HHS Public Access

Author manuscript

Alcohol Clin Exp Res. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Alcohol Clin Exp Res. 2019 April ; 43(4): 550–563. doi:10.1111/acer.13964.

CANNABIDIOL AS A NOVEL CANDIDATE ALCOHOL USE DISORDER PHARMACOTHERAPY: A SYSTEMATIC REVIEW

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Abstract

There is substantial interest in the therapeutic potential of cannabidiol (CBD), a non-psychoactive cannabinoid found in plants of the genus *Cannabis.* The goal of the current systematic review was to characterize the existing literature on this topic and to evaluate the credibility of CBD as a candidate pharmacotherapy for alcohol use disorder (AUD). Using a comprehensive search strategy, 303 unique potential articles were identified and 12 ultimately met criteria for inclusion (8 using rodent models, 3 using healthy adult volunteers, and 1 using cell culture). In both rodent and cell culture models, CBD was found to exert a neuroprotective effect against adverse alcohol consequences on the hippocampus. In rodent models, CBD was found to attenuate alcohol-induced hepatotoxicity, specifically, alcohol-induced steatosis. Finally, findings from preclinical rodent models also indicate that CBD attenuates cue-elicited and stress-elicited alcohol-seeking, alcohol self-administration, withdrawal-induced convulsions, and impulsive discounting of delayed rewards. In human studies, CBD was well tolerated and did not interact with the subjective effects of alcohol. Collectively, given its favorable effects on alcohol-related harms and addiction phenotypes in preclinical models, CBD appears to have promise as a candidate AUD

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Conflict of Interest

B.N.F has received research support from Pfizer and consultant fees from Otsuka. James MacKillop is a principal in BEAM Diagnostics, Inc. No other potential conflicts of interest to report.

pharmacotherapy. This is further bolstered by the absence of abuse liability and its general tolerability. A clear limitation to the literature is the paucity of human investigations. Human preclinical and clinical studies are needed to determine whether these positive effects in model systems substantively translate into clinically-relevant outcomes.

Keywords

cannabidiol; alcohol use disorder; CBD; alcohol; pharmacotherapy

INTRODUCTION

There is burgeoning interest in the therapeutic potential of compounds found in plants of the genus *Cannabis*. The cannabis plant contains more than 500 constituents and over 100 phytocannabinoids that actively interact with the body's endocannabinoid system (eCB), of which delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most commonly studied. The eCB is an important physiological system with broad activity impacting various functions of the human body, including brain plasticity, inflammation, appetite regulation and learning and memory among others (Aizpurua-Olaizola et al., 2017). It is comprised of at least two G-protein coupled receptors, the cannabinoid type 1 (CB_1) and type 2 (CB_2) receptors (Boggs et al., 2017). THC is a partial agonist of CB_1 and CB_2 receptors (Boggs et al., 2017), and studies using CB_1 receptor antagonists attenuate the effects of THC suggesting responsibility for its psychoactive effects (e.g., Englund et al., 2016; Justinova et al. 2008; Klumpers et al., 2013). Unlike THC, CBD is non-psychoactive which may be attributed to its function as a negative allosteric modulator of CB_1 and CB_2 receptors (Laprairie et al., 2015; Mechoulam et al., 2007). Further impact of CBD on the eCB involves blocking anandamide uptake and inhibiting its enzymatic hydrolysis (Pertwee, 2008; Thomas et al, 2007). There are also numerous non-endocannabinoid signaling systems that CBD may interact with, explaining its diverse biologic effects (Boggs et al., 2017). For instance, CBD can modulate 5-HT_{1A} receptors (Russo et al., 2005), GPR55 (Ryberg et al., 2007), TRPV1 cation channels (Bisogno et al. 2001) and μ- and δ-opioid receptors (Kathmann et al., 2006).

With numerous and diverse pharmacological effects on a wide variety of body systems, CBD has gained attention for equally numerous health applications. It has demonstrated anti-inflammatory and anxiolytic effects and reports also suggest it may have antipsychotic, antiemetic, antioxidant, and anticonvulsant effects (Hampson et al., 1998; Parker et al., 2002; Zuardi et al., 2006;). However, it is critical to note that this support is derived from a primarily preclinical literature. Despite the ubiquitous health claims of CBD, substantive support only exists in a small number of conditions. In Canada, Sativex (an oromucosal spray of THC and CBD) has been approved as an adjunctive treatment for neuropathic pain in multiple sclerosis (Health Canada, 2007). Similarly, randomized controlled trials of CBD only provide support for seizure disorders (Cunha et al., 1980; Devinsky et al., 2017; 2018a; Theile et al., 2018). Reflecting these findings, earlier this year CBD (Epidiolex ©) was approved by the Food and Drug Administration (FDA) for Lennox-Gastaut and Dravet syndrome, two rare and severe forms of pediatric epilepsy.

Given the salutary effects of CBD in preclinical studies, a variety of clinical applications have been considered, including alcohol use disorder (AUD) and other substance use disorders (SUDs). AUD is characterized by a problematic pattern of alcohol use, which leads to significant impairment and distress (APA, 2013). It is a highly disabling condition and represents a serious public health concern. The FDA has approved three medications for treating AUD including naltrexone (both oral and intramuscular formulation), acamprosate and disulfiram (Leggio & Lee, 2017); however, meta-analytic evidence only supports the use of acamprosate and naltrexone (Jonas et al., 2014). The European Medicines Agency has also approved nalmefene for AUD (Paille & Martini, 2014). These medications have distinct mechanisms of action and are effective for some patients but predicting treatment response is difficult (Jonas et al., 2014). Despite existing pharmacological or psychological therapies, substantial proportions of patients do not have successful outcomes (Aronson, 2015; e.g., Naltrexone number needed to treat (NNT) = 9) and there is a clear need for additional treatments, particularly those targeting alternative novel mechanisms (Litten et al., 2012, 2016a, 2016b), such as the eCB.

The rationale for CBD as an AUD pharmacotherapy comes from both oblique and direct evidence. First, there is evidence that AUD leads to dysfunction in a number of the biological systems for which CBD has favorable effects. For example, alcohol is a potent modulator of the immune system, potentiating alcohol-induced liver inflammation and stimulating immune cells, like monocytes, macrophages, and T lymphocytes, which in turn cause the release of pro-inflammatory cytokines (reviewed in Neupane, 2016). To address these effects, CBD's anti-inflammatory effects may prove beneficial. Oxidative stress also plays a demonstrable role in potentiating alcohol-related harms (Hernandez et al., 2016; Li et al., 2015) which may be alleviated by CBD's antioxidant properties. Further, based on the risk for seizures during alcohol withdrawal and persistent disturbances in glutamate neurotransmission (Jesse et al., 2017), CBD's anticonvulsant effects may have therapeutic potential. Second, preclinical evidence suggests that the eCB plays important roles in motivational properties of alcohol as demonstrated by studies examining CB_1 receptor modulation. More specifically, CB_1 receptor antagonism has been shown to suppress rodent alcohol consumption (Arnone et al., 1997; Colombo et al., 1998; Femenia et al., 2010; Wang et al., 2003) and can block the increased alcohol consumption noted with CB_1 receptor agonist administration (Colombo et al., 2002). Given that CBD may decrease CB_1 receptor activity (through negative allosteric modulation), and CB_1 receptor antagonism has been shown to decrease alcohol consumption in animal models, this evidence further supports the notion that CBD may be a promising treatment for AUD.

The preceding lines of research obliquely suggest that CBD may be a viable AUD pharmacotherapy, but a number of studies have also directly examined the potential role of CBD. The goal of the current systematic review was to characterize the findings from those direct investigations of CBD's effects on alcohol-related dysfunction or AUD. The broad goal was to appraise the extent to which CBD may be a credible AUD pharmacotherapy. Although a number of existing pharmacotherapies exist for AUD, suboptimal treatment outcomes remain common and the development of novel strategies remains a priority (Kranzler et al. 2018; Litten et al., 2012, 2016a, 2016b).

METHODS

Search Strategy

We applied the relevant methods outlined in the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA; Moher et al., 2009). Relevant articles on the effects of CBD on different alcohol-related harms were identified using the Boolean search terms ("cannabidiol" or "CBD") and ("ethanol" or "alcohol"). The search was conducted using PubMed/MEDLINE, EMBASE and PsycINFO in September 2018 and the initial searches were downloaded to shared drives. Titles and abstracts resulting from the initial search were screened by two reviewers for suitability for full-text review and final inclusion. To be included, an article was required to meet the following criteria: (1) an original empirical research article published in a peer-reviewed journal; (2) written in (or available in) English; (3) study design must include CBD as an experimental intervention or in an observational design; (4) the study outcomes must examine some aspect of alcohol-related harm. This systematic review was pre-registered in PROSPERO (registration number: CRD42018109578).

RESULTS

Our initial search generated 303 results, of which 12 met inclusion criteria (see PRISMA flow diagram, Figure 1). In the following sections, we review findings of the effects of CBD on alcohol-related harms in human participants (Consroe et al., 1979; Belgrave et al., 1979; Bird et al., 1980), cell culture (Brenneman et al., 2018) and animal models (Hamelink et al., 2005; Liput et al., 2013; Wang et al., 2017; Yang et al., 2014; Filev et al., 2017; Wang et al., 2017; Viudez-Martinez et al., 2018a; 2018b; Gonzalez-Cuevas et al., 2018). Table 1 provides a concise summary of the alcohol-related harm and associated outcomes of the studies included in this review. Below, the results are according to the most commonly studied outcome domains.

Protection of Cognition and Prevention of Neurodegeneration

Existing approved pharmacological interventions for AUD focus on modifying the motivational properties of alcohol (Swift, 2007). However, excessive alcohol use can give rise to neurodegeneration, which is a hypothesized cause of the observed cognitive and behavioural impairments noted in AUD (Crews & Boetigger, 2009). Previous studies have revealed that alcohol is particularly damaging to the frontal and temporal lobes (Fulton & Nixon, 2009) and the hippocampus (Wilson et al., 2017), with induction of neuroinflammatory mediators and/or oxidative stress responsible for such consequences. These brain regions are involved in problem solving, attention, information processing, learning and memory (Liput et al., 2013). Further, reduced gray cortical matter has been associated with a heightened risk of relapse (Rando et al., 2011). Thus, treatments focusing on brain regeneration or compounds with neuroprotective abilities are attractive, given that they focus on a novel therapeutic target. CBD has demonstrated neuroprotective effects, preventing oxidative damage in an in vitro model of excitotoxicity (e.g., Hampson et al., 1998), making it a highly credible pharmacotherapy for reducing adverse alcohol-related cognitive consequences. Although the exact mechanism by which it elicits these actions

remains unclear, $5HT_{1A}$ or CB_2 receptor mediation have been hypothesized (reviewed in Campos et al., 2016).

Pre-clinical Studies—Three studies were identified examining the extent to which CBD was able to prevent alcohol-induced neurodegeneration in the rat entorhinal cortex (Hamelink et al. 2005; Liput et al., 2013) and hippocampus (Brenneman et al., 2018; Hamelink et al., 2005). The first two studies utilized the Majchrowicz procedure (Majchrowicz, 1979), a widely used paradigm in studies examining AUD and alcohol-induced brain damage (Crews & Nixon, 2008). This model maintains intoxicating blood alcohol levels typical of AUD with minimal mortality and a clear pattern of neurodegeneration during a 4-day binge period (Hamelink et al., 2005; Liput et al., 2013). Compounds of interest, in this case neuroprotectants, are administered between days 2–4 of alcohol treatment as neurodegeneration is not observed prior to day 3 or 4 of the binge (Hamelink et al., 2005; Liput et al., 2013).

In the first study, Hamelink et al. (2005) evaluated the effects of several compounds on hippocampal granular and entorhinal cortical pyramidal cell death, including intraperitoneal (i.p.) administration of CBD (20 or 40mg/kg/day), α-tocopherol and butylated hydroxytoluene (antioxidants), dizocilpine, memantine and nimodipine (NMDA receptor antagonists); and furosemide, bumetanide and L-644,711 (diuretics). When 40 mg/kg/day of CBD was co-administered with alcohol, cell death was reduced by approximately 60% in both areas compared to controls. Neuronal rescue with both antioxidants and furosemide was comparable to the CBD group. Greater cell death was observed with dizocilpine, and there was no difference between the remaining NMDA receptor antagonists (Hamelink et al., 2005). Subsequently, Liput et al. (2013) determined the target CBD plasma concentration to achieve a neuroprotective effect, to be approximately 100ng/mL. This concentration was achieved on day 3 with transdermal application of a 5.0% CBD gel (but not 1.0% or 2.5%). It also resulted in a 48.8% reduction in neurodegeneration in the entorhinal cortex, a difference which approached significance. In a second experiment, an optimized CBD gel (2.5%) was evaluated in comparison to i.p. CBD and transdermal vehicle on day 3 of binge-treatment. During treatment, intoxication levels were comparable between all groups, with each group receiving 380.4 ±7.8 mg/dL of alcohol, and evidence of cell death as a result. Compared to the alcohol control condition, i.p. CBD was associated with a 50.6% reduction and transdermal CBD was associated with a 56.1% reduction in cell death of the entorhinal cortex; but they did not differ from one another (Liput et al., 2013).

Most recently, Brenneman et al. (2018) examined the effect of CBD and a novel CBD-derived compound (KLS-13019) on rat hippocampal cultures to evaluate treatment of oxidative stress as it is relevant to hepatic encephalopathy. Hippocampal cultures were co-treated with toxic levels of alcohol (30mM) and ammonium acetate (300μM) and the protective effects of CBD (concentrations ranging from 0.1 to 10μM) and KLS-13019 (concentrations ranging from 1nM to 10μM) were assessed. Both cell death and neuronal viability were measured, neuroprotection specifically was observed as an increase in fluorescence for 5,6-carboxyfluorescein diacetate, succinimidyl ester (CFDA) and decrease in fluorescence of propidium iodide (PI). The combined toxin produced a decrease in CFDA fluorescence to 76±4% for control culture. Both compounds revealed a protective ability

compared to control, although KLS-13019 exhibited substantially higher potency. Specifically, 10μM CBD and 100–700nM KLS-13019 were required for full protection in hippocampal cultures (Brenneman et al., 2018).

Adverse functional cognitive performance is a potential sequela of neurodegeneration observed in AUD. Our search revealed one preclinical study that evaluated the impact of CBD in a neurocognitive domain, specifically impulsive choice, also referred to as delay discounting (i.e., preference for small immediate rewards compared to larger delayed rewards). Impairments in impulse control are related to both alcohol use/AUD and risk of relapse (Amlung et al., 2017; MacKillop et al., 2011). In animals, impulsive choice is predictive of high alcohol intake and "loss of control" drinking (Oberlin & Grahame, 2009; Wilhelm & Mitchell, 2009). Gonzalez-Cuevas et al (2018) utilized a 7-day dependence-inducing intragastric alcohol (or vehicle) intoxication protocol, during which animals were treated with transdermal CBD (~15mg/kg) or vehicle gel every 24 hours. Effects on impulsive choice were examined after termination of the intoxication protocol and CBD was associated with significantly lower impulsive choice in the animals that received the alcohol dependence protocol. This finding provides evidence of CBD inhibiting the impaired impulse control typically seen in AUD.

Human Studies—In contrast to preclinical studies, no studies examining the effects of CBD on AUD-related cognitive dysfunction were identified in humans. However, three studies were identified that examined the effects of concurrent alcohol and CBD intake on cognitive function in healthy humans. In the earliest study, Consroe et al. (1979) recruited 10 healthy adults and administered a dose of placebo (glucose capsule and orange juice with 4mL alcohol), CBD only (200mg CBD and orange juice with 4mL alcohol), alcohol only (glucose capsule and orange juice with 1g/kg alcohol), or CBD + alcohol (200mg CBD and orange juice with 1g/kg alcohol) in a double-blind within-subjects design. Across all conditions (alcohol only and CBD +alcohol), alcohol was associated with detectable psychoactive effects and significant decrements in motor (finger tap test) and cognitive (attention and concentration) performance (Consroe et al., 1979). Thus, co-administration of CBD did not affect alcohol intoxication. Similarly, Belgrave et al (1979) examined the effect of CBD or placebo intake followed by consumption of an alcoholic (0.54 g/kg) or placebo beverage. Cognitive, perceptual and motor function tests revealed all noted deficits to be related to alcohol, while CBD was essentially inactive (Belgrave et al., 1979). Bird et al (1980) evaluated the effects of CBD (320 μg/kg), THC (215μg/kg) and cannabinol (320 μg /kg) alone or in all possible combinations with alcohol (0.54g/kg). Overall, only THC produced significant synergistic declines on all performance measures, with no interaction effects by CBD or cannabinol pre-treatment. Together these findings provide evidence that CBD is not associated with the same detrimental cognitive effects as alcohol or THC, suggesting that it may be a well-tolerated treatment from the perspective of cognition.

Alcohol motivation and relapse

Beyond excessive drug-seeking, post-treatment relapse is a primary driver of the chronicity of SUDs. Individuals with SUDs are at risk for relapse due to multiple factors including susceptibility to stress, craving induced by drug contexts and heightened anxiety (MacKillop

et al., 2010; Ramo & Brown, 2008; Singha, 2012). Unlike existing AUD treatments, CBD is pointed to as a potential treatment as it targets multiple states associated with drug addiction and heightened relapse risk. Preclinical evidence has shown the potential of CBD in opioid and psychostimulant addiction, while human studies present preliminary evidence of a beneficial impact of CBD on cannabis and tobacco dependence (reviewed in Prud'homme et al., 2015).

Pre-clinical Studies—Four studies were identified examining the effects of CBD on alcohol consumption or self-administration and processes associated with relapse and addiction (Gonzalez-Cuevas et al., 2018; Viudez-Martinez et al., 2017; 2018; Filev et al., 2017). One of these studies examined the effects of CBD when combined with naltrexone (Viudez-Martinez et al., 2018). Some of the most compelling evidence for CBD's therapeutic capacity is derived from animal models of addiction and relapse. For example, Gonzalez-Cuevas et al. (2018) systematically demonstrated the potential of CBD treatment on a number of risk factors of relapse. Using an established protocol, rats were trained to self-administer oral alcohol in daily 30-minute sessions. Vehicle pre-treatment for 4 days was followed by a 7-day treatment phase where groups were randomized to receive either CBD (15 mg/kg) or vehicle gel. Testing on reinstatement (drug seeking) occurred during treatment and the post-treatment phase. Reinstatement was provoked by exposure to drug-associated environmental stimuli (an olfactory and auditory component) and an acute stressor (yohimbine administration). Compared to vehicle treatment, CBD reduced both context- and yohimbine-induced drug seeking when applied acutely (day 1) and with repeated treatment (day 7). The effect of CBD did not diminish with multiple administrations, implying no development of tolerance. Rather, both forms of reinstatement remained significantly reduced up to 138 days after CBD treatment was discontinued. In contrast, vehicle treatment was associated with increased drug seeking behaviours with yohimbine administration. CBD also reduced experimental anxiety as demonstrated by greater duration of time CBD treated animals spent in the open arms of the elevated plus maze compared to vehicle treatment. Specifically, CBD did not alter open arm crossings (locomotor activity) compared to vehicle; effects on closed arm entries, a more common indicator of anxiety, was not reported. In addition, CBD also did not interfere with context-induced or yohimbine-stress induced reward seeking of a glucose-saccharin sweet solution, suggesting that the behavioural changes associated with CBD were likely not due to sedative or amotivational effects.

Two studies investigated the effects of CBD on motivation for alcohol (Viudez-Martinez et al., 2018a; 2018b) using a 3-stage operant oral alcohol self-administration paradigm (Navarette et al., 2014). In this paradigm, animals underwent 5 daily sessions on a fixed ratio (FR)1 reinforcement schedule and then a FR3 schedule with a final session on a progressive ratio (PR) schedule. Once alcohol intake was normalized, mice underwent FR1 (5 days), FR3 (5 days) and PR (1 day) again. The first study revealed decreased voluntary alcohol consumption with i.p. CBD treatment (60 and 120 mg/kg/d) using the two-bottle choice test (Viudez-Martinez et al., 2018a). To examine the effects of CBD on relapse-like behaviour, a separate group of animals underwent a period of deprivation (where food and water was still provided ad libitum) following the oral alcohol self-administration protocol to normalize

post-alcohol exposure. In these animals with a history of alcohol dependence, 60mg/kg and 120 mg/kg of i.p. CBD reduced alcohol-induced relapse behaviour. In addition, less withdrawal (handling-induced convulsion score) was observed in CBD (+ saline or alcohol) treated animals following a single dose of i.p. alcohol (4g/kg) than the vehicle + alcohol group. Furthermore, acute administration of i.p. alcohol (30mg/kg/d) did not alter basal temperatures of CBD treated mice, while those treated with vehicle revealed decreased temperature within 30 minutes. Subcutaneous administration of a microparticle formulation of CBD via continuous controlled release (30mg/kg/d) also significantly reduced alcohol self-administration and motivation to drink. Finally, CBD treatment significantly reduced relative gene expression of *Th* gene in the ventral tegmental area, *Oprm1*, *Cnb*$_1$ and *Gpr55* on the nucleus accumbens (NAcc), and increased CB_2 receptors in the NAcc.

Another study examined the effects of combining a subcutaneous controlled release microparticle CBD formulation (20mg/kg) and naltrexone (0.7mg/kg) in reducing alcohol self-administration and motivation compared to either compound alone (Viudez-Martinez et al., 2018b). In this case, the combined CBD and naltrexone group or either treatment independently reduced operant response and reduced alcohol self-administration on days 8–10 when compared to the control group (vehicle + vehicle). However, only the combined treatment was able to significantly reduce alcohol self-administration in all phases of the alcohol administration paradigm. Of note, the authors remarked that lowering the dose from the previous study (Viudez-Martinez et al., 2018a; from 30 mg/kg/d to 20mg/kg/d) may have altered CBD's ability to reduce alcohol motivation. Combined treatment also revealed greater reduction of gene expression of *Th* and *Oprm1* in the NAcc, dorsal raphe nucleus and ventral tegmental area. In addition, CBD alone or in combination with naltrexone reduced $5HT_{1A}$ receptor gene (*Htr1a*) expression and administration of a $5HT_{1A}$ receptor antagonist blocked the reduction in alcohol motivation induced by the alcohol administration paradigm.

Finally, one study examined the effect of CBD on an animal model of locomotor sensitization (Filev et al., 2018). The rationale for this model is that repeated administration of substances of abuse (e.g., alcohol) typically induce progressive and persistent increase of locomotor activity, even after withdrawal (Coelhoso et al., 2013). Evaluating locomotor sensitization is a common tool as rodent sensitization to the rewarding effects of a drug of abuse is directly related with the sensitization to its locomotor effects (Vanderschuren & Pierce, 2010). Once acquired, this effect is long lasting and is temporally related to morphological and neurochemical changes in the mesolimbic pathway and in the encephalic nuclei interacting with this dopaminergic tract (Vanderschuren & Pierce, 2010). Filev et al (2018) examined the effects of 4 days of pre-treatment with only CBD (2.5mg/kg), THC (2.5mg/kg), or the combination of both compared to vehicle. Only the THC and THC+CBD group revealed reduced expression of locomotor sensitization; no effects were observed with CBD alone. This suggests CBD does not attenuate alcohol-induced locomotor sensitization.

Human Studies—No studies on human populations examining the effects of CBD alcohol-related motivation or treatment response were identified.

Hepatotoxicity

Chronic alcohol consumption is a leading cause of liver disease worldwide (Leggio & Lee, 2017). Alcohol-related liver disease ranges in severity from mild and reversible fatty liver (steatohepatitis), to more severe forms including hepatitis, cirrhosis or even hepatic failure (Leggio & Lee, 2017). In terms of mechanisms, both oxidative stress and inflammation have been implicated in the induction of alcohol-related liver injury, including steatohepatitis. In this context, CBD may be a credible pharmacotherapy based on existing evidence regarding its effects as an anti-inflammatory and antioxidant molecule. Specifically, in non-alcohol related liver injury, CBD has improved brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy (Avraham et al., 2011) and hepatotoxicity resulting from cadmium (Fouad et al., 2013) and cocaine (Vilela et al., 2015).

Preclinical studies—Our search revealed two studies examining the effects of CBD on alcohol-induced liver steatosis (Wang et al., 2017; Yang et al., 2014). While both studies utilized a “binge-drinking” animal model, the Wang et al. (2017) paradigm was unique in that it incorporated chronic alcohol consumption via a diet containing 5% alcohol for 10 days. CBD (or vehicle) was administered by an i.p. injection (5 or 10mg/kg/day) throughout the alcohol exposure. On day 11, mice were gavaged with a single dose of alcohol or isocaloric dextrin-maltose. Yang et al (2014) utilized a more conventional approach, where mice were gavaged with alcohol (or vehicle) every 12 hours for 5 days and CBD (5mg/kg) or vehicle was injected intraperitoneally 30 minutes prior to alcohol administration.

In both studies, alcohol led to elevated liver enzymes (AST [Wang et al., 2017; Yang et al. 2014] and ALT [Wang et al., 2017]) and hepatic triglycerides (Wang et al., 2014; Yang et al., 2017), demonstrating liver injury. CBD treatment reversed these effects with liver injury appearing at a level similar to vehicle + vehicle treated mice (no alcohol exposure) and significantly less than alcohol + vehicle (no CBD exposure) treated mice. Staining of liver sections (H&E and oil red O) also revealed significant liver injury with alcohol exposure which was prevented in CBD treated mice (Wang et al., 2017; Yang et al., 2014).

Of particular interest, Wang et al (2017) evaluated CBD’s role in modulating genes involved in metabolism and liver steatosis, neutrophil accumulation, and liver inflammation. Alcohol enhanced expression of several genes involved in fatty acid biosynthesis and decreased those involved in fatty acid oxidation. Further significant hepatic neutrophil accumulation was noted with alcohol; however, CBD treatment markedly attenuated such effects. CBD suppressed the alcohol induced increases in mRNA expression of chemokines (macrophage inflammatory protein alpha-1 (MIP-2, chemokine ligand 2 (CXCL2), monocyte chemotactic protein (MCP-1)), cytokines (tumour necrosis factor alpha (TNF-α), interleukin-1beta (IL-1β) and adhesion molecules (E-selectin). These findings suggest the protective effects of CBD were at least partially a result of anti-inflammatory mechanisms (Wang et al., 2017).

Beyond inflammation, findings from both studies also supported antioxidant activity of CBD, with CBD inhibiting hepatic increase in reactive oxygen species induced by alcohol exposure. However, the proposed mechanisms of action differed. Yang et al. (2014) suggested that CBD’s effects may be mediated by activation of autophagy, inhibition of the JNK MAPK pathway (which is active with acute alcohol exposure), and direct inhibition of

oxidative stress. However, Wang et al. (2017) isolated granulocytes from human blood and noted that CBD, in a CB_2 receptor independent manner, was able to inhibit the rapid release of reactive oxygen species in human neutrophil cells exposed to alcohol. Furthermore, Wang et al. (2017) demonstrated that CBD's actions attenuated an inflammatory response involving E-selectin and neutrophil recruitment, and it was this anti-inflammatory effect that reduced oxidative stress.

Human Studies—No studies have examined the effect of CBD intake on alcohol-related hepatic activity in humans.

DISCUSSION

The purpose of the current systematic review was to consider the viability of CBD as a novel prospective pharmacotherapy for AUD or specific adverse alcohol-related medical consequences. Overall, the literature was limited to a small number of primarily preclinical studies, and there was an absence of studies in human clinical samples. Nonetheless, the results were consistently supportive of the potential therapeutic benefits of CBD for AUD, particularly in the areas of neurodegeneration, hepatotoxicity, cognition and risk of relapse. Arguably of greatest promise was consistent evidence that CBD is neuroprotective against alcohol-induced brain insults in preclinical models, specifically in the hippocampus and entorhinal cortex (Brenneman et al., 2018; Liput et al.,2013; Hamelink et al., 2005). The selective vulnerability of these two brain regions is notable given that it may lead to the significant behavioural sequelae which go on to impact daily functioning and cognitive ability (Hamelink et al., 2005). Aptly, this leads to the suggestion that neuroprotective compounds may prevent the cognitive deficits that contribute to relapse in some (Stevens et al., 2015).

Direct evidence regarding CBD's effect on cognition in the context of alcohol-related harms was specific to a favourable effect on impulsive behaviour in animal model of alcohol dependence (Gonzalez-Cuevas et al., 2018). This is a critical finding given that diminished impulse control is thought to play a significant role in the relapsing nature of AUD (Stevens et al., 2015) and this specific form of impulsivity (delay discounting) has been robustly associated with AUD and other forms of addictive behaviour (Amlung et al., 2017; MacKillop et al., 2011). Furthermore, precipitous delay discounting has been found to predict formal addiction treatment outcome (e.g., MacKillop & Kahler, 2009; Sheffer et al., 2012) and natural resolution of alcohol problems (Tucker et al., 2002; 2008).

More generally, the literature examining relapse-like behaviours highlighted the potential benefit of CBD in this domain, particularly in animals that underwent a dependence induction protocol (Gonzalez-Cuevas et al., 2018; Viudez-Martinez et al., 2018a, 2018b). Although the mechanism by which CBD elicits these effects is unclear, CBD prevented reinstatement of alcohol seeking in contexts that trigger relapse while also limiting risk factors associated with relapse (i.e. high anxiety and low impulse control). These findings suggest that CBD may attenuate cue-elicited craving or stress-elicited craving in humans, although that is clearly a hypothesis to be tested. Another preclinical study illustrated that combined CBD and naltrexone was more effective at reducing alcohol consumption than

CBD or naltrexone alone (Viudez-Martinez et al., 2018b). They illustrated downregulated gene expression in brain regions responsible for reward and habit formation, relevant to AUD, suggesting a shared putative mechanism of action as demonstrated by the additive effect on treatment outcome (Viudez-Martinez et al., 2018a).

Finally, two small preclinical studies suggest that CBD may have therapeutic potential in alcohol-induced steatohepatitis (Wang et al., 2017; Yang et al, 2014). There was clear consensus among findings from both studies, revealing that markers of liver damage consequent to binge-drinking are prevented by CBD (Wang et al., 2017; Yang et al, 2014). This is promising with the suggestion that perhaps CBD treatment may slow the development of more complicated and severe hepatic problems consequent to alcohol overuse.

The prior findings were restricted to preclinical models, and the only studies identified that utilized human participants used healthy volunteers, not clinical samples. This work revealed that CBD does not alter the acute cognitive effects of alcohol (Belgrave et al., 1979; Bird et al., 1980; Consroe et al., 1975), which does not directly speak to CBD as a treatment for AUD given the single-dose non-therapeutic nature of the studies. On the other hand, these findings provide oblique insights into drug interactions if AUD patients drink while taking CBD, suggesting a relatively tolerable side effect profile of CBD. Ultimately, translational studies in humans exploring these candidate mechanisms identified by the existing preclinical literature are critical to evaluate the potential of CBD as an AUD pharmacotherapy.

The potential therapeutic benefit of CBD can be further derived from the substantial evidence supporting its use in seizure disorders. While the relevance of this indication may seem obscure, other anticonvulsants, specifically topiramate, have shown substantial promise in AUD (Johnson et al., 2003; 2007). In addition to seizure prevention during alcohol withdrawal, topiramate has a large effect on abstinence (g=0.468) and heavy drinking (g=0.406) in AUD as demonstrated by meta-analytic evidence (Blodgett et al., 2014). Moreover, a recent meta-analysis suggested that topiramate was superior to nalmefene, baclofen, naltrexone and acamprosate on alcohol consumption outcomes (Palpacuer et al., 2018). Despite the moderate effect size of topiramate therapy in AUD, side effects (i.e. cognitive impairment, paresthesia, taste abnormalities) reduce topiramates tolerability clinically. This has led to evaluations of other anticonvulsants in AUD. For instance, zonisamide, another anticonvulsant that shares structural features with topiramate, has revealed promising preclinical (Knapp et al., 2007; Sarid-Segal et al., 2009), open-label (Knapp et al., 2010; Rubio et al., 2010) and randomized controlled trial evidence (Arias et al., 2010). However, cognitive impairment of zonisamide may be comparable to topiramate, excluding mental slowing which is only increased in topiramate (Knapp et al., 2015). Levetiracetam is another anticonvulsant that has been examined in AUD. Although it produces fewer adverse effect on cognition (Gomer et al., 2007), research on its efficacy in AUD is not consistent (Fertig et al., 2012; Richter et al., 2012; Sarid-Segal et al., 2008). Other anticonvulsants that have shown promise in AUD include divalproex (Brady et al., 2002) and gabapentin (Leung et al., 2015).

Taken together, the literature signals that CBD may be efficacious in the context of alcohol-related harms by way of its neuroprotective, anti-relapse, and anticonvulsant mechanisms. Despite these potential therapeutic effects, this review highlights the need for further translational studies given that the current literature is limited to a small number of preclinical studies using animal models of AUD phenotypes. It has been previously suggested that CBD may influence specific phases of addiction for different substances of abuse (Prud'homme et al., 2014). Considering the AUD literature, there is merit to exploring CBD's effects on relapse (Gonzalez-Cuevas et al., 2018; Viudez-Martinez et al., 2018a; 2018b). Moreover, it may prove particularly beneficial in the early stages of treatment given its neuroprotective ability in hippocampal and entorhinal cortical cells (Brenneman et al., 2018; Hamelink et al., 2005; Liput et al., 2013), potential benefit to cognitive function (Gonzalez-Cuevas et al., 2018) and prevention of alcohol-related liver problems (Yang et al., 2014; Wang et al., 2017). Although the animal studies included in this review used robust paradigms for investigating alcohol-related harms, the promise of this literature is from a purely preclinical standpoint. In order to appropriately appraise the utility of a pharmacotherapy, human laboratory and clinical studies (and integrated bench-to-bedside studies) in humans are imperative. More specifically, there is a need for studies that evaluate whether these mechanisms identified in preclinical work will translate to clinical populations. Figure 2 concisely articulates the candidate mechanisms by which CBD may be useful in the treatment of AUD that warrant direct empirical investigation. If positive short-term effects of CBD are present in one or more of these domains, there would be a strong basis for randomized controlled trials in individuals with AUD. However, rather than prioritizing one specific mechanism or phase of treatment, the existing literature suggests investigations that broadly screen the effects in these domains are warranted.

Dosing and route of administration present some of the primary challenges in designing clinical trials to evaluate the therapeutic benefit of CBD. For instance, a majority of the animal studies reviewed above administered CBD transdermally or by injection. This may be relevant as the bioavailability of oral CBD in humans is relatively low, approximately 6% (Agurell et al., 1981). However, recent trials of CBD in the form of Epidiolex© (an oral solution) to treat pediatric seizure disorders may inform dosing and route of administration. These studies revealed that 14 weeks of 10 mg/kg/day or 20 mg/kg/day of Epidiolex© was efficacious in reducing seizure frequency (Devinsky et al, 2017; 2018a; Theile et al., 2018). As a recently approved indication, the FDA recommends a titration schedule involving a starting dose of 5mg/kg/d (administered as doses of 2.5 mg/kg b.i.d); and after one week the dosage may be increased to 10mg/kg/d (5mg/kg b.i.d). In those tolerating this dose but requiring further seizure reduction, a maximum recommended maintenance dose of 10mg/kg b.i.d is recommended (20mg/kg/d)(FDA, 2018). When considering a target dose for AUD, 10 mg/kg/d may be more appropriate for a number of reasons. First, only one of the Epidiolex© seizure trials examined efficacy of both 10mg/kg/d and 20 mg/kg/d and the higher dose provided limited additional benefit in reducing seizure severity (median reduction −42% vs. −37%) (Devinsky et al., 2018a), although these groups were not compared statistically. Moreover, while CBD presents a good safety profile (Bergamaschi et al., 2011), the FDA has recommended a dose adjustment in those with hepatic impairment based on transaminase elevations observed in patients receiving 20mg/kg/d (FDA, 2018).

Liver damage is commonly seen in AUD patients (Leggio & Lee, 2017), and the FDA recommends a maximum dosage of 10mg/kg/d for patients with moderate hepatic impairment making this an appropriate target for AUD. Interestingly, the studies on hepatotoxicity as discussed in the current review revealed that CBD was able to prevent development of signs of liver pathology noted with excessive alcohol exposure (Wang et al., 2017; Yang et al., 2014) and safety data from Devinsky et al (2018b) also revealed that patients with elevated transaminase levels received concomitant valproate. An alternative candidate route of administration is inhalation of combusted or vaporized plant material of high CBD composition. However, none of the studies identified in this review used inhalation as a route of administration; all used oral administration, which was tolerated well by participants. Furthermore, variation in topography (e.g., number of puffs, puff duration, inhalation volume and duration) has the potential to create substantial differences in dosing and heterogeneity of effects. Collectively, oral route of administration appears to be most appropriate at this stage.

In addition to the parameters outlined above, the literature discussed in this review identifies target outcomes that would be of interest, including the effects of CBD on alcohol consumption, liver pathology, and cognition. First, measuring abstinence or change in heavy drinking could be quantified by self-report (e.g., timeline followback interview) and could be complemented with more objective biomarkers of alcohol consumption or heavy drinking (e.g., ethyl glucuronide or carbohydrate-deficient transferrin) (Jastrzebska et al., 2016). While serum liver enzymes have low specificity for detecting alcohol use, they would be reliable markers of liver damage. Studies on hepatotoxicity revealed that CBD treatment prevented increases in ALT and AST that were noted in response to heavy alcohol consumption in animals (Wang yet al., 2017; Yang et al., 2014). As such, measuring baseline to endpoint change in these liver enzymes would not only describe the effects of CBD on liver function in AUD patients, but also provide safety data regarding the hepatic impairment noted in Epidiolex© trials. Finally, given the neuroprotective effects of CBD on the hippocampus and entorhinal cortex (Brenneman et al., 2018; Hamelink et al., 2005; Liput et al., 2013), and benefits in impulsive choice (Gonzalez-Cuevas et al., 2018) general changes in neurocognitive function throughout treatment would be of interest.

In sum, this systematic review suggests that CBD may be a credible therapeutic for a wide variety of alcohol-related harms based on the preclinical literature. Several candidate mechanisms by which CBD may produce therapeutic effects in AUD were identified, providing clear avenues for future research. Fundamentally, empirical studies are needed to determine whether these effects translate into favorable outcomes in human preclinical and clinical models and, ultimately, to inform the appropriateness of CBD as a potential pharmacotherapy for AUD.

Acknowledgments

This work was supported by the Michael G. DeGroote Centre for Medicinal Cannabis Research, the Peter Boris Chair in Addictions Research, and NIH grants AA025849 and AA025911. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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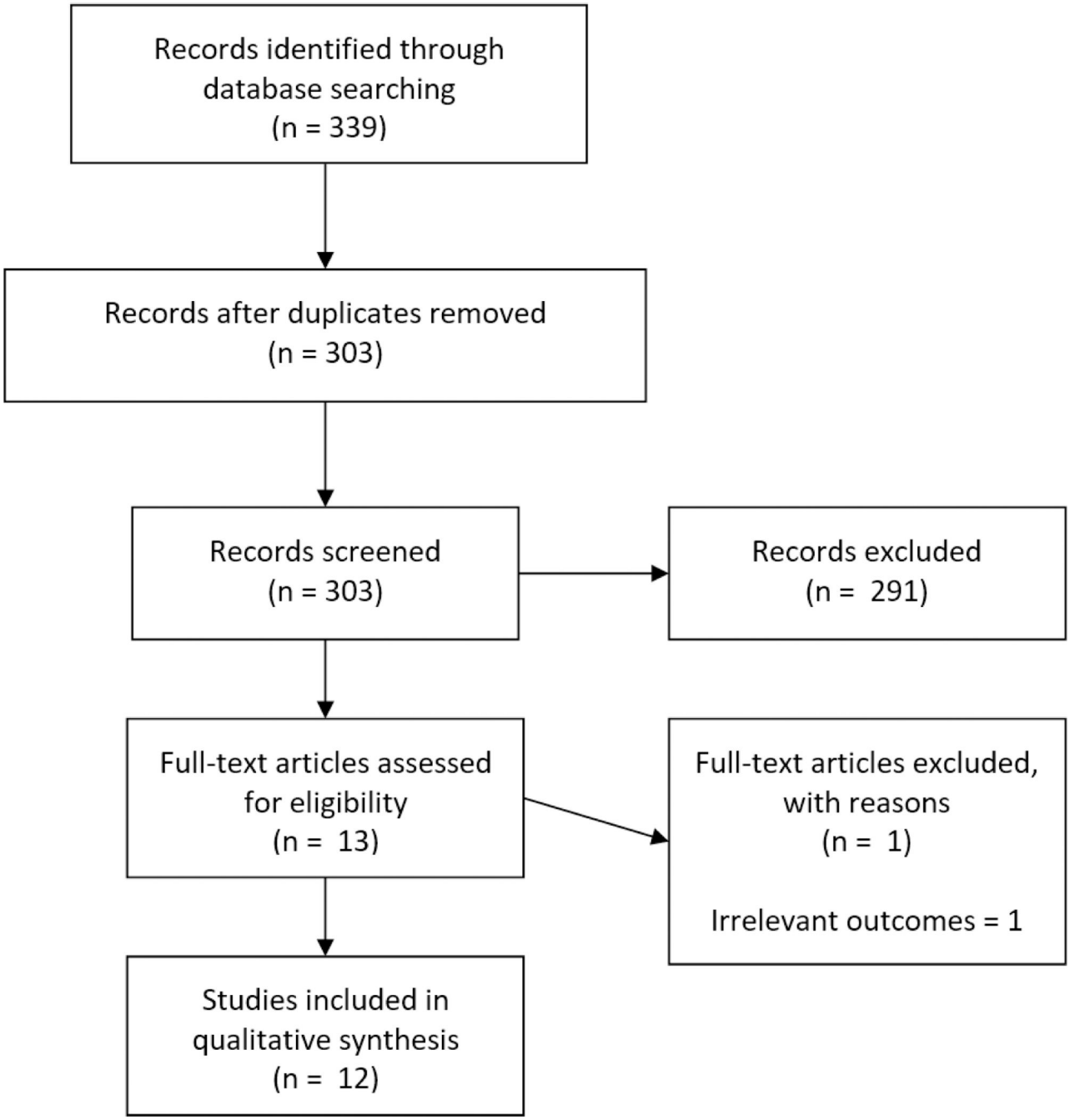

Figure 1.
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram.

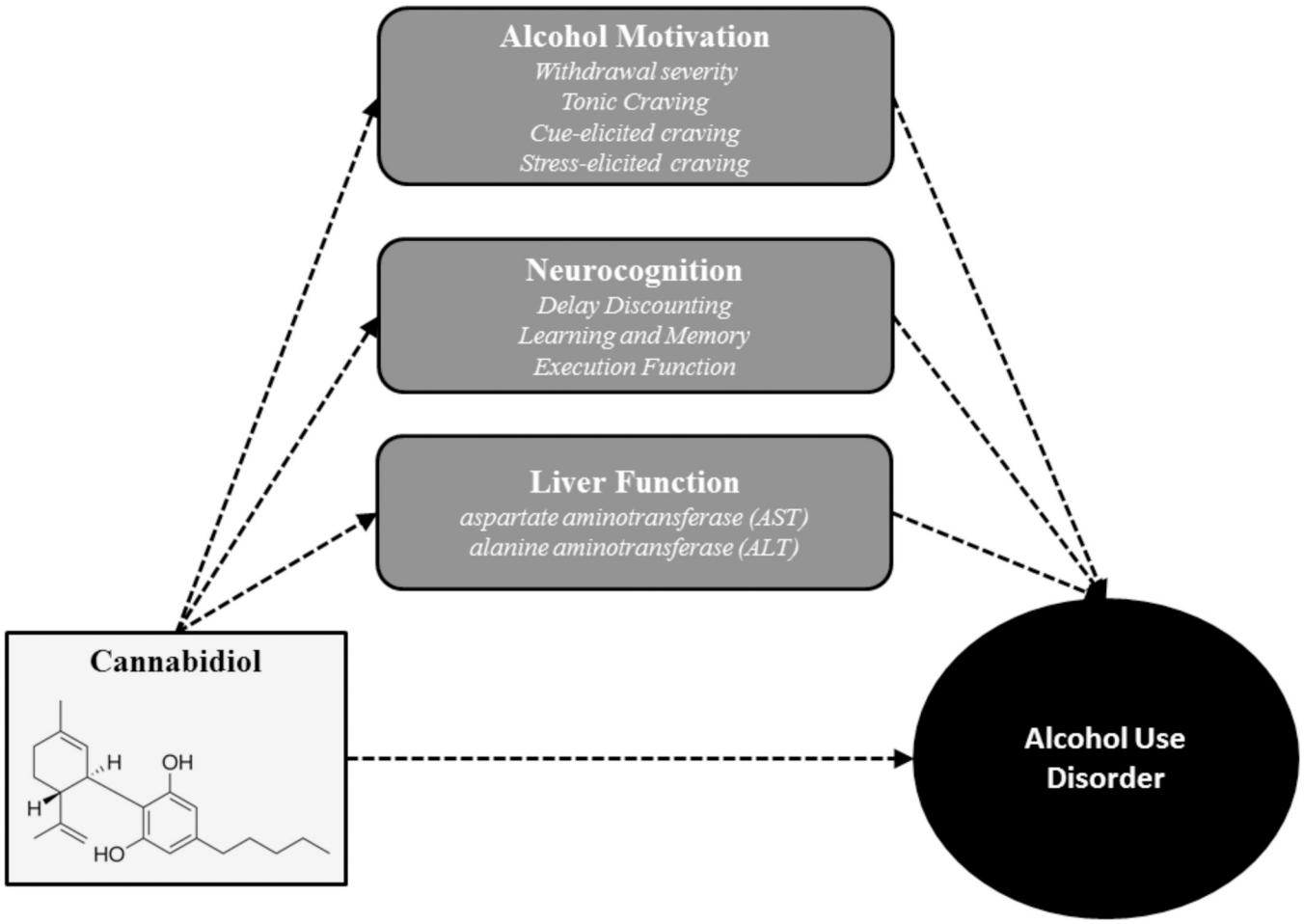

Figure 2.

Candidate mechanisms by which cannabidiol may be an efficacious pharmacotherapy for alcohol use disorder. Mechanisms are denoted by rounded rectangles, with titles indicating domains and italics indicating specific processes or measures.

Table 1.

Summary of outcomes associated with alcohol-related harms of all studies included in the review

Study	Group (n)	Model/Paradigm	Assessed outcomes
		HUMAN STUDIES	
Consroe et al. (1979)	Total n = 10 PBO; CBD; EtOH; CBD+EtOH	Healthy human (post-graduate volunteers) Within-subject design, double-blind, 1 week between sessions	- Cancellation Test: measure psychomotor processes of attention and concentration. - Differential Aptitude Test: Visual-motor test measuring attention and concentration - Time Production Task: Internal perceptual function - Finger Tap Test: Undirected motor speed - Subjective Drug Reaction scale (DRS) - BAC
Belgrave et al. (1979)	Total n = 15 CBD+EtOH; PBO+EtOH; CBD+PBO; PBO +PBO	Healthy humans (primarily undergraduates) Within-subjects design, double-blind, 1 week between sessions.	- Standing steadiness (eye open and closed) - Visual, auditory, and complex reaction time - Vienna Determination Apparatus: to measure coordination - The pursuit rotor - Arithmetic concentration and attention task - “Boggles” word construction task - BAC
Bird et al. (1980)	Total n = 161 CBD, cannabinol, THC and EtOH administered in 16 combinations	Healthy humans Double-blind	- As described in Belgrave et al., 1979
		CELL CULTURE	
Brenneman et al. (2018)	CBD KLS-13019	Dissociated hippocampal cell cultures Oxidative stress-related toxicity in hepatic encephalopathy	- Fluorescent dye-based assays: Propidium iodide (cell death) and CFDA (neuronal viability)
		ANIMAL STUDIES	
Hamelink et al., (2005)	N=6/group CBD, antioxidants (α-tocopherol, butylated hydroxytoluene), NMDAR antagonists (dizocilpine, memantine), diuretics (furosemide, bumetanide, L-644,711)	Rats (Male Sprague Dawley) 4-day binge drinking	- Quantification of hippocampal (ventral) and right/left entorhinal cortex neurodegeneration - BAC
Liput et al., 2013	Expt 1: EtOH+VEH; EtOH+ CBD (either 1%, 2.5% or 5%) Expt 2: EtOH; VEH IP; CBD IP; VEH gel; CBD gel; Total n=148	Rats (Male Sprague Dawley) Binge-drinking model	- Expt 1: Determine optimal CBD dose for neuroprotective effects (intoxication behaviour, quantification of entorhinal cortex neurodegeneration) - Expt 2: Quantification of entorhinal cortex neurodegeneration
Yang et al., 2014	n=4–6/group VEH+VEH; EtOH+VEH; VEH+CBD; EtOH+CBD	Mice (C57BL/6) Alcohol-induced liver steatosis model (gavaged with EtOH for 5 days) – 30%EtOH	- EtOH-induced hepatotoxicity (ATP levels, AST, triglycerides) - Oxidative stress in liver - JNK activation
Wang et al., 2017	n=4–7/group Pair-fed; Pair-fed+CBD; EtOH; EtOH+CBD	Mice (C57BL/6) Hepatic failure-induced model of hepatic encephalopathy (Lieber-DeCarli diet – 5% EtOH for 10 days)	- Liver triglycerides, ALT an AST levels - Hepatic nitrotyrosine and hydroxynonenal content - Liver histology and immunochemistry - Hepatic leukocytes and flow cytometry analysis

Study	Group (n)	Model/Paradigm	Assessed outcomes
Filev et al., 2017	Total n=84 Saline or EtOH plus, CBD, THC or THC +CBD	Male adult mice (DBA/2) Model of locomotor sensitization Daily intraperitoneal EtOH injections (2.5g/kg, 12 days)	- Effect on EtOH induced locomotor sensitization
Viudez-Martinez et al. (2018)	N= 10/group CBD+EtOH; VEH+EtOH	Male (C57BL/6) mice EtOH-induced relapse and acute EtOH administration Oral EtOH self-administration paradigm	- BAC - Hypothermia - Handling-induced convulsions with acute EtOH administration - Two-bottle choice paradigm - Oral EtOH self-administration (3 dosages of CBD): Experiment 1: Reinforcement and motivation for EtOH; Experiment 2: Reinforcement and motivation for water; Experiment 3: EtOH-induced relapse - Gene expression: tyrosine hydroxylase in VTA and μ-opioid receptor, CB1 and CB2 receptors and GPR55 in NAcc
Viudez-Martinez et al. (2018)	Total n=140 Expt 1: VEH+VEH; VEH+NTX; CBD+VEH; CBD+NTX) Expt2: VEH+VEH; WAY+VEH; WAY+CBD; WAY+CBD+NTX	Male (C57BL/6) mice Oral EtOH self-administration paradigm	- Experiment 1: EtOH consumption and motivation to drink (oral EtOH self-administration) - Gene expression - Experiment 2: Role of 5-HT1A receptors
Gonzalez-Cuevas et al. (2018)	n=9–12/group CBD or VEH	Rats (Male Wistar) Model of drug seeking and relapse	- Drug self-administration and reinstatement (context and stress related) - Delay discounting - Locomotor activity - Elevated plus maze - Plasma/brain CBD levels

Notes: PBO: placebo; CBD: cannabidiol; EtOH: alcohol; BAC: blood alcohol concentration; VEH: vehicle; CFDA: 6-carboxyfluoresceine diacetate; ATP: adenosine triphosphate; AST: aspartate aminotransferase; ALT: alanine transferase; THC: tetrahydrocannabinol; WAY: WAY 100635 (a piperazine drug); NTX: naltrexone; NAcc: nucleus accumbens VTA: central tegmental area CB: cannabinoid