossover study across three treatment conditions. Randomised to treatment order using a Williams Square Design.	Oromucosal spray THC 10 mg + CBD 10mg; oromucosal spray THC 10 mg; oromucosal spray Placebo	Blood samples, clinical chemistry, ECG recordings, palatability, self-rating of subjective intoxicating effects, urinalysis.	Active treatments intoxication scores were low, and effects not related to plasma concentrations THC T_{max} statistically significantly later following CBD+THC than THC alone ↓ It is possible that the presence of CBD in the CBD+THC formulation delays the absorption of THC ↓ Wide inter- and intra-subject variability	Low

Haney et al. (2016), United States	To assess the influence of oral CBD on the reinforcing, subjective, cognitive, and physiological effects of smoked THC.	31heathy volunteers (14 women; 17 men) 18-50 years, with self-reported current cannabis use; an additional 19 participants withdrew or were excluded. Urine drug screen, breathalyser and carbon monoxide test. No cannabis, alcohol, cannabis or tobacco 12hr before testing.	Placebo-controlled double-blind, crossover study across eight treatment conditions. Randomised to treatment order.	Pre-treatment (T-90mins) oral CBD 200, 400, 800 mg followed by smoked THC 42 mg; pre-treatment (T-90mins) oral Placebo followed by smoked THC 42 mg	Blood pressure, CPT, heart rate, DSST, self-rating of mood and subjective intoxicating effects.	CBD did not significantly alter the increase subjective intoxication effects or increased estimates of the street value of the cannabis smoked associated with THC alone = CBD did not significantly influence the significant increase in peak heart rate following THC =	Low
Hindocha et al. (2015); Morgan et al. (2018); Wall et al. (2019) United Kingdom	To determine the effects of THC and CBD, both alone and in combination on emotional facial affect recognition subjective effects and memory function. Secondary analyses: To investigate psychosis-like effects.	48 heathy volunteers (14 women; 34 men) 18-26 years, with either daily (24) or recreational (24) self-reported cannabis use. No alcohol or illicit drug use 24hr before testing.	Placebo-controlled, double-blind, crossover study across four treatment conditions. Analysed by four groups: high vs low SPQ score; and frequency of cannabis use: daily vs recreational. Randomised using a Latin squares design.	Vaporised THC 8 mg + CBD 16 mg; vaporised THC 8 mg; vaporised Placebo	BSS, dot-probe task, emotional processing task, genotyping, MCQ, N-back, prose recall, self-rating of subjective intoxicating effects, trail making task.	Primary outcomes: CBD reduced the impairment of recognition of ambiguous faces of 40% intensity associated with THC ↓ THC alone and combined THC+CBD equally increased feelings of being 'stoned' = Secondary outcomes: Both THC alone and in combination with CBD increased negative symptoms on the BPRS, perceptual distortions & cognitive disorganisation on the PSI = The influence of CBD on THC may differ according to variation in endocannabinoid system genetics.	Low

Hollister and Gillespie (1975), United States	To test if CBD and CDN interact with the effects of THC.	15 healthy volunteers (men) 18+ years, with self-reported cannabis use at least once. Abstinence not reported.	Crossover study across three treatment conditions. Randomised using Latin Squares design.	Oral THC 20 mg + CBD 40 mg; oral THC 20 mg; oral Placebo	ARCI, conjunctival hyperaemia, drug intensity rating, pulse rate, self-rating of subjective intoxicating effects, urinalysis.	The onset of effects measured by a narrative summary of subjective effects of THC+ CBD compared to THC alone was slightly slower ↓ Pulse rate changes were similar across treatments = Metabolites in urine samples were more numerous following the THC + CBD combination than after THC alone ↑	Some concerns
Hunt et al. (1981), United States	To investigate the effect of CBD on THC pharmacokinetics.	Four healthy volunteers (men) 22-30 years, with self-reported cannabis use 4-10 times; and cigarettes per week for an average of 8.3 years before the study. Participants remained on-site to ensure abstinence from drugs and medication 48hrs before testing.	Placebo-controlled, double-blind, crossover study across two treatment conditions. Participants counterbalanced to receive treatments in a different order.	Pre-treatment (T-480, -300, -120 mins) oral CBD 500 mg followed by intravenous THC 2 mg; pre-treatment (T-480, -300, -120 mins) oral Placebo followed by intravenous THC 2 mg	Blood sample, fingertip temperature, heart rate pharmacokinetics, self-rating of subjective intoxicating effects, urinalysis.	Pre-treatment with CBD did not alter the pharmacokinetic or pharmacodynamic effects of THC = There may be minimal effect on the formation and excretion of metabolites. Total (metabolic) blood clearance of THC 17ml/min/kg without CBD and 20.9ml/min/kg with CBD ↑	Some concerns
Karniol et al. (1974)[c], Brazil	To investigate whether THC + CBD would induce less 'high' or psychosis-like effects that would be expected from THC alone.	50 recruited (10 excluded before assignment to a group) healthy volunteers (men), 21-34 years, 22 with self-reported cannabis use at least once; 18 had never used cannabis. No alcohol 24hr before testing.	Placebo-controlled, double-blind, parallel study across eight treatment conditions. Groups balanced for age and weight.	Oral THC 30 + CBD 15, 30 or 60 mg; oral THC 30 mg; oral Placebo	Pulse rate, self-rating of subjective intoxicating effects, time production task.	CBD seemed to block the anxiety-provoking effects of THC ↓ CBD was found to attenuate several effects of THC, such as pulse rate acceleration, time production impairment and psychological disturbances ↓	Some concerns

T. P. Freeman, Pope, et al. (2018); Lawn et al. (2016); Wall et al. (2019), United Kingdom	To examine acute effects of THC + CBD and THC alone on effort-related decision-making. Secondary aims: Investigate response to music in brain regions sensitive to reward and emotion, and subjective ratings following THC and test if offset by CBD.	17 healthy volunteers (nine women; eight men) 18-70 years, with self-reported cannabis use (≥4 times in the last year, ≤3 times/week; one participant excluded in T.P. Freeman et al. 2018. Urine drug screen at each session, no alcohol or illicit drugs 24hr before each testing session.	Placebo-controlled, double-blind, crossover study across four treatment conditions. Randomised to treatment order using a Latin squares design.	Vaporised THC 8 mg + CBD 10 mg; vaporised THC 8 mg; vaporised Placebo	Blood pressure, EEfRT, fMRI, heart rate, SDS Snaith Hamilton pleasure scale, self-rating of subjective intoxicating effects, temporal experiences of pleasure scale.	Primary outcomes: CBD did not affect reduced motivation for high-effort choice associated with THC to make a to earn rewards = CBD altered increased sensitivity to monetary value following THC ↓ Secondary outcomes: Higher enhanced sound perception after THC+CBD than THC ↓ THC alone dampened the response to music in several reward and emotion brain regions, THC+CBD did not differ from placebo and showed greater connectivity ↓ THC alone reduced connectivity within the salience network when compared to THC + CBD ↓	Low
Juckel et al. (2007); Nadulski et al. (2005); Roser et al. (2009); Roser et al. (2008); (Stadelmann et al., 2011)[d], Germany	To investigate the effects of CBD on the pharmacokinetics of THC. Secondary analyses: investigate psychotic states and schizophrenic conditions; acute effects of cannabinoids on P300 amplitude; psychomotor performance by using	28 healthy volunteers recruited [a], 20-24 included depending on the analysis (up to 12 women; 12 men). Three participants had a panic attack. For others there were technical issues with ERP recording or quality of recording. Participants were 18-45 years with self-reported cannabis use at least once, but never regular use. Urine	Placebo-controlled, double-blind, crossover study across three treatment conditions. Randomised to treatment order.	Oral THC 10 mg + CBD 5.4 mg; oral THC 10 mg; oral Placebo	AIR-scales, auditory evoked MMN recorded via ERP recording, blood plasma levels, DNA genotyping, eye-movement finger tapping asymmetry, inter-manual coordination.	Primary outcomes: CBD inhibits the metabolic hydroxylation of THC; but the effect is small ↓ Secondary outcomes: Greater auditory evoked MMN amplitude following THC+CBD but not THC alone ↓ No difference in P300 amplitudes under THC and THC+CBD =	Some concerns

	a finger tapping test series; if (AAT)n polymorphism differentially modulates cannabinoid effect on P300 generation during an auditory choice reaction task.	screen for illicit drugs before each testing session, self-report no cannabis one month; no alcohol, caffeine, 48hrs before; no nicotine 12hrs.				THC+CBD but not THC alone reduced right-hand tapping frequencies ↑ >10/>10 genotypes showed a decrease of P300 amplitude and prolongation of P300 latency under THC alone but not THC+CBD ↓ Correlation between AAT repeats and P300 variables for THC alone.	
Nicholson et al. (2004), United Kingdom	To assess the effects of cannabis extracts on nocturnal sleep, early morning performance, memory, and sleepiness.	Eight healthy volunteers (four women; four men) 18-35 years, with self-reported cannabis use at least once, but never regular use. No cannabis for a month; no alcohol 48hrs.	Placebo-controlled, double-blind, crossover study across four treatment conditions. Randomisation not indicated.	Oromucosal spray THC 15 mg + CBD 15 mg; oromucosal spray THC 15 mg; oromucosal spray Placebo	Blood plasma levels, choice reaction time, delayed and immediate word recall, digit symbol, heart rate, letter and digit memory recall, multi-attribute task battery, pulse rate, self-rating of subjective intoxicating effects, sleepiness, sustained attention, sleep latency.	THC alone and in combination with CBD increased sleepiness 30minutes after waking, negatively affected mood = THC+CBD but not THC alone decreased stage 3 sleep and increased time spent awake ↑ THC decreased latencies to early morning sleep and impaired episodic memory, not present with THC + CBD ↓	Low
Zuardi et al. (1982), Brazil	To investigate whether CBD diminished the anxiety produced by THC in healthy volunteers, and to verify whether this effect occurs through a	Eight healthy volunteers (two women; six men) 20-38 years, with self-reported cannabis use at least once, three had never used cannabis. 15 days	Placebo-controlled, double-blind, crossover across six treatment conditions. Participants	Oral THC 0.5 mg/kg + CBD 1 mg/kg; oral THC 0.5 mg/kg; oral Placebo	ARCI-Ma, interviews of subjective effects, pulse rate, Scale of Bodily Symptoms, self-rating of subjective	THC increased pulse rate, CBD did not alter this effect = When combined with CBD blocks the anxiety provoked by THC ↓ CBD blocks subjective effects measured on the ARCI-Ma ↓	Some concerns

	general block of the action of THC or a specific effect on the anxiety.	abstinence of cannabis before testing.	received treatments in a different order.	intoxicating effects; STAI; self-rating of subjective intoxicating effects.

Notes. effect: ↑ increases effects of THC; ↓ decreases effects of THC, = no difference of effect; *interventions – only interventions relevant to the review are reported; Risk of bias tool: Cochrane's risk of bias tool (either for parallel/crossover study design); Where multiple publications for single study first publication reported as primary outcomes, all subsequent as secondary outcomes. AIR-scale: visual Analogue Intoxication Rating Scales; ARCI-Ma: Addiction Research Center Inventory for Marihuana Effects; BSS: Bodily Symptoms Scale; CBD: cannabinol; CMI: Cornell Medical Index; CPT Continuous Performance Task; DAF: Delayed Auditory Feedback; DAT: Divided attention task; DSST: Digit Symbol Substitution Task; DSST: Digit Symbol Substitution Task; ECG: electrocardiogram; EEfRT: Effort expenditure for rewards task; ERP: event-related brain potential; fMRI: functional magnetic resonance imaging; hr: hours; HVLT-R: Hopkins Verbal Learning Task-Revised; iv: intravenous; MCCB: MATRICS Consensus Cognitive Battery; MCQ: Marijuana Craving Questionnaire; MMN: mismatch negativity; n: total number of participants; NAB: Neuropsychological Assessment Battery; PANSS: Positive and Negative Syndrome Scale; PASAT: Paced Auditory Serial Addition Task; SDS: Severity of Dependence Scale;; SPSS The State Social Paranoia Scale, STAI: Spielberger's State-Trait Anxiety Inventory; THC: delta-9-tetrahydrocannabinol; UMACL: University of Wales Mood Adjective Checklist; VDA: Vienna Determination Apparatus; a. 166 divided into 16 groups; b. placebo n= 22 CBD n=26, c. 8 groups of 5; d. not all participants completed all measures in this study 2 men, and 2 women did not complete ERP recording due to technical issues and three women had a panic attack. Therefore Roser et al. (2008) and Stadlemann et al. (2011) included 20 participants; Nadulski et al. (2005) and Roser et al. (2009) included 24 participants; Juckel et al. (2007) included 22 participants. Underlined study is first publication of the study.

3.2. **Participants**

All studies included healthy volunteers, and all except two (Karniol et al., 1974; Zuardi et al., 1982) included only participants with previous experience of cannabis use.

3.3. **Treatment characteristics**

Table 1 shows the treatment characteristics of each study. There was considerable variability in the doses of both THC and CBD, and in the ratio of THC to CBD. There was also heterogeneity in the route of administration used across treatments and studies. For CBD administration, eight studies used oral doses (5.4mg-800mg), one intravenous (5mg), two vaporised (4mg-16mg), two smoked (0.150-0.320mg/kg), and two used an oromucosal spray (10mg-15mg). For THC administration, six studies used oral (10mg-40mg), three intravenous (1.25mg-2mg), three smoked (42mg or 0.215-0.025mg/kg), two vaporised (8mg), and two used an oromucosal spray (10mg-15mg). Five studies used a design where a dose of CBD or placebo was administered as a pre-treatment before THC administration. These were administered either orally (200-1500mg) 480 to 90 minutes before, via a smoked joint (0.150mg/kg), 30 minutes ahead, or intravenously immediately before THC. Where studies used a design that included a pre-treatment, they did not include a pure placebo condition and used baseline measurements which were administered before any drug. The remaining studies all used a design which included a treatment condition where participants received placebo only.

3.4. **Risk of bias within studies**

Only ten studies were found to be at low risk of bias (Arkell et al., 2019; Bhattacharyya et al., 2010; Dalton et al., 1976; Englund et al., 2013; Guy & Robson, 2003; Haney et al., 2016; Hindocha et al., 2015; Lawn et al., 2016; Nicholson et al., 2004); some concerns were found for six studies (Bird et al., 1980; Hollister & Gillespie, 1975; Hunt et al., 1981; Karniol et al., 1974; Nadulski et al., 2005; Zuardi et al., 1982); none were evaluated as high risk of bias. A table summarising the findings from the risk of bias assessment can be found in Appendix G.

3.5. **Risk of bias across studies**

Indicators for risk of bias across studies were assessed (Boutron et al., 2019). Overall this area of research has low risk of publication bias as many studies report a mixture of significant and non-significant findings. This review only included studies published in the English language and therefore may have missed important findings reported in different languages. Some studies were funded by an industry sponsor and therefore present a potential conflict of interest (Guy & Robson, 2003; Nicholson et al., 2004). One possible bias across studies is recreational use of cannabis external to the study, which may have resulted in residual drug effects, and could have affected participants' performance. Another bias across studies may have been that individuals were able to identify the placebo condition over active treatment conditions, although this would not be expected to be a concern for the comparison between the THC versus THC+CBD conditions.

3.6. **Synthesis of results**

Table 1 summarises the findings of comparisons between THC with and without CBD for the studies included in this review. A narrative synthesis of the findings from the review was conducted because the heterogeneity of outcomes used across studies precluded meta-analysis.

3.6.1. Pharmacokinetic effects

Pharmacokinetics were assessed in eight studies. Overall, typically studies reported that CBD did not significantly alter the pharmacokinetic profile of THC. Although three studies suggested that CBD may have a small effect on the metabolism of THC, findings were inconsistent. Three out of the eight studies were rated as having some concerns in at least one domain of the risk of bias assessment (Hollister & Gillespie, 1975; Hunt et al., 1981; Nadulski et al., 2005).

In a study of 14 participants, the combination of vaporised THC (13.75mg) and vaporised CBD (13.75mg) was associated with significantly increased peak plasma concentrations of THC when compared to vaporised THC (13.75mg) alone (Arkell et al., 2019). Although not statistically significant, the area under the curve (0-3 hours) for plasma THC was higher for the combined THC+CBD treatment than THC alone. Nadulski et al. (2005) showed that co-administration of oral CBD (5.4mg) altered the metabolism of oral THC (10mg) by partially inhibiting the cytochrome P450 enzymes, which hydroxylate THC to its metabolite 11-hydroxy-THC. The authors suggest this may lead to a slight rise and earlier peak in THC concentration when THC is combined with CBD. However, in this study of 24 participants there was wide inter-participant variability. In a later publication of the same study, Roser et al. (2009) report

significantly higher levels of 11-OH-THC and THC-COOH in women compared to men following THC with CBD, but not following THC alone. In a study of 24 participants, Guy and Robson (2003) found the time taken to reach the maximum plasma concentration for THC was significantly later following oromucosal spray of THC (10mg) and CBD (10mg) combined when compared to oromucosal spray of THC (10mg) alone. The authors concluded that CBD might delay the absorption of THC. However, this study also reported wide inter- and intra-participant variability in pharmacokinetic parameters. There were no other significant differences in the pharmacokinetic profiles between the two test treatments.

In a study of only four participants, Hunt et al. (1981) concluded that pre-treatment with three doses of oral CBD at eight, six and two hours (total dose 1500mg) before intravenous THC (2mg) had no significant effect on the pharmacokinetics of THC when compared to pre-treatment with placebo. The authors report, however, that there may be a "real but slight" effect of CBD on the metabolism of THC, where total (metabolic) blood clearance of THC averaged 17ml/min/kg without CBD and 20.9ml/min/kg with CBD. In a study of 15 participants, Hollister and Gillespie (1975) found that compared to oral THC (20mg) administered alone, when combined with oral CBD (40mg) THC was associated with increased concentrations of THC metabolites in urine. However, they attributed this to the additional presence of CBD rather than a change in the metabolism of THC.

A small crossover study (n=6) found that pre-treatment with intravenous CBD (5mg) did not influence blood levels (area under the curve from 0 to 120 minutes) of

THC following intravenous THC (1.25mg) when compared to placebo (Bhattacharyya et al., 2010). Similarly, a parallel group study (n=36) found no significant difference in plasma concentration of THC following pre-treatment with oral CBD (600mg) or placebo (Englund et al., 2013). Nicholson et al. (2004) reported plasma concentrations for THC, OH-THC and COOH-THC but did not report comparisons between the treatment groups.

3.6.2. Pharmacodynamic effects

3.6.2.1. Pulse rate

Of the ten studies that reported outcomes for the effects of cannabinoids on pulse rate, the risk of bias assessment found some methodological concerns for four studies (Bird et al., 1980; Hollister & Gillespie, 1975; Karniol et al., 1974; Zuardi et al., 1982). Eight studies found that both THC alone and the combination of THC and CBD increased pulse rate when compared to baseline measurements or placebo, but there was no significant difference between the THC alone and the combination of the two drugs (Bird et al., 1980; Dalton et al., 1976; T. P. Freeman, Pope, et al., 2018; Guy & Robson, 2003; Haney et al., 2016; Hollister & Gillespie, 1975; Zuardi et al., 1982). Another study, which investigated the effect of THC and CBD on sleep in just eight participants, found no differences in pulse rate between treatments (sublingual drops of a placebo, THC 10mg, THC 10mg + CBD 10mg) during the 30 minutes following drug administration (Nicholson et al., 2004). However, on waking the next morning both the THC alone and in combination with CBD were associated with postural systolic hypotension, with compensatory increases in supine and erect pulse rate when compared to placebo.

In contrast, Karniol et al. (1974) reported results from a very small parallel group study (n=40; n=5 per group) where oral THC (30mg) alone significantly increased pulse rate, but when THC was combined with low dose oral CBD (15mg), it seemed to increase pulse rate further. However, when THC (30mg) was combined with higher doses of oral CBD (30mg or 60mg), the combination seemed to have the opposite effect, reducing the acceleration of pulse rate associated with THC alone.

3.6.2.2. Blood pressure

Three studies reported outcomes for blood pressure. There were no concerns about the risk of bias. Findings of two studies suggest that CBD might alter the effect of THC on blood pressure. Guy and Robson (2003) reported no notable changes in diastolic blood pressure, however, three hours after drug administration the mean systolic blood pressure decreased by 10.3 mmHg following THC (10mg) alone; by 4.4 mmHg following sublingual THC (10mg) and CBD (10mg) condition; and 5.1 mmHg during the placebo period. In a crossover study of 17 participants, T. P. Freeman, Pope, et al. (2018) reported increased systolic blood pressure following both THC (8mg) alone and the combination of THC (8mg) and CBD (10mg) when compared to placebo, whereas diastolic blood pressure increased after drug administration in the THC alone condition, but not following co-administration of THC and CBD. However, Haney et al. (2016) did not find significant differences in blood pressure across their different treatment groups (n=31) in a study of pre-treatment (90mins) with either oral CBD (200, 400, 800 mg) or placebo 90 minutes before smoking a joint of THC (~42 mg).

3.6.3. Subjective intoxicating effects

There was much variation in the way studies measured subjective effects. Of the nine studies, most included visual analogue scales (VAS) where participants self-rated

feelings of intoxication. Two studies presented some concern about the potential risk of bias (Bird et al., 1980; Zuardi et al., 1982). The evidence for CBD potentially reducing the acute subjective effects of THC comes from two small experimental studies. In Dalton et al.'s (1976) double-blind, crossover study (n=15), smoked THC (0.025mg/kg) alone was associated with an increase in feeling "high" and increased drug-related effects on a modified version of the Cornell Medical Index (CMI) symptoms (a list of symptoms self-rated for intensity on a 0 to 4 scale). CBD (0.150mg/kg) significantly reduced the effects of THC. Similarly, Zuardi et al. (1982) found in a small double-blind crossover study (n=8), that oral THC (0.5mg/kg) and CBD (1mg/kg) combined reduced the increase in subjective feelings on the Addiction Research Center Inventory for marihuana effects (ARCI-Ma) associated with oral THC (0.5mg/kg) alone. In contrast to these findings, seven studies found no evidence for CBD moderating the subjective intoxicating effects of THC (Arkell et al., 2019; Bird et al., 1980; Dalton et al., 1976; T. P. Freeman, Pope, et al., 2018; Haney et al., 2016; Hindocha et al., 2015; Roser et al., 2009).

3.6.4. Anxiety

Three studies, two of which have an unclear risk of bias (Karniol et al., 1974; Zuardi et al., 1982), reported outcomes for anxiety-related symptoms. The interaction of CBD on the anxiety-inducing effects of THC was first described by (Karniol et al., 1974) in a placebo-controlled, double-blind, parallel group study (n=40; n=5 per group). The study used a specially developed scale (Appendix H) where subjective drug effects were graded (from 0 to 4) if the participant reported at least three symptoms listed in each grade (Karniol & Carlini, 1973). The scale lists anxiety and psychosis-related items, for example, Grade 0 "nothing or slight anxiety", to Grade 4, "panic; intense

sensation of being watched; impossibility to have coherent thoughts due to the rapid flow of ideas". Oral THC (30mg) induced Grade 4 effects in four out of five participants. However, when oral CBD (15mg, 30mg & 60mg respectively) was combined with oral THC (30mg), 3 participants out of 15 experienced these effects. A dose-dependent effect was suggested, where no participants in the high CBD group met criteria for Grade 4. Zuardi et al.'s (1982) double-blind, crossover study (n=8) found that when oral CBD (1mg/kg) was administered together with oral THC (0.5mg/kg), it attenuated the significant increase in anxiety symptoms on the State-Trait Anxiety Inventory (STAI; Spielberger, 2010) associated with oral THC (0.5mg/kg) alone. Arkell et al. (2019) reported in a study of 14 participants that vaporised THC (13.75 mg) both with and without vaporised CBD (13.75 mg) produced small but significant increases in ratings of anxiety and increases on the STAI 15 minutes after the drug was administered. However, only after vaporised THC (13.75 mg) alone were these ratings still increased after an hour.

3.6.5. Psychotomimetic and psychosis-like experiences

Three studies included in this review investigated psychotomimetic and psychosis-like effects following the acute administration of THC. There were no concerns about potential bias. THC induced acute psychosis-like effects on the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987), following intravenous THC (1.25mg) in three out of six participants (Bhattacharyya et al. 2010). This double-blind, pseudo-randomised, crossover study, found that pre-treatment with intravenous CBD (5mg), when compared to placebo, ameliorated the psychotomimetic effects of THC. Comparable effects were seen in Englund et al.'s (2013) randomised, double-blind, parallel study (n=48), which showed that although there was no statistical difference

in the mean increase in scores on the PANSS after intravenous THC (1.5mg) following pre-treatment of placebo or oral CBD (600mg), fewer participants treated with CBD showed a clinically significant increase in positive symptoms (≥3 points). Paranoia rated on the State Social Paranoia Scale (SSPS; D. Freeman et al., 2007) was lower in the group of participants who received pre-treatment with CBD when compared to those who received pre-treatment with placebo (Englund et al., 2013).

In contrast to these findings, however, Morgan et al. (2018) did not find any difference in acute psychotomimetic effects between two treatment conditions of vaporised THC (8mg) with or without vaporised CBD (16mg) respectively. The double-blind, placebo-controlled, crossover study (n=48), showed that THC both alone and THC combined with CBD increased negative symptoms on the Brief Psychotic Rating Scale (BPRS; Overall & Gorham, 1962) and total scores on the Psychotomimetic States Inventory (PSI; Mason, Morgan, Stefanovic, & Curran, 2008). In particular scores on the perceptual and cognitive distortion subscales of the PSI were significantly higher than scores on placebo. The study did not find any differences in these effects based on frequency of cannabis use or trait schizotypal symptoms.

3.6.6. Cognitive effects

Seven studies reported outcomes related to cognitive tasks including those focused on memory, auditory processing, emotion and reward. Two studies presented some concerns on the risk of bias assessment (Juckel et al., 2007; Karniol et al., 1974; Roser et al., 2008; Stadelmann et al., 2011).

3.6.6.1. Episodic memory

As previous studies have shown, THC alone had an acute detrimental effect on episodic memory in five studies (Dalton et al., 1976; Englund et al., 2013; Karniol et al., 1974; Morgan et al., 2018; Roser et al., 2008). Whether CBD is protective against these effects was less clear. Englund et al.'s (2013) study (n=48) showed that intravenous THC (1.5mg) alone impaired episodic memory on both the immediate and delayed recall tasks from the Hopkins Verbal Learning Task-Revised (HVLT-R; Brandt & Benedict, 2001) when compared to baseline. Participants allocated to pre-treatment with oral CBD (600mg) resulted in the same level of immediate recall following THC, but the impairment for delayed recall was ameliorated following CBD pre-treatment. In a cross over study (n=48) Morgan et al. (2018) found that vaporised THC (8mg) both alone and when combined with vaporised CBD (16mg) showed the same level of impairment in episodic memory on prose recall in the story recall task from the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn, Baddeley, & Hiorns, 1989), when compared to placebo.

3.6.6.2. Attention and working memory

Morgan et al. (2018) found that vaporised THC (8mg) both alone and when combined with vaporised CBD (16mg) impaired working memory on the N-back task (Kirchner, 1958). Karniol et al. (1974) showed that CBD reduced impairments on a time production task, which taps working memory processes (Lewis & Miall, 2006). Participants were instructed to estimate 60-second time intervals, and the study (n=40; n=5 per group) demonstrated a phenomenon where administration of oral THC (30mg) alone led to an acceleration of the 'internal clock,' which was not present when oral THC (30mg) was co-administered with oral CBD (15mg, 30mg or 60mg). However, a parallel group study (n=48) by Englund et al. (2013) found that pre-treatment with

oral CBD (600mg) did not seem to alter the impairing effects of intravenous THC (1.5mg) on working memory tasks, including digit span forward and backwards. Arkell et al. (2019) found that vaporised THC (13.75mg) alone, but not THC combined with vaporised CBD (13.75mg), induced impairments after 20 minutes on the Digit Symbol Substitution Test (McLeod, Griffiths, Bigelow, & Yingling, 1982) compared to placebo in 14 participants. However, on the Divided Attention Task (Kleykamp, Griffiths, & Mintzer, 2010) participants showed impaired performance 20 minutes following THC combined with CBD compared to THC alone or placebo.

3.6.6.3. Semantic memory

In a crossover study which included 48 participants, Morgan et al. (2018) found that verbal fluency was enhanced when vaporised THC (8mg) was combined with CBD (16mg), but there was no difference in verbal fluency performance between vaporised THC (8mg) alone and placebo.

3.6.6.4. Auditory processing

Juckel et al. (2007) aimed to investigate a component of auditory evoked brain potential (ERP) called mismatch negativity (MMN) amplitude which is an automatic, and pre-attentive event-related potential component associated with auditory processing and working memory. MMN processing is impaired in people who have a diagnosis of schizophrenia (Javitt, Doneshka, Grochowski, & Ritter, 1995). The analysis (n=22) showed that the combination of oral THC (10mg) and oral CBD (5.4mg), but not oral THC (10mg) alone, was associated with higher amplitudes at the central electrode compared to placebo. No deficits were found in the THC alone condition. The authors suggest the improvement in performance may occur due to the improved processing due to the effect of CBD on auditory information processing. In

the same study Roser et al. (2008) analysed the amplitudes of auditory evoked P300 in the same sample, to investigate the effect of THC alone and in combination with CBD on electroencephalography (EEG) correlates of working memory and attentional functioning during a choice reaction time task. The analysis (n=20) showed that THC alone, and when administered with CBD, significantly reduced P300 amplitude at midline frontal, central and partial electrodes and therefore CBD did not prevent the acute impairment of THC alone.

Stadelmann et al. (2011) later investigated whether the (AAT)*n* polymorphism differentially modulates the effects of THC alone and THC combined with CBD on P300 generation during an auditory choice reaction task in the same sample (n=20). There was a significant decrease of P300 amplitude and prolongation of P300 latency for both >10 genotypes in the THC alone condition, but not in the condition where THC and CBD were combined. There was a significant correlation between the number of AAT repeats and P300 variables for the THC condition. The authors suggest that this finding seems to indicate that the CNR1 gene may differentially alter sensitivity to the acute effects of cannabinoids on P300 generation.

Dalton et al. (1976) reported that smoked THC (0.025mg/kg) decreased the frequency of verbal responses and increased errors on delayed auditory feedback (DAF) both alone and in combination with smoked CBD (0.150 mg/kg) in 16 participants. In a randomised, double-blind, crossover study (n=14) participants showed transient impairments following vaporised cannabis containing THC (13.75mg) both with and without CBD (13.75mg) on the Paced Auditory Serial Addition Task (Herrmann et al., 2015) when compared to placebo (Arkell et al., 2019).

3.6.7. Emotion and reward processing

Two studies investigated the differential effects of THC and CBD during emotion and reward processing tasks. These studies presented a low risk of bias. Hindocha et al. (2015) demonstrated impairments in emotional processing on a task which assessed participants' emotional facial affect recognition (happy, sad, fearful, angry, disgust and surprise) following vaporised THC alone (8mg). The study (n=48) found that the impairment induced by vaporised THC (8mg) in emotional processing was blocked when it was combined with vaporised CBD (16mg).

In a similar study, Lawn et al. (2016) investigated the effects of cannabis containing different doses of cannabinoids on a task which taps effort-related decision making, the effort expenditure for rewards task (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). The study (n=17) demonstrated that vaporised THC (8mg) increased sensitivity to probability and magnitude of reward (expected monetary value) relative to both placebo, and vaporised THC (8mg) administered with vaporised CBD (10mg). In a later publication from the same study (T. P. Freeman, Pope, et al., 2018), the researchers investigated the effects of cannabinoids while participants listened to music during functional magnetic resonance imaging (fMRI). Participants reported enhanced sound perception following co-administered THC and CBD when compared to THC alone. THC alone dampened the haemodynamic response to music in the bilateral auditory cortex, right amygdala, right hippocampus and para-hippocampal gyrus, and right ventral striatum. However, when THC was combined with CBD, this effect was offset, and the response to music in these brain regions did not differ from placebo. Additionally, THC with CBD caused greater functional

connectivity between the ventral striatum and auditory cortex during musical listening when compared to THC alone.

In the same study, Wall et al. (2019) investigated the effects of THC alone, THC in combination with CBD, and placebo during resting state fMRI. THC alone, and in combination with CBD, reduced connectivity across the default mode network (DMN). The DMN is a network of brain regions which are active in periods of wakeful rest and internally focused states and was defined in this study as brain regions showing positive connectivity with the posterior cingulate cortex (PCC). THC reduced connectivity within the DMN, and this effect correlated with increased subjective intoxicating effects (feeling "stoned" and "high"). THC and THC+CBD showed spatially dissociable effects on the salience network (SN) (Seeley et al., 2007) which toggles between internally focused states and external action and goal directed behaviours, defined in this study as brain regions showing positive connectivity with the anterior insula. Treatment effects across the whole SN indicated that THC alone showed an overall reduction in connectivity within the salience network when compared to THC co-administered with CBD.

3.6.8. Psychomotor performance

Four studies investigated the effects of cannabinoids on psychomotor performance. One study presented some concerns in a risk of bias assessment (Roser et al., 2009). Roser et al. (2009) investigated impairments in psychomotor performance which have been consistently associated with schizophrenia. In a randomised crossover study outcomes are reported on a finger tapping task in 24 healthy volunteers, following either oral THC (10mg) with CBD (5.4mg) combined, oral THC (10mg) alone, or oral placebo. On each of the three testing days participants completed a task which involved

five 15-second, finger tapping 'sessions' (right- and left-hand tapping), with two sessions involving tapping while completing other tasks (humming or reading) and a final session with alternate tapping. The study reported that THC co-administered with CBD, led to significantly reduced right-hand tapping frequencies compared to placebo in all but the alternate tapping sessions. There were no differences between placebo and the THC only condition. However, THC alone impaired left-handed frequencies in sessions without distraction tasks (two out of the five sessions); this impairment was associated with increased plasma concentrations of 11-OH-THC.

In a study investigating the effects of cannabinoids on a driving simulation task (n=14), both vaporised THC (13.75mg) with and without CBD (13.75mg) were found to increase lane weaving during a car following task (Arkell et al., 2019) when compared to placebo. Bird et al. (1980) did not find any evidence for oral CBD (0.320mg/kg) moderating the effects of oral THC (0.215mg/kg). This parallel study (16 groups, n=116) combined several outcomes to create three factors. Visual, auditory, and complex reaction time were combined to create a reaction speed factor (factor 1), a standing steadiness factor included scores from eyes open and closed standing steadiness tasks (factor 2), and a third factor included the pursuit rotor and a psychomotor coordination and the Vienna determination apparatus (VDA) data (factor 3). THC alone impaired both standing steadiness and psychomotor coordination, but CBD did not moderate this effect. Dalton et al. (1976) also found in a crossover study (n=16) that both combined smoked THC (0.025mg/kg) and CBD (0.150mg/kg) and smoked THC (0.025mg/kg) alone, when compared to placebo, reduced standing steadiness using a wobble board, hand-eye coordination on an attentive motor performance task, using a modified pursuit meter (Evans et al., 1973) and manual coordination and dexterity using a pegs test.

3.6.9. Sleep

One study assessed the acute effects of THC, with and without CBD, on sleep. Nicholson et al. (2004) investigated the effect of oromucosal spray containing THC (15mg) and CBD (15mg) when compared to oromucosal spray containing THC (15mg) alone in eight participants. The study found that THC had sedative qualities, however, when THC was combined with CBD the spray increased the duration of wakefulness and stage 3 nocturnal sleep suggesting that CBD may have some activating properties. There were no differences in participants' ratings of sleep onset, duration or quality between treatments. However, THC alone was associated with increased sleepiness 30 minutes after waking, and decreased latencies to early morning sleep (Nicholson et al., 2004).

3.6.10. Genetic vulnerability to the effects of cannabis

Hindocha et al. (2019) analysed the effects of cannabinoids on addiction endophenotypes. The study (n=48) found that carriers of the CNR1 rs1049353 GG genotype reported decreased desire to smoke a joint after both vaporised THC (8mg), and vaporised THC (8mg) with vaporised CBD (16mg) when compared to placebo. Those with the A allele did not experience this reduction. There was no difference between THC with or without CBD. Those with the FAAH rs324420 genotype CC had lower attentional bias to appetitive cues following THC only when compared to A carriers. By contrast, CC and A carriers did differ on attentional bias following THC+CBD. These findings suggest that the ability of CBD to influence the effects of THC may differ according to variation in endocannabinoid system genetics.

4. Discussion

In the first systematic review of how CBD influences the acute effects of THC, 23 eligible papers were identified reporting on 16 studies, including a total of 466 participants. All studies employed experimental designs with adequate control conditions, enabling comparison of the acute effects of THC with those of a matched dose of THC combined with CBD. The risk of bias across within and across studies was typically low.

When taken together, these results suggest that CBD may moderate some of the effects of THC, most commonly resulting in a reduction in its acute effects. However, the moderating effect of CBD was not consistent across all studies. There was some disparity in findings, and although the direction of associations was consistent in many studies associations did not reach statistical significance in all studies. There was also considerable heterogeneity in the interventions used across studies, including different routes of administration (oral, sublingual, smoked, vaporised, mixed with food, or made into a drink), doses of THC and CBD, and the ratio of THC to CBD. No consistent pattern of effects across these factors was found, consequently, it was not possible to determine whether there is a dose-response relationship influencing how CBD moderates the effects of THC. Several studies included an oral dose of CBD (5.4mg-800mg). As oral CBD has been shown to have low bioavailability (13-19%; Mechoulam, Parker, & Gallily, 2002) the findings from studies administering low doses of oral CBD should be interpreted with caution. Additionally, other factors may have influenced the effects of cannabinoids within studies and this may explain why several studies reported large variability in effects across participants. For example, cannabis use history, including the potency and frequency of previous cannabis used (Curran et al., 2002; Curran et al., 2018; D'Souza et al., 2008; Desrosiers, 2015),

psychosis-proneness (Mason et al., 2009), gender (Cooper & Haney, 2014; Klumpers et al., 2012) and genetic factors (Hindocha et al., 2019; Morgan, Freeman, Powell, & Curran, 2016) can influence the acute effects of cannabinoids. The majority of studies did not assess for these issues which, alongside some very small sample sizes, may have contributed to variability in findings. It is recommended that future research should take these factors into account.

4.1. **Pharmacokinetic and pharmacodynamics effects**

The results obtained in this review show mixed findings and it is not clear how CBD influences the way THC is metabolised. While two studies showed that combining CBD with THC may lead to an increased peak plasma of THC (Arkell et al., 2019; Nadulski et al., 2005) another showed that when CBD was combined with THC the time to reach peak plasma concentrations was delayed (Guy & Robson, 2003). Four studies showed non-significant findings when investigating the pharmacokinetic interactions between THC and CBD (Bhattacharyya et al., 2010; Englund et al., 2013; Hollister & Gillespie, 1975; Hunt et al., 1981). In animal studies (Paton & Pertwee, 1972), CBD has been found to inhibit the metabolism of THC and potentially other drugs when administered together. There was some indication that gender may contribute to differences in metabolism of cannabinoids, as Roser et al. (2009) reported higher levels of 11-OH-THC and THC-COOH in women compared to men following THC with CBD, but not following THC alone, which is consistent with some evidence showing that women experience more intense subjective effects than men (Cooper & Haney, 2014; Haney et al., 2016). However, most studies in this review were small and did not report any significant differences in the pharmacokinetic profile of THC when it was combined with CBD. More extensive studies are needed to investigate

these effects, particularly because there seems to be substantial variability between participants.

In terms of the pharmacodynamic profile, across studies, THC with and without CBD generally increased pulse rate. Outcomes on blood pressure were mixed, with two studies reporting that CBD reduced the effect of THC on diastolic and systolic blood pressure respectively. A recent study of a single dose of CBD (600mg) alone showed that it increases heart rate but reduces systolic blood pressure (Jadoon, Tan, & O'Sullivan, 2017). These effects may be a consideration for prescribing clinicians and as well as recreational users of the drug.

4.2. **Subjective intoxication**

Participants predominantly experienced the subjective intoxicating effects of THC and THC combined with CBD similarly. These findings suggest that co-administration of THC and CBD may not reduce the desired effects of cannabis (Curran & Morgan, 2014).

4.3. **Anxiety and psychosis-like experiences**

Three studies included in this review showed that significantly fewer participants experienced extreme feelings of anxiety and psychotic-like effects when THC was co-administered with CBD. A recent study showed that the therapeutic properties of CBD within specific prefrontal brain regions in rats might be present only during pathologically aberrant states induced by THC (Szkudlarek et al., 2019). A mechanism whereby CBD only regulates THC when it has extreme effects may explain findings where CBD reduced clinically significant increases in psychosis-like effects, but not

increases in these experiences overall (Englund et al., 2013). This may be an important consideration for future research, as previous studies may have excluded participants at risk of adverse effects of cannabis (such as acute psychotic symptoms) due to concerns about safety. However, the moderating effects of CBD may only be apparent in those who experience more severe responses to THC.

4.4. **Cognitive effects**

While some studies found that CBD was protective against the acute memory-impairing effects of THC on tasks which tapped episodic memory and working memory, findings were not consistent. Schoeler and Bhattacharyya (2013) suggested that cannabis with higher doses of THC and lower CBD content produces robust acute memory deficits and that other factors may also contribute (e.g. tolerance, heavy early use). Regarding the specific components of memory that are affected, the studies included report outcomes for the number of items recalled correctly, consistent with an impairment in the encoding of episodic memories (Ballard, Gallo, & de Wit, 2012, 2013). However, it is not clear whether these effects are also present for the retrieval of episodic memories which can be measured by comparing the recall of false intrusions (Doss, Weafer, Ruiz, Gallo, & De Wit, 2018). Evidence suggests that THC impairs encoding but not retrieval of episodic memory (Ranganathan et al., 2017), but the specific effects of CBD on encoding versus retrieval are currently unclear. Collectively, studies included in the current review which investigated effects on memory included a wide range of doses and routes of administration of both THC and CBD, and no clear pattern of results emerged.

One study found that verbal fluency was enhanced when vaporised THC was combined with CBD but there was no difference in verbal fluency performance between vaporised THC alone and placebo (Morgan et al., 2018). However, a previous study has shown that oral THC alone can dose-dependently enhance verbal fluency (Curran et al., 2002) while another study found that vaporized cannabis impaired verbal fluency (Kowal et al., 2015). This suggests that the effects of THC on verbal fluency are inconsistent, and may be moderated by other factors in addition to CBD.

There was some evidence to suggest that CBD may influence the effects of THC on emotion and reward processing. When combined with THC, CBD attenuated impairments associated with THC (Hindocha et al., 2015; Lawn et al., 2016). These findings, however, come from only two studies. CBD did not reduce the impairments of THC across a range of psychomotor tasks (such as standing steadiness) in two studies (Bird et al., 1980; Dalton et al., 1976). One study found differences in finger tapping, where THC with CBD, but not THC alone, impaired performance on a task which is found to be related to impairments seen in schizophrenia (Roser et al., 2009).

4.5. **Genetics**

There was also evidence from two studies that genetic variants of the CNR1 gene may also influence the relationship between CBD and THC where the effects of the drugs alone and in combination depend on individual endocannabinoid system genetics (Hindocha et al., 2019; Stadelmann et al., 2011). Variations of the CNR1 gene may differentially alter sensitivity to the acute effects of cannabinoids on P300 generation (Stadelmann et al., 2011). Hindocha et al. (2019) found endocannabinoid system genetics may influence vulnerability to satiety, attentional bias towards appetitive cues

and craving which suggests that these differences may influence markers of vulnerability to cannabis use disorders.

4.6. **The role of CBD in harm reduction**

Although some studies reported that CBD may reduce the potentially harmful effects of cannabis, evidence suggests that combining THC with CBD may not necessarily reduce the desired intoxicating effects of the drug. More research is needed to fully elucidate how CBD influences the effects of THC. This is a complex issue as CBD has multiple mechanisms of action that may interact with THC to determine the health effects of the drug. For example, CBD may act to reduce some acute effects of THC through negative allosteric modulation of the CBR1 receptor (Hayakawa et al., 2008; Laprairie et al., 2015). There is however, also some evidence that CBD may increase plasma concentrations of THC (Arkell et al., 2019; Nadulski et al., 2005). The extent to which CBD acts via contrasting mechanisms such as these within and across individuals could account for the mixed and sometimes opposing effects of CBD reported in the literature to date. Further research should focus on establishing standardised methods for investigating these effects. One option might be for future research to focus on administration routes and doses which have the most ecological validity (such as vaporised or smoked cannabis, or sublingual methods for medicinal use). It may be helpful to establish standardised units of measurement of THC and CBD in cannabis to allow for more meaningful comparisons to be made between studies (T. P. Freeman & Lorenzetti, in press). Further evidence is needed to strengthen the evidence base on how CBD influences the effects of THC, and to establish dose-response. As policymakers aim to guide regulation strategies and

educate consumers on how to minimise the risks of cannabis use, this is an important issue for future research.

4.7. **Strengths and limitations**

This review followed PRISMA guidelines for conducting and reporting systematic reviews (Higgins & Green, 2008; Liberati et al., 2009). Two independent raters were used for both searches and data extraction. This study used the Cochrane risk of bias tool (Higgins et al., 2016) to evaluate methodological criteria. This is the first systematic review to assess outcomes for human studies evaluating the moderating effects of CBD on the acute effects of THC. This review aimed to provide a narrative synthesis of a large variety of outcomes using a wide range of measures. To give a comprehensive picture of findings, where possible this review has incorporated all outcomes reported where THC with and without CBD were compared. In order to directly assess the acute effects of THC with and without CBD, it was necessary only to include studies that directly compared a matched dose and route of administration of THC with and without CBD. Therefore, repeated dosing studies and studies which looked at a range of administration methods were excluded. Cannabis contains over a hundred cannabinoids (such as cannabinol and tetrahydrocannabivarin). Similarly, there are more than a hundred terpenoids and some of these have the potential to moderate the effects and interactions of cannabinoids (Russo, 2011). Further research is needed to investigate how terpenoids and cannabinoids other than THC and CBD influence the effects of cannabis in humans.

Methodological issues with the identified studies included: limited information about how withdrawals were managed; inadequate description or randomisation; treatment

allocation blinding and information about whether order effects were accounted for in statistical analyses. An additional limitation in some studies is that they included very small sample sizes. Although rigorous experimental designs which use repeated measures may afford higher statistical power, some studies may have nevertheless been underpowered when taking into account the effect sizes reported (Machin, Campbell, Tan, & Tan, 2018). Not all studies accounted for multiple analyses in their statistical analysis plan. Correlations for treatment response across conditions for individual participants was not considered in the analysis plan of several studies, which may have reduced power in crossover studies (Sedgwick, 2015).

4.8. **Conclusions**

The cannabis plant contains more than a hundred different cannabinoids and many of these may interact to determine the drug's effects. At present, there is some evidence to suggest that CBD may reduce some of the effects of THC. However, significant variability was reported in the effects of these compounds both between studies and across individuals within studies. Further research is needed to investigate how CBD interacts with THC across a range of doses and routes of administration to gain further insight into how it might influence the benefits and harms of THC.

5. Appendices

Appendix A. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9, 10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11, 54
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	11

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	25
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13-22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	24
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-22
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	25-38
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	24

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	39-44
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	45
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	46
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Appendix B. Review Protocol

How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (Δ9-THC) in humans? A systematic review

Abigail Freeman, Rachel Lees, Katherine Petrilli, Rob Saunders, Chandni Hindocha, Claire Mokrysz, Tom Freeman, Valerie Curran

Citation

Abigail Freeman, Rachel Lees, Katherine Petrilli, Rob Saunders, Chandni Hindocha, Claire Mokrysz, Tom Freeman, Valerie Curran. How does cannabidiol (CBD) influence the acute effects of delta-9- tetrahydrocannabinol (Δ9-THC) in humans? A systematic review. PROSPERO 2019 CRD42019126994 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019126994

Review question

How does CBD influence the acute effects of Δ9-THC?

Searches

We will search the following electronic bibliographic databases: MEDLINE, EMBASE, PsycINFO, and CINAHL Plus. The search strategy will include only terms relating to or describing the intervention (Δ9-THC and CBD). The terms will be combined with the Ovid filter for human studies and studies published in English. The search terms will be adapted for use with other bibliographic databases in combination with database-specific filters for human trials and peer-reviewed articles, where these are available.

There will be no date restrictions. The searches will be re-run just before the final synthesis and further studies retrieved for inclusion. Papers must be published in English.

Types of study to be included

Inclusion criteria: We will include human studies with an experimental design which include random allocation to (i) a fixed dose of THC (THC), and (ii) the same fixed dose of THC administered with CBD (THC+CBD). Participants must be compared to a matched control group, or act as their own controls (crossover design). The included papers must be peer-reviewed.

Exclusion criteria:

Conference extracts or abstracts, theses, reviews, supplements, editorial reports, correspondence, non-peer reviewed material e.g., books extracts, notes, and letters.

Animal studies.

Condition or domain being studied

The acute administration of Δ9-THC and CBD in humans.

Participants/population

Inclusion: Human participants

Exclusion: None

Intervention(s), exposure(s)

Studies must include both a) a condition or group in which delta-9-tetrahydrocannabinol (Δ9-THC/ THC/tetrahydrocannabinol/dronabinol) is acutely administered under experimental conditions, and b) a matched condition or group where the same dose of Δ9-THC is acutely administered together with cannabidiol (CBD).

Comparator(s)/control

Placebo or a control condition where there is no drug administered, for example, a pre-drug measurement or baseline measurement. This is necessary to evaluate the acute effects of THC.

Context

Human laboratory studies which include healthy or clinical populations.

Main outcome(s)
Establishing how CBD influences the acute effects of THC in humans (change in THC-induced effect when THC is administered with CBD).

Additional outcome(s)
None.

Data extraction (selection and coding)
Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two reviewers to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer.
A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and details of the dose and route of administration for THC and CBD, THC:CBD ratio; study methodology; recruitment and study completion rates; outcomes and times of measurement; information for assessment of the risk of bias. Two reviewers will extract data, discrepancies will be identified and resolved through discussion with a third reviewer where necessary. A subset of the extracted data will be randomly checked by a third reviewer.

Risk of bias (quality) assessment
Two reviewers will independently assess the risk of bias in included studies by considering the criteria set out by the Cochrane's risk of bias (RoB2) assessment tool as appropriate for the study design. Disagreements between the reviewers over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.

Strategy for data synthesis
We will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention, type of outcome and intervention content. We will provide summaries of intervention effects for each study. From initial scoping of the existing literature, we anticipate that the opportunity for meta-analysis may be limited because of the range of different outcomes measured across studies.

Analysis of subgroups or subsets
It is not expected that the studies will be reviewed separately for different groups. However, outcomes for different drug doses may be presented separately.

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Type and method of review

Narrative synthesis, Systematic review

Anticipated or actual start date
24 February 2019

Anticipated completion date
01 October 2019

Funding sources/sponsors
None

Conflicts of interest
None

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Cannabidiol; Dronabinol; Humans

Date of registration in PROSPERO
18 March 2019

Date of publication of this version
18 March 2019

Details of any existing review of the same topic by the same authors
None

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

18 March 2019

Appendix C. Search strategy

Search Strategy: **Embase** 1974 to 2019 February 27

#	Searches	Results
1	cannabis*.tw.	19528
2	THC*.tw.	12293
3	tetrahydrocannabinol*.tw.	7913
4	delta-9-tetrahydrocannabinol*.tw.	1913
5	dronabinol*.tw.	490
6	Dronabinol/	7043
7	Dronabinol/	30687
8	cbd*.tw.	12647
9	Cannabidiol*.tw.	2835
10	Cannabidiol/	3660
11	marijuana*.tw.	14832
12	8 or 9 or 10	14970
13	(books or review or erratum or note or editorial or letter or "short survey" or tombstone or "conference paper" or "conference abstract").pt.	9350415
14	tetrahydrocannabinol/ or dronabinol/ or cannabis/	38377
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 11 or 14	55349
16	12 and 15	3241
17	16 not 13	1820
18	limit 17 to (human and English language)	721

Search Strategy: **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to February 27, 2019

#	Searches	Results
1	cannabis*.tw.	14086
2	THC*.tw.	8799
3	tetrahydrocannabinol*.tw.	6408
4	delta-9-tetrahydrocannabinol*.tw.	3234
5	dronabinol*.tw.	308
6	Dronabinol/	6606
7	Cannabis/	8197
8	cbd*.tw.	7736
9	Cannabidiol*.tw.	2052
10	Cannabidiol/	1255
11	marijuana*.tw.	11743
12	8 or 9 or 10	8769
13	(books or review or erratum or note or editorial or letter or "short survey" or tombstone or "conference paper" or "conference abstract").pt.	3959425
14	tetrahydrocannabinol/ or dronabinol/ or cannabis/	13133
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 11 or 14	35691
16	12 and 15	1765
17	16 not 13	1399
18	limit 17 to (human and English language)	535

Search Strategy: **PsycINFO** 1806 to February Week 1 2019

#	Searches	Results
1	cannabis*.tw.	9350
2	THC*.tw.	2179
3	tetrahydrocannabinol*.tw.	2240
4	delta-9-tetrahydrocannabinol*.tw.	892
5	dronabinol*.tw.	95
6	cbd*.tw.	846
7	Cannabidiol*.tw.	555
8	marijuana*.tw.	9477
9	(books or review or erratum or note or editorial or letter or "short survey" or tombstone or "conference paper" or "conference abstract").pt.	0
10	exp CANNABIS/	7501
11	exp MARIJUANA/	2902
12	exp Marijuana/ or exp Tetrahydrocannabinol/ or exp Cannabis/	8462
13	1 or 2 or 3 or 4 or 5 or 8 or 10 or 11 or 12	19213
14	6 or 7	1031
15	13 and 14	459
16	15 not 9	459
17	limit 16 to (human and English language)	250

CINHAL Plus up to February Week 1 2019

(MH "cannabis" or “cannabis” or “THC” or “tetrahydrocannabinol” or “delta-9-tetrahydrocannabinol or “dronabinol”) AND (cbd or “cannabidiol")

Appendix D. Data extraction form

Table D.1. Study Characteristic extraction template	
Reviewer:	Notes
Study ID	
Experimental design? Type of study: (e.g. placebo-controlled, double-blind, parallel, crossover, non-RCT)	
Random allocation? How as it randomised, Unit of randomisation (by individuals, groups)	
Placebo or a control condition where measurement is taken with no drug administered?	
Types of intervention: (i) a fixed dose of THC, and (ii) the same fixed dose of THC administered with CBD (THC+CBD)? Any other interventions?	
Assessment of acute effects: i.e. single dose or multiple doses in a single session	
Include or Exclude	
Reason: repeated dosing study, no baseline measurement, No THC+CBD or meets inclusion criteria - list	
Do not proceed if excluded.	
Aim of study as stated	
Population description: For example, healthy current users, healthy ever users, clinical population, CUD	
Abstinence: How many hours drug-free before dosing?	
Inclusion criteria/Exclusion criteria	
Number of participants	
If parallel Include information for each group (i.e. intervention and controls) under study	
Withdrawals and exclusions	
Were there any significant baseline imbalances?	
Were patients who entered the study adequately accounted for?	
Age; range, median mean, SD	
Sex (M, F)	
Race/Ethnicity	
Cannabis use status: current and historical	
Co-morbidities & other relevant demographics	
Intervention & control (route of admin, content, dose, schedule) For example, smoked THC 8mg; oral CBD 800mg	
Dosing schedule: For example, CBD administered one hour before THC dose	
Sample size calculation: What assumptions were made? Were these assumptions appropriate?	
A potential conflict of interest from funding? Y / N / unclear	
Types of outcome measures: e.g. fMRI, psychological, pharmacokinetic	
Outcomes comparing THC vs THC+CBD: 1/2 short sentences for each outcome	
Key conclusions of the study	
Notes	
Limitations/strengths	

Appendix E. Studies excluded in full-text search

Table E. 1. Study characteristics for inclusion criteria for each study excluded in a full-text search

Study	Design	Randomisation	Placebo or baseline	Intervention	Treatment schedule	Reason for exclusion
Agurell et al. (1981)	Crossover study	Balanced crossover sequence	No placebo or baseline measurement	Oral 20 mg of THC and placebo; oral 20 mg of THC, and oral 40 mg of CBD; oral 20 mg of THC and oral 40 mg of CBN.	Single dose, weekly interval	No baseline measurement pre-THC
Babalonis et al. (2017)	Double-blind, crossover study	Random allocation	Placebo	Oral cannabidiol (0, 200, 400, 800 mg) alone and in combination with smoked marijuana 0.01%; 5.3–5.8% THC	8 once-weekly outpatient sessions (7.5 h)	No active THC+CBD condition
Berman, Symonds, and Birch (2004)	Double-blind, crossover study	Randomly allocated to treatment order by a computer	Placebo	Oromucosal spray GW-1000-02: Sativex THC:CBD) 1:1 ratio; GW-2000-02 THC; placebo	Baseline period of 2 weeks, followed by three, 2-week treatment periods	Repeated dosing study
Brady et al. (2004)	Crossover study	NA	Open label	Sublingual spray THC (2.5mg); THC (2.5mg) +CBD (2.5mg)	Repeated dosing 16 weeks	Repeated dosing study
Efron and Freeman (2018)	NA	NA	NA	NA	NA	Commentary
Guy and Flint (2003)	Partially double-blind, crossover study	Partially randomised,	Placebo	Sublingual drops placebo; THC (20mg); THC (20mg) + CBD (20mg)	Single dose	THC+CBD condition is open label
Guy and Robson (2004)	Four-way crossover study	Randomised; Williams Square Design	Open label	Sublingual, buccally, oro-pharyngenally, or oral THC 10mg + CBD 10mg	Single dose; 6 day washout	No THC only comparator
Ilan, Gevins, Coleman, ElSohly, and de Wit (2005)	Double-blind, crossover study	Randomised	Placebo	Smoked Placebo; smoked THC 1.91%, Low CBC 0.6% and Low CBD 0.2%; smoked THC 2.86%, Low CBC 0.1% and High CBD	Single dose, weekly interval	Not comparable matched doses for THC in both THC

				1.0%; smoked THC1.88%, Low CBC 0.1% and High CBD 1.52%; smoked THC 3.09%, High CBC 0.5% and Low CBD 0.08%		and THC+CBD condition
Johnson et al. (2010)	Double-blind, parallel study	Randomised	Placebo	Oromucosal spray THC (2.7mg) THC (2.7mg) + CBD (2.5mg) extract and placebo	Repeated dosing over 2 weeks	Repeated dosing study
Karniol and Carlini (1974)	NA	NA	NA	NA	NA	Unable to access
Karschner 2011 Karschner et al. (2011)	Double-blind, crossover study	Randomised	Placebo	Oral THC (5mg), oral THC (15mg); oromucosal spray THC (5.4mg) + CBD (5mg), spray THC (16.2mg) + CBD (15.0mg) or placebo	Single dose, 5 days washout	Different routes of administration
Karschner et al. (2011)	Double-blind, crossover study	Randomised	Placebo	Oral THC (5mg), oral THC (15mg); oromucosal spray THC (5.4mg) + CBD (5mg), spray THC (16.2mg) + CBD (15.0mg) or placebo	Single dose	Different routes of administration
Lee et al. (2013)	Double-blind, crossover study	Randomised	Placebo	Oral THC (5mg), oral THC (15mg); oromucosal spray THC (5.4mg) + CBD (5mg), spray THC (16.2mg) + CBD (15.0mg) or placebo	Single dose	Different routes of administration
Leweke et al. (2000)	Double-blind, crossover study	No	Baseline	Oral placebo+ nabilone (1mg); nabilone (1mg) +CBD (200mg); CBD (200mg) + placebo	Single dose	Not randomised
Notcutt et al. (2004)	34 ‘n of 1’ studies	Randomised	Placebo	Sublingual spray THC (2.5mg); THC (2.5mg); THC (2.5mg) + CBD (2.5mg); placebo	12 weeks repeated dosing	Repeated dosing study
Perez-Reyes et al. (1973)	Crossover study	Randomised	Placebo	THC (0.53mg/kg); CBD (0.27mg/kg); CBN (0.27mg/kg); placebo	Single dose	No THC+CBD condition

Perry, Ton, and Allan (2018)	NA	NA	NA	NA	NA	Review
Solowij et al. (2019)	Crossover study	Randomised	Placebo	THC 8 + CBD 4 mg; THC 8 mg, THC 12 + CBD 400; CBD 400mg, Placebo	Single dose	No comparison between THC 8 + CBD 4 mg; THC 8 mg alone; only linear function across all THC conditions
Strasser et al. (2006)	Double-blind, placebo-controlled study	Randomly assigned (2:2:1)	Placebo	Oral cannabis extract (standardized for 2.5 mg THC and 1 mg cannabidiol); THC (2.5 mg); placebo	Twice daily for 6 weeks	Repeated dosing study
Schoedel et al. (2011)	Double-blind, crossover study	Randomised	Placebo, and baseline	Oromucosal spray THC (10.8 mg) + CBD (10 mg); THC (21.6 mg) + CBD (20mg); THC (43.2 mg) + CBD (40 mg); oral dronabinol (20 mg); dronabinol (40 mg), placebo	Single dose, 2 day washout	Not matched control/dose
Valle et al. (2015)	Double-blind, crossover study	Randomised	Placebo	Sublingual THC (7.5mg); CBD (7,5mg), THC (7.5mg) + CBD (7.5mg)	Single dose	Abstract only
Wade et al. (2003)	Single-patient, crossover study	Randomised	Placebo	Sublingual spray THC (2.5mg); CBD (2.5mg); THC (2.5mg) + CBD(2.5mg); placebo	Two week repeated dosing	Repeated dosing study
Wade, Makela, Robson, House, and Bateman (2004)	Double-blind, parallel study	Randomised	Placebo	Sublingual spray THC (2.5mg); CBD (2.5mg); THC (2.5mg) + CBD(2.5mg); placebo	Six week repeated dosing	Repeated dosing study 1
Yuan et al. (2017)	Case report	NA	NA	3-4 joints a day THC (18.6%)	Repeated dosing	Case report

Appendix F. PRISMA flowchart

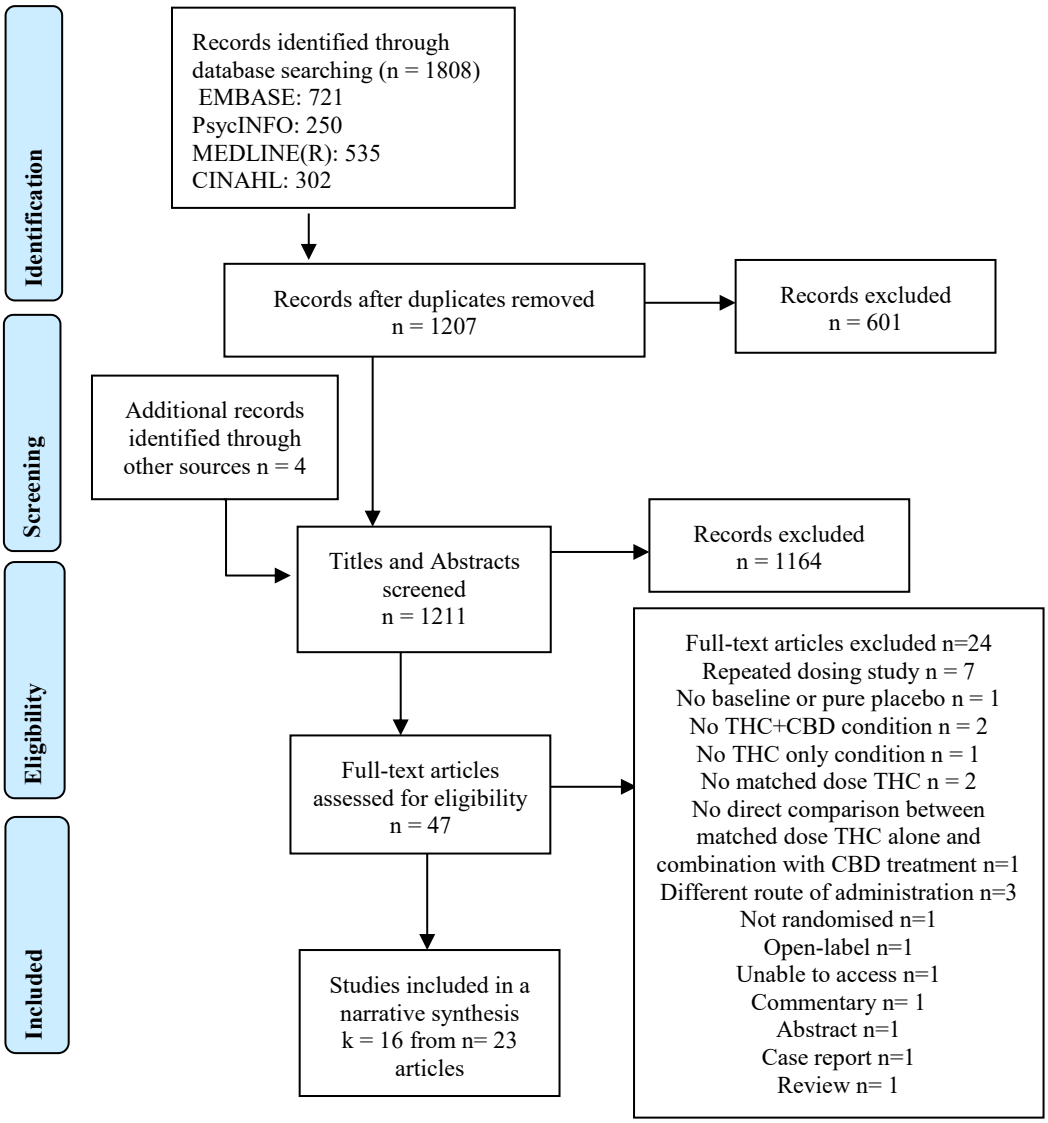

Figure 1. PRISMA flow diagram (Moher, Liberati, Tetzlaff, Altman, & Group, 2009)

Appendix G. Risk of bias assessment for each study

Study	Randomisation process	Deviations from intended interventions[a]	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall bias
Arkell et al. (2019)						
Bhattacharyya et al. (2010)						
Bird et al. (1980)[b]						
Dalton et al. (1976)						
Dalton et al. (1976)						
Englund et al. (2013)						
Guy and Robson (2003)						
Haney et al. (2016)[c]						
Hindocha et al. (2015); Morgan et al. (2018)						
Hollister and Gillespie (1975)[d]						
Hunt et al. (1981)						
Karniol et al. (1974)						
T. P. Freeman, Pope, et al. (2018); Lawn et al. (2016); Wall et al. (2019)						
Juckel et al. (2007); Nadulski et al. (2005); Roser et al. (2009); Roser et al. (2008); Stadelmann et al. (2011)[e]						
Nicholson et al. (2004)						
Zuardi et al. (1982)[f]						

Notes.

a. Studies were assessed for both potential bias arising from intevention assignment and assessment
b. Whether groups were balanced, and how many per group is not reported, the total number of particpants does not devide equally between the groups

c. 31/50 participants completed raising some concerns about potential bias.
d. No indication of blinding, study states randomisation process so at least participant concealment is assumed by some concern noted. Study does not report statistics.
e. Study had fewer than 90-95% of particpants who were randomised complete the intervention
f. Some concerns about the randomisation and blinding of the study as this is not indicated in the article it seems reasonable to assume that as it was placebo cotrolled it would also be blinded. Treatments allocated in a different order but so each followed eachother, so its possible the experimeter would have been able to guess the drug allocation.


No issues


Some concerns

Appendix H. Psychological effects of drug action scale

The psychological effects of drug action were graded from 0 to 4, according to the subjective report of at least three symptoms in a grade:

Grade 0: nothing or slight anxiety.

Grade 1: slight feeling of well-being; feeling of lightness; paraesthesia in extremities; slight difficulty in concentration; dizziness; somnolence; cold hands and sweating.

Grade 2: definite feeling of well-being; euphoria; colours are brighter; intense paraesthesia; uninterested by the surroundings; some difficulty in reporting feelings; sometimes slight sensation of fear; intense difficulty in concentration.

Grade 3: marked sensation of euphoria intercalated with moments of apprehension; intense introspection with resistance to describing feelings; sensation of being watched; sounds are clearer and colours are brighter; laughing without reason; concentration almost impossible due to the rapid flow of ideas; extremities very heavy; unable to visualize intact objects with eyes closed (e.g. watch seen without numbers or hands).

Grade 4: feelings of well-being followed later by panic; intense sensation of being watched; coherent thoughts impossible due to the rapid flow of ideas; in general, subject knows what is happening, but loses the knowledge from time to time and panic starts; cenesthesia; striking visual hallucinations.

Taken from: Carlini, Karniol, Renault, and Schuster (1974)

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