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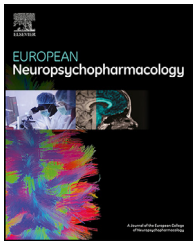

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Co-exposure of cocaine and cannabinoids and its association with select biological, behavioural and health outcomes: A systematic scoping review of multi-disciplinary studies

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List of abbreviations: AOR, adjusted odds ratio; BF, Bayes factor; BNDF, brain-derived neurotrophic factor; BOLD, blood-oxygen-level-dependent; CBD, cannabidiol; CBI, credible intervals; CB1R, cannabinoid receptor type 1; CI, confidence interval; DAT, dopamine active transporter; DSM, Diagnostic and Statistical Manual of Mental Disorders; ERK1/2, Extracellular signal-regulated kinases 1/2; HIV, human immunodeficiency virus; HR, hazard ratio; i.p., intraperitoneal; i.v., intravenous; MeSH, Medical Subject Headings; NeuN/BrdU+, Neuronal Nuclei/5-bromo-2′-deoxyuridine; OR, odds ratio; RCT, randomised controlled trial; RMSEA, root-mean-square error of approximation; PRESS, Peer Review Electronic Search Strategies; PTSD, post-traumatic stress disorder; RR, risk ratio; s.c., subcutaneous; SRA-DM, The Systematic Review Assistant-Deduplication Module; SRMR, root-mean-square residual; TH, tyrosine hydroxylase; THC, tetrahydrocannabinol; US, United States; 5-HT, 5-Hydroxytryptamine (serotonin).

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Review

Abstract
Cocaine use entails severe health- and social-related harms globally. Treatment options for cocaine dependence are highly limited. Benefits of cannabinoids for addiction have been documented, making it opportune to examine existing data on the possible outcomes associated with cannabinoids and cocaine co-use. We conducted a systematic scoping review following the PRISMA guidelines of peer-reviewed, English-language studies published from 2000 to 2021 in four databases (Medline, Web-of-Science, CINAHL Plus, and PsycInfo), assessing the co-exposure of cannabis/cannabinoids with cocaine on behavioural, biological or health outcomes. Both quantitative and qualitative, as well as humans and pre-clinical animals' studies (n=46) were included. Pre-clinical studies (n=19) showed mostly protective effects of cannabidiol (CBD) administration on animal models of addiction (e.g., cocaine-craving, -relapse, and -withdrawal) and cocaine-toxicity. Tetrahydrocannabinol (THC) had more inconsistent results, with both protective and counter-protective effects. Human studies (n=27) were more heterogeneous and assessed natural ongoing cannabis and cocaine use or dependence. Quantitative-based studies showed mostly enhanced harms in several outcomes (e.g., cocaine use, mental health); two available clinical trials found no effect upon CBD administration on cocaine-related treatment outcomes. Qualitative data-based studies reported cannabis use as a substitute for or to alleviate harms of crack-cocaine use. While pre-clinical studies suggest a potential of cannabinoids, especially CBD, to treat cocaine addiction, the few trials conducted in humans found no benefits. Cannabis co-use by cocaine users commonly presents a risk factor, entailing enhanced harms for users. More rigorous, controlled trials are still necessary to investigate cannabinoids' potential considering pre-clinical findings and reported benefits from specific drug users.

1. Introduction

Estimates suggest that some 0.4% (approximately 19 million people) of the world's adult population use cocaine, with some 3.9 million people cocaine dependent in 2015, rendering cocaine products to be among the most widely used illicit drugs globally (Degenhardt et al., 2013; Peacock et al., 2018; UNODC, 2020). Use of cocaine – particularly in distinct regions and/or user populations – occurs in a variety of different forms and formulations (e.g., cocaine powder and crack-cocaine), involving different use modes, such as inhalation, smoking or injection (Fischer et al., 2013; Goldstein et al., 2009; Warner, 1993). Cocaine use is associated with elevated risks for multiple morbidity and mortality outcomes involving cardiovascular and infectious diseases, mental health problems (e.g., depression, psychosis, suicide) and violence (Afonso et al., 2007; Butler et al., 2017; Dackis and O'Brien, 2001; Ford et al., 2009). Cocaine users' mortality risk is multi-fold higher than that of the general population (Degenhardt et al., 2011). In 2017, an estimated 0.3% (approximately 178,000 people) of global all-cause mortality was associated with cocaine dependence (Farrell et al., 2019). Commonly, people who use psychostimulants, including cocaine, also co-use multiple other psychoactive drugs (e.g., opioids), amplifying risks for adverse health outcomes, such as overdose risk and mortality (Coffin et al., 2003; Kohut, 2017; Leri et al., 2003; Motta-Ochoa et al., 2017). Recent changes in illegal drug production, especially with substantive expansion in cocaine manufacturing in Latin America, suggest that cocaine supply/use have been increasing globally (UNODC, 2020).

Currently, no pharmaco-therapies have been approved for any of the main stages of treatment for cocaine (or other psychostimulants) use disorder (e.g., risk reduction, targeted prevention for use or intoxication, withdrawal or abstinence-oriented treatment, relapse prevention) (Farrell et al., 2019; Fischer et al., 2015b). In addition, the application range and outcomes of psychosocial (e.g., targeted prevention or treatment) interventions for cocaine use are overall highly limited, with mainly selected cognitive-behavioural interventions, including contingency management approaches, showing some positive effects (Knapp et al., 2007; Minozzi et al., 2016; Penberthy et al., 2010; Schierenberg et al., 2012; Shearer, 2007). This underscores the need for examination of putative therapeutic strategies for psychostimulant use, and specifically problematic cocaine use or cocaine use disorders (Fischer et al., 2015a; Fischer et al., 2015b; Kogan and Mechoulam, 2007; Shorter et al., 2015). Cannabinoids have emerged as one potential therapeutic avenue for addictive disorder and specifically stimulant-related adverse effects; they are increasingly accessible for therapeutic usage through 'medical cannabis' provisions in different jurisdictions (Abrams, 2018; Crippa et al., 2018; Hill, 2015; NASEM, 2017; Rodrigues et al., 2020; Walsh et al., 2017). Cannabis products are widely used around the world for both 'non-medical' and 'medical' purposes. More generally, the non-medical use of cannabis is associated with risk for a variety of adverse health out-

comes, including acute and chronic neuro-cognitive impairment, mental health problems (e.g., psychosis, depression, suicide), cannabis use disorder (dependence), injuries (e.g., related to cannabis-impaired driving), and select others (Hall et al., 2019; Hasan et al., 2020; Lorenzetti et al., 2020; Memedovich et al., 2018; Scott et al., 2018; Volkow et al., 2014). The risks for these adverse outcomes are substantially elevated for use at young age, and frequent use involving high-potency (THC) products (Fischer et al., 2017; Hines et al., 2020; Kiburi et al., 2021; Leung et al., 2021)

Notwithstanding the aforementioned cannabis use-related risks, there has been growing interest in the endocannabinoid system as a possible target for treating craving and addiction (Manzanares et al., 2018; Parsons and Hurd, 2015; Spanagel, 2020). Notably, different cannabinoids that target the endocannabinoid system exhibit distinct properties on addictive behaviour. Most studies have focused on Δ^9-tetrahydrocannabinol (THC), the principal psychoactive constituent of the *cannabis* plant, as the compound that drives the rewarding effects of cannabis through activation of central nervous system CB_1 receptors (Spanagel, 2020). Blockade of this receptor through antagonists have been proposed for the treatment of substance use disorder (Manzanares et al., 2018; Robinson et al., 2018; Soyka et al., 2008). Recently, interest has focused on cannabidiol (CBD), a non-intoxicating phyto-cannabinoid, based on evidence that CBD may act as an inverse agonist or negative allosteric modulator of CB_1 receptors (Ibeas Bih et al., 2015; Laprairie, Bagher, Kelly, and Denovan-Wright, 2015; Spanagel, 2020). Other potential targets of CBD have been identified, including transient receptor potential vanilloid 1/2 proteins, fatty acid amide hydrolase (a hydrolysing enzyme of the endogenous cannabinoid anandamide) and 5-hydroxytryptamine (5-HT) 1A serotoninergic receptors (Parsons and Hurd, 2015). Furthermore, user self-reports have described the intentional use of cannabinoids to modulate psycho-stimulant (e.g., crack-cocaine) use or adverse effects. On this basis, beneficial properties or effects from cannabinoids may exist for addictive behaviours related to a range of different psychoactive substance categories (e.g., opioids, nicotine, alcohol) yet specifically for psychostimulants (Abrams, 2018; Calpe-López et al., 2019; Fischer et al., 2015b; Prud'homme et al., 2015).

Given the overall substantial use prevalence of and harms related to cocaine use, and the general lack of effective therapeutic interventions, we sought to systematically examine and review existing, multi-disciplinary data on possible associations of cannabinoid use or exposure on cocaine use and adverse outcomes from animal (e.g., pre-clinical) as well as human (e.g., clinical, epidemiological, observational) study populations.

2. Methods

2.1. Study aims and scope

The review's principal objective was to systematically identify and summarize data on the effects and associations of experimental or natural co-use of cannabinoids on cocaine use-related biological, behavioural, and health outcomes from different methodological or disciplinary studies (e.g., pre-clinical, human experimental, observational approaches). Considering the marked diversity and heterogeneity of available studies, and their methods and outcome data, we conducted a systematic scoping review, as indicated appropriate for such a review approach and landscape of evidence (Peters et al., 2015). The review adhered to essential steps and procedures for a systematic review, including a structured search strategy and reporting, following the PRISMA guidelines (Munn et al., 2018; Page et al., 2021; Tricco et al., 2018). We considered cannabinoids as all-natural cannabis product forms or compositions (e.g., THC, CBD) and cocaine as any cocaine-based product (e.g., crack-cocaine), regardless of mode of use (e.g., smoking, ingestion), subject status (e.g., dependence) or intended purpose of use (e.g., medical, non-medical).

2.2. Search strategy

The systematic search strategy focused on cannabis/cannabinoid- and cocaine-related words and MeSH terms related to cannabinoids, cannabis and cocaine. The full search strategy details for the different databases searched are available as supplementary material (Supplementary Material 1 & 2). The search strategy was developed for MEDLINE through an interactive process by the co-authors, revised using the Peer Review Electronic Search Strategies (PRESS) checklist (McGowan et al., 2016) and adjusted for application in other databases. The following four databases were accessed: MEDLINE (PubMed), Web of Science (core collection), CINAHL plus and PsycInfo. The results were collated and de-duplicated using The Systematic Review Assistant-Deduplication Module (SRA-DM) (Rathbone et al., 2015) and then uploaded to Endnote (v.X9.2), where all screening and management tasks were performed. Complementary search strategies included manual searching of reference lists of included studies.

2.3. Study selection

Screening and studies selection involved the following inclusion criteria: 1) original studies based on primary study data; 2) studies explicitly examining the co-use or co-exposure of cannabinoid products with cocaine products in human or animal model populations; 3) reporting biological, behavioural or health-related measures or outcomes (e.g., brain activity/function, craving, drug use/dependence); 4) with measures or outcomes that comparatively addressed cocaine-only and cocaine and cannabinoid co-use or -exposure; 5) studies in English-language published from 2000 to 9 February 2021. Given the aim of a comprehensive, multi-disciplinary scoping review, both quantitative and qualitative studies were included. We excluded studies not meeting the above criteria, as well as reviews, commentaries, case reports and case-control studies with other non-target drug use (e.g., comparing cocaine to alcohol and cannabis). Moreover, studies with specific other disease populations (e.g., HIV-positive, PTSD sample) were excluded.

Following de-duplication, titles and abstracts were screened by one lead reviewer (DDB), with potentially unclear or ambiguous cases arbitrated towards consensus together with a second reviewer. Then, full-text review of studies for possible inclusion was performed by the same procedure. Studies excluded predominantly did not match the content or outcome specific criteria for the review (e.g., no clear cannabis/cocaine comparison, no current cannabis use). In accordance with systematic review principles (Page et al., 2021), the attached PRISMA-based flowchart (Fig. 1) reports the review's main process steps and outcome information.

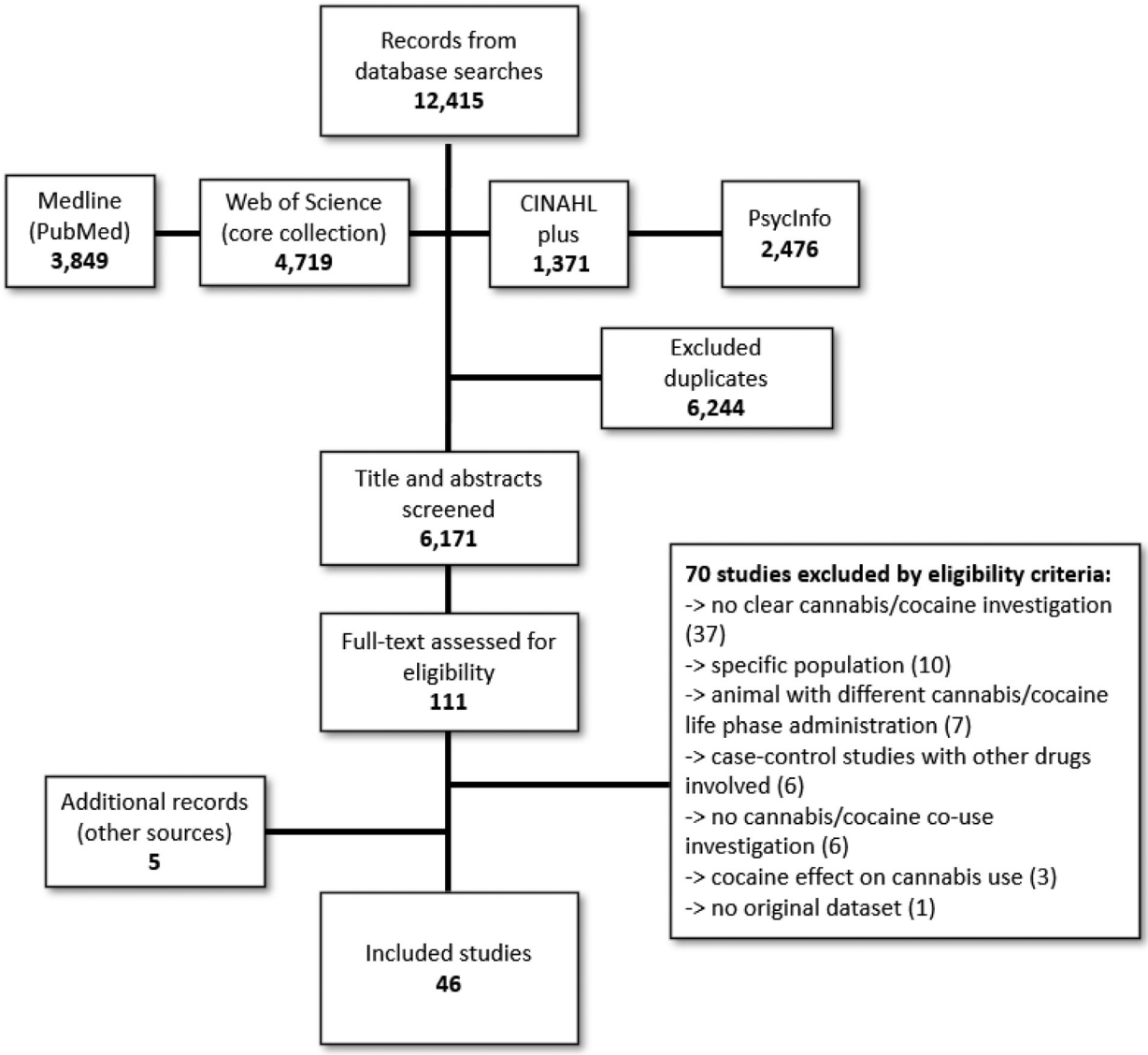

Fig. 1 Flowchart of the selection process of studies.

2.4. Data synthesis

Data was extracted by the lead author (DDB). For results documentation, we inductively grouped the included studies by study design or outcome characteristics, further dividing them into study subcluster, and narratively summarized the individual studies' scopes, measures and results. No risk of bias or quality assessment and no meta-analysis were conducted (also due to the heterogeneity of individual study designs and outcomes), as is common for a scoping review (Arksey and O'Malley, 2005).

3. Results

3.1. Characteristics of included studies

Overall, 12,415 article citations were identified from the database searches, which, after de-duplication, resulted in a total of 6,171 potentially relevant abstracts screened. From these, 113 abstracts were selected for full-text review, and a final set of 46 articles, including 5 from secondary searches, were included in the present review (Fig. 1). Thirty-four (74%) of the studies were published from 2010 onward. Articles were broadly divided into studies with animal experimental models (n=19) and human populations (n=27). Animal studies mostly involved rodent- (i.e., rats and mice), but also monkey-based animal experiments with CBD or THC administration compared to controls (i.e., vehicle administration) divided into three clusters: non-contingent animal models of addiction (e.g., conditioned place-preference and sensitization experiments) (n=7), contingent models of addiction (drug self-administration or brain self-stimulation experiments) (n=8), and cocaine pharmacokinetics and induced toxicity (n=4). Human subject studies were more heterogeneous involving addiction treatment, hospitalisation, and community-based epidemiologic studies, specifically consisting of clinical or case-control, longitudinal, cohort, or observational studies assessing several outcomes (e.g., co-

caine use and treatment outcomes, neurocognitive functions, mental health) based on biological, quantitative or qualitative measures; therefore, topically divided into cocaine use behaviours (n=11), cannabis-based risk-reduction for cocaine (n=12), and health and miscellaneous outcomes (n=4). Key methods and results details of all studies included are presented in Tables 1 and 2.

3.2. Animal/pre-clinical studies (see Tables 1 for study and results details)

3.2.1. Non-contingent models of addiction (n=7)

Four studies investigated the effect CBD (10-60 mg/kg), THC (0.5 mg/kg) or vehicle administration using cocaine-conditioning place preference paradigms in rodents (n=8-15/group). Single CBD (10 mg/kg, s.c.) administration immediately after cocaine-paired memory reactivation decreased cocaine-conditioned memory reconsolidation ($F[1,60]=5.38$, $p<0.01$, post-hoc $p<0.05$) (de Carvalho and Takahashi, 2017). Single CBD (30 and 60 mg/kg, i.p.) administration 60 minutes before pharmacological- (cocaine, 5 mg/kg, i.p.) or stress-induced (social defeat) cocaine-reinstatement prevented, at both dose-levels, both mechanisms of cocaine-reinstatement ($F[9,117]=2.300$, $p<0.02$; $F[9,99]=2.005$, $p<0.01$, post-hoc $p<0.05$) and cocaine-induced increase of DAT gene in the ventral tegmental area ($F[3,40]=9.347$, $p<0.001$, post-hoc $p<0.05$; CBD alone did not reinstate cocaine-induced place preference ($p=1.00$) (Calpe-López et al., 2021). CBD (10 mg/kg, i.p.) administration immediately after cocaine condition sessions or 30 minutes before cocaine-induced reinstatement or conditioning and extinction sessions reduced preference for a cocaine-paired context 20 days after CBD cessation ($F[3,48]=4.1$, $p=0.01$, post-hoc $p<0.05$) and reduced cocaine memory consolidation ($F[5,140]=3.2$, $p=0.001$, post-hoc $p<0.05$) but did not affect cocaine-related memory reconsolidation, extinction and reinstatement ($F[4,88]=0.1$, $p=0.9$; $F[5,80]=0.9$, $p=0.5$; $F[1,16]=0.1$, $p=0.9$) (Chesworth and Karl, 2020). Moreover, single CBD (5 mg/kg, i.p.) or THC (0.5 mg/kg, i.p.) administration 30 minutes before the extinction of cocaine-induced place-preference conditioning potentiated the extinction of cocaine-induced place-preference learning ($F[3,76]=4.6$, $p<0.01$, post-hoc $p<0.05$) (Parker et al., 2004).

Three studies using rodents investigated the effects of CBD (10-40 mg/kg, i.p.) or THC (3, 10 mg/kg, i.p.) on cocaine-induced sensitization (n=8-16/group). Single CBD (10, 20, and 40 mg/kg, i.p.) administration 90 minutes before an induced model of cocaine withdrawal (15-60 mg/kg, i.p., 12-days of increasing doses) blocked, at all doses, cocaine-induced hyperlocomotion and anxiety ($F[4,48]=4.173$, $p=0.006$; $F[4,48]=12.573$, $p<0.001$). At different doses, CBD normalized somatic withdrawal behaviours (e.g., increased rearing, digging, rubbings) ($F[4,48]=4.589$-15.025, all $p<0.005$) and reduced cocaine-induced DAT and TH gene expression in the ventral tegmental area ($F[4,47]=5.019$, $p<0.01$; $F[4,42]=4.878$, $p<0.01$) (Gasparyan et al., 2020). Daily THC (3 mg/kg, i.p.) administration for eight days before cocaine administration (1-30 mg/kg, i.p.) increased cocaine-induced locomotor activity in adolescent rats while decreasing locomotor activity in adults ($F[4,232]=3.38$, $p\leq0.01$; $F[1,52]=5.75$, $p\leq0.02$, post-hoc $p<0.001$) (Dow-Edwards and Izenwasser, 2012). Daily THC with/without CBD (each 10 mg/kg, i.p.) administration for five days, 30 minutes before daily cocaine administration (15 mg/kg, i.p.) did not affect cocaine-sensitization ($F[1,56]=0.03$, $p=0.8$) and locomotor activity after a drug-free period ($p>0.05$) (Gerdeman et al., 2008).

3.2.2. Contingent models of addiction (n=8)

Eight studies investigated the effect of CBD (3-40 mg/kg) or THC (0.1-8 mg/kg) administration on rodents or monkeys trained to self-administrate cocaine (0.03-0.75 mg/kg/infusion, i.v.) or to self-stimulate intracranially (n=4-33/group). Single CBD (20 mg/kg, i.p.) administration before cocaine self-administration acquisition sessions reduced cocaine consumption and cocaine-paired compartment preference ($t[71]=2.00$, $p=0,049$; $F[4,176]=5.71$, $p=0.001$, post-hoc $p<0.001$), but daily CBD administration for ten days (5, 10, 20 and 30 mg/kg, i.p.) before cocaine-sensitization and place preference conditioning (10 mg/kg, i.p) had no effect on cocaine-sensitization and -reinstatement ($F[1,44]=0.34$, $p=0.558$; $F[1,15]=7.51$, $p=0.015$, post-hoc $p>0.05$). Hippocampal molecular markers (e.g., CB1R, ERK1/2, BDNF, $p<0.05$) were higher in CBD-treated animals (Luján et al., 2018). Single CBD (3, 10, 20, 40 mg/kg, i.p.) administration 30 minutes before cocaine self-administration test dose-dependently (10-40 mg/kg) inhibited low-doses (0.03-0.12 mg/kg) of cocaine self-administration ($F[10,120]=2.33$, $p<0.05$, post-hoc $p<0.05$), and diminished cocaine self-administration break-points under a progressive-ratio schedule of reinforcement ($F[2,20]=6.25$; $p<0.01$, post-hoc $p<0.05$). When administered 30 minutes before cocaine (2 or 10 mg/kg, i.p.), CBD (3-20 mg/kg) attenuated cocaine-enhanced brain-stimulation reward and cocaine-induced increases of dopamine in the nucleus accumbens in a dose-dependent manner ($F[3,30]=3.17$; $p<0.05$, post-hoc $p<0.05$; $F[14,147]=4.28$, $p<0.001$, post-hoc $p<0.001$) (Galaj et al., 2020). Single CBD (5 and 10 mg/kg, i.p.) administration 30 minutes and 24 hours before cocaine self-administration test or before cocaine-reinstatement test had no effect on cocaine self-administration under a progressive ratio schedule of reinforcement ($F[1.87,16.88]=0.31$, $p=0.82$; $F[1.93,17.37]=0.53$, $p=0.59$), nor on cocaine-seeking and cue-induced cocaine-reinstatement after 14 withdrawal days ($F[2,7]=2.31$, $p=0.17$; $F[2,14]=0.59$, $p=0.57$) (Mahmud et al., 2017). Single CBD (5 mg/kg, i.p.) administration after intracranial self-stimulation learning and 20 minutes before cocaine (5 mg/kg, i.p.) administration had no impact on the reward-facilitating effects of cocaine ($p>0.05$) (Katsidoni et al., 2013). CBD (20 mg/kg, i.p.) administration daily for ten days, immediately before cocaine self-administration acquisition learning sessions reduced cocaine self-administration acquisition ($x2=18.1$, $p<0.001$), intake ($F[1,36]=13.74$, $p<0.001$) and increased the number of NeuN/BrdU+ cells and neurogenesis in the hippocampus ($F[1,13]=47.87$, $p<0.001$; $F[1,12]=4.75$, $p<0.05$) (Luján et al., 2020). Daily CBD (15 mg/kg, transdermal) administration for seven days after cocaine self-administration extinction attenuated context- and pharmacological stress-induced cocaine-seeking ($F[1,20]=8.93$, $p<0.01$; $F[1,19]=11.71$, $p<001$, post-hoc $p<0.05$), and reduced

Table 1 Animal pre-clinical studies with cannabinoids and cocaine co-administration.

Authors	Sample (sample size)	Cannabinoid	Intervention/Design	Outcome measures	Pattern of cannabinoid administration	Main results
Non-contingent models of addiction						
Calpe-López, Gasparyan, Navarrete et al., 2021	Mice (12/group)	CBD 30 and 60 mg/kg, i.p.	Effects of CBD on drug- and stress-induced cocaine reinstatement (vehicle-controlled study)	CBD-, cocaine- and social defeat-induced reinstatement of cocaine-induced place preference; DAT gene in the ventral tegmental area	Single CBD dose 60 min before cocaine- or social defeat-induced reinstatement	↑ CBD prevented cocaine- and stress- induced cocaine-reinstatement ($F[9,117]=2.300$, $p<0.02$; $F[9,99]=2.005$, $p<0.05$) and cocaine-induced DAT gene increase in the ventral tegmental area ($F[3,40]=9.347$, $p<0.001$)
Chesworth and Karl, 2020	Mice (9–15/group)	CBD 10 mg/kg, i.p.	Effects of CBD on cocaine-environment memory (vehicle-controlled study)	Cocaine-place preference acquisition, consolidation, reconsolidation, extinction and cocaine-induced reinstatement	Single CBD dose right after cocaine place preference conditioning sessions or 30 min before cocaine-induced cocaine-reinstatement or conditioning and extinction sessions	↑ CBD reduced preference for a cocaine-paired environment and reduced cocaine memory consolidation ($F[3,48]=4.1$, $p=0.01$; $F[5,140]=3.2$, $p=0.001$), but did not affect cocaine memory reconsolidation, extinction or reinstatement ($F[4,88]=0.1$, $p=0.9$; $F[5,80]=0.9$, $p=0.5$; $F[1,16]=0.1$, $p=0.9$).
Gasparyan, Navarrete, Rodríguez-Arias et al., 2020	Mice (8–10/group)	CBD 10, 20, 40 mg/kg, i.p.	Effect of CBD on cocaine-withdrawal (vehicle-controlled study)	Cocaine-induced hyperlocomotion, anxiety, and withdrawal behaviours; DAT and TH gene expression in the ventral tegmental area	Single CBD dose six hours after increasing daily cocaine administration and 90 min before tests	↑ CBD at all doses blocked cocaine-induced hyperlocomotion and anxiety ($F[4,48]=4.173$, $p=0.006$; $F[4,48]=12.573$, $p<0.001$), at different doses normalized withdrawal behaviours ($F[4,48]=4.589$–15.025, all $p<0.005$) and reduced cocaine-induced DAT and TH expression ($F[4,47]=5.019$, $p<0.01$; $F[4,42]=4.878$, $p<0.01$)

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Table 1 (*continued*)

Authors	Sample (sample size)	Cannabinoid	Intervention/Design	Outcome measures	Pattern of cannabinoid administration	Main results
de Carvalho and Takahashi, 2017	Rats (10/group)	CBD 10 mg/kg, s.c.	Effects of CBD on the reconsolidation of cocaine-environment memory (vehicle-controlled study)	Cocaine place preference memory reconsolidation	Single CBD dose immediately after the reactivation of cocaine-paired place preference memory	↑ CBD decreased reconsolidation of cocaine-paired place preference ($F[1,60]=5.38$, $p<0.01$)
Dow-Edwards and Izenwasser, 2012	Rats (14–16/group)	THC 3 mg/kg, i.p.	Effects of THC on cocaine-stimulated activity in different ages (vehicle-controlled study)	Cocaine sensitization in adolescent and adult rats; locomotor activity	Daily THC dose for eight days, followed by cocaine administration after four drug-free days	↓ THC increased cocaine-sensitization in adolescents and decreased locomotor activity in adult rats ($F[4,232]=3.38$, $p\leq0.01$; $F[1,52]=5.75$, $p\leq0.02$)
Gerdeman, Schechter, and French, 2008	Mice (9–10/group)	THC with/without CBD, 10 mg/kg each, i.p.	Effects of THC with/without CBD on cocaine-sensitization (vehicle-controlled study)	Cocaine sensitization; locomotor activity	Daily THC or THC+CBD dose, 30 min before daily cocaine administration for five days, except for the first and last day	↔ CBD alone or combined with THC had no effect on cocaine-sensitization ($F[1,56]=0.03$, $p=0.8$) or locomotor activity ($p>0.05$)
Parker, Burton, Sorge et al., 2004	Rats (8–12/group)	CBD (5 mg/kg) or THC (0.5 mg/kg), i.p.	Effects of CBD or THC on cocaine-environment memory extinction (vehicle-controlled study)	Extinction of cocaine-induced place preference	Single CBD or THC dose 30 min before cocaine-induced place preference extinction trial	↑ CBD and THC potentiated the extinction of cocaine-induced place-preference learning ($F[3,76]=4.6$, $p<0.01$)

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Table 1 (*continued*)

Authors	Sample (sample size)	Cannabinoid	Intervention/Design	Outcome measures	Pattern of cannabinoid administration	Main results
Contingent models of addiction						
Galaj, Bi, Yang et al., 2020	Rats (6–12/group)	CBD 3, 10, 20, 40 mg/kg, i.p.	Effects of CBD on cocaine reward effects (vehicle-controlled study)	Cocaine self-administration; brain-stimulation reward; dopamine levels in the nucleus accumbens	Single CDB dose 30 min before cocaine self-administration tests or 30 min before cocaine administration	↑ CBD attenuated cocaine-enhanced brain-stimulation reward, dose-dependently inhibited low doses of cocaine self-administration ($F[3,30]=3.17$; $p<0.05$; $F[10,120]=2.33$, $p<0.05$), lowered cocaine self-administration break-points and attenuated cocaine-induced increases of dopamine ($F[2,20]=6.25$; $p<0.01$; $F[14,147]=4.28$, $p<0.001$)
Luján, Cantacorps and Valverde, 2020	Mice (10/group)	CBD 20 mg/kg, i.p.	Effects of CBD on cocaine-intake (vehicle-controlled study)	Cocaine self-administration and molecular markers in the hippocampus dentate gyrus	Single CBD dose before each cocaine self-administration acquisition sessions	↑ CBD reduced cocaine self-administration acquisition ($x2=18.1$, $p<0.001$), intake ($F[1,36]=13.74$, $p<0.001$) and increased the number of NeuN/BrdU+ cells and neurogenesis in the hippocampus ($F[1,13]=47.87$, $p<0.001$; $F[1,12]=4.75$, $p<0.05$)

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Table 1 (*continued*)

Authors	Sample (sample size)	Cannabinoid	Intervention/Design	Outcome measures	Pattern of cannabinoid administration	Main results
John, Martin and Nader, 2020	Monkeys (4)	THC 0*, 0.03, 0.1, 0.3 mg/kg, i.v.	Effects of THC on cocaine self-administration within a food-drug choice paradigm (vehicle-controlled study)	Cocaine choice, cocaine injections, food reinforcers earned and total reinforcers earned per session	Single THC dose immediately before each food-cocaine choice sessions	↓ THC increased cocaine lowest dose choice ($F[12,51]=4.08$, $p<0.001$), and decreased total reinforcers earned per session ($F[3,9]=20.06$, $p<0.001$)
Gonzalez-Cuevas, Martin-Fardon, Kerr et al., 2018	Rats (9-12/group)	CBD 15 mg/kg, transder-mal	Effects of CBD on cocaine self-administration reinstatement (vehicle-controlled study)	Context- and stress-induced cocaine reinstatement; anxiety	Daily CBD dose for seven days, after cocaine-extinction	↑ CBD attenuated context- and stress-induced cocaine-seeking ($F[1,20]=8.93$, $p<0.01$; $F[1,19]=11.71$, $p<001$) and reduced anxiety during cocaine-abstinence period ($t[19]=2.76$, $p<0.05$)
Luján, Castro-Zavala, Alegre-Zurano et al., 2018	Mice (11-33/group)	CBD 5, 10, 20, 30 mg/kg, i.p.	Effects of CBD on cocaine-intake and neural proliferation (vehicle-controlled study)	Cocaine-reinstatement, -sensitization, self-administration, place preference and hippocampus molecular markers	Experiment 1: Daily CBD dose for ten days, followed by five free-drug days before cocaine-sensitization and place preference conditioning Experiment 2: Single CBD dose before each cocaine self-administration acquisition sessions	↑ CBD reduced cocaine consumption and cocaine-environment preference ($t[71]=2.00$, $p=0,049$; $F[4,176]=5.71$, $p=<0.001$), increased molecular markers in the hippocampus (e.g., CB1R, ERK1/2, BNDF, $p<0.05$) and had no effect on cocaine-reinstatement and -sensitization ($F[1,15]=7.51$, $p=0.015$, post-hoc $p>0.05$; $F[1,4]=1.72$, $p=0,191$; $F[1,44]=0.34$, $p=0.558$)

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Table 1 (*continued*)

Authors	Sample (sample size)	Cannabinoid	Intervention/Design	Outcome measures	Pattern of cannabinoid administration	Main results
Mahmud, Gallant, Sedki et al., 2017	Rats (10/group)	CBD 5 and 10 mg/kg, i.p.	Effects of CBD on cocaine self-administration, cocaine-seeking and -reinstatement (vehicle-controlled study)	Cocaine self-administration and cue-induced cocaine-reinstatement	Experiment 1: Single CBD dose after cocaine self-administration learning and 30 min and 24 h before cocaine-self administration test Experiment 1b and 2: Single CBD dose (with/without previous CBD exposure) during the withdrawal period and one day before cocaine-reinstatement test	↔ CBD had no effect on cocaine self-administration ($F[1.87,16.88]=0.31$, $p=0.82$; $F[1.93,17.37]=0.53$, $p=0.59$), cocaine- seeking ($F[2,7]=2.31$, $p=0.17$) and cue-induced cocaine-reinstatement ($F[2,14]=0.59$, $p=0.57$)
Katsidoni, Anagnostou and Panagis, 2013	Rats (6/group)	CBD 5 mg/kg, i.p.	Effects of CBD on the reward-facilitating effects of cocaine (vehicle-controlled study)	Intracranial self-stimulation threshold; reward-facilitating effect of cocaine	Single CBD dose after intracranial self-stimulation learning and 20 min before cocaine administration	↔ CBD had no effect on intracranial self-stimulation threshold and on the reward-facilitating effect of cocaine (data not shown)
Panlilio, Solinas, Matthews et al., 2007	Rats (15/group)	THC 2–8 mg/kg, i.p.	Effects of THC on cocaine reinforcing efficacy (vehicle-controlled study)	Cocaine-seeking, -sensitization and acquisition of cocaine self-administration	Increasing THC doses, twice a day for three days, before cocaine self-administration training	↑ THC had no effect on cocaine self-administration acquisition ($F[9,399]=2.28$, $p<0.05$, post-hoc $p>0.05$) and sensitization ($p>0.05$) but reduced cocaine seeking ($F[1,100]=4.38$, $p<0.05$)

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Table 1 (*continued*)

Authors	Sample (sample size)	Cannabinoid	Intervention/Design	Outcome measures	Pattern of cannabinoid administration	Main results
Cocaine pharmacokinetics and toxicity						
Zou, Zuo, Chen et al., 2020	Mice (6–7/group)	CBD (3, 10, 30 mg/kg) or THC (1, 5, 10mg/kg), i.p.	Effects of CBD or THC on cocaine-induced seizure (vehicle-controlled study)	Cocaine-induced seizure score, latency and duration	Single CDB or THC administration 15 min before cocaine-induced seizure	↑ THC accelerated seizure onset at all doses but dose dependently reduced seizure severity and duration ($p<0.05$). CBD at 10 and 30 mg/kg delayed seizure onset and dose dependently reduced seizure duration and severity ($p<0.05$)
Gobira, Vilela, Gonçalves et al., 2015	Mice (5–13/group)	CBD 15, 30, 60, 90 mg/kg, i.p.	Effects of CBD on cocaine-induced seizures (vehicle-controlled study)	Duration and onset latency of cocaine-induced seizure	Single CBD dose 30 min before cocaine-induced seizure	↑ CBD reduced seizures duration in all doses ($F[4,48]=2.61$, $p=0.046$) and at 30 mg/kg increased onset latency ($F[4,48]=5.11$, $p=0.001$)
Vilela, Gomides, David et al., 2015	Mice (6/group)	CBD 30 mg/kg, i.p.	Effects of CBD on cocaine toxicity (vehicle-controlled study)	Cocaine-induced seizure and liver damage	Single CBD dose 30 min before cocaine administration	↑ CBD prevented cocaine-induced liver injury, reduced cocaine-induced seizure duration and increased seizure latency (all $p<0.05$)
Reid and Bornheim, 2001	Mice and rats (4–6/group)	CBD or THC 15, 30, 120 mg/kg, i.p.	Effects of CBD or THC on cocaine brain pharmacokinetics (vehicle-controlled study)	Cocaine-induced locomotion and cocaine brain and blood levels	Single CBD or THC doses 1 h before cocaine administration	↓ CBD at 30 mg/kg and 120 mg/kg increased cocaine-levels in brain and blood ($p<0.05$) and at 30 mg/kg increased cocaine-induced locomotion ($p<0.01$); THC at 120 mg/kg increased cocaine brain levels ($p<0.05$)

*Controls were the same animals in sessions receiving vehicle. Legends: Protective (↑), counter-protective (↓) or no effect (↔) of cannabis/cannabinoid co-use exposure with cocaine on related outcomes. Abbreviation codes can be found at the abbreviation list.

Table 2 Human studies with cannabis and cocaine/crack-cocaine co-use.

Authors	Sample/ groups (sample size)	Participant characteristics	Intervention/Design	Outcome measures	Temporality of cannabis use or measure	Main results
Cocaine use behaviours						
Mongeau-Pérusse, Brissette, Bruneau et al., 2021	CBD (40) Placebo (38)	Men/women with cocaine use disorder (DSM-IV)	Single-site, double-blind, randomised controlled trial on CBD efficacy on cocaine use disorder	Cue-induced cocaine craving and cocaine relapse	Daily dose (300-800 mg) for 92 days, being the first 10 days an inpatient detoxification	↔ CBD had no effect on cue-induced craving (CI=-0.33, 3.04; p=0.069; BF=0.498) and relapse risk (HR=1.20, CI=0.65, 2.20; p=0.512; BF=0.152)
Liu, Cheong, Setlow et al., 2021	Cocaine (186) Cocaine + cannabis (2,782)	Men/women with lifetime cocaine use or cocaine use disorder (DSM-5) with/without lifetime cannabis use	Case-control study on the mediation effects of cannabis use upon cocaine use	Cocaine use quantity, frequency, duration and disorder	Lifetime cannabis use (self-report)	↑ Cannabis use was a protective factor for cocaine use quantity, disorder (-0.09, 95%CI[-0.19, -0.001]), and for risky use pattern controlled by the quantity, frequency and duration of cocaine use and presence/absence of cocaine use disorder (-0.43 95%CI[-0.78, -0.07])
Meneses-Gaya, Crippa, Hallak et al., 2020	CBD (14) Placebo (17)	Men with crack-cocaine use disorder (DSM-IV)	Randomised, double-blind, placebo-controlled trial on CBD efficacy on crack-cocaine craving	Cue-induced crack-cocaine craving, anxiety, depression and sleep quality	Daily dose (300 mg) for 10 days	↔ CBD had no effect on cue-induced crack-cocaine craving scores (F[10,230]=2.663; p=0.116; F[10,230]=2460; p=0.130); there were no differences on anxiety and depression symptoms and sleep quality scores (data not shown)
Viola, Sanvicente-Vieira, Kluwe-Schiavon et al., 2020	Cocaine (138) Cocaine + occasional (29) or frequent cannabis use (47)	Women with cocaine use-disorder (DSM-5) with/without occasional or frequent cannabis use (</>5 prior use days/month)	Longitudinal case-control study on cannabis use and cocaine-related symptoms among inpatients of a 3-week cocaine use disorder treatment	Cocaine withdrawal and depressive symptoms at baseline and discharge	Last month cannabis use (self-report) at time of experiment	↓ Frequent cannabis users had higher cocaine withdrawal and depressive symptoms at discharge than cocaine-only users (p=0.028, 95%CI[0.61, 14.32], d=0.431; p=0.030, 95%CI[0.31, 8.62], d=0.437)

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Table 2 (*continued*)

Authors	Sample/ groups (sample size)	Participant characteristics	Intervention/Design	Outcome measures	Temporality of cannabis use or measure	Main results
Giasson-Gariépy, Potvin, Ghabrash et al., 2017	Cocaine (12) Cocaine + cannabis (16)	Men with cocaine use disorder (DSM-IV) abstinent for 72 h and with/without cannabis use disorder (DSM-IV) with at least 25 use days/month in prior trimester	Case-control study on cannabis use and cue-induced cocaine-craving in cocaine-dependents	Mental health status, affect, cocaine-withdrawal and -craving at baseline; cocaine-craving before and after video sequences with neutral or cocaine-cue stimuli	Current cannabis use (self-report) at time of experiment	↔ No inter-group differences in psychiatric symptoms ($p=0.1$), cocaine craving ($p=0.38$), positive and negative affect ($p=0.1$ and 0.19), withdrawal symptoms ($p=0.56$) and cue-induced craving ($F[1,26]=0.75$, $p=0.394$)
Viola, Tractenberg, Wearick-Silva et al., 2014	Cocaine + early- (62) or late-onset (31), and short- (44) and long-term (49) cannabis use	Women with cocaine use disorder (DSM-IV) and early- or late-onset (first use mean age cut-off) or short- and long-term (thrice/weekday use for five years cut-off) cannabis use	Longitudinal case-control study of cannabis use effects on cocaine-related symptoms among inpatients of a 3-week cocaine use disorder treatment	Cocaine withdrawal and craving symptoms at 4th, 9th and 14th treatment days and re-hospitalisation at 2.5-year follow-up	Lifetime cannabis use (self-report) at treatment admission	↓ Early-onset cannabis use was associated with higher cocaine withdrawal and craving ($p=0.044$; $p=0.004$); long-term use was associated with increased withdrawal ($p=0.016$; $p=0.041$) at select time-points and predicted higher re-hospitalisation ($p=0.036$)
Green, Schmitz, Lindsay et al., 2012	Cocaine dependents with cannabis co-use receiving pharma-cotherapy (113) or placebo (64)	Men/women with cocaine use disorder (DSM-IV) and cannabis use (use days/prior month)	Retrospective assessment (secondary data) on baseline cannabis use in two 9-week RCT with levodopa/carbidopa pharmacotherapy for cocaine use disorder	Treatment effectiveness score based on cocaine-negative urine tests; cannabis use at baseline	Last month cannabis use (self-report) at time of experiment	↔ For every day of cannabis use, treatment effectiveness in the pharmacotherapy group decreased 5.4% (RR:0.946, 95%CBI[0.864, 1.069]) while increased in the placebo group 4.9% (RR:1.049, 95%CBI[1.002, 1.115]) even when controlling for baseline cocaine use

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Authors	Sample/ groups (sample size)	Participant characteristics	Intervention/Design	Outcome measures	Temporality of cannabis use or measure	Main results
Alessi, Rash and Petry, 2011	Cocaine (315) Cocaine + cannabis (78)	Men/women with cocaine use disorder (DSM-IV) and cannabis use (use days/prior month)	Retrospective study (secondary data) of cannabis use effects on three 12-months outpatient RCTs on contingency management treatment for cocaine use disorder	Drug use severity at baseline, treatment retention and cocaine-abstinence during treatment	Last month cannabis use (self-report) at time of experiment	↔ No inter-group differences on cocaine use disorder, time of abstinence and treatment retention ($p=0.81$–0.95); cannabis users had more severe baseline drug problems and better treatment improvement than non-users ($x^2(3)=4.261$, $p=0.23$/RMSEA=0.03, SRMR=0.04)
Lindsay, Stotts, Green et al., 2009	Cocaine (634) Cocaine + occasional (403) and frequent cannabis use (146)	Men/women with cocaine use disorder (DSM-IV) and occasional or frequent cannabis use, defined by prior month use days (</>10 days)	Case-control study on clinical outcomes of cannabis use among patients in a 12-week outpatient cocaine use disorder treatment	Cocaine use, medical, legal and psychiatric problems and drug use severity at baseline	Last month cannabis use (self-report) at treatment admission	↓ Frequent cannabis co-users had more cocaine use ($f/x^2=13.5$, $p<0.001$), legal ($f/x^2=3.37$, $p=0.034$) and psychiatric problems ($f/x^2=4.32$, $p=0.014$) than other groups
Aharonovich, Liu, Samet et al., 2005	Cocaine (144) Cocaine + cannabis (55)	Men/women with cocaine use disorder (DSM-IV) and cannabis use (minimum of 1-2 days/week) after treatment discharge	Retrospective study (secondary data) on the effects of post-discharge cannabis use upon inpatient cocaine use disorder treatment	Sustained remission (26 weeks without use), cocaine use and relapse after treatment discharge	Cannabis use (self-report) after treatment discharge (median: 91 weeks follow-up)	↓ Post-discharge cannabis use increased the likelihood of cocaine use and reduced remission duration (HR:5.57, 95%CI[3.17, 9.77]; HR:0.29, 95%CI[0.10, 0.80]) but not relapse-risk (HR:2.95, 95%CI[0.97, 8.94])
Epstein and Preston, 2003	Cocaine/heroin (188) Cocaine/heroin + occasional (125) or frequent (95) cannabis use	Men/women with heroin/cocaine use disorder (DSM-III) with/without occasional or frequent cannabis use (</>2 positives urine tests/month)	Retrospective study (secondary data) on cannabis use effects on drug-related outcomes of three 25–29 weeks outpatient behavioural treatments while in methadone maintenance treatment	Psychosocial problems, cocaine use severity during/after treatment (follow- up to a year), treatment retention	Cannabis use (self-report) and urinalysis throughout treatment	↔ No inter-group differences on retention or cocaine use during/after treatment ($p>0.5$); cannabis use predicted less cocaine use ($t=-1.66$, $p=0.098$)* during treatment but not psychosocial problems (data not shown)

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Table 2 (*continued*)

Authors	Sample/ groups (sample size)	Participant characteristics	Intervention/Design	Outcome measures	Temporality of cannabis use or measure	Main results
Cannabis-based risk-reduction for cocaine						
Socías, Kerr, Wood et al., 2017	Crack-cocaine pre-, during-, and after-period of cannabis use (122)	Men/women with crack-cocaine use and intentional cannabis use (prior six months) to reduce crack-cocaine consumption	Retrospective cohort study on intentional cannabis use to reduce crack-cocaine use among three cohorts of illicit drug users	Crack-cocaine use frequency in relation to before, during and after the first report of intentional cannabis use	Cannabis use (self-report) throughout the study	↑ Cannabis-use after-period was associated with decreased frequency of crack-cocaine use compared to before- and during- use periods, even when controlling for socio-demographics (AOR=1.89, 95%CI:[1.02, 3.45])
Gonçalves and Nappo, 2015	Crack-cocaine users with cannabis co-use (27)	Men/women with crack-cocaine use disorder (DSM-IV) with at least 25 concurrent cannabis use occasions	Descriptive qualitative in-depth interview study on crack-cocaine use combined with cannabis	Reasons to combine crack-cocaine and cannabis use	Natural history	↑ Cannabis use was described as a health protection strategy for adverse effects experienced with crack-cocaine, specifically to reduce craving, improve sleep, appetite and quality-of-life
Teixeira, Kantorski, Corrêa et al., 2015	Crack-cocaine (5)	Men with at least one year of crack-cocaine use	Descriptive qualitative interview study on strategies developed by crack-cocaine users to deal with use risks	Strategies to deal with crack-cocaine use risks	Natural history	↑ Cannabis consumption was reported to decrease crack-cocaine use related health risks, specifically by decreasing fissure, facilitating sedation and rest, and enhancing appetite
Lau, Sales, Averill et al., 2015	Long-term cannabis users with other drugs exposure (97)	Men/women with at least 24 cannabis use occasions in the prior 6-months	Descriptive qualitative life history interview study on cannabis use as a substitute for other drugs	Cannabis use as a substitute for other drugs	Natural history	↑ Cannabis use was reported as an alternative for alcohol, pharmaceutical and illicit drugs (including crack-cocaine) based on perceptions of more manageable or lesser adverse side-effects and addiction-risk
Lucas, Reiman, Earleywine et al., 2013	Cannabis (404)	Men/women medical cannabis dispensary users	Descriptive survey study on cannabis use as a substitute for other drugs	Cannabis use as a substitute for other drugs use	Cannabis use (self-report) at time of survey	↑ Cannabis use was reported as a substitute for illicit drugs, including crack-cocaine (n=21) due to lesser withdrawal, fewer side-effects, and better symptom management

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Authors	Sample/ groups (sample size)	Participant characteristics	Intervention/Design	Outcome measures	Temporality of cannabis use or measure	Main results
Chaves, Sanchez, Ribeiro et al., 2011	Active (n=31) and former crack-cocaine users (9)	Men/women with current and former crack-cocaine use (no criteria specified)	Descriptive qualitative in-depth interview study on crack-cocaine use behaviours and coping strategies	Behaviours and coping strategies for adverse crack-cocaine use effects	Natural history	↑ Cannabis use was were reported as a self-protective strategy to address/reduce crack-cocaine use and craving
Andrade, Santiago, Amari et al., 2011	Crack-cocaine users (4) Community service workers (2)	Crack-cocaine users (sex not specified) with cannabis co-use	Descriptive qualitative in-depth interviews study on crack-cocaine and cannabis co-use	Reasons to combine crack-cocaine with cannabis use	Natural history	↑ Cannabis co-use was reported to reduce adverse behavioural and physical effects of crack-cocaine use
Ribeiro, Sanchez and Nappo, 2010	Crack-cocaine (28)	Men/women with at least four years of crack-cocaine use	Descriptive qualitative in-depth interview study on crack-cocaine users' behaviours	Crack-cocaine risk reduction strategies developed by users	Natural history	↑ Cannabis use was described as a self-administered protection strategy to control crack-cocaine's adverse effects
Reiman, 2009	Cannabis (350)	Men/women medical cannabis patients	Descriptive survey on cannabis use as a substitute for alcohol and other drugs	Cannabis use as a substitution for other drugs use	Current cannabis use (self-report) at survey time	↑ Cannabis use was reported as a substitute for illicit drugs (n=91), including cocaine, due to lesser adverse side-effects (65%), better symptom management (57%) and fewer withdrawal effects (34%)
Oliveira and Nappo, 2008	Active (45) and former (17) crack-cocaine users	Men/women with at least 25-lifetime crack-cocaine use occasions and former users (at least six months abstained)	Descriptive qualitative interview and ethnographic study to characterize crack-cocaine use behaviours	Pattern of crack-cocaine use	Natural history	↑ Cannabis co-use was reported as a self-employed strategy to alleviate crack-cocaine craving and abstinence

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Authors	Sample/ groups (sample size)	Participant characteristics	Intervention/Design	Outcome measures	Temporality of cannabis use or measure	Main results
Reiman, 2007	Cannabis (130)	Men/women medical cannabis patients	Descriptive survey study on cannabis use as a substitute for alcohol and other drugs	Cannabis use as a substitute for other drugs use	Current cannabis use (self-report) at time of survey	↑ Cannabis use was reported (n=61) as a substitute for illegal drugs, including cocaine, due to fewer side effects (63%) and withdrawal symptoms (43%)
Dreher, 2002	Active (17) and former (14) crack-cocaine users	Women with current crack-cocaine use and former users (no criteria specified)	Longitudinal (nine months) descriptive qualitative interview and ethnographic, participant observation study on intentional co-use of cannabis with crack-cocaine	Cannabis and crack-cocaine co-use motivations and practices	Natural history	↑ Cannabis was intentionally co-used with crack-cocaine to minimize undesirable effects, specifically paranoia and weight loss; most former users (92%) attributed their ability to quit crack-cocaine use to cannabis use
Health and miscellaneous outcomes						
Oliveira, Gonçalves, Ometto et al., 2019	Cocaine (24) Cocaine + cannabis (63) Non-drug users controls (36)	Men with cocaine use disorder (DSM-IV) with/without cannabis use (</>50-lifetime use occasions)	Longitudinal case-control study on cocaine and cannabis co-use effects on neurocognitive functioning and drug-related outcomes after a 4-week inpatient cocaine use disorder treatment	Neurocognitive functions two weeks after discharge and cocaine-relapse at one, three- and six-months follow-up	Lifetime cannabis use (self-report) at treatment admission	↓ Cannabis co-users had lower speed processing, inhibitory control and sustained attention, but better mental flexibility than the cocaine-only group (F=9.87-19.79, p=0.01); no association was found between cannabis co-use and cocaine-relapse at follow-up (p>0.1)

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Authors	Sample/ groups (sample size)	Participant characteristics	Intervention/Design	Outcome measures	Temporality of cannabis use or measure	Main results
Gilmore, Zorland, Akin et al., 2018	Cocaine (49) Cocaine + cannabis (21)	Men/women with cocaine use with/without moderate cannabis use-risk (ASSIST cut-off of 11)	Longitudinal case-control study on mortality rate of emergency department patients with cocaine and cannabis use	Mortality rate by drug use at three years	Last three months cannabis use (self-report) at admission	↓ Cocaine + cannabis co-users had greater mortality risk (HR=13.74, 95%CI[2.92, 64.61] than cocaine-only users (HR=0.89, 95%CI[0.28, 2.76])
Butelman, Bacciardi, Maremmani et al., 2017	Cocaine (615)**	Men/women with cocaine use disorder (DSM-IV) with/without lifetime cannabis use	Case-control study on substance use effects on depressive symptoms	Depressive symptoms	Lifetime cannabis use (self-report)	↓ Cannabis use was associated with the presence of depressive symptoms when controlling by demographics and other drugs use (OR:1.07, $p<0.05$)
Li, Milivojevic, Constable et al., 2005	Cocaine (18) Cocaine + cannabis (8)	Men/women with cocaine use disorder (DSM-IV) and cannabis use	Case-control study on the impact of recent cannabis use on stress-induced BOLD signals in cocaine dependent brain areas	fMRI imaging, anxiety and cocaine-craving before/after neutral and stress imagery induction	Last three months cannabis use (self-report) at time of experiment	↔ No differences in anxiety and cocaine-craving during stress-induced imagery ($F[1,48]=1.35$, $p=0.250$; $F[1,48]=0.20$, $p=0.656$) but there was a general decrease in frontal brain area (including the perigenual anterior cingulate cortex) activity among cannabis users during stress induction ($p=0.001$)

*Authors considered a p-value threshold <0.1 significative. **Number of cannabis users not disclosed. Legends: Protective (↑), counter-protective (↓) or no effect (↔) of cannabis/cannabinoid co-use exposure with cocaine on related outcomes. Abbreviation codes can be found at the abbreviation list.

anxiety during cocaine abstinence period (t[19]=2.76, p<0.05) (Gonzalez-Cuevas et al., 2018).

In regards to THC, increasing (2–8 mg/kg, i.p.) administration twice per day for three days before cocaine self-administration training within a progressive ratio schedule had no impact on cocaine self-administration acquisition (F[9,399]=2.28, p<0.05, post-hoc p>0.05) and sensitization (p>0.05), but reduced cocaine-seeking (F[1,100]=4.38, p<0.05, post-hoc p<0.005) (Panlilio et al., 2007). In rhesus monkeys trained to self-administrate cocaine, single THC (0.03–0.3 mg/kg, i.v.) exposure immediately before food-cocaine choice sessions within an alternative food reinforcer context increased, as compared to vehicle, cocaine lowest-dose choice (F[12,51]=4.08, p<0.001, post-hoc p<0.001), and decreased total reinforcers earned per session (F[3,9]=20.06, p<0.001) (John et al., 2020).

3.2.3. Cocaine pharmacokinetics and toxicity (n=4)

Three studies in mice investigated the effects of single CBD (30–90 mg/kg, i.p.) or THC (1–10 mg/kg, i.p.) administration 15–60 minutes before cocaine-induced (40–80 mg/kg, i.p.) seizure (n=6–13/group). CBD at 15, 30, 60 and 90 mg/kg reduced seizure duration (F[4,48]=2.61, p=0.046) and at 30 mg/kg it increased seizure latency (F[4,48]=5.11, p=0.001) (Gobira et al., 2015). In another study, administration of 30 mg/kg of CBD increased seizure latency, decreased duration and prevented cocaine-induced liver injury (all p<0.05) (Vilela et al., 2015). Zou et al. (2020) showed that CBD administration, at 10 and 30 mg/kg, decreased seizure latency and reduced the duration and severity in a dose-dependent manner, while THC accelerated seizure latency but dose-dependently reduced the duration and decreased severity (all p<0.05) (Zou et al., 2020). Finally, when administrated (15, 30 and 120 mg/kg, i.p.) one hour before cocaine (40 mg/kg, i.p.), CBD (30 mg/kg and 120 mg/kg) increased cocaine-levels in brain and blood samples (p<0.05) and at 30 mg/kg increased cocaine-induced locomotion (p<0.01), while 120 mg/kg of THC increased brain levels of cocaine (p<0.05) (Reid and Bornheim, 2001).

3.3. Human (clinical, epidemiological and other) studies (see Table 2 for study and results details)

3.3.1. Cocaine use behaviours (n=11)

Two randomised, double-blind, placebo-controlled trials investigated CBD effects on treatment outcomes among cocaine-dependent participants. A Canadian-based single-site trial with participants with cocaine use disorder (DSM-IV) (CBD, n=40; placebo, n=38) found no effect of daily CBD (800 mg for 92 days) dose during a 10-day inpatient detoxification and a 12-week outpatient follow-up on cue-induced cocaine craving scores (CI=-0.33, 3.04; p=0.069; BF=0.498) and in the risk of cocaine relapse (HR=1.20, CI=0.65, 2.20; p=0.512; BF=0.152) (Mongeau-Pérusse et al., 2021). Similarly, a Brazilian-based study with daily CBD (300 mg) dose for 10 days in crack-cocaine dependent participants (DSM-IV) (CBD, n=14; placebo, n=17) found no effect on audiovisual cue-induced crack-cocaine craving scores, even when controlling for cannabis use (F[10,230]=2.663; p=0.116; F[10,230]=2460 p=0.130); there were also no differences on anxiety and depression symptoms and sleep quality scores (data not shown) (Meneses-Gaya et al., 2020).

Seven studies investigated possible influences of baseline cannabis use on cocaine-related treatment outcomes of interventions for cocaine use disorder. A Brazilian-based study with women undergoing a three-week inpatient treatment for cocaine use disorder (DSM-5) with occasional (n=29), frequent (n=47) or without (n=138) pre-enrolment cannabis use found frequent cannabis users to have higher cocaine withdrawal (p=0.028, 95%CI[0.61, 14.32], d=0.431) and depressive symptoms (p=0.030, 95%CI[0.31, 8.62], d=0.437) than non-cannabis users at treatment discharge (Viola et al., 2020). Data from a two-week inpatient cocaine detoxification treatment, also in Brazil, showed early-onset cannabis use (n=62) to be associated with elevated cocaine withdrawal and craving (p=0.044; p=0.004); long-term cannabis use (n=49) was associated with increased withdrawal symptoms (p=0.016; p=0.041) at select time-points and predicted higher re-hospitalisation at 2.5 years follow-up (p=0.036) (Viola et al., 2014). Another study among 1,183 individuals undergoing an outpatient-based treatment for cocaine use disorder, found that frequent (last 30 days, n=146) cannabis users had more cocaine use (f/x^2=13.5, p<0.001), legal (f/x^2=3.37, p=0.034) and psychiatric problems (f/x^2=4.32, p=0.014) than occasional (n=403) or non- (n=634) cannabis users (Lindsay et al., 2009). Post-discharge cannabis use (n=55) at 18-month follow-up of an inpatient cocaine use disorder (DSM-IV) treatment compared to no cannabis use (n=144) increased the likelihood of cocaine use and reduced remission likelihood (HR:5.57, 95%CI[3.17, 9.77]; HR:0.29, 95%CI[0.10, 0.80]) but did not increase relapse risk (HR:2.95, 95%CI[0.97, 8.94]) (Aharonovich et al., 2005).

Using data from three outpatient-based randomised trials of contingency management, involving patients with (n=78) and without (n=315) pre-treatment cannabis use, Alessi and colleagues (Alessi et al., 2011) found no differences in cocaine use, abstinence duration, and treatment retention (p=0.81–0.95), but pre-cannabis users showed more severe baseline drug problems and better improvement relative to non-cannabis users (x^2(3)=4.261, p=0.23/RMSEA=0.03, SRMR=0.04). Secondary analysis of two US-based randomized, double-blind, placebo-controlled trials with levodopa/carbidopa pharmacotherapy for cocaine use disorder (DSM-IV, n=64 and 113) reported that, for every day of baseline cannabis use, the intervention group had a 5.4% decrease (RR:0.946, 95%CBI[0.864, 1.069]), while the placebo group had a 4.9% increase (RR:1.049, 434 95%CBI[1.002, 1.115]), in treatment effectiveness (i.e., cocaine-negative urine sample scores) even when controlling for cocaine baseline use (Green et al., 2012). A study using data from three trials involving contingency management behavioural intervention for cocaine use among no (n=188), occasional (n=125) and frequent (n=95) cannabis users, found no inter-group differences for retention or cocaine use during or after treatment (p>0.5); however, cannabis use predicted less cocaine (t=-1.66, p=0.098) use during treatment but not psychosocial problems (data not shown) (Epstein and Preston, 2003).

A US-based study using population survey data of cocaine (n=186) and cocaine + cannabis (n=2,782) users (NESARC-III; 2012–2013) found, through mediation analysis, that

cannabis was a protective factor for cocaine use disorder (DSM-5) by reducing the quantity of cocaine used (-0.09, 95%CI[-0.19, -0.001]), and for risky cocaine use pattern when controlling for the amount, cocaine use frequency and duration and presence/absence of cocaine use disorder (-0.43, 95%CI [-0.78, -0.07]) (Liu et al., 2021). However, a Canada-based study among cocaine dependents with (n=16) and without (n=12) cannabis co-use dependence (DSM-IV) found no inter-group differences in the effects of drug cue-induced craving (F[1,26]=0.75, p=0.394), psychiatric symptoms (p=0.1), cocaine craving (p=0.38), positive and negative affect (p=0.1 and 0.19) or withdrawal symptoms (p=0.56). (Giasson-Gariépy et al., 2017).

3.3.2. Cannabis-based risk-reduction for cocaine (n=12)

Four studies used quantitative-based designs to evaluate cannabis use in regards to other drugs substitution or risk-reduction. A study involving three prospective cohorts of urban street drug users in Canada (n=122) found that the after-period of intentional cannabis use to reduce crack-cocaine use was associated with decreased frequency of crack-cocaine use compared to before- and during- intentional cannabis use periods, even when controlling for socio-demographics (AOR=1.89, 95%CI[1.02, 3.45]) (Socías et al., 2017). The remaining three studies drew on self-administrated survey data among medical cannabis patients. A Canada-based sample of medical cannabis dispensary users (n=404) found that 36% of the participants reported past-month cannabis use as a substitute for illicit drugs use, including crack-cocaine (n=21), due to perceived lesser withdrawal, fewer side-effects and better symptom management characteristics ascribed to cannabis (Lucas et al., 2013). Participants from US-based medical cannabis dispensaries also reported cannabis use as a substitute for cocaine and other illicit drugs (n=91) due to fewer adverse side-effects (65%), better symptom management (57%) and fewer withdrawal effects (34%) (Reiman, 2009). Similarly, about half (47%) of participants of a medical cannabis patients survey in San Francisco (n=130) reported having used cannabis as a substitute for illegal drugs, including cocaine, due to a perception of fewer side effects (63%) and withdrawal symptoms (43%) (Reiman, 2007).

Eight studies used qualitative methods to investigate self-reported health- and addiction-related outcomes of combining crack-cocaine with cannabis use. Long-term (median: 42 years) US-based cannabis users with other drug exposure (n=97) described, through semi-structured in-depth interviews, cannabis as an alternative for alcohol, pharmaceutical, and illicit drug (including crack-cocaine) use based on perceived more manageable or lower adverse side-effects and addiction-risk (Lau et al., 2015). An ethnographic, participant observation-based study in Jamaica with a community-recruited sample of former (n=14) or active (n=17) female crack-cocaine users reported using cannabis in conjunction with crack-cocaine to minimize undesirable effects, specifically paranoia and weight loss. Most of the former crack-users (92%) attributed their ability to quit crack-cocaine use to cannabis use and characterized it as the cheapest, most effective and readily available therapeutic intervention practically available to them (Dreher, 2002).

The remaining six studies employed in-depth, qualitative interview data to explore crack-cocaine and cannabis co-users' perspectives on drug use and health-related consequences in low-economic or socially-marginalized (e.g., homeless) urban Brazilian sub-populations. Cannabis use was self-described as a protection strategy for adverse health effects experienced with crack-cocaine, specifically to reduce craving, improve sleep, appetite and quality-of-life in a community-recruited, street-based sample in São Paulo (n=27) (Gonçalves and Nappo, 2015). A sample of men (n=5) with >5 years of crack-cocaine use in Pelotas reported cannabis use after crack-cocaine use, among other risk-reduction strategies, to decrease fissure, facilitate sedation and rest, and enhance appetite (Teixeira et al., 2015). Similarly, former (n=9) and current crack-cocaine users (n=31) in São Paulo reported cannabis use among several auto-behavioural (e.g., eating, leisure, work) self-protective strategies to manage crack-cocaine use and craving (Chaves et al., 2011). Crack-cocaine users (n=4) and community service workers (n=2) in Salvador reported cannabis use as reducing adverse behavioural and physical effects associated with crack-cocaine use (Andrade et al., 2011). A male sample with long (at least four years of use, average >10 years) crack-cocaine use histories (n=28) in São Paulo described cannabis use as a self-administered protection strategy towards controlling crack-cocaine adverse effects, including craving and paranoia (Ribeiro et al., 2010). Finally, another São Paulo-based study among active (n=45) and former crack-cocaine users (n=17) found cannabis co-use as a self-selected strategy to alleviate crack-cocaine craving and abstinence (Oliveira and Nappo, 2008).

3.3.3. Health and miscellaneous outcomes (n=4)

At the end of a two-week inpatient cocaine detoxification program in Brazil, cocaine + cannabis (n=63) and cocaine-only (n=24) users had worse scores than non-drug user controls (n=36) in several neurocognitive (e.g., working memory, decision-making) functions (F=4.67-15.33, p=0.01, post-hoc p<0.05); moreover cocaine + cannabis co-users performed worse on speed processing, inhibitory control and sustained attention, yet better on mental flexibility compared to the cocaine-only group (F=9.87-19.79, p=0.01, post-hoc p≤0.01). No association was found between cannabis co-use and relapse at follow-ups (p>0.1) (Oliveira et al., 2019). Three-year follow-up data of two urban emergency-department patient samples in Georgia (US) showed cocaine + cannabis users (n=21) to have a vastly greater mortality risk (HR=13.74, 95%IC[2.92, 64.61]) than cocaine-only users (n=49, HR=0.89, 95%IC[0.28, 2.76]) (Gilmore et al., 2018). In regards to depression, a US-based case-control study using data from two methadone maintenance and community-based cohorts, found lifetime cannabis exposure in cocaine dependents (DSM-IV, n=615) to be associated with higher depressive symptoms scores, even when controlling for demographics and other drug use (OR:1.07, p<0.05) (Butelman et al., 2017). Finally, a functional magnetic resonance imaging study with blood-oxygen-level-dependent (BOLD) contrast during script-guided imagery for emotional stress induction in cocaine-dependents with (n=8) and without (n=18) recent cannabis use found no between-group differences in

anxiety and cocaine-craving during stress-induced imagery ($F[1,48]=1.35$, $p=0.250$; $F[1,48]=0.20$, $p=0.656$). However, there was a general decrease in frontal brain area activity among recent cannabis users during emotional stress induction, including the perigenual anterior cingulate cortex ($p=0.001$). (Li, Milivojevic et al., 2005).

4. Discussion

The present study reviewed multi-disciplinary studies that assessed cannabis use or co-exposure with cocaine on behavioural, biological and health outcomes in both animal and human populations. Animal-based studies investigated the effect of THC or CBD on several models of cocaine addiction that mimic drug-reinforcement patterns such as cocaine-seeking, -craving, -relapse and -withdrawal in humans (Kuhn et al., 2019; Spanagel, 2017), but also on cocaine induced-toxicity. THC-exposure overall showed mixed protective/counter-protective effects: while potentiating cocaine-related memory extinction, reducing cocaine-seeking and protecting from cocaine-induced toxicity, it also enhanced cocaine-reinforcement, brain cocaine-levels, and induced cocaine-sensitization in rodents. A potential factor contributing to the variability of results may be related to other effects of THC, for example, the alteration in spatial memory, catalepsy, and hypomotility (Fujiwara and Egashira, 2004; Sano et al., 2008; Varvel et al., 2005) that may influence the cocaine-related results based on behavioural assessment. In addition, a wide range of THC dosing has been examined (from 0.5 mg/kg to 120 mg/kg i.p.), while especially the physiological relevance of high dosing on outcomes of cannabis use is not yet established. In contrast, CBD results were mostly protective, with pro-neurogenic effects in cocaine-consuming animals, potentiating cocaine-related memory extinction, alleviating cocaine-induced toxicity and reducing cocaine-relapse. Many differences in THC and CBD's pharmacological actions, including the reinforcing properties, may account for the observed differences in outcomes. While drugs that block CB1 receptors – which are involved in THC's rewarding effects – may offer therapeutic value for substance use disorder treatment, CBD's central actions are yet to be fully understood (Laprairie et al., 2015; Manzanares et al., 2018; Parsons and Hurd, 2015; Spanagel, 2020).

CBD could alleviate cocaine addiction through its pharmacological action on the endocannabinoid or other neurotransmitter system (e.g., serotonin, glutamate), by normalizing cocaine-induced dopaminergic alteration, modulating signal transduction pathways, decreasing inflammation and reversing cocaine-induced toxicity as well as alleviating comorbidities (e.g., anxiety) (Calpe-López et al., 2019; Rodrigues et al., 2020). A relevant mechanism in play for protective outcomes could be related to the serotoninergic system, since psychostimulant drugs increase serotonin levels (Müller and Homberg, 2015). Specifically, it has been hypothesized that CBD could prevent the rewarding effects of psychostimulants through its agonist action on post-synaptic 5-HT1A receptors, as the activation of this receptor can inhibits addiction-related behaviours (Calpe-López et al., 2019; Müller and Homberg, 2015). In addition, CBD has been suggested to facilitate partial agonist action on dopaminergic D2 receptors, given that other D2 partial agonists have shown to attenuate cocaine self-administration in pre-clinical models (Calpe-López et al., 2019; Feltenstein et al., 2009; Pulvirenti et al., 1998). Actions on other neurotransmitter systems, such as the non-competitive inhibition of acetylcholine receptor or allosteric modulation of opioid receptors, could also play an important role in CBD protective effects for addiction (for a review of mechanisms, see (Calpe-López et al., 2019)). However, confounding interpretation of CBD data is the observation that while many potential mechanisms have been described in vitro, their relevance to therapeutic effect in a clinical population is far from established (Ibeas Bih et al., 2015).

In contrast, clinical studies utilizing quantitative-data mostly investigated naturalistic cannabis use or exposure (instead of isolated cannabinoids with controlled content and dosage regimen), and despite a few exceptions, showed mostly counter-protective or neutral effects when co-used with cocaine. These included worsened neurocognitive functions, mental and general health, and, more frequently, negative cocaine-treatment related outcomes (e.g., craving, abstinence, treatment retention, etc.). These studies have highly heterogeneous designs (e.g., intervention or epidemiologic studies), and many did not primarily investigate cannabis use (e.g., secondary results, cannabis moderating effect), therefore involving possible uncontrolled confounders, such as co-morbidities, relevant to addiction. Specifically, cannabis use was assessed as naturally ongoing use or dependence, often among other drugs, which may entail a poly-substance use scenario. The co-use of cannabis with other substances, especially with cocaine, is a common phenomenon (Liu et al., 2018; White et al., 2013), and it is well-known that poly-substance users commonly experience more severe problems, including populations seeking cannabis treatment (Connor et al., 2013; Connor et al., 2014). Potentially related, these studies show that cannabis – and especially problematic cannabis use, may entail increased risks and comorbidities that are not limited to cocaine-related outcomes; overall, highlighting the importance to address cannabis use as one risk-element among cocaine and poly-substance users.

Furthermore, animal studies did not evaluate cannabinoids within an abuse model (e.g., cannabinoid self-administration, conditioned place preference). Rather, they used cannabinoids as an intervention to evaluate cocaine-related outcomes. Such differences hinder translational properties and may account, at least partially, for the discrepancies between pre-clinical and human studies results. However, two randomised clinical trials – which control for more confounders - did not find effects of CBD on cocaine-related outcomes, including craving and relapse. These results contrast with both pre-clinical studies and trials with humans using CBD for use disorders of other substances (e.g., heroin, cannabis, tobacco) which have shown promising results (Freeman et al., 2020; Hurd et al., 2019; Meneses-Gaya et al., 2020; Mongeau-Pérusse et al., 2021; Morgan et al., 2013). These results indicate that, contrary to what pre-clinical studies suggest, CBD alone may not be sufficient as a therapeutic agent for cocaine use disorder; rather, instead of acting in preventing craving and relapse, it may be more efficient to alleviate cocaine-use comorbidi-

ties or detrimental effects, such as neuronal or hepatic toxicity.

Several descriptive studies comprising mostly (qualitative) self-report data of cannabis use as a self-medication adjuvant for cocaine-use related risk and adverse experiences, together with select quantitative-based studies, suggested a protective effect of cannabis use. Some aspects of drug addiction known to influence drug-craving and relapse, such as motivation, drug use pattern (e.g., differences in cue-drug associative learning) and social interactions (Bardo et al., 2013; O'Brien et al., 1998; Pelloux et al., 2019) related to intentional cannabis use could explain some of the cocaine-related benefits reported. For example, cocaine users with comorbid conditions could seek cannabis use to self-regulate negative psychological states. In that sense, cannabis use has previously been suggested to substitute for cocaine or reduce related harms (Labigalini et al., 1999; Mikuriya, 2004; Paul et al., 2020). However, these qualitative-based results should be interpreted with caution given that they are extensively based on descriptive reports, being subject to participants' perceptions of experiences, and lacking rigorous parameters for validation (e.g., control group, measurable outcome). Therefore, the external validity and efficacy, if any, could be limited to a specific population, e.g., people with intentional cannabis use to modulate cocaine or other drugs use.

There is a clear and substantial need for future research in this area. Concretely, studies should clarify the neurobiological mechanisms involved in CBD's potential to alleviate cocaine use disorder, for example the mechanisms through which CBD prevents the stress-induced reinstatement of cocaine and cocaine withdrawal, to what extend different CBD doses influences cocaine-context memory, and non-cannabinoid neuronal pathways (e.g., 5-HT) involvement on cocaine-self administration (Calpe-López et al., 2021; Chesworth and Karl, 2020; Gasparyan et al., 2020). More controlled trials in humans with different approaches (e.g., varying dose levels, administration time, and study populations) remain required to clarify the translational potential of pre-clinical findings related to CBD, especially considering CBD's pharmacological complexity (Laprairie et al., 2015; Linares et al., 2019; Spanagel, 2020). More research on CBD potentials to decrease the biological burden of cocaine use, e.g., protective effect on oxidative stress and inflammation, are also of interest to reduce the health-related harms associated with cocaine use. In regards to THC, additional studies on pre-clinical models of cocaine addiction are warranted since they are less frequent and have less consistent results. Related investigations should consider potential confounders of THC behavioural effects (e.g., catalepsy) when designing new studies based on the behavioural assessment of cocaine-related outcomes. Furthermore, when administered together, THC and CBD have complex interactions; therefore, studies examining a range of different combinations of THC and CBD and their effect on cocaine use behaviours could take advantage of the apparent synergy observed from the combination of these compounds.

Finally, there are a number of potential limitations of this review, including the number of databases searched, the inclusion of English-only studies, and the absence of gray literature, risk of bias evaluation and meta-analysis (due to the heterogeneity of data). In conclusion the available multi-disciplinary data suggest that the potential benefits of cannabis/cannabinoid on cocaine related outcomes reported by specific samples of users have not been confirmed to date in clinical studies; however, in light of the preclinical and qualitative human data, exploring other influences, such as dose, population, presence of comorbidities, may be justified

Contributors

BF and DDB co-developed the concept for the study. DDB developed the review strategy, led the data collection and writing for the paper. DDB and LOM extracted, collated and analysed the study data. All co-authors contributed to data/results analyses and interpretation, and provided substantial intellectual content towards iterative drafts and revisions of the paper. All authors approved the final version of the paper submitted.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2021.06.002.

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