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REVIEW

Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ^9-Tetrahydrocannabinol

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The plant *Cannabis sativa*, commonly called cannabis or marijuana, has been used for its psychotropic and mind-altering side effects for millennia. There has been growing attention in recent years on its potential therapeutic efficacy as municipalities and legislative bodies in the United States, Canada, and other countries grapple with enacting policy to facilitate the use of cannabis or its constituents for medical purposes. There are >550 chemical compounds and >100 phytocannabinoids isolated from cannabis, including Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is thought to produce the main psychoactive effects of cannabis, while CBD does not appear to have similar effects. Studies conflict as to whether CBD attenuates or exacerbates the behavioral and cognitive effects of THC. This includes effects of CBD on THC-induced anxiety, psychosis, and cognitive deficits. In this article, we review the available evidence on the pharmacology and behavioral interactions of THC and CBD from preclinical and human studies, particularly with reference to anxiety and psychosis-like symptoms. Both THC and CBD, as well as other cannabinoid molecules, are currently being evaluated for medicinal purposes, separately and in combination. Future cannabis-related policy decisions should include consideration of scientific findings, including the individual and interactive effects of CBD and THC.

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INTRODUCTION

The plant *Cannabis sativa*, or cannabis, has been used for millennia for its medicinal, psychotropic, and mind-altering effects (Callaway, 2004). Clinical and preclinical research efforts over the past decades have defined many effects of cannabis on physiology and behavior and more recent research has focused its efficacy for various medicinal purposes (Izzo *et al*, 2009; Pertwee, 2008). There are >550 chemical compounds and >100 plant cannabinoids or phytocannabinoids isolated from *Cannabis sativa*, including Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (ElSohly *et al*, 2017). THC is the most studied of these phytocannabinoids and likely the most psychoactive. Research from the 1960s and 1970s identified THC as the main cause of the psychoactive effects of cannabis (Grunfeld and Edery, 1969; Mechoulam *et al*, 1970), and further research led to the introduction of synthetic THC for medicinal use (Pertwee, 2008). Unlike THC, CBD does not appear to have psychotomimetic effects but it may interact with some of the effects of THC when co-administered (Morgan and Curran, 2008; Morgan *et al*, 2010a; Morgan *et al*, 2011; Morgan *et al*, 2010b). CBD is also currently being researched for medicinal purposes (Izzo *et al*, 2009; Pertwee, 2008). This article aims to review the interactive effects of CBD and THC on several domains from preclinical, human field/epidemiological and human laboratory studies. Further, there is a paucity of research on the interactive effects of THC and CBD, and several studies compare the effects of THC and CBD rather than their interactive effects. Nevertheless, a consideration of what is known about THC/CBD interactions will help to better understand gaps in knowledge and frame directions for future research.

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ENDOCANNABINOID SYSTEM

Cannabis and its component cannabinoids exert their effects primarily via the endogenous cannabinoid system. The two primary receptors of the endogenous cannabinoid system are cannabinoid 1 receptors (CB_1Rs) and cannabinoid 2

receptors (CB_2Rs)(Cabral *et al*, 2008; Devane *et al*, 1988). Both CB_1Rs and CB_2Rs are G-protein coupled receptors with CB_1Rs predominantly located on neurons in the central and peripheral nervous systems and CB_2Rs primarily located in immune cells, although also found in some neurons (Onaivi *et al*, 2006). CB_1Rs are located in several areas of the brain, including the basal ganglia, frontal cortex, hippocampus, and cerebellum, on GABAergic and glutamatergic terminals and cannabinoids produce their psychotomimetic effects primarily via activation of CB_1Rs (Huestis *et al*, 2007). The primary endogenous cannabinoid ligands (endocannabinoids) identified thus far are anandamide (AEA) (Devane *et al*, 1992) and 2-arachidonoyl-glycerol (2-AG) (Mechoulam *et al*, 1995; Sugiura *et al*, 1995), both of which act as retrograde messengers at synapses in the central nervous system. They are produced on demand based on neuronal activity, released from postsynaptic neurons, and diffuse backward across the synapse to presynaptic neurons where they bind and activate CB_1Rs (Hashimotodani *et al*, 2007). Binding and activation of CB_1Rs cause inhibition of voltage-sensitive N-type and P/Q-type calcium channels, which inhibits further release of neurotransmitters, including GABA, glutamate, and acetylcholine (Parsons and Hurd, 2015). The primary source of catabolism of AEA and 2-AG are the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (Justinova *et al*, 2015). FAAH is found in the dendrites and somas of neurons and MAGL is found in presynaptic neurons (Hashimotodani *et al*, 2007). Both FAAH and MAGL have become potential targets for new medications aimed at enhancing levels of endocannabinoids as treatment of pain and depression (Justinova *et al*, 2015).

EXOGENOUS CANNABINOIDS

Exogenous cannabinoids include compounds extracted from herbal cannabis (phytocannabinoids), such as THC and CBD as well as synthetic cannabinoids (compounds included in spice/K2) that are increasing in popularity recreationally particularly among youth (Spaderna *et al*, 2013).

Δ^9-Tetrahydrocannabinol

THC's structure and stereochemistry were determined in the 1960s. (Gaoni and Mechoulam, 1964). THC is a partial agonist at both CB_1R and CB_2R. THC's psychoactive effects are principally mediated by agonist effects at CB_1R and its potential immunological or anti-inflammatory effects are likely mediated via CB_2Rs (Pertwee, 2008). Intravenous (i.v.) THC administration produces a wide range of psychoactive effects, including feeling 'high', anxiety, paranoia, perceptual alterations, and cognitive deficits, particularly deficits in verbal recall (D'Souza *et al*, 2004) in healthy individuals and exacerbates psychotic symptoms in patients with schizophrenia (D'Souza *et al*, 2005). Cannabis users, however, often report stress as a primary factor for chronic use (Hyman and Sinha, 2009). Activation of CB_1R by THC results in perturbation of GABA/glutamatergic neurotransmission as well as dopamine release; although the magnitude of THC-induced dopamine release is small compared with drugs such as amphetamine and cocaine, which produce larger striatal dopamine release (Bossong *et al*, 2015). The disruption of inhibitory/excitatory balances could contribute to THC's psychotomimetic effects (Farkas *et al*, 2010; Hampson *et al*, 2011; Li *et al*, 2010). Cognitive deficits seen with acute exposure to THC are generally acute, transient, and self-limited. However, chronic use of cannabis, especially in adolescents, is associated with more chronic deficits in memory (Meier *et al*, 2012; Ranganathan and D'Souza, 2006), though other studies have not replicated this finding (Jackson *et al*, 2016; Mokrysz *et al*, 2016).

Synthetic THC formulations. Currently, two synthetic pharmaceutical forms of cannabinoids are approved for administration in the United States, nabilone (a synthetic derivative of THC) (Ward and Holmes, 1985) and dronabinol (synthetic THC). Clinically, the effects of both are similar to oral administration of cannabis (Badowski, 2017). Both synthetic forms of THC are approved for the treatment of chemotherapy-induced nausea and vomiting in patients who failed to respond to conventional antiemetic medications (Marinol (package insert), 2017,Cesamet (package insert), 2013). Additionally, dronabinol is approved to treat anorexia associated with weight loss in people with AIDS.

Cannabidiol

CBD was originally isolated in 1940 and its structure and stereochemistry were determined in the 1960s (Adams *et al*, 1940; Mechoulam *et al*, 2002). It was originally proposed that CBD functions as an allosteric negative modulator (antagonist) at CB_1R and CB_2R (Laprairie *et al*, 2015; Mechoulam *et al*, 2007; Petitet *et al*, 1998; Thomas *et al*, 2007; Turkanis and Karler, 1986). Further studies have identified pharmacological promiscuity of CBD (Campos *et al*, 2012; De Petrocellis and Di Marzo, 2010; Pertwee, 2009), therefore it is probably premature to draw firm conclusions about all of the compound's mechanisms of action. There is mounting evidence that CBD produces many of its effects *in vivo* via facilitatory interactions with serotonin 1A ($5\text{-}HT_{1A}$) receptors (Gomes *et al*, 2012; Magen *et al*, 2010; Resstel *et al*, 2009; Stern *et al*, 2012) in rodents. CBD reduces immobility in a forced swim in a manner that depends on $5\text{-}HT_{1A}$ activity in male rats (Sartim *et al*, 2016). The anxiolytic effects of intralimbic administration of CBD are blocked by an $5\text{-}HT_{1A}$ antagonist in male rats (Fogaca *et al*, 2014) as are the anxiolytic effects of intraperiaqueductal gray CBD on elevated plus maze in male rats (Campos and Guimaraes, 2008); these latter are unaffected by the CB_1R antagonist AM251. The evidence also extends to nonhuman primate models as the subjective effects of CBD in male rhesus monkeys are overlapping with those observed for a $5\text{-}HT_{1A}$ agonist 8-hydroxy-2-dipropylaminotetralin and do not exhibit significant CB_1R agonist or antagonist-like activity (McMahon, 2016). There is also evidence for activity of CBD

at the μ and δ opioid receptors and transient receptor potential vanilloid type-1 (TRPV1) cation channels (Pertwee, 2008). CBD also increases levels of AEA due to AEA reuptake inhibition and FAAH inhibition (Bisogno *et al*, 2001; Ligresti *et al*, 2006). Unlike THC, CBD has no psychotomimetic effects and, instead, may have antipsychotic effects. CBD may also have potential clinical effects on anxiety disorders, movement disorders, neuropathic pain, epilepsy, and cancers as well as anti-inflammatory effects (Izzo *et al*, 2009).

Δ^9-Tetrahydrocannabinol/cannabidiol. Combinations of THC/CBD available for clinical use or nabiximols (Sativex) are prescription botanical drug substances developed from a 1 : 1 combination of two selected cannabis strains. One strain (Tetranabinex) yields a high THC content and the other (Nabidiolex) yields a high CBD content. The flowers are dried, extracted, and utilized to formulate nabiximols. Nabiximols is comprised mainly of THC and CBD (70% w/w) but also contains other phytocannabinoids derived from the plant material (Russo and Guy, 2006). The 1 : 1 combination of THC:CBD appears to allow for higher doses of THC without increasing the risk of adverse side effects, as CBD acts to antagonize some of the psychoactive and sedative effects of THC without interfering with intended THC effects, such as muscle relaxation and reduction of spasticity.

MECHANISMS OF POTENTIAL CBD/THC INTERACTIONS

Pharmacodynamic Effects

In contrast with THC, which acts primarily as a CB_1R receptor partial agonist, the pharmacological mechanism of action of CBD is less well understood (see above). The diametrically opposing actions of CBD on CB_1Rs provides a potential pharmacological mechanism for any *in vivo* effects that appear to oppose those of THC. As one review argues, however, CBD influence on THC-related effects may also be mediated through non-CB_1R mechanisms (McPartland *et al*, 2014), consistent with evidence that human cognitive effects of CBD may not depend solely on CB_1R activity (Stadelmann *et al*, 2011). Thus, given its wide pharmacological targets, the precise mechanism underlying CBD and THC interactions need further work to be fully understood.

Pharmacokinetic Effects

Consideration of the pharmacokinetic distribution and metabolism of THC in the presence and absence of CBD should be included in any interpretation of the interactive effects. As briefly reviewed (Zuardi *et al*, 2012), the direction of CBD/THC interactions in preclinical models, particularly rodents, may depend on the pretreatment offset. In some cases, when CBD is administered 30 min (or up to 24 h) prior to THC in rats or mice a potentiation can be observed, whereas co-administration results in blockade or amelioration of THC effects. In contrast, the beneficial effects of CBD in a monkey model of THC-induced behavioral impairment were present when CBD was either administered simultaneously with or 30 min prior to the THC (Wright *et al*, 2013). The fact that significant pretreatment intervals for CBD in rodent models potentiate the effects of THC may be related to an increase in the effective brain exposure to THC via alterations in pharmacokinetic distribution and metabolism. Co-administration of an equal CBD dose roughly doubled brain THC levels 30 min after i.p. injection in male adolescent rats (Klein *et al*, 2011). CBD pretreatment also increased plasma THC levels and the distribution of THC to the brain of mice (and vice versa), likely because CBD inhibits the hepatic metabolism of THC (Bornheim *et al*, 1995; Reid and Bornheim, 2001). Prolongation of THC-appropriate responding by CBD in one rat study (Hiltunen and Jarbe, 1986) may be a consequence of this pharmacokinetic effect. The picture is complicated even further by a suggestion that CBD/THC ratios on the order of 8 may be necessary for antagonistic properties and only 1.8 for potentiation of THC-related effects in rodents (Zuardi *et al*, 1984). In contrast, CBD administered in 1 : 1–3 : 1 ratios relative to THC are effective in attenuating cognitive effects of THC in monkeys (Jacobs *et al*, 2016; Wright *et al*, 2013).

Although overwhelming evidence on pharmacokinetic interactions of CBD and THC in humans are not available, one study reported that oral co-administration of 5.4 mg CBD with 10 mg THC in humans did not alter the pharmacokinetic distribution of THC in plasma (Nadulski *et al*, 2005). Oral administration of 1500 mg CBD likewise did not alter the pharmacokinetics of i.v. THC (Hunt *et al*, 1981). Furthermore, Karschner *et al* (2011a) found that maximum plasma levels of THC after oral administration (5, 15 mg, p.o.) were similar to levels obtained after oromucosal administration of 5.4 and 16.2 mg THC combined with 5.0 and 15.0 mg of CBD, respectively.

PRECLINICAL STUDIES OF CBD AND THC INTERACTIONS

Cannabis and THC induce a 'tetrad' of behavioral effects characterized by hypolocomotion, hypothermia, catalepsy, and analgesia reliably in rodents (Metna-Laurent *et al*, 2017). This preclinical model is often used to examine the effects of cannabinoid agonists (such as THC) and drugs that may interact with it. Below, we first briefly review the effects of CBD on some of the THC-induced tetrad of effects followed by effects on anxiety and cognition.

EFFECTS OF CBD ON THC-INDUCED HYPOTHERMIA AND HYPOLOCOMOTION

A profound and lasting reduction in body temperature is a consistent effect of THC in laboratory monkeys (Matsuzaki

et al, 1987; McMahon *et al*, 2005; Taffe, 2012) and rodents (Tulunay *et al*, 1981; Vann *et al*, 2008). THC also reduces the spontaneous activity of rats (Smirnov and Kiyatkin, 2008; Taffe *et al*, 2015; Whitlow *et al*, 2002). These measures are two of the canonical tetrad of signs of cannabinoid activity in rodent models and thus useful to examine potential interactive effects of CBD with THC, even though there are no established, direct parallels of these preclinical models with the effects of THC on human thermoregulation or spontaneous activity thus far.

The effects of CBD on the locomotor and thermoregulatory effects of THC in rodents may vary depending on species, dose ratios, and the experimental measure. For example, CBD both potentiated locomotor suppression and attenuated hypothermia caused by THC when administered in 1 : 1 CBD:THC ratio in mice (Todd and Arnold, 2016) but potentiated locomotor suppression and hypothermia caused by THC when administered in 10 : 1 or 50 : 1 ratio (Hayakawa *et al*, 2008). CBD appears to slightly potentiate the locomotor-suppressive and hypothermic effects of a threshold dose of THC (0.3 mg/kg, i.v.; 10–100 : 1 CBD:THC ratio) in mice but had no influence on the effects of a 10-fold higher dose of THC (Varvel *et al*, 2006). CBD increased the hypothermia and locomotor suppression caused by THC in rats when equal doses (20 mg/kg, i.p.) were administered simultaneously (Fernandes *et al*, 1974). In that study, CBD acted mostly to prolong the duration of hypothermia and hypolocomotion, whereas in our recent study (Taffe *et al*, 2015) CBD also increased the magnitude of temperature reduction in rats when administered at a 1 : 1 dose ratio either simultaneously or at a 15 min CBD:THC offset. CBD had negligible effects by itself on locomotor activity and body temperature in mice and rats (Fernandes *et al*, 1974; Taffe *et al*, 2015; Todd and Arnold, 2016; Wiley *et al*, 2005) and did not interact with the hypothermic or hypolocomotor effects of another cannabinoid, cannabinol, in male rats (Hiltunen *et al*, 1988).

EFFECTS OF CBD ON THC-INDUCED ANTINOCICEPTION

A decrease in the sensitivity to a noxious stimulus (such as immersion of the tail in a ~50 °C warm water bath or intraplantar injection of formalin) is another consistent effect of THC in rodents (Martin *et al*, 1998; Reche *et al*, 1996). Similar antinociceptive effects of THC or cannabis are also reported in humans (Cooper and Haney, 2016) and nonhuman (Vivian *et al*, 1998) primates. This item from the tetrad of cannabinoid activity in rodents may therefore offer enhanced translational and interpretive relevance. It has been shown that CBD potentiated the antinociceptive effects of a threshold dose of THC (0.3 mg/kg, i.v.) when administered in a 10–100 : 1 CBD:THC ratio in mice but had no influence on the effect of a 10-fold higher dose of THC (Varvel *et al*, 2006). Finn *et al* (2004) reported no effect of CBD on THC-induced antinociception in rats when administered in 2.5–5.0 : 1 CBD:THC ratios. There is also some evidence that CBD can act via CB_1, serotonin 1A, adenosine, and TRPV1 receptors to decrease nociception (Maione *et al*, 2011) in anesthetized rats, but these may not synergize with the effects of THC in the awake animal. At present, the available preclinical evidence does not support a general conclusion that CBD consistently alters the antinociceptive effects of THC. Nevertheless, these data are from rodent models. As no similar evidence is available in human or nonhuman primates at present, it would be premature to overgeneralize the potential for CBD to alter the antinociceptive effects of THC.

EFFECTS OF CBD ON THC-INDUCED ANXIETY- AND DEPRESSION-LIKE BEHAVIOR

Evidence for the effects of CBD on THC-induced anxiety- and depression-like behavior in animal models is limited. CBD potentiated the anxiogenic effects of THC in rats treated chronically in a 1 : 1 CBD:THC ratio assessed on both an open field test and an elevated plus maze (Klein *et al*, 2011). In a separate study, intralimbic administration of CBD was either anxiogenic or anxiolytic in rats depending on the behavioral assay (Fogaca *et al*, 2014); this could be related to the specific brain site of CBD action (Campos and Guimaraes, 2008). Further, acute administration of CBD attenuated the THC-induced reduction in social interaction, another putative anxiety-like behavior (Malone *et al*, 2009). Together, these results suggest that CBD may have mixed effects on THC-induced affective-like behaviors in rodent models, in some cases by attenuating the effect of THC. Interpretation is complicated, however, by the fact that CBD may have effects on these measures by itself. For instance, CBD administered alone reduced marble-burying behavior in mice (Nardo *et al*, 2014), a putative anticompulsive effect. Given a substantial interest in the therapeutic use of CBD and cannabis for anxiety symptoms and disorders, this may be an area of pressing interest for additional preclinical investigation.

EFFECTS OF CBD ON THC-INDUCED COGNITIVE DEFICITS

Animal models are useful in probing the putative protective effect of CBD on THC-induced effects, particularly given the inherent limitations of human studies. These limitations include being unable to control for environmental and preexisting differences in the individuals who are exposed to CBD-rich *vs* -poor cannabis as well as the inability to accurately determine users' ongoing history of exposure in terms of CBD/THC dose or ratio. In contrast, preclinical investigations can use random assignment of drug-naive populations or fully balanced repeated-measures designs to minimize such confounds. In addition, human laboratory studies can be limited with respect to the ranges of CBD and

THC doses that participants may be exposed to, unlike animal studies in which a full dose range can be assessed.

An early study conducted in rhesus macaque monkeys reported that a 30 mg/kg, i.m., CBD blocked THC-induced reductions in fixed-interval responding for food when administered 60 min prior to 0.3 mg/kg, i.m., THC in macaques but had no effect when administered prior to 1.0 mg/kg, i.m., THC (Brady and Balster, 1980). This study also reported a minor performance impairment following 30 mg/kg, but not 10 mg/kg, i.m., CBD when administered alone. This latter is consistent with a demonstration that CBD by itself did not have any effects on repeated acquisition accuracy in Old World monkeys over a range of 0.32–3.2 mg/kg, i.m. (Winsauer *et al*, 1999). A study by our group (Taffe *et al*, 2015) found that CBD could ameliorate or reverse some of the detrimental effects of THC on bimanual motor coordination and object-spatial memory tasks in macaque monkeys (Wright *et al*, 2013). These latter effects were observed when CBD and THC were administered in equal amount (0.5 mg/kg, i.m.) that may be critical, as CBD:THC ratios in street cannabis do not typically exceed 1 : 1 (Burgdorf *et al*, 2011; Morgan *et al*, 2010a). Similarly, Jacobs *et al* (2016) showed that CBD attenuated the detrimental effect of THC (0.32 mg/kg, i.m.) on go-trial success in a stop-signal task in male macaque monkeys. In this case, CBD was effective when administered in a 3 : 1 CBD:THC ratio. In these nonhuman primate studies, CBD administered by itself had negligible or no behavioral effects. The use of repeated-measures designs in these two nonhuman primate laboratory studies enhances confidence that the protective effects of CBD in the study of human recall (Morgan *et al*, 2010b) was due, at least in part, to pharmacological interactions and not to preexisting differences in cognitive capability.

In contrast with the effects in monkeys, the data from rodent models do not consistently confirm any ability of CBD to ameliorate the detrimental effects of THC on learning and memory. In fact, CBD may exacerbate some of the effects of THC. CBD further impaired spatial working memory in male rats beyond that associated with THC alone when administered in a 5 : 1 ratio (Fadda *et al*, 2004); there was no effect of CBD when administered with THC in a 5 : 2 ratio in that study. In another study, the reconsolidation of fear memory in male rats was disrupted by either THC or CBD with approximately 10-fold higher CBD required to produce similar effects (Stern *et al*, 2012; Stern *et al*, 2015). When subthreshold doses of THC and CBD were co-administered, they combined additively to disrupt the reconsolidation of fear memory (Stern *et al*, 2015). Despite the interaction with the effects of THC, CBD does not produce any detrimental effects on spatial working memory or delayed match-to-sample performance in rats (Fadda *et al*, 2004; Heyser *et al*, 1993; Lichtman *et al*, 1995) when administered by itself. These data suggest that rodent models may not be ideal for preclinical modeling of the effects of THC and CBD on complex cognitive tasks.

CBD/THC INTERACTIONS ON REWARD, AVERSION, AND INTEROCEPTIVE CUES

The subjective effects of THC in animal models appear to depend in large part on the dose. Lower doses of THC decreased the self-stimulation brain reward threshold of rats while higher doses increased reward thresholds, indicating an aversive state (Katsidoni *et al*, 2013). The i.v. self-administration of THC has so far only been established in one species of New World monkey by one laboratory (Justinova *et al*, 2005; Justinova *et al*, 2004; Justinova *et al*, 2003) but this may not generalize to Old World monkeys (John *et al*, 2017) or rats (Lefever *et al*, 2014; Panlilio *et al*, 2010). Perhaps as a consequence of the lack of consistent self-administration models, the interactive effects of CBD and THC have only been assessed in drug-discrimination and place-conditioning assays. CBD prevented the establishment of a conditioned place aversion produced by 10 mg/kg THC in rats when administered in a 1 : 10 or 1 : 1 (but not 3 : 1) ratio with THC (Vann *et al*, 2008). Interestingly, CBD did not have any effect on the subjective, discriminative stimulus effects of THC in a drug-discrimination assay in the same study. This may be dose related, as CBD in 30 : 1 ratio did prolong the duration of THC-appropriate responding in rats (but not pigeons) in another drug-discrimination study (Hiltunen and Jarbe, 1986). CBD also increased the potency of THC in a drug-discrimination assay in male rhesus monkeys, while not substituting for THC when administered by itself (McMahon, 2016); However, the interactive effect was only observed with a 100 : 1 CBD:THC ratio. Thus the evidence for CBD effects on subjective effects in preclinical models is mixed but overall it appears that very high CBD:THC ratios result in an additive or potentiating effect. The study by Vann *et al* (2008) is one of the few to show that CBD can attenuate the effects of THC in rodents. In combination with the finding of Malone *et al* (2009) (see above), this may indicate that CBD has a specific role in ameliorating aversive subjective effects of THC in rodent models.

In humans as well, the effects of CBD on the rewarding effects of THC are mixed. Morgan *et al* (2010b) reported that in recreational cannabis users high CBD:THC ratio was associated with a reduced attentional bias to cannabis and food-related cues, suggesting that it may reduce THC-associated reward. In contrast, others have reported that oral CBD at several doses had no rewarding effects on its own nor did it alter the subjective high associated with smoked THC (Babalonis *et al*, 2017; Haney *et al*, 2016). Thus further studies are needed to examine the effects of CBD on THC-associated reward.

THC–CBD INTERACTIONS IN HUMANS

Several investigators have examined the interactive effects of THC and CBD over the past few decades; however, much of this data comes from preclinical studies. Human data on THC–CBD interactions come largely from cross-sectional

population-based studies and a handful of clinical trials comparing the effects of THC and CBD and/or examining their interactive effects.

ANXIETY

THC reliably increases subjective effects of anxiety acutely in a biphasic dose-related manner—with lower doses producing decreases in anxiety and higher doses being anxiogenic. In contrast, CBD may have anxiolytic properties. A few clinical studies have examined the interaction of THC and CBD on anxiety. In one of these earliest studies, Karniol *et al* (1974) examined the effects of oral CBD by itself and on THC-induced effects. Although oral CBD (15, 30, and 60 mg) did not reduce anxiety on its own, it did reduce oral THC (30 mg) induced anxiety when given simultaneously (Karniol *et al*, 1974). This was replicated by Zuardi *et al* (1982) using a combination of oral CBD (1.0 mg/kg) and oral THC (0.5 mg/kg). In contrast, Karschner *et al* (2011b) reported no effect of CBD on THC-induced anxiety. They examined the effects of two doses of oral THC (5 mg; 15 mg) with oramucosal nabiximols (low dose: 5.4 mg THC, 5.0 mg CBD; and high dose: 16.2 mg THC, 15.0 mg CBD). All four conditions produced anxiety relative to placebo, but there were no differences between THC alone and the combination on measures of anxiety.

A series of studies have compared the effects of oral CBD (600 mg) and THC (10 mg) in healthy volunteers who were shown fearful faces designed to elicit anxiety (Fusar-Poli *et al*, 2010; Fusar-Poli *et al*, 2009). As expected, THC alone increased subjective anxiety as well as the skin conductance response to the fearful faces while CBD alone trended toward a reduction in anxiety. Furthermore, CBD reduced the blood-oxygenation-level-dependent (BOLD) signal in the amygdala and the anterior and posterior cingulate cortex during the viewing of the fearful faces and disrupted connectivity between the amygdala and anterior cingulate during this task. The CBD-associated reduction in BOLD response was correlated with the reduction in skin conductance response, suggesting that this underlies CBD's anxiolytic effects. Of note, though, these studies did not examine the interactive effects of THC and CBD.

Thus CBD may attenuate the anxiolytic effects of THC acutely although the data remain mixed. Further studies are required to understand the potential dose/route-related interactive effects of THC and CBD on anxiety and the neural substrate of CBD's anxiolytic effects.

COGNITION

The endocannabinoid system is important to cognitive processes, including learning and memory (Marsicano and Lafenetre, 2009), and prolonged use of cannabis (Meier *et al*, 2012) has been associated with cognitive impairment. Meier *et al* (2012) reviewed records of 1037 individuals born between 1972 and 1973 in New Zealand. Neuropsychiatric testing was conducted before age 13 years and again at age 38 years. At several yearly intervals, participants were followed and questioned about their cannabis use. These who reported persistently using cannabis at $\geqslant 3$ interval times had a full-scale intelligence quotient that was about 10 points lower at age 38 years than those that reported never using cannabis or never regularly using cannabis.

Acute exposure to THC as well (D'Souza *et al*, 2004; Ranganathan and D'Souza, 2006) produces acute, transient, and dose-related cognitive impairments in executive function, abstract ability, and decision making. The most robust effects are on verbal learning, short-term memory, working memory, and attention (Hart *et al*, 2001; Heishman *et al*, 1990; Hooker and Jones, 1987; Leweke *et al*, 1998; Marks and MacAvoy, 1989; Miller *et al*, 1977; Ranganathan and D'Souza, 2006), consistent with effects in rodents and nonhuman primates (Lichtman *et al*, 2002; Wilson and Nicoll, 2002). CBD by itself does not appear to produce cognitive deficits. On the other hand, some studies suggest that CBD may decrease the cognitive impairing effects of THC, although the results are mixed.

Morgan *et al* (2010b) have conducted a series of cross-sectional studies examining the subchronic and acute effects of cannabis in recreational and heavy cannabis users. Cannabis-using individuals completed the same verbal memory at baseline and then returned 7 days later with their own supply of cannabis and completed the verbal memory task while intoxicated (Morgan *et al*, 2010b). Cognition was examined at baseline when subjects were not acutely intoxicated as well as after acute cannabis ingestion. Samples of cannabis smoked were assayed for the levels of THC and CBD. In this study, specimens with higher levels of CBD were associated with better prose recall (Morgan *et al*, 2010b). In a follow-up study, recreational and heavy users were examined while not intoxicated (subchronic THC exposure). Hair samples were obtained to assay for the THC/CBD levels. Daily cannabis users with high hair THC concentrations performed worse on verbal recall. Although CBD was not associated with a difference in prose recall in this sample, the presence of CBD was associated with better recognition recall (Morgan *et al*, 2012). Taken together, these data suggested that the presence of CBD in recreational cannabis may protect against the memory-impairing effects of THC. However, it must be noted that these cross-sectional studies are limited by self-report with regard to dose, frequency, and potency of cannabis used, possible relationship of type of cannabis with individual factors (eg, it cannot be determined whether individuals who sought more perceptual-altering effects used cannabis with greater THC content or vice versa), and recall bias regarding the types of symptoms experienced. Furthermore, the studies relied on individuals who continued to use cannabis and therefore possibly excluded those who may have had worse experiences.

Experimental laboratory-based studies can address some of these limitations of epidemiological studies and have also examined the effects of THC and CBD on cognition in

humans. In a series of experiments, the effects of oral CBD (600 mg) and oral THC (10 mg) in a healthy cohort have been examined on verbal memory, executive function, and attention (Bhattacharyya *et al*, 2010; Borgwardt *et al*, 2008). Interestingly, in these studies, neither CBD nor THC significantly affected performance on cognitive tasks in these studies, although there were differences in brain-activation patterns as described below. It is possible that the lack of effects on performance reflects load/timing of the task or the dose/oral route of THC and CBD. Of note, these studies compared the effects of THC and CBD but did not examine the interactive effects. In contrast, Englund *et al* (2013) pretreated healthy subjects with CBD (600 mg PO)/placebo prior to receiving i.v. THC and demonstrated a protective effect on CBD on THC-induced verbal learning deficits.

Wade *et al* (2003) evaluated the effects of both THC and CBD in a clinical population of 24 individuals with a range of neurological symptoms, including multiple sclerosis, spinal cord injuries, brachial plexus damage, and neurofibromatosis. Individuals were given a 2.5 mg sublingual dose of CBD and then evaluated on the Short Orientation-Memory Concentration (SOMC) test (Wade and Vergis, 1999). CBD did not affect memory and concentration when administered alone but reversed the deficits on the SOMC seen with sublingual THC (2.5 mg).

The effects of cannabinoids on social cognition have also been evaluated. A large randomized double-blind placebo controlled crossover study of 48 cannabis users ($n = 24$ light users, $n = 24$ heavy users) examined the effects of oral CBD (16 mg), oral THC (8 mg), placebo, or the combination of THC+CBD on an emotional facial recognition task (Hindocha *et al*, 2015). The task consisted of showing a range of emotions of varying intensities from 20 to 100%. The results found that CBD improved facial recognition at the 60% emotional intensity, while THC impaired facial recognition of ambiguous faces at 40% intensity. The combination of THC+CBD resulted in no difference in emotion recognition from placebo, suggesting that CBD attenuated the THC-induced impairments.

Data from Neuroimaging Studies

Brain imaging studies employing functional magnetic resonance imaging (fMRI) and electrophysiology outcome measures provide an opportunity to assess the effects of THC/CBD in the brain during various perceptual/cognitive tasks. One of the earliest reported fMRI studies on the interactions of THC and CBD examined the effects of oral THC 10 mg, oral CBD 600 mg, and placebo on a go/no go task on three separate test days in 15 healthy volunteers in a double-blind randomized study (Borgwardt *et al*, 2008). In general, performance was similar on the task during all 3 test days. However, CBD decreased the BOLD response in the left insula and left superior/transverse gyri relative to placebo and THC decreased the BOLD response in the right inferior frontal gyrus, anterior cingulate gyrus, and bilaterally in the precuneus. THC also increased the BOLD response in the right hippocampus/para hippocampal gyrus, temporal gyrus, caudate and fusiform gyrus, and in the left posterior cingulate gyrus, suggesting that THC may specifically target areas involved in response inhibition, unlike CBD.

The same research group has published several other fMRI studies with oral THC 10 mg, oral CBD 600 mg, and placebo in healthy volunteers (Bhattacharyya *et al*, 2015; Bhattacharyya *et al*, 2010; Fusar-Poli *et al*, 2010; Fusar-Poli *et al*, 2009). Fusar-Poli *et al* (2009) evaluated the BOLD response related to THC and CBD during a fearful face task. Relative to placebo, CBD decreased activation in the left medial temporal region (including the amygdala and anterior para hippocampal gyrus), the anterior and posterior cingulate gyrus, the left middle occipital gyrus, and the right lobe of the cerebellum. THC increased BOLD response in the left precuneus and bilaterally in the primary sensory cortex, but decreased BOLD response bilaterally in the middle frontal gyrus and in the posterior cingulate gyrus. A connectivity analysis showed that CBD but not THC decreased forward connectivity with the amygdala and the anterior cingulate cortex (Fusar-Poli *et al*, 2010), suggesting that CBD may target a neural mechanism underlying anxiety disorders or posttraumatic stress disorder.

Bhattacharyya *et al* (2010) demonstrated that THC and CBD had diametrically opposite effects on BOLD response relative to placebo in the striatum during verbal recall, in the hippocampus while conducting an inhibition task, in the amygdala during a fearful face task, in the superior temporal cortex during a verbal listening task, and in the occipital cortex during a visual processing task. During an oddball salience processing task, THC and CBD also had opposite effects on functional connectivity between the dorsal striatum, prefrontal cortex, and hippocampus. These studies show opposing actions on regional activation by THC and CBD but need replication given their relatively small sample size. Significantly larger fMRI studies with behavioral outcomes will be required to continue to determine the neurobiological interactions of THC and CBD with acute administration.

To summarize, limited epidemiological and experimental data suggest that CBD may have a protective effect against THC-induced learning deficits. Further studies with larger sample sizes are needed to examine dose-related acute as well as chronic effects and to examine the interactive effects of CBD on THC rather than comparative effects on patterns of brain activation.

PSYCHOSIS

Separate from the subjective effects of feeling high, relaxed, or altered, cannabis extracts as well as THC alone, in susceptible individuals, can produce subjective effects, including suspiciousness, paranoia, conceptual disorganization, and perceptual alterations, that can be measured on standardized rating scales such as the Positive and Negative Syndrome Scale (PANSS), Clinician Administered

Dissociative Symptoms Scale, Psychotomimetic States Inventory, Brief Psychiatric rating scale, etc. (D'Souza *et al*, 2004; Kleinloog *et al*, 2012; Liem-Moolenaar *et al*, 2010; Morrison and Stone, 2011; Morrison *et al*, 2009). In contrast to THC, CBD does not produce acute psychotomimetic effects and in fact may have potential antipsychotic effects (Iseger and Bossong, 2015). The interaction of THC and CBD on psychosis-like symptoms is one that has been extensively studied in humans.

Schubart *et al* (2011) conducted a web-based survey where information on the amount and the type of cannabis consumed by individuals ($n=1877$) was collected and psychiatric symptoms were evaluated using the Community Assessment of Psychic Experiences (CAPE). Self-reported use of cannabis with high CBD content was correlated with lower CAPE-positive symptoms ($p<0.001$). Similarly, a linear regression showed a positive relationship of THC/CBD ratio with positive symptoms ($p<0.001$). In two separate population-based studies by Morgan and colleagues, greater psychosis proneness was observed in individuals using THC alone *vs* THC+CBD using the Oxford Liverpool Inventory of Life Experiences (Morgan and Curran, 2008) and the Schizotypal Personality Questionnaire (Morgan *et al*, 2012). CBD may have a protective influence on long-term effects from frequent cannabis use. However, as discussed above, as these are based on a retrospective population analysis, it is not known if individuals with higher psychosis proneness are more likely to use cannabis with lower CBD content.

Several human laboratory studies have compared the effects of THC and CBD on psychotomimetic effects and a few have also examined their interactive effects on this parameter. As expected, THC acutely produced intoxication and positive psychotic symptoms in healthy volunteers, whereas CBD alone did not. Furthermore, pretreatment with CBD was associated with lower acute THC-induced psychotomimetic effects, including paranoia (Bhattacharyya *et al*, 2010; Englund *et al*, 2013). Consistent with this, in one of the first human laboratory studies of CBD on psychosis, nine healthy individuals participated in a visual processing binocular depth perception task (Leweke *et al*, 2000). Binocular depth perception is a model of illusionary perception and is found to be altered in people with schizophrenia (Schneider *et al*, 2002). The study found that oral CBD (200 mg) had no effect on visual processing on its own. However, CBD reversed the acute impairment in binocular depth perception by the CB_1R agonist nabilone.

The experimental and epidemiological data suggest that CBD reduces the psychosis-like effects of THC. These data as well as others suggesting endocannabinoid system alterations in psychosis give support to the hypothesis that CBD may have antipsychotic effects on its own—a hypothesis that has been tested in clinical populations as discussed below.

An early case report (Zuardi *et al*, 1995) and a case series (Zuardi *et al*, 2006) in patients with psychosis also supported the antipsychotic potential of CBD. Leweke *et al* (2012) in a 4-week randomized double-blind study of acutely psychotic patients with schizophrenia compared the effects of CBD 800 mg/day ($n=21$) with amisulpride 800 mg/day ($n=21$). Treatment with both medications resulted in a clinically and statistically significant decrease in PANSS total, positive, negative, and general scores. However, no significant difference was seen in PANSS change scores between CBD and amisulpride. CBD was well tolerated and resulted in significantly less extrapyramidal symptoms, weight gain, and prolactin increase than amisulpride. Although not placebo controlled, this is the first controlled study suggesting CBD could be an effective antipsychotic in the treatment of schizophrenia.

Effects of Nabiximols: Interactions of CBD and THC

The putative beneficial effects of CBD in attenuating the unwanted psychotomimetic, anxiogenic, or cognitive impairing effects of THC have been harnessed in nabiximols. Nabiximols is approved for treatment of symptoms of spasticity in adults with multiple sclerosis (MS) in several countries (Vermersch, 2011) and is available as an oromucosal spray (Russo and Guy, 2006) as described above.

In a placebo-controlled crossover study (Aragona *et al*, 2009) of 17 individuals, MS patients were evaluated after nabiximols administration. No significant deficits in cognition were detected *vs* placebo. However, these results need to be taken with caution due to the small sample size and short duration of treatment. In a larger crossover study, multiple doses of nabiximols (10.8, 21.6, and 43.2 mg THC) was compared with placebo and the synthetic THC dronabinol (20, 40 mg) in recreational cannabis users (Schoedel *et al*, 2011). Few significant differences were seen between nabiximols and dronabinol on psychomotor speed, attention, and short-term memory. One concern of the study is the lack of difference in cognitive outcomes with dronabinol and placebo. Only reaction time for the short-term memory test was different for dronabinol 40 mg and placebo. The results suggest the doses of THC used in this study do not cause significant cognitive deficits that could be reversed by CBD.

To summarize, clinical data on THC-CBD interactions suggest that the data are mixed, although some studies suggest that CBD may attenuate some effects of THC such as anxiety, cognitive deficits, and psychosis. The literature is limited not only by the scarcity of published studies but also by confounds such as recall bias in self-reported consumption of cannabis, variability in the amount, duration and amount of prior exposure to cannabis and cannabinoids even within the same individual over a given time, difference in methodology and outcome measures over studies, inadequate assessment of dose response, and reliance on self-report for subjective outcome measures. Despite this, there is a growing interest in the ability of CBD to attenuate unwanted effects of THC (eg, Sativex).

Preclinical studies may be better designed to address some of these limitations and to examine THC–CBD interactions in a systematic manner as reviewed above.

FUTURE DIRECTIONS

As discussed above, the existing clinical and preclinical data suggest that CBD may attenuate several acute and chronic effects of THC. However, the existing literature has several limitations that need further study as discussed below.

Acute Dose–Response Relationship

Clinical data on the interactions between THC and CBD rely on a very limited dose range of CBD. Further, several of the existing studies on the acute interactions of THC and CBD include oral CBD that is limited by poor and variable bioavailability. Thus future studies should include a wider dose range of CBD and alternate routes of administration.

Effects of CBD on Chronic THC Exposure

Both recreational and putative therapeutic human use of cannabis involve repeated exposure, yet the majority of the information on potential interactive effects of CBD and THC from preclinical models results from acute dosing. In the one noted exception, Klein *et al* (2011) found that chronic co-administration of CBD and THC produced more anxiety-like behavior and a greater reduction in social interaction compared with chronic THC alone. Additional studies of chronic dosing would be critical to support translational inferences regarding the potential interactive effects of CBD and THC. As a related issue, the majority of human cannabis consumption is via inhalation and yet only limited information exists on the preclinical effects of inhaled THC (Ali *et al*, 1991; Lichtman *et al*, 2000; Lichtman *et al*, 2001) and there is as yet none on the effects of inhaled CBD. Recent development of techniques to deliver cannabinoids to rodents using e-cigarette or Volcano technologies that are increasingly popular with human cannabis users are highly promising for future investigations (Manwell *et al*, 2014; Nguyen *et al*, 2016).

Species Differences

One of the greater limitations in translating preclinical research into predictions for human exposure to CBD, THC, and the combination lies in what appear to be significant order differences in the results from nonhuman primate and rodent laboratory models. The clearest parallels to the memory-sparing effects of CBD in the studies by Morgan and colleagues (Morgan *et al*, 2011; Morgan *et al*, 2010b) derive from the results from nonhuman primate models (Jacobs *et al*, 2016; Wright *et al*, 2013). In contrast, most of the behavioral rodent studies suggest that CBD either fails to attenuate the effects of THC or instead potentiates such effects. Unfortunately, the relative paucity of information from nonhuman primate models on interactive effects of CBD and THC make definitive conclusions about possible order differences difficult. In addition, the route of administration may be a critical contributor to apparent species differences if the metabolic effects on THC and CBD following i.m. or i.p. administration vary significantly within or across species. This consideration raises the further concern that, while humans frequently consume cannabis by inhalation, preclinical models of THC inhalation are only infrequently used (eg, Ali *et al*, 1991; Nguyen *et al*, 2016; Varvel *et al*, 2006). This is an area in which understanding would benefit greatly from additional research efforts.

POLICY IMPLICATIONS

As various municipalities and legislative bodies in the United States, Canada and other countries grapple with enacting policy to shape the use of both medical and recreational cannabis, the constituents of that cannabis (most importantly, the behaviorally active constituents) may come under regulatory guidance. Although this review focused on THC and CBD, there are other pharmacologically active cannabis constituents that may also be important to study for properties relevant to regulation and personal decision making. For example, if CBD (or another cannabis constituent) is found to have negligible negative effects on the main desired target of cannabis (such as the recreational 'high' or pain/spasticity), while providing some beneficial effects (such as sparing cognition), then a THC+high-CBD strain of cannabis may be warranted. The initial findings of Morgan and colleagues are promising, but it is difficult to establish the potential benefit of such approaches as typical strains of recreational market cannabis are limited in CBD: THC ratio (Burgdorf *et al*, 2011; Morgan *et al*, 2010b). A somewhat greater diversity of cannabis is emerging, particularly in medical-marijuana-permitting jurisdictions and some of this cannabis may be focused on high CBD with low THC content (Kolikonda *et al*, 2016; Maa and Figi, 2014). Thus future epidemiological studies may better address interactive effects of CBD and THC, particularly in the context of regular consumption. Relevant to THC/CBD interactions, whether CBD has an effect on the unwanted effects of THC is not the only important question. If, for example, CBD is found to potentiate the medically desired effects of cannabis (eg, analgesia), then this may permit lower THC content strains or products that contain substantial amounts of CBD to succeed. There are indeed recent efforts to validate high CBD/low THC strains of cannabis to treat refractory seizures in children (O'Connell *et al*, 2017; Sulak *et al*, 2017). Thus a better understanding of THC/CBD interactions on several domains may help identify strains with specific ratios for different indications. Clearly, further work is needed to definitively establish these interactions in preclinical and clinical research so that future policy decisions may rely on scientific findings as much as possible.

Summary

As has been made clear by this review, there are currently many unanswered questions about the potentially interactive

effects of the cannabis constituents, CBD and THC. There are studies in humans, nonhuman primates, and rodents that suggest some potential for CBD to attenuate the effects of THC, with the most direct parallels in the memory/cognition-protecting effects observed in recreational users and verified in monkey findings. There are also indications, primarily from preclinical research, that CBD may, in fact, potentiate some effects of THC. The mechanism of such interactions is unknown given the diversity of potential pharmacological targets of CBD and a propensity for CBD to interfere with the distribution, metabolism, and/or excretion of THC. Ultimately, there is a profound lack of research on the manner by which CBD may affect the actions of THC across a wide range of behavioral and physiological effects. This paucity is particularly acute when attempting to compare across human and nonhuman experimental studies that may use very different behaviors to assess cannabinoid activity. Cannabis use is expanding in many regions of the world as prohibitions against recreational use are relaxed and as permission for medical use grows. In the medical context particularly, there are claims of efficacy for CBD, THC, and other constituents that are only poorly evaluated or understood at present. This is particularly acute when it comes to potentially interacting effects of key cannabis constituents, such as THC or CBD. Personal and public decision making on the use of cannabis would be improved by additional research that can evaluate claims and establish potential mechanisms of action.

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REFERENCES

Adams R, Hunt M, Clark JH (1940). Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. *J Am Chem Soc* **62**: 196–200.

Ali SF, Newport GD, Scallet AC, Paule MG, Bailey JR, Slikker W Jr (1991). Chronic marijuana smoke exposure in the rhesus monkey. IV: Neurochemical effects and comparison to acute and chronic exposure to delta-9-tetrahydrocannabinol (THC) in rats. *Pharmacol Biochem Behav* **40**: 677–682.

Aragona M, Onesti E, Tomassini V, Conte A, Gupta S, Gilio F *et al* (2009). Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. *Clin Neuropharmacol* **32**: 41–47.

Babalonis S, Haney M, Malcolm RJ, Lofwall MR, Votaw VR, Sparenborg S *et al* (2017). Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend* **172**: 9–13.

Badowski ME (2017). A review of oral cannabinoids and medical marijuana for the treatment of chemotherapy-induced nausea and vomiting: a focus on pharmacokinetic variability and pharmacodynamics. *Cancer Chemother Pharmacol* (doi:10.1007/s00280-017-3387-5; e-pub ahead of print).

Bhattacharyya S, Falkenberg I, Martin-Santos R, Atakan Z, Crippa JA, Giampietro V *et al* (2015). Cannabinoid modulation of functional connectivity within regions processing attentional salience. *Neuropsychopharmacology* **40**: 1343–1352.

Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T *et al* (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* **35**: 764–774.

Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I *et al* (2001). Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* **134**: 845–852.

Borgwardt SJ, Allen P, Bhattacharyya S, Fusar-Poli P, Crippa JA, Seal ML *et al* (2008). Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. *Biol Psychiatry* **64**: 966–973.

Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ (1995). Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metab Dispos* **23**: 825–831.

Bossong MG, Mehta MA, van Berckel BN, Howes OD, Kahn RS, Stokes PR (2015). Further human evidence for striatal dopamine release induced by administration of 9-tetrahydrocannabinol (THC): selectivity to limbic striatum. *Psychopharmacology* **232**: 2723–2729.

Brady KT, Balster RL (1980). The effects of delta 9-tetrahydrocannabinol alone and in combination with cannabidiol on fixed-interval performance in rhesus monkeys. *Psychopharmacology* **72**: 21–26.

Burgdorf JR, Kilmer B, Pacula RL (2011). Heterogeneity in the composition of marijuana seized in California. *Drug Alcohol Depend* **117**: 59–61.

Cabral GA, Raborn ES, Griffin L, Dennis J, Marciano-Cabral F (2008). CB2 receptors in the brain: role in central immune function. *Br J Pharmacol* **153**: 240–251.

Callaway J (2004). Hempseed as a nutritional resource: an overview. *Euphytica* **140**: 65–72.

Campos AC, Guimaraes FS (2008). Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology (Berl)* **199**: 223–230.

Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimaraes FS (2012). Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philos Trans R Soc Lond Ser B Biol Sci* **367**: 3364–3378.

Cesamet (package insert) (2013) Meda Pharmaceuticals Inc.: Somerset, NJ, USA.

Cooper ZD, Haney M (2016). Sex-dependent effects of cannabis-induced analgesia. *Drug Alcohol Depend* **167**: 112–120.

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G *et al* (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* **57**: 594–608.

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT *et al* (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* **29**: 1558–1572.

De Petrocellis L, Di Marzo V (2010). Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. *J Neuroimmune Pharmacol* **5**: 103–121.

Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* **34**: 605–613.

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G *et al* (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **258**: 1946–1949.

ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A. Phytochemistry of *Cannabis sativa* L*Phytocannabinoids*. A. Douglas Kinghorn, Heinz Falk, Simon Gibbons, Jun'ichi Kobayashi (eds). Springer: Switzerland, 2017, pp 1–36.

Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S *et al* (2013a). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol* **27**: 19–27.

Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G (2004). Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. *Neuropharmacology* **47**: 1170–1179.

Farkas I, Kallo I, Deli L, Vida B, Hrabovszky E, Fekete C *et al* (2010). Retrograde endocannabinoid signaling reduces GABAergic synaptic transmission to gonadotropin-releasing hormone neurons. *Endocrinology* **151**: 5818–5829.

Fernandes M, Schabarek A, Coper H, Hill R (1974). Modification of delta9-THC-actions by cannabinol and cannabidiol in the rat. *Psychopharmacologia* **38**: 329–338.

Finn DP, Beckett SR, Roe CH, Madjd A, Fone KC, Kendall DA *et al* (2004). Effects of coadministration of cannabinoids and morphine on nociceptive behaviour, brain monoamines and HPA axis activity in a rat model of persistent pain. *Eur J Neurosci* **19**: 678–686.

Fogaca MV, Reis FM, Campos AC, Guimaraes FS (2014). Effects of intra-prelimbic prefrontal cortex injection of cannabidiol on anxiety-like behavior: involvement of

5HT1A receptors and previous stressful experience. *Eur Neuropsychopharmacol* **24**: 410–419.

Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S *et al* (2010). Modulation of effective connectivity during emotional processing by Delta 9-tetrahydrocannabinol and cannabidiol. *Int J Neuropsychopharmacol* **13**: 421–432.

Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R *et al* (2009). Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Arch Gen Psychiatry* **66**: 95–105.

Gaoni Y, Mechoulam R (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *J Am Chem Soc* **86**: 1646–1647.

Gomes FV, Reis DG, Alves FH, Correa FM, Guimaraes FS, Resstel LB (2012). Cannabidiol injected into the bed nucleus of the stria terminalis reduces the expression of contextual fear conditioning via 5-HT1A receptors. *J Psychopharmacol* **26**: 104–113.

Grunfeld Y, Edery H (1969). Psychopharmacological activity of the active constituents of hashish and some related cannabinoids. *Psychopharmacology* **14**: 200–210.

Hampson RE, Miller F, Palchik G, Deadwyler SA (2011). Cannabinoid receptor activation modifies NMDA receptor mediated release of intracellular calcium: implications for endocannabinoid control of hippocampal neural plasticity. *Neuropharmacology* **60**: 944–952.

Haney M, Malcolm RJ, Babalonis S, Nuzzo PA, Cooper ZD, Bedi G *et al* (2016). Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis. *Neuropsychopharmacology* **41**: 1974–1982.

Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW (2001). Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology* **25**: 757–765.

Hashimotodani Y, Ohno-Shosaku T, Kano M (2007). Endocannabinoids and synaptic function in the CNS. *Neuroscientist* **13**: 127–137.

Hayakawa K, Mishima K, Hazekawa M, Sano K, Irie K, Orito K *et al* (2008). Cannabidiol potentiates pharmacological effects of Delta(9)-tetrahydrocannabinol via CB(1) receptor-dependent mechanism. *Brain Res* **1188**: 157–164.

Heishman SJ, Huestis MA, Henningfield JE, Cone EJ (1990). Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. *Pharmacol Biochem Behav* **37**: 561–565.

Heyser CJ, Hampson RE, Deadwyler SA (1993). Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: alterations in short-term memory associated with changes in task specific firing of hippocampal cells. *J Pharmacol Exp Ther* **264**: 294–307.

Hiltunen AJ, Jarbe TU (1986). Interactions between delta 9-tetrahydrocannabinol and cannabidiol as evaluated by drug discrimination procedures in rats and pigeons. *Neuropharmacology* **25**: 133–142.

Hiltunen AJ, Jarbe TU, Wangdahl K (1988). Cannabinol and cannabidiol in combination: temperature, open-field activity, and vocalization. *Pharmacol Biochem Behav* **30**: 675–678.

Hindocha C, Freeman TP, Schafer G, Gardener C, Das RK, Morgan CJ *et al* (2015). Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. *Eur Neuropsychopharmacol* **25**: 325–334.

Hooker WD, Jones RT (1987). Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. *Psychopharmacology* **91**: 20–24.

Huestis MA, Boyd SJ, Heishman SJ, Preston KL, Bonnet D, Le Fur G *et al* (2007). Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. *Psychopharmacology* **194**: 505–515.

Hunt CA, Jones RT, Herning RI, Bachman J (1981). Evidence that cannabidiol does not significantly alter the pharmacokinetics of tetrahydrocannabinol in man. *J Pharmacokinet Biopharm* **9**: 245–260.

Hyman SM, Sinha R (2009). Stress-related factors in cannabis use and misuse: implications for prevention and treatment. *J Subst Abuse Treat* **36**: 400–413.

Iseger TA, Bossong MG (2015). A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophr Res* **162**: 153–161.

Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R (2009). Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci* **30**: 515–527.

Jackson NJ, Isen JD, Khoddam R, Irons D, Tuvblad C, Iacono WG *et al* (2016). Impact of adolescent marijuana use on intelligence: results from two longitudinal twin studies. *Proc Natl Acad Sci USA* **113**: E500–E508.

Jacobs DS, Kohut SJ, Jiang S, Nikas SP, Makriyannis A, Bergman J (2016). Acute and chronic effects of cannabidiol on Delta(9)-tetrahydrocannabinol (Delta(9)-THC)-induced disruption in stop signal task performance. *Exp Clin Psychopharmacol* **24**: 320–330.

John WS, Martin TJ, Nader MA (2017). Behavioral determinants of cannabinoid self-administration in old world monkeys. *Neuropsychopharmacology* **42**: 1522–1530.

Justinova Z, Goldberg SR, Heishman SJ, Tanda G (2005). Self-administration of cannabinoids by experimental animals and human marijuana smokers. *Pharmacol Biochem Behav* **81**: 285–299.

Justinova Z, Panlilio LV, Moreno-Sanz G, Redhi GH, Auber A, Secci ME *et al* (2015). Effects of fatty acid amide hydrolase (FAAH) inhibitors in non-human primate models of nicotine reward and relapse. *Neuropsychopharmacology* **40**: 2185–2197.

Justinova Z, Tanda G, Munzar P, Goldberg SR (2004). The opioid antagonist naltrexone reduces the reinforcing effects of Delta 9 tetrahydrocannabinol (THC) in squirrel monkeys. *Psychopharmacology (Berl)* **173**: 186–194.

Justinova Z, Tanda G, Redhi GH, Goldberg SR (2003). Self-administration of delta9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. *Psychopharmacology (Berl)* **169**: 135–140.

Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA (1974). Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. *Eur J Pharmacol* **28**: 172–177.

Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA (2011a). Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. *Clin Chem* **57**: 66–75.

Karschner EL, Darwin WD, McMahon RP, Liu F, Wright S, Goodwin RS *et al* (2011b). Subjective and physiological effects after controlled Sativex and oral THC administration. *Clin Pharmacol Ther* **89**: 400–407.

Katsidoni V, Kastellakis A, Panagis G (2013). Biphasic effects of Delta9-tetrahydrocannabinol on brain stimulation reward and motor activity. *Int J Neuropsychopharmacol* **16**: 2273–2284.

Klein C, Karanges E, Spiro A, Wong A, Spencer J, Huynh T *et al* (2011). Cannabidiol potentiates Delta(9)-tetrahydrocannabinol (THC) behavioural effects and alters THC pharmacokinetics during acute and chronic treatment in adolescent rats. *Psychopharmacology* **218**: 443–457.

Kleinloog D, Liem-Moolenaar M, Jacobs G, Klaassen E, de Kam M, Hijman R *et al* (2012). Does olanzapine inhibit the psychomimetic effects of {Delta}9-tetrahydrocannabinol? *J Psychopharmacol* **26**: 1307–1316.

Kolikonda MK, Kavitha Srinivasan ME, Sagi V, Lippmann S (2016). Medical marijuana for epilepsy? *Innov Clin Neurosci* **13**: 23.

Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM (2015). Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *Br J Pharmacol* **172**: 4790–4805.

Lefever TW, Marusich JA, Antonazzo KR, Wiley JL (2014). Evaluation of WIN 55,212-2 self-administration in rats as a potential cannabinoid abuse liability model. *Pharmacol Biochem Behav* **118**: 30–35.

Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C *et al*. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012; **2**: e94

Leweke FM, Schneider U, Radwan M, Schmidt E, Emrich HM (2000). Different effects of nabilone and cannabidiol on binocular depth inversion in man. *Pharmacol Biochem Behav* **66**: 175–181.

Leweke M, Kampmann C, Radwan M, Dietrich DE, Johannes S, Emrich HM *et al* (1998). The effects of tetrahydrocannabinol on the recognition of emotionally charged words: an analysis using event-related brain potentials. *Neuropsychobiology* **37**: 104–111.

Li Q, Yan H, Wilson WA, Swartzwelder HS (2010). Modulation of NMDA and AMPA-mediated synaptic transmission by CB1 receptors in frontal cortical pyramidal cells. *Brain Res* **1342**: 127–137.

Lichtman AH, Dimen KR, Martin BR (1995). Systemic or intrahippocampal cannabinoid administration impairs spatial memory in rats. *Psychopharmacology (Berl)* **119**: 282–290.

Lichtman AH, Peart J, Poklis JL, Bridgen DT, Razdan RK, Wilson DM *et al* (2000). Pharmacological evaluation of aerosolized cannabinoids in mice. *Eur J Pharmacol* **399**: 141–149.

Lichtman AH, Poklis JL, Poklis A, Wilson DM, Martin BR (2001). The pharmacological activity of inhalation exposure to marijuana smoke in mice. *Drug Alcohol Depend* **63**: 107–116.

Lichtman AH, Varvel SA, Martin BR (2002). Endocannabinoids in cognition and dependence. *Prostaglandins Leukot Essent Fatty Acids* **66**: 269–285.

Liem-Moolenaar M, te Beek ET, de Kam ML, Franson KL, Kahn RS, Hijman R *et al* (2010). Central nervous system effects of haloperidol on THC in healthy male volunteers. *J Psychopharmacol* **24**: 1697–1708.

Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L *et al* (2006). Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther* **318**: 1375–1387.

Maa E, Figi P (2014). The case for medical marijuana in epilepsy. *Epilepsia* **55**: 783–786.

Magen I, Avraham Y, Ackerman Z, Vorobiev L, Mechoulam R, Berry EM (2010). Cannabidiol ameliorates cognitive and motor impairments in bile-duct ligated mice via 5-HT1A receptor activation. *Br J Pharmacol* **159**: 950–957.

Maione S, Piscitelli F, Gatta L, Vita D, De Petrocellis L, Palazzo E *et al* (2011). Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. *Br J Pharmacol* **162**: 584–596.

Malone DT, Jongejan D, Taylor DA (2009). Cannabidiol reverses the reduction in social interaction produced by low dose Delta(9)-tetrahydrocannabinol in rats. *Pharmacol Biochem Behav* **93**: 91–96.

Manwell LA, Ford B, Matthews BA, Heipel H, Mallet PE (2014). A vapourized Delta-tetrahydrocannabinol (Delta-THC) delivery system. Part II: Comparison of behavioural effects of pulmonary versus parenteral cannabinoid exposure in rodents. *J Pharmacol Toxicol Methods* **70**: 112–119.

Marinol (package insert) (2017). AbbVie Inc.: North Chicago, IL, USA, 2017.

Marks DF, MacAvoy MG (1989). Divided attention performance in cannabis users and non-users following alcohol and cannabis separately and in combination. *Psychopharmacology* **99**: 397–401.

Marsicano G, Lafenetre P (2009). Roles of the endocannabinoid system in learning and memory. *Curr Top Behav Neurosci* **1**: 201–230.

Martin WJ, Tsou K, Walker JM (1998). Cannabinoid receptor-mediated inhibition of the rat tail-flick reflex after microinjection into the rostral ventromedial medulla. *Neurosci Lett* **242**: 33–36.

Matsuzaki M, Casella GA, Ratner M (1987). delta 9-Tetrahydrocannabinol: EEG changes, bradycardia and hypothermia in the rhesus monkey. *Brain Res Bull* **19**: 223–229.

McMahon LR (2016). Enhanced discriminative stimulus effects of Delta(9)-THC in the presence of cannabidiol and 8-OH-DPAT in rhesus monkeys. *Drug Alcohol Depend* **165**: 87–93.

McMahon LR, Amin MR, France CP (2005). SR 141716A differentially attenuates the behavioral effects of delta9-THC in rhesus monkeys. *Behav Pharmacol* **16**: 363–372.

McPartland JM, Duncan M, Di Marzo V, Pertwee R (2014). Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. *Br J Pharmacol* **172**: 737–753.

Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR *et al* (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* **50**: 83–90.

Mechoulam R, Parker LA, Gallily R (2002). Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol* **42**(11 Suppl): 11S–19S.

Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO (2007). Cannabidiol–recent advances. *Chem Biodivers* **4**: 1678–1692.

Mechoulam R, Shani A, Edery H, Grunfeld Y (1970). Chemical basis of hashish activity. *Science* **169**: 611–612.

Meier MH, Caspi A, Ambler A, Harrington HL, Houts R, Keefe RSE *et al* (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci* **109**: E2657–E2664.

Metna-Laurent M, Mondesir M, Grel A, Vallee M, Piazza PV (2017). Cannabinoid-induced tetrad in mice. *Curr Protoc Neurosci* **80**: 9.59.1–9.59.10.

Miller LL, McFarland D, Cornett TL, Brightwell D (1977). Marijuana and memory impairment: effect on free recall and recognition memory. *Pharmacol Biochem Behav* **7**: 99–103.

Mokrysz C, Landy R, Gage SH, Munafo MR, Roiser JP, Curran HV (2016). Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. *J Psychopharmacol* **30**: 159–168.

Morgan CJ, Curran HV (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry* **192**: 306–307.

Morgan CJ, Freeman TP, Schafer GL, Curran HV (2010a). Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology* **35**: 1879–1885.

Morgan CJ, Gardener C, Schafer G, Swan S, Demarchi C, Freeman TP *et al* (2012). Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. *Psychol Med* **42**: 391–400.

Morgan CJ, Schafer G, Freeman TP, Curran HV (2010b). Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. *Br J Psychiatry* **197**: 285–290.

Morrison PD, Stone JM (2011). Synthetic delta-9-tetrahydrocannabinol elicits schizophrenia-like negative symptoms which are distinct from sedation. *Hum Psychopharmacol* **26**: 77–80.

Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF *et al* (2009). The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychol Med* **39**: 1607–1616.

Nadulski T, Pragst F, Weinberg G, Roser P, Schnelle M, Fronk EM *et al* (2005). Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of Delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. *Ther Drug Monit* **27**: 799–810.

Nardo M, Casarotto PC, Gomes FV, Guimaraes FS (2014). Cannabidiol reverses the mCPP-induced increase in marble-burying behavior. *Fundam Clin Pharmacol* **28**: 544–550.

Nguyen JD, Aarde SM, Vandewater SA, Grant Y, Stouffer DG, Parsons LH *et al* (2016). Inhaled delivery of Delta(9)-tetrahydrocannabinol (THC) to rats by e-cigarette vapor technology. *Neuropharmacology* **109**: 112–120.

O'Connell BK, Gloss D, Devinsky O (2017). Cannabinoids in treatment-resistant epilepsy: a review. *Epilepsy Behav* **70**: 341–348.

Onaivi ES, Ishiguro H, GONG JP, Patel S, Perchuk A, Meozzi PA *et al* (2006). Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. *Ann NY Acad Sci* **1074**: 514–536.

Panlilio LV, Justinova Z, Goldberg SR (2010). Animal models of cannabinoid reward. *Br J Pharmacol* **160**: 499–510.

Parsons LH, Hurd YL (2015). Endocannabinoid signalling in reward and addiction. *Nat Rev Neurosci* **16**: 579–594.

Pertwee RG (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol* **153**: 199–215.

Pertwee RG (2009). Emerging strategies for exploiting cannabinoid receptor agonists as medicines. *Br J Pharmacol* **156**: 397–411.

Petitet F, Jeantaud B, Reibaud M, Imperato A, Dubroeucq MC (1998). Complex pharmacology of natural cannabinoids: evidence for partial agonist activity of delta9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life Sci* **63**: PL1–PL6.

Ranganathan M, D'Souza DC (2006). The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology* **188**: 425–444.

Reche I, Fuentes JA, Ruiz-Gayo M (1996). A role for central cannabinoid and opioid systems in peripheral delta 9-tetrahydrocannabinol-induced analgesia in mice. *Eur J Pharmacol* **301**: 75–81.

Reid MJ, Bornheim LM (2001). Cannabinoid-induced alterations in brain disposition of drugs of abuse. *Biochem Pharmacol* **61**: 1357–1367.

Resstel LB, Tavares RF, Lisboa SF, Joca SR, Correa FM, Guimaraes FS (2009). 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol* **156**: 181–188.

Russo E, Guy GW (2006). A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* **66**: 234–246.

Sartim AG, Guimaraes FS, Joca SR (2016). Antidepressant-like effect of cannabidiol injection into the ventral medial prefrontal cortex-possible involvement of 5-HT1A and CB1 receptors. *Behav Brain Res* **303**: 218–227.

Schneider U, Borsutzky M, Seifert J, Leweke F, Huber T, Rollnik J *et al* (2002). Reduced binocular depth inversion in schizophrenic patients. *Schizophr Res* **53**: 101–108.

Schoedel KA, Chen N, Hilliard A, White L, Stott C, Russo E *et al* (2011). A randomized, double-blind, placebo-controlled, crossover study to evaluate the subjective abuse potential and cognitive effects of nabiximols oromucosal spray in subjects with a history of recreational cannabis use. *Hum Psychopharmacol* **26**: 224–236.

Schubart CD, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP (2011). Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res* **130**: 216–221.

Smirnov MS, Kiyatkin EA (2008). Behavioral and temperature effects of delta 9-tetrahydrocannabinol in human-relevant doses in rats. *Brain Res* **1228**: 145–160.

Spaderna M, Addy PH, D'Souza DC (2013). Spicing thing up: synthetic cannabinoids. *Psychopharmacology* **228**: 525.

Stadelmann AM, Juckel G, Arning L, Gallinat J, Epplen JT, Roser P (2011). Association between a cannabinoid receptor gene (CNR1) polymorphism and cannabinoid-induced alterations of the auditory event-related P300 potential. *Neurosci Lett* **496**: 60–64.

Stern CA, Gazarini L, Takahashi RN, Guimaraes FS, Bertoglio LJ (2012). On disruption of fear memory by reconsolidation blockade: evidence from cannabidiol treatment. *Neuropsychopharmacology* **37**: 2132–2142.

Stern CA, Gazarini L, Vanvossen AC, Zuardi AW, Galve-Roperh I, Guimaraes FS *et al* (2015). Delta9-Tetrahydrocannabinol alone and combined with cannabidiol mitigate fear memory through reconsolidation disruption. *Eur Neuropsychopharmacol* **25**: 958–965.

Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K *et al* (1995). 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun* **215**: 89–97.

Sulak D, Saneto R, Goldstein B (2017). The current status of artisanal cannabis for the treatment of epilepsy in the United States. *Epilepsy Behav* **70**: 328–333.

Taffe MA (2012). Delta9-Tetrahydrocannabinol attenuates MDMA-induced hyperthermia in rhesus monkeys. *Neuroscience* **201**: 125–133.

Taffe MA, Creehan KM, Vandewater SA (2015). Cannabidiol fails to reverse hypothermia or locomotor suppression induced by Delta(9) -tetrahydrocannabinol in Sprague-Dawley rats. *Br J Pharmacol* **172**: 1783–1791.

Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG (2007). Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol* **150**: 613–623.

Todd SM, Arnold JC (2016). Neural correlates of interactions between cannabidiol and Delta(9) -tetrahydrocannabinol in mice: implications for medical cannabis. *Br J Pharmacol* **173**: 53–65.

Tulunay FC, Ayhan IH, Portoghese PS, Takemori AE (1981). Antagonism by chlornaltrexamine of some effects of delta 9-tetrahydrocannabinol in rats. *EurJ Pharmacol* **70**: 219–224.

Turkanis SA, Karler R (1986). Cannabidiol-caused depression of spinal motoneuron responses in cats. *Pharmacol Biochem Behav* **25**: 89–94.

Vann RE, Gamage TF, Warner JA, Marshall EM, Taylor NL, Martin BR *et al* (2008). Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of Delta(9)-tetrahydrocannabinol. *Drug Alcohol Depend* **94**: 191–198.

Varvel SA, Wiley JL, Yang R, Bridgen DT, Long K, Lichtman AH *et al* (2006). Interactions between THC and cannabidiol in mouse models of cannabinoid activity. *Psychopharmacology* **186**: 226–234.

Vermersch P (2011). Sativex(R) (tetrahydrocannabinol+cannabidiol), an endocannabinoid system modulator: basic features and main clinical data. *Expert Rev Neurother* **11**(4 Suppl): 15–19.

Vivian JA, Kishioka S, Butelman ER, Broadbear J, Lee KO, Woods JH (1998). Analgesic, respiratory and heart rate effects of cannabinoid and opioid agonists in rhesus monkeys: antagonist effects of SR 141716A. *J Pharmacol Exp Ther* **286**: 697–703.

Wade DT, Robson P, House H, Makela P, Aram J (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil* **17**: 21–29.

Wade DT, Vergis E (1999). The short orientation-memory-concentration test: a study of its reliability and validity. *Clin Rehabil* **13**: 164–170.

Ward A, Holmes B (1985). Nabilone. A preliminary review of its pharmacological properties and therapeutic use. *Drugs* **30**: 127–144.

Whitlow CT, Freedland CS, Porrino LJ (2002). Metabolic mapping of the time-dependent effects of delta 9-tetrahydrocannabinol administration in the rat. *Psychopharmacology (Berl)* **161**: 129–136.

Wiley JL, Burston JJ, Leggett DC, Alekseeva OO, Razdan RK, Mahadevan A *et al* (2005). CB1 cannabinoid receptor-mediated modulation of food intake in mice. *Br J Pharmacol* **145**: 293–300.

Wilson RI, Nicoll RA (2002). Endocannabinoid signaling in the brain. *Science* **296**: 678–682.

Winsauer PJ, Lambert P, Moerschbaecher JM (1999). Cannabinoid ligands and their effects on learning and performance in rhesus monkeys. *Behav Pharmacol* **10**: 497–511.

Wright MJ Jr, Vandewater SA, Taffe MA (2013). Cannabidiol attenuates deficits of visuospatial associative memory induced by Delta(9) tetrahydrocannabinol. *Br J Pharmacol* **170**: 1365–1373.

Zuardi AW, Hallak JE, Crippa JA (2012). Interaction between cannabidiol (CBD) and (9)-tetrahydrocannabinol (THC): influence of administration interval and dose ratio between the cannabinoids. *Psychopharmacology (Berl)* **219**: 247–249.

Zuardi AW, Hallak JE, Dursun SM, Morais SL, Sanches RF, Musty RE *et al* (2006). Cannabidiol monotherapy for treatment-resistant schizophrenia. *J Psychopharmacol* **20**: 683–686.

Zuardi AW, Morais SL, Guimaraes FS, Mechoulam R (1995). Antipsychotic effect of cannabidiol. *J Clin Psychiatry* **56**: 485–486.

Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG (1982). Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology* **76**: 245–250.

Zuardi AW, Teixeira NA, Karniol IC (1984). Pharmacological interaction of the effects of delta 9-trans-tetrahydrocannabinol and cannabidiol on serum corticosterone levels in rats. *Arch Int Pharmacodyn Ther* **269**: 12–19.