The Efficacy of Cannabidiol in Mitigating Delta-9-Tetrahydrocannabinol-Induced Harms: A Systematic Review

by

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Institute of Medical Science
University of Toronto

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Abstract

Introduction: Delta-9-tetrahydrocannabinol (THC) produces acute and chronic psychological, cognitive, and physiological effects, and increases the risk for dependence in certain individuals. Cannabidiol (CBD), in contrast, displays anxiolytic, neuroprotective and anti-inflammatory properties when administered alone. **Methods:** A systematic review of human randomized controlled trials (n=19) was conducted to determine whether chemovars that include CBD are more protective over the THC-only aforementioned effects. **Results:** THC+CBD chemovars may mitigate anxiety, symptoms of psychosis and certain cognitive impairments provoked by THC-dominant chemovars, particularly when administered orally. Abuse liability and physiological parameters appear to be unaltered by THC+CBD chemovars compared to THC, although THC+CBD may exert greater protective properties among infrequent users. **Discussion:** Findings from this review indicate that the effects of THC+CBD cannabis may be protective for psychological and certain cognitive outcomes, certain individuals, and perhaps at certain ratios of THC:CBD. Future research should design longitudinal investigations exploring the effects of differing doses and ratios of THC:CBD based on current frequency of use.

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Statement of Contributions

Dr. Sergio Rueda provided funding for the current study and oversaw the development of the research question, study protocol, methodology, data analysis and interpretation of the findings. Dr. Rueda also provided feedback and revisions of this thesis.

Dr. Bernard Le Foll and Dr. Benedikt Fischer provided guidance and assistance regarding framing the research question, interpreting findings as well as editing and suggesting important considerations for this thesis.

Sarah Bonato helped to craft the literature search strategy for this thesis.

Thepikaa Varatharajan was the second reviewer for the first round of abstract and full-text screening. Erik Blondal assisted as the second reviewer in the second round of abstract and full-text screening. Laura Best analyzed risk of bias among included studies as a second reviewer.

Dr. Wei Wang assisted with the statistical analyses, specifically in determining whether or not a meta-analysis was appropriate to conduct.

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List of Abbreviations

Δ_8THC	(–)-Δ_8-trans-Tetrahydrocannabinol
Δ_9THC	Delta-9-Tetrahydrocannabinol
11-OH-THC	11-Hydroxy-Delta-9-Tetrahydrocannabinol
2AG	2-Arachidonoylglycerol
5-HT$_{1A}$	5-hydroxytrptamine 1A (serotonin) receptor
A2AR	Adenosine 2A Receptor
AC/cAMP	Adenyl Cyclase/3',5'-cyclic Adenosine Monophosphate
ACMPR	Access to Cannabis for Medical Purposes
AEA	Anandamide
AIR-Scales	Analogue Intoxication Rating Scales
ARCI	Addiction Research Centre Inventory
BDI	Binocular Depth Inventory
BP	Blood Pressure
BQMI	Bett's Questionnaire upon Mental Imagery
CB1	Cannabinoid Receptor 1
CB2	Cannabinoid Receptor 2
CB3	Cannabinoid Receptor 3
CBC	Cannabichromene
CBD	Cannabidiol
CBDA	Cannabidiolic Acid
CBE	Cannabielsoin
CBG	Cannabigerol
CBGA	Cannabigerolic Acid
CBL	Cannabicycol
CBN	Cannabinol
CBND	Cannabinodiol
CBT	Cannabitriol
CMI	Cornell Medical Index
CNS	Central Nervous System
CRT	Choice Reaction Time
CYP2C19	Cytochrome Protein 2C19
CYP3A4	Cytochrome Protein 3A4
CYP450	Cytochrome Protein 450
D2	Dopamine Receptor 2
DAGL	Diacylglycerol Lipase
DSST	Digit Symbol Substitution Test
ECS	Endocannabinoid System
EEfRT	Effort Expenditure for Rewards Task
EPT	Emotional Processing Task
ERP	Event Related Potential
FAAH	Fatty Acid Amide Hydrolase
FTA	Finger Tapping Asymmetry
G-Protein	Guanine-binding Protein
GABA	Gamma-Aminobutyric Acid
GPR55	G-Protein Coupled Receptor 55
GPR18	G-Protein Coupled Receptor 18

HR	Heart Rate
HVLT-R	Hopkin's Verbal Learning Test – Revised
IMC	Intermanual Coordination
LP	Licensed Producer
MAPK	Mitogen-Activated Protein Kinase
MAGL	Monoacylglycerol Lipase
MMN	Mismatch Negativity paradigm
MRF	Marijuana Rating Form
NAPE-PLD	N-Acyl Phosphatidylethanolamine-Specific Phospholipase D
NAB	Neuropsychological Assessment Battery
NIDA	National Institute on Drug Abuse
PANSS	Positive and Negative Symptom Scale
PPFIA2	Protein Tyrosine Phosphatase Receptor Type F Polypeptide-Interacting-Protein Alpha-2
PSI	Psychotomimetic States Inventory
ROA	Route of Administration
SDS	Severity of Dependence Scale
SDV	Subjective Drug Value
SOMC	Short Orientation Memory Concentration Test
SSPS	State Social Paranoia Scale
STAI	State Trait Anxiety Inventory
STWT	Spot the Word Test
SVR	Street Value Ratings
TEPS	Temporal Experiences of Pleasure Scale
THCA	Tetrahydrocannabinolic Acid
THC-COOH	11-nor-9-Delta-Tetrahydrocannabinol
THCV	Tetrahydrocannabivarin
TRPV1	Transient Receptor Potential Vanilloid Type 1
VAS	Visual Analogue Scale

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1 Introduction

"Cannabis", the common name for the phyla, *Cannabaceae*, has been used for its medicinal and mind-altering properties for millennia, being indigenous to Central and South Asia since 4000 BC (Small, Beckstead, & Chan, 1975; Amar, 2006). Traditionally, Cannabis has been used in Chinese medicine to treat many conditions including pain, convulsions, mania, and insomnia, as well as in Indian medical contexts for digestive, analgesic, sedative, aphrodisiac, anti-viral and stimulating properties (Nuutinen, 2018).

Cannabis has since undergone significant fluctuations in public opinion and legality, coinciding with societal views on drugs and addiction, particularly over the last 100 years. Cannabis-related acute impairments such as cannabis-induced anxiety, paranoia and acute psychotic phenomenon, as well as chronic outcomes such as dependence and development of psychosis led to recognition that like most substances, in addition to its benefits, cannabis could also produce some harms.

The advent of the 21st century brought about advances in preclinical and clinical cannabis-related research which elucidated various chemicals in the plant and highlighted its therapeutic potential in different medical contexts, ensuing the gradual liberalization globally. As of 2016, an estimated 192.2 million individuals worldwide consume cannabis, with a trend for increased use over the next few years in North America (United Nations, 2018). Roughly two-thirds of American states and the District of Columbia have legalized cannabis for medical and/or recreational use (Hasin et al., 2015; Johnson, Hodgkin, Harris, 2017) leading to a decreased perception of risk and increased availability (Goldenberg et al., 2017). Australia, Israel and the majority of the European Union permit the use of cannabis for medical purposes and in addition to Canada, Uruguay has legalized cannabis for both medicinal and recreational purposes. This, in part, has led to misconceptions on either extreme, that cannabis is a dangerous drug that should be avoided, or that cannabis is largely without harm and that claims are exaggerated.

Although cannabis use appears to have remained stable in states that have legalized cannabis (Hasin et al., 2015) except for Washington which has noticed an increase in adolescent cannabis use (Cerdá et al., 2017), without proper regulations in place, those at increased risk of harm for use, such as adolescents and those with mental health predispositions/comorbidities, may fare

worse off. Subsequent to medical and recreational legalization, in 2009 and 2014, respectively, Colorado experienced a significant rise in adolescent cannabis-related emergency department and urgent care visits (1.8 per 1,000 in 2009 to 4.9 in 2015), with approximately 71% of the 4,202 visits identified involving a psychiatric diagnosis and 62% of codes indicating cannabis abuse was present (Wang et al., 2018). Therefore, there is still much controversy regarding the consequences of cannabis use, largely due to a lack of high-quality, rigorous research, now underway in various countries, especially where legalization has taken place such as Canada and the United States.

Canada has one of the highest rates of cannabis use globally, with approximately 4.6 million Canadians (16%) above the age of 15 reported consuming cannabis in the past three months (Statistics Canada 2018a) and 1.8 million consuming cannabis daily or near daily (Statistics Canada, 2018b). This reported use varies across provinces and territories, however, with Nova Scotia (21%) and Ontario (18%) residents consuming above the national average (Statistics Canada 2018a). Nova Scotia has long historical ties to cannabis production, being the first recorded site for cultivation of North American hemp in 1606 (Small, Beckstead, & Chan, 1975), which, in conjunction with its proportion of use, may have contributed to the 50% increase in cannabis-related treatment admission outcomes in Nova Scotia despite stable cases nationally (Fischer et al., 2018).

With the Access to Cannabis for Medical Purposes Regulations (ACMPR) in place for medical patients, cannabis newly legalized across Canada for recreational purposes as of October 17, 2018, and the recent legalization of cannabis edibles, extracts and topicals in October 2019, there is a need to investigate if and how cannabis-induced outcomes differ depending on plant compositions. Specifically, an exploration of whether certain varieties of cannabis can produce less harmful individual and public health outcomes is warranted.

1.1 The Endocannabinoid System

Cannabis exerts its effects through the manipulation of the endocannabinoid system (ECS). The ECS, however, was only recently discovered in the 1990s upon the elucidation of delta-9-tetrahydrocannabinol (THC) and its signal transduction activity within neuronal cells, which was similar to neurotransmitters and hormones (Howlett, 1995; Howlett et al., 2004; Howlett, 2005). The ECS is one of the most vital, versatile and ubiquitously expressed systems in the mammalian

brain, responsible for homeostatic and behavioural regulation (Katona & Freund, 2008; Ronan, Wongngamnit, & Beresford, 2016). Development of the ECS begins prenatally, having a pivotal impact on neuronal development, migration, connectivity patterns, and specificity (Fernández-Ruiz et al., 2000; Berghuis et al., 2005; Mulder et al., 2008; Castillo et al., 2012) and continues to influence growth throughout the lifespan, controlling brain plasticity, learning and memory, as well as other crucial physiological processes such as appetite, metabolism, digestion, energy, sleep, thermogenesis, nociception, and psychomotor performance (Ronan, Wongngamnit, & Beresford, 2016; Aizpurua-Olaizola et al., 2017). The ECS also has a large influence in psychological processes including the regulation of emotions, stress, anxiety, fear, as well as reward processing and addiction (Serrano & Parsons, 2011).

The ECS is comprised of endogenous ligands, ('endocannabinoids'; see, '1.1 Endogenous Cannabinoids' below), their associated receptors, cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2), regulatory proteins, and the enzymes responsible for the degradation and synthesis of the endocannabinoids. Noncanonically, the ECS uses retrograde transmission to communicate via neural networks. Endocannabinoids are synthesized 'on demand' post-synaptically and bind to cannabinoid receptors on the presynaptic membrane, preventing the release of neurotransmitters, namely GABA, glutamate, dopamine and/or acetylcholine at the presynaptic terminal (Halah et al., 2016; Jacobson et al., 2019). The endocannabinoids are then degraded by their respective enzymes when homeostatic balance is restored. By regulating neurotransmission at GABAergic and glutaminergic terminals, the inhibitory and excitatory synapses within the brain, the ECS is critical to functioning and survival (Marco et al., 2011).

Despite the ongoing discovery of novel ECS receptors, the two most well-known cannabinoid receptors are CB_1 and CB_2, which are seven-transmembrane guanine-binding regulatory protein (G-protein) coupled receptors of $G_{\alpha i/o}$ type. They are responsible for mediating neuronal transmission by reducing calcium influx and promoting potassium efflux along the cell membrane, resulting in hyperpolarization of the cell and inhibition of neurotransmitter release (Ronan, Wongngamnit, & Beresford, 2016; Mandelbaum & de la Monte, 2017; Mlost, Wasik, & Starowicz, 2019). In the brain, CB_1 receptors are located on axons and presynaptic terminals, being most highly expressed in the hippocampus, prefrontal cortex, basal ganglia and cerebellum, followed by the midbrain, basolateral amygdala and hypothalamus (Devane et al., 1988; Herkenham et al., 1990; Marco et al., 2011), however, there have also been receptors

found in the periphery, namely, in reproductive, gastrointestinal, endocrine and vascular networks (Rodriguez de Fonseca et al., 2004).

It was initially thought that CB_1 was exclusively found throughout the central nervous system, influencing cognitive and neural processes solely, whereas CB_2 was associated with the periphery and vascular permeability, displaying a multitude of anti-inflammatory and analgesic effects (Halah et al., 2016). CB_2 receptors were found to be connected with immunologic cells such as splenocytes, macrophages, monocytes and B- and T-cells, and to a lesser degree with muscle, liver, intestine, testis and adipose tissue (Munro et al., 1993; McPartland et al., 2015). More recently, the discovery of CB_2 receptors in the brainstem and cerebellum led to further studies identifying both gene and protein expression in crucial brain centres including the cortex, striatum, hippocampus and amygdala. CB_2 receptors are located on microglia and blood vessels within the brain, displaying their neural immunomodulatory properties, as well as on cortical tissues where they potentially regulate regions high in dopamine (Minichino et al., 2019). In addition to their neuronal attachments, CB_1 and CB_2 have been discovered in non-neuron cells such as oligodendrocytes and astrocytes in addition to microglia (Marco et al., 2011).

The ECS achieves homeostatic balance through binding endocannabinoids to CB_1 receptors, leading to decreased glutamate released from the presynaptic terminal and thereby preventing excitotoxic damage. Communication within the ECS takes place not only neuronally but involves crosstalk with the CNS and organs of the periphery, resulting in physiological alterations of a vast number of systems and tissues throughout the body, including the digestive, immune, cardiovascular, and musculoskeletal systems (Maccarrone et al., 2015). Activation of CB_2 also has been shown to suppress neuroinflammation in cortical regions, and release proinflammatory cytokines in the periphery (Benito et al., 2008).

1.1.1 Endogenous Cannabinoids

The two most well-studied endocannabinoids are N-arachidonylethanolamine or “anandamine” (AEA) (Devane et al., 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam et al., 1995), both of which are lipophilic in nature, allowing them to move freely through cell membranes. AEA and 2-AG are agonists at CB_1 and CB_2, however, both preferentially bind with CB_1 versus CB_2. Moreover, 2-AG is a slightly more potent agonist than AEA at both receptors (Pertwee, 2008). Agonism of cannabinoid receptors increases mitogen-activated protein kinase (MAPK) activity

and inhibits the AC/cAMP cascade, voltage-sensitive N-type and P/Q-type calcium channels, inhibiting further neurotransmitter release (Aizpurua-Olaizola 2017; Boggs et al., 2018a). The type of neuron a cannabinoid receptor is on and what neural network they belong to will dictate the effect produced when agonized by AEA or 2-AG.

Diacylglycerol lipase (DAGL) is responsible for the synthesis of 2-AG and N-acyl phosphatidylethanolamine (NAPE)-specific phospholipase D (PLD) aids in the rate-limiting step of AEA synthesis (Basavarajappa, 2007), both which occur within the postsynaptic membrane. Rather than kept stored in vesicles like most neurotransmitters, endocannabinoids are synthesized perpetually on demand, diffusing backward across the synapse to bind to cannabinoid receptors on the presynaptic membrane, allowing endocannabinoids to respond and adapt quickly to fluctuating conditions.

Prior to degradation, AEA is shuttled back into the postsynaptic terminal via an anandamide membrane transporter where it is then degraded into arachnoid acid and ethanolamine by the enzyme, fatty acid amide hydrolase (FAAH). FAAH also hydrolyzes various biologically active amides in addition to AEA including, palmitoylethanolamide, oleoylethanolamide, and to a lesser degree, 2-AG. In contrast to AEA degradation, 2-AG enters the presynaptic terminal and is hydrolyzed by monoacylglycerol lipase (MAGL) into arachnoid acid and glycerol in the presynaptic membrane (Jacobson et al., 2019).

Although FAAH and MAGL are responsible for the hydrolysis of AEA and 2-AG, respectively, other receptor channels have been implicated working in synergy with the ECS including G-Protein-coupled Receptors (GPR), GPR55 (also known as CB_3; Ronan, Wongngamnit, & Beresford, 2016) and GPR18, both presumed to be cannabinoid receptors, along with $5\text{-}HT_{1A}$ and transient receptor potential vanilloid type 1 (TRPV1) calcium channels (Baron et al., 2018). AEA can activate TRPV1, having implications for nociception modulation and recovery.

The ECS plays a critical role in emotional and cognitive regulation, interacting with the dopaminergic system and modulating the expression of N-methyl-D-aspartate receptors which are implicated in the development of psychosis (Minichino et al., 2019). Pathological mental health conditions that develop as a result of its imbalance, such as schizophrenia, provide insight into this connection. Particularly, changes in endocannabinoid levels, namely, an increase of AEA in cerebrospinal fluid, have been implicated in schizophrenia (Leweke et al., 1999; Leweke

et al., 2007). Interestingly, this is proposed to involve a negative feedback loop as levels of AEA and psychotic symptoms are negatively correlated, suggesting AEA's protective role in counterbalancing these effects (Zuardi et al., 2012). Furthermore, high levels of CB_1 receptors are found in key regions that mediate pathology to schizophrenia, such as the cerebellum, hippocampus, basal ganglia and dorsolateral prefrontal cortex, consistent with psychomotor performance impairments observed in this population (Roser et al., 2009). These findings were confirmed in a recent systematic review and meta-analysis that showed significantly greater AEA levels in the cerebrospinal fluid (SMD = 0.97; 95% CI, 0.67-1.26; $p < 0.001$; $I^2 = 54.8\%$) and blood (SMD = 0.55; 95% CI, 0.05-1.04; $p = 0.03$; $I^2 = 89.6\%$) of patients with psychotic disorders compared to controls which appeared to be normalized after successful treatment (Minichino et al., 2019). Patients with psychosis also had a significantly greater expression of CB_1 receptors on peripheral immune cells compared to controls (SMD = 0.57; 95% CI, 0.31-0.84; $p < 0$ .001; $I^2 = 0\%$). An increase in CB_2 receptor production is also observed in certain other pathological conditions and is hypothesized to be a compensatory mechanism for increased inflammation as well as with influencing long-term brain structure and functionality (Minichino et al., 2019). CB_2 may add a neuroprotective role by dimerizing with CB_1, interfering with CB_1 signaling and reducing the cellular response, preventing further damage (Pacher & Mechoulam, 2011).

The critical influence endocannabinoid signaling has on maintaining homeostasis is depicted in further instances where it is out of balance. Evidence for an altered ECS is apparent in neurological conditions such as multiple sclerosis, epilepsy, Parkinson's Disease, Huntington Disease and Alzheimer's Disease (Iannotti, Di Marzo, & Petrosino, 2016).

1.1.2 Exogenous Cannabinoids

Cannabis has several different species including the most well-known and important for discussion: Cannabis *sativa*, Cannabis *indica*, and Cannabis *ruderalis.* Centuries of crossbreeding, however, likely suggests that the majority of plants today are 'hybrids' (Small, 2015). There are over 400 chemical compounds that comprise Cannabis, with a specific set of at least 116 known as 'cannabinoids'. Exogenous cannabinoids, unlike endogenous cannabinoids, are not produced in the body but are ingested and interact with the ECS receptors to produce the majority of the effects experienced. Delta-9-tetrahydrocannabidiol (Δ_9-THC or simply, THC) is

the most well-studied and -known cannabinoid, responsible for the intoxication users attribute to cannabis. In contrast to THC, the second cannabinoid gaining great interest, cannabidiol (CBD), is said to produce no adverse effects when administered on its own. Other prominent cannabinoids within the plant include cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), cannabicycol (CBL), cannabielsoin (CBE), cannabinodiol (CBND), cannabitriol (CBT), (–)-Δ_8 -trans-Tetrahydrocannabinol (Δ_8-THC), tetrahydrocannabivarin (THCV) among others (ElSohly & Slade, 2005).

Various cannabinoids come from the same precursor, cannabigerolic acid (CBGA), including THC and CBD. CBGA is broken down by tetrahydrocannabinolic acid synthase and cannabidiolic-acid synthase to form tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) respectively. THCA and CBDA are the direct precursor molecules for THC and CBD, respectively, and are present in the unheated or raw form (Shoyama et al., 2005).

In contrast to endocannabinoids which act locally in response to biological demands and are degraded upon homeostatic restoration, exogenous cannabinoids (namely, THC) flood the central nervous system and bind with less affinity, but in greater proportions, to a multitude of centres in the brain. Given the location of CB_1 brain receptors, it has been proposed that cannabinoids disrupt the normal transmission of sensory information from certain regions of the brain to the cerebral cortex, resulting in the disintegration of neurophysiological communication (Lundqvist, 2005). Specifically, CB_1 receptors located on the soma of cholecystokinin-positive interneurons contribute to the synchronicity of cortical firing by pyramidal cells, which is responsible for the generation of gamma oscillations (Minichino et al., 2019). In comparison to brief, acute binding of endocannabinoids to CB_1 receptors which results in the termination of signaling and rapid internalization and recycling of CB_1 receptors to the cell membrane, extended exposure from exogenous cannabinoids results in the degradation of these receptors, requiring new CB_1 synthesis (Aizpurua-Olaizola et al., 2017). This mechanism is thought to be responsible for tolerance among cannabis users.

Plant-derived cannabinoids, such as THC and CBD are more accurately known as ‘phytocannabinoids’, to distinguish them from other varieties such as synthetic cannabinoids. Illicit synthetic cannabinoids such as “spice” and “K2” are potent or ‘full’ agonists of CB_1 receptors in the brain, producing more severe and intense adverse effects (i.e., tachycardia,

seizures, recurrent psychosis, increased hospitalization duration) and a greater propensity to abuse liability than the natural plant (Ford et al., 2017; Cohen & Weinstein, 2018). A recent systematic review determined from preclinical and clinical studies that both acute and repeated exposure to illicit synthetic cannabinoids is associated with pronounced impairments in executive function as well as tachycardia and seizures (Cohen & Weinstein, 2018). Therapeutic explorations have led to pharmaceutical synthetic cannabinoid preparations, which will be described under section *1.2.8 Therapeutic Advancements*.

1.2 Manipulation of the ECS by Exogenous Cannabinoids

The manipulation of the ECS by exogenous cannabinoids has been shown to resemble pathological states of when the ECS is out of balance (e.g., schizophrenia) and can potentially lead to chronic, molecular adaptations within the brain. A review of neuroanatomic alterations in cannabis users revealed that compared to controls, cannabis users have consistent hippocampal and orbitofrontal cortex volumetric reductions (Lorenzetti et al., 2019). Moreover, reduced volume and increased grey matter density are observed in the amygdala, prefrontal cortex, parietal cortex, insular cortex and striatum (however, some increased volumes are also observed in the striatum; Lorenzetti, Solowij, & Yücel, 2016). Chronic cannabis abuse induces white matter atrophy where CB_1 receptors are located particularly in frontal lobes, the hippocampus, corpus collosum and frontal-limbic networks, producing neurobehavioural deficits and symptoms of psychosis (Mandelbaum & de la Monte, 2017). Importantly, not only did locations with high concentrations of CB_1 receptors correspond to areas of neuroanatomic alterations in cannabis users, but functional and structural connectivity between high- and low-density CB_1 regions were impaired also. Impaired structural-functional connectivity in the hippocampus and caudate, two areas of high CB_1 density, is also shown in cannabis users compared to abstainers, with findings implicating alterations in learning and addiction (Kim et al., 2019). Functional alterations in cannabis users compared to nonusers include decreased activation in the anterior cingulate cortex (co-activated with frontal, parietal and limbic regions) and dorsolateral prefrontal cortex (co-activated with frontal and occipital regions) and increased activation in the striatum (co-activated with frontal, parietal and associated limbic structures) (Yanes et al., 2018). These results, obtained via a meta-analysis of a large neuroimaging repository, suggest cannabis is linked with decreases in cognitive and attentional functioning and increased/altered reward processing.

Cannabis consistently produces some level of acute perceptual alterations and cognitive impairment, with strongest evidence in acute inhibition predominantly modulated through the inferior frontal gyrus as well as acute deficits in psychomotor performance (Martin-Santos et al., 2010; Broyd et al., 2016; Sahlem et al., 2018; Oomen, Hell & Bossong, 2018). Evidence for cannabis-induced effects include impairments in acute verbal learning, memory and concentration (Broyd et al., 2016) as well as object distance, tracking behaviour, information processing and slowed time perception (Ries et al., 2014), whereas other findings implicate they are less clearly associated (Oomen, Hell & Bossong, 2018). An explanation for these impairments lies in cannabis' ability to interrupt ECS signaling in long-term depression and long-term potentiation, causing alterations in synaptic communication for extended periods. Alternate explanations, outside the scope of this review, could extend to interactions with the gut microbiota whereby cannabis use is associated with flora alterations having implications on cognitive processes (Panee, Gerschenson, & Chang, 2018).

Cannabis most notably produces acute increases in anxiety, paranoia and symptoms of psychosis, particularly in novice users. However, using cannabis frequently is also associated with double the risk of developing a chronic psychotic disorder compared to abstaining from cannabis (Marconi et al., 2016). Cannabis use can also lead to worsening mental health trajectories, problematic use and potentially dependence in individuals vulnerable to these risks (see, 1.2.5 Genetic, Environmental and Behavioural Considerations, below). Problematic cannabis use is defined as use that results in negative intra- and/or inter-personal social or health-related issues (Sznitman & Room, 2018). Chronic social impairments and decreased social interactions arising from dependence may be the product of altered processing of natural rewards, as preclinical work demonstrates deficient striatal sensitivity in long-term cannabis exposure (Zimmerman et al., 2019). Cannabis dependence has been shown to be associated with decreased levels of CB_1 receptors (D'Souza et al., 2016), reduced striatal dopamine synthesis capacity (Bloomfield et al. 2014), and reduced AEA levels in cerebrospinal fluid (Morgan et al., 2013). Downregulation of CB_1 receptors is also observed following both chronic and recent cannabis consumption, as evidenced by a recent systematic review and meta-analysis (Jacobson et al., 2019). Individuals seeking treatment for Cannabis Use Disorder (CUD) also experience low rates of abstinence (Sahlem et al., 2018; Nielsen et al., 2019), indicating poor long-term individual outcomes.

Physiologically, upon CB_1 activation, cannabis increases heart rate and has been shown to promote hypotension as a result of this centrally mediated sympathetic stimulation and decreased parasympathetic activity (Oomen, Hell & Bossong, 2018; Drummer et al., 2019). There are mixed findings relating to cannabis' influence on blood pressure, with some noticing increases in systolic pressure and decreases in diastolic pressure and others noting no significant changes. Cannabis use has been said to increase the risk of myocardial infarction and the rate of overall cardiovascular mortality, producing respiratory symptoms such as coughing and wheezing (Sahlem et al., 2018). Risk of chronic obstructive pulmonary disease (COPD), lung cancer and other respiratory diseases remain unclear as data is typically cofounded by alcohol, tobacco and/or other substances. Cannabis is now considered a risk factor for cardiovascular disorders including heart failure, with slightly increased rates of emergency department visits related to cannabis-induced cardiovascular events (Monte et al., 2019; Drummer et al., 2019).

1.2.1 THC-Mediated Effects

Although THC is a partial agonist at CB_1 and CB_2, it displays lower affinity than both AEA and 2-AG towards these endocannabinoid receptors (Pertwee, 2008). Unlike endocannabinoids that act locally upon injury or insult to a specific area of the brain and is often transient in nature (< 1 minute), THC instead 'floods' the brain, partially binding to different receptors within different cortical regions and can last hours to days (Ronan, Wongngamnit, & Beresford, 2016). By binding to CB_1 receptors, THC disrupts normal GABA and/or glutamatergic neurotransmission, and increases dopamine release, activating the mesolimbic dopamine or 'reward' system (Budney & Borodovsky, 2017; Boggs et al., 2018a). THC is first hydroxylated by cytochrome P450 (CYP450) enzymes, then undergoes a process of glucuronidation prior to elimination (Jacobson et al., 2019) to produce its major metabolites, 11-hydroxy-THC (11-OH-THC), a major psychoactive metabolite which is then oxidized to 11-nor-9-carboxy-THC (THC-COOH) (Hollister, 1974; Newmeyer et al., 2016).

Through this interaction with the ECS, THC is able to exert many of its well-known rewarding and reinforcing effects. THC interacts with CB_2 receptors to produce anti-inflammatory and muscle relaxant properties, mainly mediated through CB_2 receptor binding (Russo & Guy, 2006; Boggs et al., 2018a). However, THC is also the cannabinoid responsible for producing the typical psychoactive effects, or intoxication, experienced when consuming cannabis, chiefly

mediated through interactions with CB_1 brain receptors in a dose-dependent manner (Hoch et al., 2015; Jacobson et al., 2019).

Specifically, THC produces acute transient psychological phenomenon such as anxiety, paranoia, and perceptual alterations in healthy individuals (D'Souza et al., 2004; Boggs et al., 2018b; Colizzi & Bhattacharyya, 2018; Doss et al., 2018) as well as worsening symptoms of psychosis in individuals with schizophrenia (Fadda et al., 2004; D'Souza et al., 2005; D'Souza, Sewell & Ranganathan, 2009; Leweke & Rohleder, 2017; Borodovsky & Budney, 2018). THC produces some biphasic psychological effects, with low doses of THC eliciting anxiolytic properties and high doses (>10 mg of THC) producing anxiety (Childs, Lutz, & de Wit, 2017; Boggs et al., 2018a; Borodovsky & Budney, 2018). When anxiogenic, THC alters activation in the right amygdala during processing fearful stimuli (Bhattacharyya et al., 2017; Fusar-Poli et al., 2009). The severity of THC-induced psychotic symptoms decrease activation in the ventral striatum and anterior cingulate gyrus during retrieval, and the right temporal lobe when processing auditory stimuli (Winton-Brown et al., 2011; Bhattacharyya et al., 2012).

THC produces dose-related deficits in psychomotor coordination, reaction time, information processing, attention, verbal learning and memory deficits (Hall & Degenhardt, 2009; Broyd et al., 2016). There has been debate concerning whether impairments in cognition as a result of cannabis use are acute and transient (dissipating some weeks to months upon abstinence) or whether they are chronic, with structural and functional impairments even two years post-cessation of use having been observed (Solowij, 2006; Oomen, Hell & Bossong, 2018).

Consumption of THC dose-dependently increases the propensity for abuse and dependence in preclinical studies and in human observational, longitudinal and clinical trials. Potency of cannabis is typically reflected in THC concentration. Potency can vary from ~20-30% THC in dried flower to 80-90% THC in cannabis concentrates. These high-potency varieties, commonly referred to as 'skunk' or *sinsemilla*, interact more intensely with the ECS, modestly increasing dopamine release in the striatum and have been associated with greater abuse and dependence (Bossong et al., 2015). Moreover, acute consumption of THC, especially synthetic preparations, can induce acute increases in heart rate, cardiac output, vasospasms, arrhythmias and acute myocardial infarctions (Mittleman et al., 2001; Aryana & Williams, 2007; Goyal, Awad & Ghali, 2017; Drummer et al., 2019). The effects of potency on adverse outcomes are discussed below.

1.2.2 CBD-Mediated Effects

CBD is posited to act as an allosteric modulator at neuronal CB_1 and CB_2 receptors, potentially inhibiting agonistic ligands from binding to these receptor sites, however, its mechanism of action is still largely unclear. CBD's interaction with other receptors includes increasing serotonergic activity via increased $5HT_{1A}$ receptor signaling (Russo et al., 2005; McPartland et al., 2015), increasing dopamine (D_2) receptor activity (localized with CB_1 receptors on the same neurons in the striatum; Glass & Felder, 1997), as well as producing agonistic activity at vanilloid receptors TRPV1 and TRPV2 equivalent to capsaicin (Russo & Guy, 2006; Ronan, Wongngamnit & Beresford, 2016), and at sigma and mu opioid receptors (Pertwee, 2008; Lee et al., 2017; Szkudlarek et al., 2018). CBD interacts with α3 and α1 glycine receptors (Mandelbaum & de la Monte, 2017) and displays antagonistic properties at G-protein coupled receptors such as GPR55 (Ryberg et al., 2007), a putative cannabinoid receptor found throughout the dorsal striatum (putamen and caudate nucleus), implicating its potential as neuroprotective agent (Devinsky et al., 2014; Demirakca et al., 2011). More recently, the existence of presynaptic adenosine A2A receptor (A2AR) heterodimerization with CB_1 receptors in the hippocampus and CBD's functional interplay with these complexes is suggestive in its memory-protecting abilities (Aso et al., 2019). CBD also inhibits T-type calcium channels inside the cell, thereby modulating intracellular calcium concentrations and signaling (Mandelbaum & de la Monte, 2017) as well as increases levels of AEA through FAAH inhibition, allowing more AEA to be available to bind cannabinoid receptors (Bisogno et al., 2001). CBD, like THC, is metabolized by CYP450 enzymes, and the effect CBD has on these CYP enzymes influence the metabolism of THC (McPartland et al., 2015), as discussed below.

Unlike THC, CBD is said to produce no psychotomimetic effects on its own (Hollister, 1973; Cunha et al., 1980; Carlini & Cunha, 1981; Mechoulam, Parker, & Gallily, 2002; Iseger & Bossong, 2015; Boggs et al., 2018a), and can be tolerated up to 1500 mg/day or 30 mg intravenously (Bergamaschi et al., 2011a). CBD has also been investigated as an antipsychotic with some evidence of its potential and optimal tolerability profile (Zuardi et al., 1995, Zuardi et al., 2006; Zuardi et al., 2012; Campos & Guimarães, 2008; Leweke et al., 2012; Boggs et al., 2018b). Given as a single oral dose, 600 mg CBD modulates activity in the striatum, medial cortex (parahippocampal) and midbrain in high-risk individuals for psychosis during verbal

encoding and recall, normalizing dysfunctional states (Bhattyacharyya et al., 2018). When patients with schizophrenia were administered 600 and 1200 mg of CBD, it was not only well tolerated but promoted cannabis abstinence 28 days later, with the higher dose achieving greater results (McGuire et al., 2017). Considering concurrent cannabis use can adversely affect the course of psychotic disorders by exacerbating symptoms of schizophrenia, resulting in relapses, poor clinical and psychosocial outcomes, and increased inpatient treatment, irrespective of the extent of use, CBD may provide some benefit in multiple ways to this population.

CBD has shown anxiolytic and anti-depressant properties, perhaps explained through its partial agonistic activity at the 5-HT_{1A} receptor. When given to a population of Social Anxiety Disorder (SAD) patients, 600 mg of CBD significantly reduced the anxiety during a simulated speaking task, compared to placebo and similar to anxiety levels of 'healthy' controls (Bergamaschi et al., 2011a). However, CBD produces an inverted-U dose-response curve in many preclinical studies. A randomized controlled trial (RCT) examining the effects of 100, 300, and 900 mg of CBD among humans confirmed these findings in a real-life situation speaking paradigm. CBD was able to significantly reduce anxiety at 300 mg compared to placebo, however, not at the higher or lower doses (Zuardi et al., 2017).

CBD appears to reduce anxiety in SAD populations (Crippa et al., 2011) as well as 'healthy' populations. One imaging study found that 400 mg of CBD (capsules) was sufficient to produce significant anxiolytic effects in limbic and paralimbic cortical areas in healthy participants (Crippa et al., 2004). Other imaging studies administering 600 mg CBD orally noted that throughout emotional processing, CBD attenuated forward connectivity between the anterior cingulate cortex and amygdala (Fusar-Poli et al., 2009; Fusar-Poli et al., 2010), and enhanced fronto-striatal connectivity between the putamen and prefrontal cortex (Grimm et al., 2018), strengthening the previous findings. However, two separate imaging RCTs, both also administering 600 mg oral CBD to 'healthy' volunteers, did not find CBD to produce any effects on anxiety (Borgwardt et al., 2008; Bhattacharyya et al., 2009). Instead, CBD diminished activity in the left temporal cortex and insula in one of the studies (Borgwardt et al., 2008). This may suggest that CBD displays anxiolytic properties upon a trigger for anxiety. Recently, CBD has also been shown to produce some impairing effects, such as increasing anxiety, in non-clinical participants with high-paranoid traits, although it did not increase persecutory ideation (Hundal et al., 2018).

Preclinical work demonstrates CBD's potential in opioid and stimulant addiction and early studies on humans implicate its role in reducing cigarette smoking and symptoms of cannabis dependence (dos Santos et al., 2017). CBD poses low risk for abuse liability as evidenced by previous studies administering doses of typically 200-800 mg orally producing no intoxication in participants (Carlini & Cunha, 1981; Crippa et al., 2004; Bhattacharrya et al., 2009; Bergamaschi et al., 2011a; Winton-Brown et al., 2011; Martin-Santos et al., 2012; Babalonis et al., 2017; Solowij et al., 2018). Recent studies, in addition to Hundal et al. (2018), have also discovered that CBD may be impairing at certain doses in certain individuals (Meier et al., 2018; Solowij et al., 2019). A recent RCT investigating the abuse potential of purified oral doses of 750, 1500 and 4500 mg of CBD (Epidiolex®; see 1.2.7 Therapeutic Advancements) among heavy recreational polydrug users, determined CBD to be intoxicating at doses of 1500 and 4500 mg compared to placebo ($p = 0.04$ and 0.002, respectively), specifically for subjective ratings of "Drug Liking" but not on cognitive nor psychomotor tasks (Schoedel et al., 2018). Positive subjective effects tended to subside within two to three hours post-consumption. Although significantly more intoxicating than placebo, CBD was less intoxicating than purified oral doses of oral synthetic THC (dronabinol; see 1.2.7 Therapeutic Advancements) at both 10 and 30 mg.

CBD does not appear to influence physiological parameters such as heart rate and blood pressure when administered on its own in ranges of 3-30 mg/kg in preclinical studies, with observational studies in humans reporting similar findings (Bergamaschi et al., 2011b). More recent evidence suggests that 600 mg (oral dose) of CBD on its own increases heart rate and decreases blood pressure among healthy men compared to placebo (Jadoon, Tan, & O'Sullivan, 2017).

CBD has garnered much attention due to the favourable therapeutic properties aforementioned as well as for its potential anti-inflammatory, anti-oxidative, anticonvulsive and anti-necrotic effects all-the-while having a superior safety and tolerability profile to typical pharmaceuticals (Millar et al., 2018). CBD has therefore additionally been investigated in preclinical models for Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, Multiple Sclerosis, and epilepsy with promise (Hill et al., 2012; Fernández-Ruiz, Moro, & Martínez-Orgado, 2015).

1.2.3 The 'Entourage Effect'

Early research into the effects of cannabis extracts versus THC isolates revealed that whole-plant derivatives produced 2-4 times the effects than THC-only (Russo, 2006). This is echoed through

patient preferences, with a US survey discovering participants prefer whole-plant derived cannabis compared to synthetic THC (Marinol) in treating symptoms (Russo, 2001). Russo (2011), posited that other cannabinoids, along with plant-derived secondary metabolites, known as 'terpenoids' produce synergistic effects when combined together that are not observed when administered as pure isolates, known as the 'entourage effect'.

Terpenoids are aromatic compounds found in essential oils of many plants species and are responsible for the flavour and aroma of cannabis, evolutionarily produced for protection from insects and the environment (Aizpurua-Olaizola et al., 2016). Although they typically constitute <1% of cannabis assays, they can make up to 10% of trichrome content (Russo, 2011). Terpenoid production and concentration, dependent on light and soil fertility, varies substantially, even within the same chemovar, and can therefore produce differing effects.

Importantly, when terpenoids are in concentrations greater than 0.05% (Russo, 2011), they may produce pharmacological phenomena including anti-inflammatory, anticonvulsant, neuroprotective, anti-anxiety and anti-depressant properties, which is thought to potentially enhance the effects of cannabinoid compounds, namely THC and CBD (Baron et al., 2018; Nuutinen, 2018). Terpenes (as essential oil aromatherapies) have been investigated in clinical trials, proving efficacious in treating psychiatric disorders, with stress-relieving effects most often reported (Perry & Perry, 2006).

Monoterpenes such as limonene, myrcene and pinene are typically more dominant, prior to processing, drying and storing cannabis, compared to sesquiterpenes such as caryophyllene (Lewis, Russo & Smith, 2017). Their lipophicity, ability to interact with cell membranes, ion channels, secondary messenger enzymes as well as G-protein coupled and neurotransmitter receptors is suggestive of their role in the ECS (McPartland & Russo, 2001; Russo, 2011). Specifically, evidence that sesquiterpene, β-caryophyllene, is a selective full agonist at CB_2, implicates an important role for terpenoids in inflammation and neuroprotection without producing intoxicating effects through microglial activation (Aizpurua-Olaizola et al., 2017; Nuutinen, 2018). Terpenoids such as β-caryophyllene, limonene, nerolidol, myrcene and pinenes have lethal doses of 5000 mg/kg or greater, signifying that a good therapeutic index of 1% can be achieved with administration of 50 mg/kg (Nuutinen, 2018). Other terpenoids display high selectivity for dopaminergic and GABAergic receptors as well as TRP channels. Although most

of the work on the pharmaceutical properties of terpenoids is preclinical and therefore still debated, it is widely accepted that health benefits from plant foods, vegetables and fruits are due to the synergy of whole-plant differing bioactive compounds, rather than just one (Liu, 2013). For an in-depth review of potential therapeutic uses and combinations of terpenoids to enhance cannabinoid activity see McPartland & Russo (2001), Russo (2011) and Nuutinen (2018).

Cannabinoids can also influence one another, and it is said that CBD may act synergistically with THC, having an impact on its associated effects via a variety of potential mechanisms. CBD appears to prevent THC transformation to its more potent metabolite, 11-OH-THC, evidenced via enhanced blood and urine concentrations of THC when administered concomitantly (Russo & Guy, 2006; Meier et al., 2018). CBD may also influence THC-induced activity through its inhibition of FAAH, prolonging AEA in the synaptic cleft so that it can bind to CB_1 and CB_2. Promoting increased circulation of AEA prevents THC from acting upon the CB_1 receptors (Bisogno et al., 2001). Although increased circulating levels of AEA found in patients with psychosis appear to be inversely related to psychotic symptoms experienced (Leweke et al., 1999; Giuffrida et al., 2004; Leweke et al., 2007), administration of CBD in this population increases AEA levels, corresponding to improved outcomes (Leweke et al., 2012; McGuire et al., 2017). Only when the "tone" of the endocannabinoid system is disturbed by a stimulus, such as THC, is the effect of CBD expressed (McPartland et al., 2015). However, evidence is inconclusive whether CBD can attenuate and/or potentiate certain THC-attributable effects.

1.2.4 Chemovars

Different varieties of cannabis, dependent on the chemical and cannabinoid composition, are correctly referred to as *chemovars* (derived from the phrase 'chemical varieties') rather than 'strains', which instead reflects microbiological organisms such as bacteria and viruses (Lewis, Russo & Smith, 2017). Before the entourage effect theory was proposed, scientists investigating the evolution of breeding and resulting cannabinoid phenotypes of 350 different chemovars across 50 different countries, elucidated three distinct cannabis types (Small, Beckstead & Chan, 1975). Briefly, Phenotype I was considered THC-dominant and defined as >0.3% THC with <0.5% CBD; Phenotype II consisted of >0.3% THC and >0.5% CBD; and Phenotype III as CBD predominant, with <0.3% THC and >0.5% CBD (later referred to as Type 1, Type 2 and Type 3; MacCallum & Russo, 2018). Although this work was pivotal in defining chemovars, the authors

grew these chemovars in Ottawa, Canada, and unfortunately 30% of them did not flower and therefore this data was not included in the findings.

More recently, an analysis of cannabis samples in the United States was conducted from Denver, Oakland, Sacremento, and Seattle as well as samples from the National Institute on Drug Abuse (NIDA) by plotting THC concentrations against CBD concentrations for all samples (Vergara et al., 2017). For the purposes of this review, we built upon the work of Small, Beckstead, & Chan (1975) and the more recent work of Vergara et al. (2017) recognizing cannabis should fall into categories of THC-only, THC with CBD, and CBD-only. However, an attempt to examine differences among THC:CBD ratios is needed as CBD may potentiate THC in low ratios and be protective in higher ratios. Minimal effects from cannabis are produced when concentrations are less than 1% of THC or CBD, which also coincides with Swiss law's definition of hemp (must contain <1% THC; Meier et al., 2018) but is more liberal than the US definition (< 0.3% THC; Cherney & Small, 2016). Any chemovar that contains less than 1% of one cannabinoid is dominant in the other cannabinoid (i.e., if a chemovar contains <1% THC but >1% CBD it would be classified as Type 3, CBD-dominant; >1% THC and <1% CBD would be classified as Type 1, THC-dominant). This review divided Type 2 cannabis into three distinct subcategories (see *2.3 Secondary Analysis: Conceptualization of Cannabis Categorical Domains*, below) where THC and CBD both had to be in concentrations greater than or equal to 1%.

1.2.5 Genetic, Environmental and Behavioural Considerations

Genetic, environmental and behavioural risk factors contribute to differing rates of cannabis-induced adverse effects, with a specific set of 10 core indicators identified that are associated with cannabis-incurred risk and harms (Fischer et al., 2018). Cannabis-induced adverse effects that are most important in the context of public health include CUD and developing/worsening of mental health trajectories, with some populations more vulnerable than others to harm. Individuals' 'endocannabinoid tone' (the make-up and functioning of their ECS) contributes to the heterogenous effects cannabis produces on humans. Preclinical evidence highlights THC neurotoxicity in regions of the brain dense with CB_1 receptors such as the hippocampus, amygdala, striatum, and prefrontal cortex (Lorenzetti, Solowij, & Yücel, 2016). CB_1 receptor availability is positively correlated with modulation of amygdala function by THC, with males containing greater CB_1 concentrations and experiencing increased anxiety during fear-processing

(Bhattacharyya et al., 2017). Males also present a 2.46 greater risk of problematic use compared to females (Bonner et al., 2017). Gender aside, neuroimaging studies reveal that compared to controls, cannabis users, particularly those using higher doses and at an earlier age of onset, have either decreased hippocampal, amygdala and/or prefrontal cortex volume, or increased density of grey matter in the left nucleus accumbens to the subcallosal cortex, hypothalamus and parts of the amygdala (Gilman et al., 2014; Lorenzetti, Solowij, & Yücel, 2016).

Canadians between 15–24 years old are 15 times greater than those over 65 years old to be current cannabis users and are 10 times more likely to exhibit problematic use (Bonner et al., 2017). Although largely inconclusive, early, heavy use in crucial periods of neuronal development (i.e., adolescence, prior to the age of 15) has been associated with mental illness and cognitive impairments, including a lower IQ as well as school dropout (Meier et al., 2012; Lubman, Cheetham, & Yucel, 2015; Mandelbaum & de la Monte, 2017; Hasin, 2018; Fischer et al., 2018). A recent systematic review and meta-analysis (n = 69 cross-sectional studies) suggested that chronic cognitive deficits as a result of heavy cannabis use in adolescence may be overestimated in terms of magnitude and prevalence (d, -0.25; 95% CI, -0.32 to – 0.17; $p<0.001$), with effects typically dissipating after 72 hours (Scott et al., 2018). However, the greatest concern is the increased risk of developing psychosis and/or addiction-related issues (Jacobson et al., 2019). This "critical period" theory emerged upon discovery of increased ECS activity at the onset of puberty, whereby the brain is increasing its cognitive capacities (i.e., pre-frontal cortical maturation leading to increased executive functioning, particularly in the frontal cortex and limbic system) and is most vulnerable to the drug's effects (Schneider, 2008; Satterthwaite et al., 2013). Preclinical studies are suggestive of this plausible connection between early use and psychological impairments, with intensive use in adolescence (daily/near daily use) associated with worsening outcomes (Levine et al., 2017). Adolescents consuming cannabis prior to the age of 18, after controlling for baseline depression, are at risk for developing major depression and increased suicidal attempt in early adulthood with an OR of 1.37 (95% CI, 1.16-1.62, $I^2 = 0\%$) and 3.46 (95% CI, 1.53-7.84 = 61.3%), respectively, but are not significantly at risk for the development of anxiety or suicidal ideation later in life (Gobbi et al., 2019). The effect of adolescent cannabis use on developing depression among women later in life was present even when cannabis use was stopped after adolescence (Brook et al., 2011; Gobbi et al., 2019). However, this systematic review and meta-analysis excluded 24 longitudinal studies from the

quantitative synthesis. The Adolescent Brain Cognitive Development (ABCD) Study (National Institute of Health), currently underway, will help to clarify this risk by conducting neurocognitive and neuroimaging assessments on children prior to use, following them longitudinally over time (Volkow et al., 2018).

Behavioural choices such as frequency of use, dose and potency used at each occasion, history of use (how many years of frequent and infrequent use) as well as preferred route of administration to use cannabis, such as 'smoking' cannabis via 'joints', using 'pipes' or 'bongs' (see, *1.2.6. Routes of Administration & Pharmacokinetic Considerations*, below), will impact the corresponding effects produced by cannabis. Frequent and occasional/nonusers also present differing acute and chronic risks. 'Frequent' cannabis users are defined by Newmeyer et al. (2017) as ≥ 5x/week plus a positive urine screen for metabolites, whereas 'occasional' users are classified as consuming cannabis ≥ 2x/month and ≤ 3 times per week plus a positive urine test as well. In novice or naïve users, cannabis induces acute anxiogenic and psychotic symptoms more frequently than in regular users upon consumption, especially elicited by the use of high-potency cannabis that contain greater levels of THC (Martín-Sánchez et al., 2009; Martin-Santos et al., 2012; Hunault et al., 2014). THC administration in nonusers (< 5 times of lifetime use) produced greater anxiety and psychotomimetic effects compared to cannabis users ($p = 0.04$), with severity of symptoms correlating with more pronounced neurophysiological alterations (Colizzi & Bhattacharyya, 2018). Even among abstinent modest cannabis users (24.5 ± 9 lifetime cannabis joints smoked), neurophysiological alterations are observed, with increased right hemispheric activation coupled with worse performance compared to nonusers (Colizzi & Bhattacharyya, 2018). However, chronic cognitive impairments in abstract thinking, concentration, memory, learning and psychomotor performance among regular users may no longer be detectable with one month of abstinence (Hoch et al., 2015). Using cannabis less than weekly is also associated with decreased risk of chronic psychological, cognitive and physiological harms although acute intoxication and psychomotor impairment are still present upon use (Halah et al., 2016).

Chronic use that is intensive (daily or near-daily) is associated with worsening mental health and cognitive trajectories. Resulting from structural changes and repeated use, cannabis manipulation of the ECS has led to postulations of a cannabis-induced 'amotivational syndrome', defined as decreased motivation to perform daily activities, blunted affect and impairments in concentration and attention (Hirst et al., 2017; Lac & Luk, 2018; Pacheco-Colón, Limia, & Gonzalez, 2018),

although this has been widely debated and may be attributed to underlying factors such as comorbid depression (Musty & Kaback, 1995). Prior survey-based research suggests self-reported motivation is not associated with long-term use, with impairments in effort-related decision-making being acute rather than chronic (Barnwell et al., 2006).

Additionally, the National Academies of Sciences' (2017) comprehensive review, revealed that increased levels of cannabis use led to an increased risk of developing psychosis. The risk increases further with experiences of childhood trauma or stressors early in life, making some individuals more vulnerable to cannabis' effects than others. Furthermore, a meta-analysis (Moore et al., 2007) reported frequent use was associated with an increase of experiencing a psychotic symptom (OR = 2.09) which may partly explain why more use increases the risk for developing psychosis. Another review examining 19 studies determined that younger age, genetic vulnerability, childhood maltreatment and regular cannabis use were predictive of higher psychotic-like experiences, particularly positive symptomatology, in non-clinical samples (Ragazzi et al., 2018). Twin studies reveal a close connection between cannabis exposure and genetic risk for development of psychosis, leading to delayed brain maturation from adolescence to adulthood (Grimm et al., 2018).

Genetic vulnerability, including personal or family history of psychoses/mental health disorders, and/or those presenting with prodromal signs and symptoms, are said to be at greater risk for becoming dependent on cannabis, an earlier onset of schizophrenia, or worsening current mental health trajectories even for those taking antipsychotic medications (Treffert, 1978; Moore et al., 2007; Di Forti et al., 2013; Schubart et al., 2011a; Halah et al., 2016; Bonner et al., 2017; Borodovsky & Budney, 2018; Hall et al., 2018). For instance, acute THC administration increases suspiciousness, perceptual disorganization and paranoia more so in these vulnerable individuals (Boggs et al., 2018a). Presence of a single nucleotide polymorphism in the AKT1 genotype or a Catechol-*O*-methyl transferase (COMT) gene with a valine-to-methionine (Val/Met) polymorphism has been implicated in the development of psychosis and risk for cannabis-induced psychosis especially when use commences in adolescence (Williams, Owen, & O'Donovan, 2007; Halah et al., 2016). Among a sample of 442 healthy individuals, variation at the rs2494732 locus of the AKT1 gene was predictive of acute psychotic symptomatology, cannabis dependence and baseline schizotypy (Morgan et al., 2016). The cannabinoid receptor type 1 (CNR1) gene, coding for cannabis receptors, along with increased protein expression of

Protein Tyrosine Phosphatase Receptor Type F Polypeptide-Interacting-Protein Alpha-2 (PPFIA2) is implicated in neuropsychological impairments associated with cannabis use as well (Hindocha et al., 2019; He et al., 2019). Twin studies also reveal heritability estimates for CUD ranging from 51 to 70% with strong expression of a particular trait locus variant for cholinergic receptor nicotinic α2 subunit (CHRNA2) associated with increased risk of CUD, worsening cognitive performance, increased risk of schizophrenia and attention deficit hyperactivity disorder (ADHD; Demontis et al., 2019). However, a retrospective Swedish cohort study on 50,087 male conscripts also found that schizophrenia and psychoses can develop in those not at risk who initiate use in adolescence, with those using before the age of 18 having a 2.4 greater risk of developing schizophrenia compared to nonusers (Andréasson et al., 1987). This study was re-examined by a different group of authors who accounted for use of other substances and drugs, other mental health illnesses and socioeconomic backgrounds and concluded that cannabis use >50 times was associated with an odds ratio of 6.7 (2.1 to 21.7) for developing psychoses (Zammit et al., 2002). Important environmental factors, such as stress from their employment, should be taken into consideration. A longitudinal New Zealand study following 1,265 children from birth, and assessing them repeatedly, determined that daily users between 18-25 years old had higher rates of psychotic symptoms even after controlling for confounders (Fergusson, Boden, & Horwood, 2015). Further modelling revealed that the causal pathway was from cannabis use to psychosis and not vice versa. A separate meta-analysis examining five studies for CUD at baseline, concluded that CUD predicted ensuing psychosis (Kraan et al., 2016). Individuals at ultra-high risk (UHR) of psychosis, compared to healthy controls, also have increased rates of cannabis use and CUD as well as increased positive symptomatology such as paranoid and unusual thought content (Carney et al., 2017).

Among those with mental health disorders and schizophrenia, ongoing cannabis use leads to an exacerbation of symptoms (including an increased number of episodes), decreased adherence to medications (as well as decreasing the treatment response) and an overall poorer prognosis, especially with frequent, high-potency cannabis use (Halah et al., 2016). Individuals with schizophrenia who were former frequent users of cannabis were significantly less likely to relapse compared to those using high-potency or ‘skunk-like’ varieties (Schoeler et al., 2016). High-potency users with schizophrenia were also at the highest risk for more relapses (1.9 times), fewer months until a relapse occurred, and a greater intensity of psychiatric treatment

even after adjusting for medication non-adherence compared to their former-using counterparts (OR 2.73; 95% CI 1.02 - 7.56; Schoeler et al., 2016). Benefits were observed among those who used cannabis less frequently in smaller doses of lower potency, although those who used cannabis on at least a monthly basis also experienced an increase in relapses. Furthermore, among a sample of 410 individuals with first-episode psychosis, those using 'skunk-like' cannabis daily presented with the earliest onset of psychosis compared to never users (Di Forti et al., 2013). It may be that patients with a psychotic disorder who consume cannabis prefer high-potency chemovars, as some state using cannabis with high levels of CBD and low levels of THC produce effects that are too short and weak (van Amsterdam et al., 2018).

Similarly, those with a mental health illness other than psychosis (anxiety and mood disorders) are more likely to engage in behaviours that contribute to this risk, such as using high-potency cannabis (Hoch et al., 2015; Borodovsky et al., 2017). Paradoxically, high-potency cannabis use in this population can lead to an exacerbation of depression (Bahorik et al., 2017; Agrawal et al., 2017) and anxiety (Mammen et al., 2018; Borodovsky & Budney, 2018; Hall et al., 2018), with doses as low as 5 mg of THC eliciting anxiogenic responses (D'Souza et al., 2004). Individuals with a short allele in the 5-HTLPR gene experience greater anxiety following cannabis, particularly upon frequent, high-potency use (Halah et al., 2016). Compared to less frequent users, regular cannabis users (reporting use over the past 30 days) experience a greater prevalence of current mental health distress (10.1% vs. 18.4%) and a greater incidence of a prior diagnosis of depression (18.4% vs. 29.9%), according to the Colorado 2014-2016 Behavioural Risk Factors Surveillance System (Hall et al., 2018). It is proposed that those with mental health disorders, in addition to seeking cannabis' euphoric effects, 'self-medicate' to relieve negative emotional states, leading to a perpetuating a cycle of constant cannabis use in some, and increasing their risk for substance abuse and potentially CUD.

Since anxiety is also a symptom of the typical cannabis withdrawal syndrome and proposed to contribute to continued cannabis use (Hasin et al., 2017), it is important to understand whether baseline anxiety contributes to use or whether anxiogenic outcomes are a result of cannabis initiation and withdrawal. Cannabis withdrawal is typically accompanied by irritability, nervousness/restlessness, low mood, reduced appetite, chills, and insomnia. Interestingly, only one-third of users in the general population experience withdrawal symptoms one-week to one-month post-cessation, compared to 50-95% of heavy users in institutional or research settings

(Hasin, 2018). Although typically not severe enough to elicit medical intervention, users report the symptoms of withdrawal make it more difficult to quit (Ronan, Wongngamnit, & Beresford, 2016). A severe CUD diagnosis (out of mild, moderate, severe) is more strongly associated with mood and anxiety disorders compared to milder diagnoses (Hasin et al., 2016). However, a 3-year longitudinal study examining cannabis use outcomes among anxiety disorders concluded worsening outcomes appear to be a result of individual baseline factors (sociodemographic and clinical parameters) rather than being attributed to cannabis use (Feingold et al., 2018).

Environmental considerations to take into account include increasing availability, accessibility and decreasing public perception of risk. There is support for decreasing perception of risk and increasing use, being strongest for those between 18-25 years old (Pacek, Mauro, & Martins, 2015; Salloum et al., 2018; Young-Wolff et al., 2019). Although conflicting data point to whether an increase in prevalence of cannabis use in states that have legalized cannabis exists (Leung et al., 2018), the public health concern that arises out of increased harmful use is among current users transitioning to problematic use. Consequences of increasing accessibility, availability and decreased perception of risk are highlighted in the US even among unlikely populations, especially within states such as California and Colorado that have had medical marijuana laws in place for some time. Cannabis use, both during pregnancy and in the year prior to pregnancy, among 276,991 women in Northern California, increased significantly from 2009-2017 (Young-Wolff et al., 2019). Alarmingly, rates for daily and weekly use increased most rapidly compared to monthly use in the year prior-to and in the year during pregnancy, despite increasing education and awareness about the harms of use throughout this time. These self-reported results are corroborated by an increase in urine toxicology screenings showing similar rises in cannabis use among pregnant women (Young-Wolff et al., 2017), suggesting there may be some problematic use involved.

Analysis of data from Statistics Canada's 2013 Canadian Tobacco, Alcohol and Drugs Survey (CTADS) (n = 13,635), revealed that despite 10% of the Canadian population using cannabis in the past three months, only 2% of this sample represents high-risk use (Leos-Toro, Rynard, & Hammond, 2017). It appears within Canada, location affects prevalence of outcomes with British Columbia and the Atlantic provinces displaying significantly greater 'desire to use' and 'failure to complete normal tasks' compared to their Prairie counterparts (Leos-Toro, Rynard, & Hammond, 2017).

It is clear that cannabis use is a prerequisite for CUD and that chronic users experience increased attentional bias to cannabis stimuli (Broyd et al., 2016), however, not all users become dependent on cannabis despite use. Two reviews highlight that this risk is heightened from using high-potency strains (Kraan et al., 2016; Gage, Hickman, & Zammit, 2016). Therefore, the composition of chemovars and route of administration (ROA) may have an influential role in whether outcomes are protective or harmful, regardless of other genetic, environmental and behavioural factors.

1.2.6 Routes of Administration & Pharmacokinetic Considerations

Cannabis can be administered, and therefore absorbed, in a variety of forms, however, historically, the most popular ROA is inhalation (smoking, vaporizing) in the form of dried flower and cannabinoid concentrates (Russell et al., 2018). Depending where in the body cannabis is absorbed will have an impact on its pharmacokinetic profile and mechanisms of action in the body, including the bioavailability of cannabinoids, their peak blood concentrations and the speed of these processes. Other ways in which cannabis has been administered in the literature include oral preparations (via the ingestion of cannabis extracts such as oils, capsules and cannabis-infused foods), oromucosal/sublingual sprays (administered as pump actuations; tinctures), intravenously, and topically (administered via creams, which typically are not potent enough to pass through the blood-brain-barrier and produce localized effects).

THC and CBD must undergo a process of transformation, known as ‘decarboxylation’ from their acid precursors, THCA and CBDA respectively, in which dried flower is heated to 200-210°C for 5 minutes (Grotenhermen, 2003). However, anecdotal reports suggest that these acid precursors may not be entirely pharmacologically inactive when ingested as previously described due to their lack of ECS receptor binding and non-psychoactive effects. THCA has been shown to produce anti-inflammatory (via tumour necrosis factor-alpha) and anti-emetic responses, additionally showing potential neuroprotective and anticonvulsant properties, while devoid of adverse effects (Russo & Guy, 2006). CBDA in addition to displaying strong anti-emetic properties has shown some analgesic and anti-inflammatory capabilities also (Bolognini et al., 2013; Rock, Limebeer, & Parker, 2018). Furthermore, certain cannabinoids must go through a process of aging, such as CBN, in order to be produced. It is important to understand how all these differing chemical compounds within the plant can influence varying outcomes.

Smoking provides a more rapid, intense delivery of THC to the nervous system compared to other ROAs since it enters the intrapulmonary system via absorption by alveoli in the lungs, rapidly entering into the bloodstream (Vandrey et al., 2017). THC reaches peak concentrations at 9-10 minutes (Huestis et al., 1992a; 1992b), followed by distribution into the tissues and slow elimination from plasma (Meier et al., 2018), with effects lasting approximately 2-4 hours (MacCallum & Russo, 2018). About 10-60% of THC reaches the systemic circulation with roughly 30-50% lost in 'side-stream' smoke (Ko et al., 2016; MacCallum & Russo, 2018).

Smoking requires cannabis to undergo combustion, heating dried flower at 600-900°C, which also releases harmful, carcinogenic byproducts such as tar, carbon monoxide, ammonia and polycyclic aromatic hydrocarbons (Russell et al., 2018), increasing the risk for acute and/or chronic pulmonary-bronchial harms (Jett et al., 2018). Vaporization requires less heat application, 200-210°C, and therefore has been increasingly popular as a 'safer' method to consume cannabis, as it results in similar onset and duration of effects as smoking cannabis, including comparable uptake of THC, but without as many toxic byproducts, including significantly decreased CO concentrations (Newmeyer et al., 2017; Russell et al., 2018). Smoking and vaporizing can both produce great variability in absorption due to factors such as depth of inhalation (volume), duration of breath held (exposure/time). Vaporizing cannabis concentrates has become increasingly popular among some recreational users, but poses risks including inducing psychotic episodes and psychomotor impairment (Russell et al., 2018; Cavazos-Rehg et al., 2016).

Oral ROAs are favourable for titration and dosing in medicinal contexts with standardized preparations, producing more latent onset of effects than intrapulmonary routes. Oral ROAs produce a slower onset and weaker effects due to first pass metabolism, being excreted via the kidneys, and degradation of THC by acid in the stomach, resulting in less cannabinoids and metabolites entering the bloodstream (Millar et al., 2018). Oral cannabis consumption leads to a decreased bioavailability of cannabinoids compared to inhalation, mainly as a result of travelling through the digestive tract, where approximately 25-30% is metabolized in the liver, producing a longer period of time before effects are experienced. Oral dosing therefore has an approximate bioavailability of 10% in comparison to intrapulmonary routes which have a ~25% bioavailability, resulting in a 2.5-fold difference (MacCallum & Russo, 2018). Additionally, oral ROA effects are typically prolonged, with an onset between 1–4 hours, (Product Monograph,

Marinol®, 2011) as there is a continued, slow reabsorption from the stomach and intestines, and can last anywhere from 4–6 hours post-consumption. For instance, increases in heart rate are observed 30 minutes post-smoking or vaporizing, whereas the onset of this increase was delayed by 3 hours post-consumption of oral cannabis dosing (Newmeyer et al., 2017).

This low bioavailability and variable, slow absorption make the oral ROA suitable for reducing the rapid onset and intensity of effects. In contrast to a recreational context where inhalation methods such as smoking and vaporizing are preferred, therapeutic advancements have led to oral cannabis preparations predominating the way cannabis is consumed medically, in the form of oils and capsules, both of which are ingested orally (see 1.2.7. Therapeutic Advancements below). However, oral preparations can also include cannabis-infused foods such as cookies and other edibles which can lead to unpredictable dosing, with individuals consuming more than intended. It is estimated that it would take 15-70 grams of ingested cannabis to be fatal for humans (Hall & Degenhardt, 2009) which is a seemingly large quantity, more so than what would be consumed by a 'heavy' user. Alarmingly however, accidental coma and death resulting from over-dosing on cannabis-infused foods have been reported (Russell et al., 2018; Monte et al., 2019). Illicit synthetic cannabinoids and concentrates have also been attributed to at least 13 deaths due to cardiovascular complications and are responsible for at least 35 cardiovascular emergencies, as outlined by a review of 31 case reports (Drummer et al., 2019). Although these numbers may seem small in comparison to mortality rates attributed to other drugs of abuse (e.g., opioids, cocaine, alcohol), considering cannabis is one of the most consumed substances globally, they are still important to take into consideration among vulnerable populations now that concentrates are soon to be legalized.

Therapeutic cannabinoid preparations have been developed that utilize cannabis in an 'untypical' fashion, i.e., via oromucosal 'spray' delivery. Sativex®, described in more detail below, is a spray formulation that patients administer sublingually, buccally, or via nasopharyngeal routes. CBD appears to produce the lowest bioavailability when administered in this form, with a half-life of 1.4–10.9 hours compared to 31 hours post-smoking and 2–5 days upon chronic oral dosing (oral bioavailability of 13–19%) (Millar et al., 2018). The oromucosal route has an intermediate onset of effects compared to intrapulmonary and gastrointestinal routes, roughly 15-45 minutes, and a duration similar to oral, 4-6 hours (Product Monograph, Sativex®, 2015; MacCallum & Russo, 2018). These oral formulations have been gaining clinical popularity over

the past decade, especially in patients presenting with chronic noncancer pain, chemotherapy-induced emesis and neurological conditions (by reducing spasticity in multiple sclerosis and seizures in epilepsy). Potential contraindications of continued and frequent use, however, include irritation of the lining of the mucosa (Schoedel et al., 2011).

CBD can also affect THC's pharmacokinetic distribution and metabolism. In preclinical models, pretreatment with CBD potentiates THC's effects as well as increases THC plasma levels and therefore distribution to the brain (Boggs et al., 2018a). Pretreatment of one cannabinoid before the other is affected by whether both are administered via the same route (i.e., inhaling each cannabinoid separately versus administering one cannabinoid orally and the other intravenously), as well as the time between delivery, which is also dependent on route of absorption. For instance, administering CBD intravenously 1-hour prior to smoking THC would not coincide with peak-intravenous effects, whereas consuming one dose of CBD orally 1-hour prior to smoking one dose of THC would be more appropriate due to the pharmacokinetics of each route described above. Intravenous preparations, typically used in research studies, are said to provide a "rush" to users as they are administered directly into the bloodstream, producing a rapid onset of subjective effects (Hollister, 1974).

CBD and THC also differ in absorbability. Due to cannabinoid lipophilicity, THC is stored in adipose tissue, reaching peak concentrations within 4-5 days, and having a half-life of approximately seven days, as it is released slowly back into the bloodstream (Ashton, 2001). Previous food intake can affect absorbability, as administration of high-fat foods with cannabinoids have been said to increase drug exposure in adults (Huestis et al., 2007; Zgair et al., 2016; Schoedel et al., 2018). Therefore, previous consumption of food or lack thereof can influence cannabinoid availability in the bloodstream. Upon absorption, THC is metabolized into 11-OH-THC and THC-COOH by the liver where these metabolites are further modulated and released during excretion. In comparison to THC, 11-OH-THC is said to be four times more potent than THC (McPartland et al., 2015) and is a strong CB_1 agonist, producing psychotropic effects similar to THC (Kogel et al., 2018), whereas THC-COOH is non-psychoactive, anti-inflammatory and analgesic (Grotenhermen, 2005). However, THC's main metabolites peak in concentrations at differing times, with 11-OH-THC peaking maximally close to smoking, and THC-COOH attaining peak levels 1-4 hours later, with all three metabolites detected in blood up to 30 days even after abstinence (Maykut, 1985; Newmeyer et al. 2016). Notably, CBD appears

to reduce concentrations of 11-OH-THC when administered concomitantly with THC (Russo & Guy, 2006).

Interindividual pharmacokinetics of cannabis ingestion vary widely, with many studies unable to achieve consistent associations with plasma cannabinoid concentrations and experienced effects. However, oral and oromucosal preparations are beneficial in their consistent dosing, minimizing variability in bioavailability due to smoking-related factors such as depth and length of inhalation. To add greater complexity, novice users experience a greater intensity of subjective effects, typically no matter the ROA, whereas frequent users show intoxication post-oral dosing but display tolerance of effects upon inhalation (Newmeyer et al. 2017). Interestingly, these authors discovered that although frequent users-only had a higher THC C_{max} upon smoking versus vaporizing cannabis, both frequent and occasional users had the highest THC C_{max} after inhaling cannabis (smoking and vaporizing) compared to oral dosing. Daily/near-daily users may prefer smoking methods as intrapulmonary absorption produces a readily available and greater supply of THC and its metabolites to the blood, and therefore increased intensity of effects and risk of harm. When assessing risk, especially concerning dependence related issues, it is important to understand the motivation and reasons behind use, noting that some ROAs produce a quicker 'reward' to the brain and can therefore impact an individual's desire to use.

1.2.7 Existing Literature on CBD's Ability to Mitigate THC-Induced Harms

Rottanburg et al. (1982) were the first to suggest a protective effect from CBD on THC's psychoactive effects by observing a high-incidence of psychosis in those who smoked strains higher in THC and lacking CBD. Ensuing years brought extensive preclinical work to determine CBD's potential in mitigating THC-induced effects (for a detailed review see, Boggs et al., 2018a). Intra-prefrontal cortex infusions of CBD in rats block both cognitive impairments and the anxiogenic effects induced by THC, providing evidence that optimal efficacy from CBD is achieved in the presence of pathologically abnormal states (Szkudlarek et al., 2018). A review of early preclinical literature by Russo & Guy (2006) illustrates that CBD was hypothesized to act in a biphasic manner with THC in rodents, potentiating depressant effects in low doses and blocking emotional and excitatory mechanisms at higher doses. Evidence of a dose-response relationship with cannabis-induced cognitive impairments is unclear, as CBD:THC ratios of 20:1, for instance, can inhibit THC decrements in variable-interval performance in mice, whereas

ratios of 5:1 instead potentiate these effects, and still other studies have found no effects of CBD on aspects of memory (Russo & Guy, 2006). However, due to many inconsistencies in effects observed in research conducted between rodents and humans as well as no direct parallels with human ROAs (particularly smoking) (Fadda et al., 2004), thermoregulation or spontaneous activity, and no consistent findings on the ability of CBD to mitigate THC-induced harms (Boggs et al., 2018a), this evidence should be interpreted with caution.

Research conducted on nonhuman primates, with close evolutionary ties to humans, may provide greater insight into translatable effects, as these two species produce similar antinociceptive outcomes (Vivian et al., 1998; Cooper & Haney, 2016). In contrast to rodent models, when CBD and THC are administered together in a 1:1 ratio, or higher, to nonhuman primates, cognitive impairments (specifically learning and memory) observed from administering THC-only doses are ameliorated (Boggs et al., 2018a). Equal amounts of CBD and THC (0.5 mg/kg) given intramuscularly to macaque monkeys, reversed impairments in object spatial memory tasks produced by THC (Wright et al., 2013). Moreover, when CBD:THC was administered in a 3:1 ratio, CBD diminished 'go-success' impairments in a stop-signal task produced by 0.32 mg/kg intramuscular THC in a group of male macaque monkeys, that was not observed when given in a 1:1 ratio (Jacobs et al., 2016). The repeated nature of these studies allows for inference and confidence that the parallels seen with CBD on cognition in human observational, cross-sectional and longitudinal studies are in part contributed by pharmacological activity rather than underlying differences in capabilities.

Cross-sectional studies assessing human hair samples reveal that frequent users consuming high ratios of THC:CBD (with no traces of CBD in their hair) scored higher on ratings of unusual experiences, increased schizotypal traits and impaired verbal recall compared to individuals with both THC and CBD in their hair (Morgan & Curran, 2008; Morgan et al., 2012). An online survey consisting of 1877 cannabis users, also examined the dose and type (concentration of THC and CBD) of cannabis consumed, along with using the Community Assessment of Psychic Experiences (CAPE) inventory to assess psychiatric symptomatology (Schubart et al., 2011b). Individuals using high-CBD strains (THC:CBD ratio of 2.0–55.0) reported less positive psychotic symptoms in a linear manner compared to low-CBD chemovars (THC:CBD ratios 75.0–81.5; $p < 0.001$), even after adjusting for age (current age and age of first use), gender and frequency of use. However, there was no significant correlation with depression or negative

symptoms. It should be noted that the high-CBD group on average used cannabis once a month, whereas the low-CBD group used cannabis weekly (< 5 times) which may also contribute to differences observed. Importantly, when heavy users were analyzed, those who used high-CBD chemovars had lower positive psychotic symptoms. This longitudinal data suggests CBD may have a protective effect despite frequency of use. As previously mentioned, patients with psychoses not only develop differing patterns of use but are more likely to use high-potency ('sinsemilla') cannabis, with little-to-no CBD, clouding the interpretation of these findings (Di Forti et al., 2009; Di Forti et al., 2013). Paradoxically, high-potency cannabis use is associated with a 3-times greater risk for development of a psychotic disorder (particularly with early-onset use in those who are vulnerable) and an increased rate in hospital admissions related to cannabis use (Lorenzetti, Solowij, & Yücel, 2016; Fischer et al., 2018).

A recent naturalistic study tracked 11,953 inhalation sessions using the StrainPrint app, among medicinal cannabis users to examine changes in negative affect (Cuttler et al., 2018). The largest changes in depression ratings were obtained among the high CBD + low THC group (9.5% CBD + 5.5% THC; ~2:1 ratio of CBD:THC), whereas the high CBD + high THC group (11% CBD + 26.5% THC; ~1:2.5 ratio of CBD:THC) was most effective at decreasing perceived stress. When CBD was low, no dose of THC (low to high) was able to mitigate patient stress, however, when CBD was high, higher levels of THC produced greater reductions in stress. Interestingly, no effect on anxiety with either THC only, CBD, or THC+CBD was observed ($p=0.55$). Of concern, depression (not anxiety nor stress) appeared to be exacerbated across tracked sessions ($p=0.006$).

THC potency is consistently shown to be associated with development of dependence. A 30-year longitudinal study conducted in Michigan examined the effect of potency on cannabis abuse liability trajectories at cannabis initiation (Arterberry et al., 2019). As the national average potency increased by 1%, there was a 1.41-times greater progression to CUD onset, indicating that higher potency leads to greater problematic use even after adjusting for sex and cohort effects ($p<0.001$). When this was adjusted for daily use, 4.9% potency compared to 12.3% potency was associated with a 1.67- and 3.60-fold increase in CUD symptom onset, respectively, within the first year of initiation (Arterberry et al., 2019). However, since potency is reflected in THC concentration, quantification of CBD concentrations among chemovars was not available and therefore not examined, making it difficult to infer whether CBD has a protective influence over increasing concentrations of THC on measures of abuse.

CBD may also be protective among cognitive and abuse liability outcomes as evidenced by naturalistic studies. Morgan et al. (2010a) examined samples of participants' cannabis for levels of THC and CBD concentrations as well as measured plasma levels of cannabinoids from each participant. They discovered that when intoxicated, those using strains high in CBD (plasma metabolite concentrations: THC = 15.97 ± 28.81 ng/ml; CBD = 2.48 ± 7.17 ng/ml) had decreased measures of abuse liability, enjoyed cannabis stimuli less and had reduced attentional bias to drug and food stimuli compared to the low-CBD group (THC = 21.20 ± 42.7 ng/ml; CBD = 0.14 ± 0.51 ng/ml). Interestingly, no difference was observed between participants for these measures when they were not intoxicated. This was replicated in a subsequent study showing that individuals in the high-CBD group (plasma metabolite concentrations: THC = 16.44 ± 34.57 ng/ml; CBD = 3.77 ± 6.64 ng/ml) display decreased levels of anxiety and memory impairment (immediate and delayed prose recall) when intoxicated compared to the low-CBD group (THC = 25.68 ± 46.77 ng/ml; CBD = 2.72 ± 7.91 ng/ml) (Morgan et al., 2010b).

These naturalistic studies provide added insight as most RCTs use higher concentrations (sometimes close to 30-fold) of CBD that are not observed in regulated markets nor in 'street' cannabis and more cannabis-related research has been turning toward this approach. Curran et al. (2018) examined 410 cannabis users, similar to the studies above, once while intoxicated with their own cannabis (average concentrations: 10% THC, <1% CBD) and once while they were not. Cannabis dependence and tolerance were associated with levels of THC concentrations, with greater psychotic symptoms associated with age of first-use, and THC-COOH/creatine predictive of greater dependence (Curran et al., 2018). CBD, however, was not protective over measures of abuse liability. Given the lack of CBD metabolite quantification, with no investigation into urinary metabolites undertaken, investigation into potential explanations for the absence of an effect for CBD over THC is restricted.

Inclusion of 200 mg of CBD in an open-label trial among daily/near-daily cannabis users continuing to smoke their own cannabis, decreased euphoria when intoxicated at the end of the 10-week trial, in comparison to when they were intoxicated at baseline (Solowij et al., 2018). Moreover, participants noted significantly decreased psychotic and depressive symptoms and improvements in memory, attentional switching and verbal learning, which were correlated with plasma CBD. However, the lack of a control group or placebo requires further replication of findings. The inclusion of CBD in a 1:1 ratio with THC (in combination with motivational

enhancement therapy and cognitive behavioural therapy) in a separate study, reduced cannabis use by 70.5% among cannabis-dependent users seeking treatment compared to a 42.6% reduction in the placebo group (Trigo et al., 2018). Despite decreasing overall use, the 1:1 ratio was unable to reduce withdrawal symptoms in this population.

1.2.8 Therapeutic Advancements

The 1990s marked the beginning of research into cannabinoid therapeutic potential which led to cannabis being granted access for medicinal purposes in California in 1996 and subsequently by Health Canada in 2001. Cannabis has had a long history medicinally for the use of pain with physicians William O'Shaughnessy in 1841 and Sir William Osler in 1982, as prominent advocates for its use (Ko et al., 2016). More recently, a systematic review and meta-analysis of RCTs and observational studies have evaluated natural and synthetic cannabinoid preparations for symptom management and alleviation with promising findings (Stockings et al., 2018).

Nabilone (Cesamet®) is a highly bioavailable (≥ 60%) synthetic analogue of THC, roughly five times more potent than plant-derived THC (Herkenham et al., 1990), which has been approved for cancer chemotherapy-induced nausea and vomiting in Canada and certain states in the US (Borodovsky & Budney, 2018). Dronabinol (Marinol®), although no longer available in Canada, is synthetic THC approved for anorexia ensuing from HIV/AIDS as well as cancer-related emesis (Health Canada, 2018). The therapeutic potential of CBD and CBDA has garnered attention, particularly as FAAH inhibitors (Leweke et al., 2016), and new preparations sought to combine these cannabinoids with THC (Aizpurua-Olaizola et al., 2017).

Nabiximols (trade name, Sativex®, developed by GW Pharmaceuticals) is a highly standardized cannabis-based medicinal product, delivering a precise 1:1 ratio of CBD:THC (roughly 2.5 mg and 2.7 mg respectively) per 100 μL pump-action spray (Russo, 2006). Specifically, Sativex contains Tetranabinex® and Nabidiolex®, two clonal cultivars of high-THC and high-CBD extracts (Guy & Stott, 2005). Unlike dried flower, which is typically favoured among nonmedical populations, Sativex is comprised of liquid carbon dioxide extracts, peppermint flavoring (0.05%), and ethanol:propylene glycol components that allow for spray formulation. In addition to CBD and THC, which comprise 70% of the total weight, it also contains minor cannabinoids (5-6%), terpenoids (6-7%), sterols (6%) and other minor excipients from the plant (Russo, 2006). It was first approved in the United Kingdom in 2010 for the treatment of

spasticity due to multiple sclerosis (MS), overactive bladder, and neuropathic pain, however is now approved in 29 countries for treatment of MS-related spasticity, meeting their safety and efficacy standards of typical pharmaceuticals (MaCallum & Russo, 2018). In Canada, it has been approved for neuropathic pain and spasticity due to MS and as adjunctive treatment in moderate to severe cancer-related pain conditions (Health Canada Fact Sheet, 2005). Recommendations to limit prescribing doses to no more than 30 mg/day of THC and to include CBD to avoid psychoactive effects and other adverse events have been put forth (MacCallum & Russo, 2018). Similarly, a maximum dose of Sativex of 12 sprays/day (32.4 mg THC + 30 mg CBD) has been proposed by GW Pharmaceuticals (2010), allowing increased dosing of THC without the increased risk of adverse effects (e.g., anxiety) seen without CBD (Boggs et al., 2018a).

Interestingly, Sativex has been investigated in the alleviation of cognitive symptoms and neurological disorders, relating to Alzheimer's Disease with CBD-only isolates showing promise in cases of pediatric epilepsy. CBD's anticonvulsant properties led to the formulation of Epidiolex®, a pure CBD-isolate extract used in Dravet and Lennox-Gastaut syndromes in sometimes doses as high as 2500 mg/day (MacCallum & Russo, 2018). Importantly, lower efficacious doses of Epidiolex have been observed in the concomitant administration of very low doses of THC and/or THCA (MacCallum & Russo, 2018). Like Sativex, Epidiolex is plant-derived from well-characterized *Cannabis sativa* cultivars.

Many systematic reviews have investigated cannabis' efficacy into treating various ailments, particularly in the context of pain, nausea and HIV/AIDS-related anorexia. However, a recent systematic review and meta-analysis of systematic reviews (n = 31 SRs) investigated the efficacy of cannabinoids for four main symptom/condition categories: pain (n = 23), spasticity (n = 5), nausea and vomiting (n = 6), and adverse events (n = 12), and found that the strongest evidence linked cannabis to adverse outcomes (Allan et al., 2018). Despite a much higher safety profile in comparison to other pharmaceutical drugs, namely opioids (Hall & Lynskey, 2016; Hasin, 2018), the authors note the most common adverse events include psychotic-like experiences and "feeling high" (35-70% of the reviewed population; Allan et al., 2018) especially in novice users. It may be that adverse events are experienced in those taking non-CBD containing products (i.e., Marinol, Cesamet), as evidence of Sativex use in a Phase III clinical trial on 160 MS patients significantly reduced spasticity without adverse cognitive or mood effects (Wade et al., 2004). It is important to note that findings from Allan et al. (2018) indicate a therapeutic benefit from

cannabis, as 35% of patients obtained a 30% improvement in spasticity with a 1:1 ratio of CBD:THC (Sativex), compared to 25% of patients with placebo; and 47% obtaining a clinically meaningful benefit for nausea and vomiting with cannabinoids compared to 13% for placebo. Findings should, however, be interpreted with caution as this study reviewed and combined low-quality studies. Findings pertaining to the use of cannabinoids for improving health-related quality of life (subjective sense of physical, mental, emotional and social wellbeing) of medical patients (pain, MS, amyotrophic lateral sclerosis, traumatic brain injury, cancer-related anorexia-cachexia syndrome, inflammatory bowel disease, and HIV) by a separate systematic review and meta-analysis were also inconclusive (Goldenberg et al., 2017). Although there was a subtle trend for cannabis producing a greater positive effect on quality of life in comparison to studies of just cannabinoids (e.g., dronabinol, nabilone).

Aside from treating various non-mental health related conditions, medicinal cannabis products have also been investigated in the treatment of CUD as well as in other substance use populations with some efficacy (Lucas & Walsh, 2017; Trigo et al., 2018). There is a distinction between problematic cannabis use and cannabis use for therapeutic purposes (e.g., if they are both aiming to 'treat' anxiety). Cannabis that is used to alleviate anxiety in medical contexts, for instance, is considered therapeutic if the frequency of use and dose remains relatively stable over time (once the optimal dose is achieved through titration) and does not interfere with social functioning and daily responsibilities (i.e., not meeting DSM-5 criteria for CUD). In contrast, recreational use of cannabis to alleviate anxiety is not therapeutic if it leads to a loss of control of use and impacts daily routines. The majority of patients initiating cannabis therapy show low risk of problematic prescription cannabinoid use over a 12-month period, scoring below versus above cutoff scores ($p < 0.001$), with only ~25% displaying problematic prescription cannabinoid use that was strongly associated with comorbid psychiatric and substance use problems ($p < 0.05$ and $p < 0.005$, respectively; Ware et al., 2018). Further, Sativex plus structured counselling has been investigated in a 12-week RCT among 128 individuals with CUD, excluding participants with additional substance use disorders or psychiatric conditions (Lintzeris et al., 2019). Individuals were allowed up to 32 sprays per day (86.4 mg THC + 80 mg CBD) but used a mean (SD) of 17.6 (9.5) sprays daily which was enough to produce an estimated difference in days using cannabis of 18.6 (95% CI, 3.5-33.7 days; $p = 0.02$) compared to the placebo plus structured counselling group.

Low levels of abuse may be observed in these therapeutic formulations in comparison to intrapulmonary modes of administration due to their slightly slower onset of effects, lower absorbability and the ability to titrate to a greater specified dose (Allsop et al., 2014). There has been no evidence to date for cannabis in the treatment of anxiety and mood disorders (Hasin, 2018), except perhaps for the potential antipsychotic and anxiety effects of CBD only. Moreover, there has been consistent debate regarding whether cannabis acts as a 'Band-Aid' strategy, acutely treating symptoms of anxiety and depression while worsening long-term trajectories overall by not addressing root-causes (Mammen et al., 2018). This group is at increased risk for abuse, problematic use and/or eventual dependence as reliance on cannabis to alleviate negative symptom states which can lead to increased, frequent use.

1.3 Aim

Recently, there has been growing attention around enacting policy and legislation to permit the use of cannabis for medicinal and recreational purposes in North America. Currently, 33 states and the District of Columbia have legalized cannabis for medicinal purposes and 10 for recreational markets (Arterberry et al., 2019). As of October 17, 2018, cannabis has been fully legalized for medical and nonmedical uses in Canada, the first G-20 nation to do so and second country to Uruguay (Fischer et al., 2018). However, neither the US nor Canada have developed any regulations pertaining to the maximum concentrations of THC within chemovars to be cultivated and sold. With the recent legalization of edible products in Canada on October 17, 2019, increasing potency trends (including in medicinal markets; Mammen et al., 2017) and rates of dependence (Jutras-Aswad et al., 2018), there is a need to further inform the Lower Risk Guidelines (Fischer et al., 2011; 2017) and examine alternative ways of making cannabis safer.

Potency has been on the rise globally, increasing on average 3 to 5-fold, (Compton, Volkow, & Lopez, 2017), with concentrations in the UK and Holland, specifically, changing from 4% THC and 4% CBD to 16–22% THC and <0.1% CBD; and concentrations in North America between 1994 – 2014 increasing from 4% THC to ~20% THC in dried flower and up to 80 – 90% THC in extracts and concentrates such as 'shatter' (Slade et al., 2012; ElSohly et al., 2016; Freeman et al., 2017a; Wu et al., 2017; Fischer et al., 2018; Hammond, 2019). Even among Canadian medicinal markets, 76% of all products from all Licensed Producers (LPs) were either THC-

dominant or THC-pure products (concentration of THC ranged from 7.44–29.1%), with 91% of all these THC-dominant products containing <1% CBD (Mammen et al., 2017).

Potency, in combination with the frequency and way in which individuals are consuming cannabis are important factors in considering harm. Current estimates of CUD among the population suggest 1 in 3 users meet criteria for CUD in comparison to older predictions of 10% (Hasin et al., 2015; Fischer et al., 2018). However, these estimates may be low when considering CUD among frequent or daily users (Curran et al., 2018). Frequent users of cannabis concentrates use cannabis with higher THC concentrations and endorse increased symptoms of CUD compared to frequent users that use concentrates rarely or those that never use concentrates (Bidwell et al., 2018). Frequent users of cannabis that use concentrates also experience more anxiety, feelings of nervousness and edginess compared to frequent non-users of concentrates (Bidwell et al., 2018) and current users of concentrates typically feel more 'worried' about their use compared to former concentrate users (Sagar et al., 2018).

It may be too premature to garner an understanding of if and how cannabis legalization impacts incidents of CUD in the population since the disorder develops over time, as even the time from use, to abuse, to dependence, does not follow a linear nor predictable time course interindividually (Ware et al., 2018). However, increased acute adverse events such as cannabis-related hospitalizations, psychiatric episodes, impaired driving and poisoning calls have been observed in Colorado and Washington have also been related to potency and frequency of use (Wang et al., 2018; Hall et al., 2018; Fischer et al., 2018). Greater regulation of cannabis may therefore reduce incidents of harm (Williams et al., 2017).

There has been extensive research conducted to determine alternate routes of consumption, and guidelines for further lower-risk use (Fischer et al., 2011; 2017) as well as practical considerations for therapeutic dosing (MacCallum & Russo, 2018). However, no study has systematically determined whether protection from harm is afforded by certain cannabinoid and/or plant compositions more so than others. It is important to understand whether the acute effects typically produced by high-THC chemovars can be influenced by alternate cannabinoid composition (i.e., by increasing CBD concentrations, or ratios of CBD:THC) to prevent increasing rates of emergency department visits, psychiatric hospitalization, worsening mental health trajectories and dependence disorders. However, varying quantification of cannabis-use

patterns (i.e., chemovars used, frequency of use, amount or dose, ROAs) combined with a lack of standard/consistent units of cannabis measurement, presents as a challenge to systematically assess outcomes in research.

The aim of this systematic review of randomized controlled trials (RCTs) is to determine whether CBD can mitigate THC-induced impairments in psychological outcomes (anxiety, paranoia, positive psychotic symptoms), cognitive outcomes (memory, attention, psychomotor performance), subjective outcomes (abuse liability, intoxication, 'liking') and physiological outcomes (heart rate, blood pressure) dependent on the route of administration. Secondary aims of this review are to determine whether Type 2 (THC with CBD) chemovars are protective at certain ratios more so than others in comparison to Type 1 and whether these results are influenced based on participants' frequency of use. If it is shown that Type 2 cannabis can mitigate Type 1-induced effects at specific ratios and/or for certain populations, this can potentially inform policy on the types of cannabis chemovars to be regulated and cultivated across Canada. Informed policy may translate into lower cannabis-induced mental health and dependence-related outcomes especially when targeted at those at-risk of negative outcomes associated with cannabis use, therefore research into chemovar-specific consequences will be of great benefit.

1.4 Hypothesis

There have been conflicting findings in the literature regarding CBD's efficacy in attenuating THC-induced adverse effects such as anxiety, paranoia, increases in heart rate, deficits in cognition as well as CBD's effects on THC's rewarding properties. Moreover, no study to date, as far as the authors of this review are aware, has been conducted examining whether these acute effects differ depending on cannabinoid (THC and CBD) ratio, or differences between Type 2 specified chemovars as well as on frequency of use. Systematic reviews investigating CBD's effects over THC-induced psychological (Niesink & van Laar, 2013; Iseger & Bossong, 2015) and cognitive effects (Batalla et al., 2014; Broyd et al., 2016; Boggs et al., 2018a) have not investigated abuse liability nor physiological outcomes as well. These reviews have also only examined whether or not an effect exists with the addition of CBD, whereas no study to date has examined the consequences of differing cannabis chemovars (as described in section 2.2 below) nor frequency of use on cannabis-induced outcomes. Other systematic reviews have limited their

populations, typically in medicinal contexts, and while this decision increases the internal validity of the study, it is also necessary to determine whether an overall trend exists. Given that pharmacokinetic data differs between frequent and occasional users (Newmeyer et al., 2016), limiting this investigation to a specific population (e.g., cannabis users-only) would preclude potential findings, as both medicinal and recreational cannabis users can be considered 'frequent' users. It is key to understand if certain ratios of cannabinoids, namely CBD and THC, are superior to other ratios in producing protective effects over cannabis-induced harms, and if so, for whom and under what conditions.

The authors of this review anticipate that the addition of CBD with THC in cannabis (i.e., Type 2 chemovars) will be associated with significantly fewer acute harmful psychological, cognitive, rewarding and physiological properties compared to THC-dominant (Type 1) chemovars. We further expect that this effect may be most prominent in non-smoking ROAs (e.g., oral administration). As CBD has been shown to produce an inverted-U dose-response curve when administered on its own (Zuardi et al., 2017), we anticipate the same would be observed in relation to THC for the secondary analysis. For instance, we predict that median ratios of CBD to THC (~1:1), or, 'Type 2b', would produce fewer adverse effects compared to high ratios of CBD to THC (Type 2c) and low ratios of CBD to THC (Type 2a). Specifically, we expect that ratios approximate to 1:1 of either cannabinoid (i.e., Type 2b) will produce the least psychological (e.g., anxiety, paranoia, psychotic symptoms), cognitive (e.g., impairments in memory, concentration, psychomotor performance), rewarding (i.e., abuse liability, feelings of intoxication, propensity for dependence), and physiological (increased heart rate and blood pressure) impairments and that lower or higher ratios of CBD:THC (Type 2a and 2c) will produce effects in between Type 1 and Type 2b. We also predict that Type 2 cannabis will be more protective over Type 1 chemovars among novice or infrequent compared to frequent users who may have developed a tolerance to cannabis' effects.

2 Methods

A systematic review of randomized controlled trials (RCTs) was conducted to determine whether CBD is efficacious in modulating THC-induced acute impairments in cognition, the increases in psychological and physiological phenomena and the propensity to become dependent on cannabis across 'healthy' volunteers and cannabis consumers. This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (Moher et al., 2009). Details of the review within the PRISMA diagram can be found in Figure 1.

2.1 Study Design

2.1.1 Search Strategy

Eligible studies were identified through a systematic search of the following databases: EMBASE, MEDLINE, PsychINFO, PubMed, Scopus, and Web of Science from inception until the date of the second search on January 25, 2019 (the initial search was conducted August 14, 2017). A CAMH librarian (S.B.) was consulted and assisted in the development of this search strategy on MEDLINE which was then translated, using as closely similar language as possible, to other databases to search. In order to capture various terms for the cannabinoid, THC, words such as "delta-9-tetrahydrocannabinol" and synthetic THC terms, "dronabinol", were 'Exploded' and used as 'Map Terms' in EMBASE, MEDLINE and PsychINFO. At the time of this search, the database only recognized the terms "tetrahydrocannabinol", "dronabinol" and "Marinol" as alternate strings for THC. Alternatively, CBD was known only as "cannabidiol" which was 'Exploded' and used as a 'Map Term' as well. All THC terms were combined using the 'or' function, similarly, the "cannabidiol" and "CBD" searches were merged using the function 'or'. The subsequent THC results and CBD results were combined using the 'and' function to yield the final search total. This search strategy was necessary to capture all potential included studies, as a previous more restricted preliminary search that limited articles to RCTs-only, excluded a few studies that were eligible for inclusion in this review. The detailed search strategy for individual databases can be found in Appendix 2.

2.1.2 Eligibility Criteria

Study Design

Inclusion criteria for this systematic review permitted human RCTs only. This review restricted study type to RCTs-only because RCTs are considered the 'gold-standard' of evidence. RCTs minimize known and unknown confounders arising from baseline characteristics through randomization of individuals to groups. Both parallel and crossover RCTs were included in this review.

Population

The population consisted of both male and female participants, with no restrictions on age or any other demographic variables. There was no limitation on patterns of cannabis consumption, as daily and infrequent cannabis users were included along with patient populations utilizing cannabis for medicinal, as opposed to recreational, purposes (i.e., various pain conditions). Although the reasoning for cannabis use may differ vastly across groups (i.e., relieving physical symptomatology such as spasticity and emesis; for recreational purposes; as 'self-medication' to alleviate negative mood states; etc.) there is still a need to examine whether CBD is protective across these populations or whether it affords protection to certain groups over others. Due to a large discrepancy among all human population studies in their specific inclusion/exclusion criteria for previous and current cannabis use, the inclusion criteria for this review had no restrictions on previous history of use nor on current patterns of use. This inclusion allows for a thorough overview of the possible mitigating effects of CBD across populations, increasing external validity while also affording potential distinctions to be made between groups via post-hoc subgroup analyses.

Intervention

To determine whether Type 2 cannabis is able to modulate Type 1-provoked adverse psychological, cognitive, subjective and physiological effects across multiple populations, studies comparing differing ratio combinations of CBD to THC were included as the intervention in this review. To be included, studies must have examined at least one dose combination of THC + CBD (i.e., Type 2 – the 'intervention'). Studies were included if the intervention contained greater than both 1% CBD and 1% THC within the chemovar(s) provided to participants. If the intervention had less than 1% of one cannabinoid but greater than 1% of the other, it was excluded from the review because it would be considered either THC- or CBD-dominant.

There were no restrictions regarding the ROA (e.g., oral/edible, inhaled/smoking, spray/oromucosal, intravenous administration, a combined approach, etc.), dosing procedure, or type of cannabis administered (e.g., dried flower, concentrate, pharmaceutical preparation [e.g., nabiximols), etc.]. 'Combined' ROAs included separate delivery of CBD and THC to participants (i.e., 'pretreated' with one cannabinoid, typically CBD, before the other, usually THC) as long as it was within the same session and in accordance with pharmacokinetic considerations pertaining to the ROAs utilized in their trial. For instance, if a study administered the first cannabinoid orally (gastrointestinal absorption), and the subsequent cannabinoid via a smoking or inhaling procedure (intrapulmonary absorption), the second cannabinoid must be administered by 4-5 hours post-inhalation, preferentially within 30-90 minutes after the first cannabinoid. Moreover, studies that combined plant-derived CBD and synthetic THC (i.e., dronabinol, nabilone), or vice versa, were included. However, the five-fold greater difference in THC potency for synthetic vs. plant-derived THC was taken into consideration when interpreting the data and comparing ratios of CBD:THC.

Studies that included differing doses of the same ratio of a cannabis chemovar (e.g., 20 mg THC + 10 mg CBD; and 30 mg THC + 15 mg CBD; both of which are a 2:1 ratio of THC:CBD) were included as long as they also assessed the effects of a Type 1 condition (see '*Comparison'* below). However, if more than one dose of the same Type 2 ratio was compared to Type 1, we selected the higher dose combination (e.g., from the previous example we would select the '30 mg THC + 15 mg CBD' to compare to Type 1). An exception to this is Schoedel et al. (2011) where we selected the low dose of Type 1 and medium dose of Type 2 as they most closely matched with the high Type 1 and high Type 2 doses from Karschner et al. (2011). If a study included more than one different ratio of THC:CBD (e.g., one 2:1 ratio of THC:CBD, one 1:1 ratio of THC:CBD and one 1:2 ratio of THC:CBD), we selected the middle dose of CBD (e.g., we would select the 1:1 ratio of THC:CBD as the comparison). If studies examined two Type 2 groups with differing ratios and neither were close to a 1:1, we examined the chemovar with a greater CBD:THC ratio. Data was extracted from all differing doses of the same ratio in these included studies as well as from all differing Type 2 ratios in order to conduct sensitivity analyses.

Comparison

To be included in the review, the study intervention must be compared to at least one Type 1 chemovar provided in any form. To be considered a Type 1 chemovar, the cannabis preparation must contain >1% THC and <1% CBD, (i.e., 'THC-dominant'). If more than one Type 1 chemovar was included, the preparation that was most similar (in THC concentration) to the study's Type 2's THC concentration was selected, otherwise the highest dose of THC was chosen. Studies were also included if they stated the presence of other cannabinoids (i.e. CBN, CBC) in low amounts in either the intervention and/or comparison groups. It is hard to control for this variability in other studies that may have not tested the presence of alternate cannabinoids in their administered preparations or did not state the presence of known cannabinoids for whatever reason. Similar to the intervention, there was no restriction on the route that cannabinoids were administered. Eligibility did not restrict for plant-derived versus pharmaceutical or synthetic-based (i.e., dronabinol, nabilone) cannabinoids.

Outcomes

The investigation into whether Type 2 cannabis is able to alter Type 1-induced adverse psychological, cognitive, subjective and physiological outcomes excluded any study that did not measure one or more of the following four outcome categories.

Psychological Outcomes:

Included outcome measures pertained to any psychological measures including acute anxiety, paranoia, psychotic symptoms, mood, and depressive symptoms. Measurement scales such as Spielberger's State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg & Jacobs, 1983), Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein & Opfer, 1987), Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), Psychotomimetic States Inventory (PSI; Mason, Morgan & Curran, 2008), and various Visual Analogue Scales (VAS) allowing participants to rate their mood or level of anxiety on a scale of 0-10, were used as instruments to quantify the previously stated acute symptomatology (Appendix 1; see Section 3, Results, for other scales utilized).

Cognitive Outcomes:

Studies that assessed any aspect of cognition including memory (working, episodic), concentration/attention, psychomotor performance (processing speed, reaction time, accuracy, coordination), and visual perception were included. There was no restriction on the type of cognitive measures and/or rating scales used as long as they assessed one or more of the aforementioned cognitive realms. Tasks such as the Digit Symbol Substitution Test (DSST; McLeod et al., 1982), Divided Attention Task (DAT; Casswell & Marks, 1973), and VAS scales including 'Concentration' and 'Memory' captured the cognitive components of this outcome domain (see Section 3, Results, for additional tests and scales used to assess cognition).

Subjective Outcomes:

Subjective outcomes, or abuse liability measures, are meant to gain insight into the reinforcing effects of cannabis, and ultimately, individual propensity to want to consume the drug again. Several abuse liability measures have been developed and utilized over the years, despite some criticism and uncertainty in their validity and reliability as being accurate measures of potential for dependence on cannabis specifically. These measures include the Addiction Center Research Inventory (ARCI), which have a number of subscales (i.e., Marijuana, Lysergide, Morphine/Benzedrine, etc.) pertaining to mood, bodily symptoms, sensations and perceptions, and some items relating to schizophrenia (Haertzen, Hill & Belleville, 1963; see Appendix 1); as well as capturing participant feelings of craving using VAS scales to quantify individuals' feelings of intoxication or 'high'/'stoned', their 'liking' of the drug administered, how much of a 'good effect' they are experiencing, and whether they are craving or 'wanting' more of the administered dose. Other measures and tasks to quantify participant's level of intoxication and impairment are described in Section 3, Results.

Physiological Outcomes:

Physiological measures were restricted to heart rate and blood pressure findings. Data pertaining to plasma concentrations was not quantitatively taken into consideration, however, it was assessed qualitatively, where applicable.

Exclusion Criteria

Studies utilizing differing doses of the same ratio of CBD:THC were eliminated (e.g., administering four capsules of a 1:1 ratio of CBD:THC to one group, and 8 capsules of the same 1:1 ratio in another group) only if they did not include a separate Type 1 group. Studies, including trials that pretreated one cannabinoid prior to the other, were excluded if they did not assess at least one outcome in accordance with pharmacokinetic parameters (e.g., administering cannabinoids at 10 pm and then assessing participants for the first time at 8 am the following morning). Similarly, this applied to trials where participants took the study medication/treatments home and were tested only after two weeks of consistent dosing with treatments. The purpose of this review is to assess the acute effects of chemovars containing CBD and THC in comparison to THC-only, and therefore the timeframe for outcome assessments needs to coincide with peak drug effects specific to the ROA. Studies were also excluded, despite meeting all inclusion criteria, if they collected and displayed their data in a manner that was impossible to extract information from and subsequent attempts to retrieve this data from the authors were unsuccessful. Additional exclusions were made if the authors planned to assess certain outcomes (as stated in their methods) but did not display or report on the data in the results. These studies were excluded only upon attempts to contact the authors for the relevant data with no response or if the authors were unable to provide the necessary data. This scenario typically happened when one of this review's four outcomes of interest were the RCT's secondary, and not primary, outcomes of interest.

2.1.3 Study Selection and Screening Process

Data collected and extracted for this review was performed by four independent reviewers using the DistillerSR software (Partners, 2011). Two reviewers (LD and TV) independently screened articles in three phases: Title/Abstracts, Abstract and full-text (see Appendix 3 for a copy of each screening form). Abstracts were screened a second time with an alternate second reviewer (EB) because some of the articles that should have been excluded from the first round made it into the second round. Conflicts were resolved on consensus upon further discussion between the reviewers or by a fourth, independent reviewer (SR).

2.1.4 Data Collection and Extraction

Upon identification of included studies, data was collected and inputted into an Excel spreadsheet, categorized based on study demographics as well as outcome measures assessed, and verified between two reviewers, LD and EB. For data that could not be extracted from the text or tables within the paper, PlotDigitizer (http://plotdigitizer.sourceforge.net/) was used to extract values from relevant graphs. The data was further sorted based on study ROA, with three categories emerging: 1) gastrointestinal absorption (oral ROA, typically in the form of capsules, edibles such as brownies, and anything that is directed to the stomach); 2) alveolar absorption (inhaled ROA, typically via smoking cannabis cigarettes, or vaporizing); and 3) combination [any study that used more than one ROA within the same session: gastrointestinal, alveolar, oromucosal / sublingual (i.e., spray ROA], and intravenous administration). Data was extracted from individual studies and grouped into one of the four outcomes, with the majority of studies assessing more than one outcome. References of included studies were manually explored for additional relevant studies that may meet inclusion criteria of this review.

2.1.5 Outcome Measurements

Outcomes measurements included any scale or measurement that assessed one or more of the four outcome categories (psychological, cognitive, subjective and physiological). To deal with the multiplicity of outcomes within one of the four outcome domains (e.g., one study examining paranoia, anxiety and acute psychotic symptoms, which would all be categorized as ‘psychological’ outcomes for this review), as well as the multiplicity of scales or tests for a specific domain (e.g., one study using STAI and VAS ‘anxious’ to measure anxiety), a hierarchy was determined by the authors of this review to select the outcome that would determine the overall finding for each outcome domain. If multiple psychological outcomes were measured, anxiety was selected first, followed by measures of acute psychotic symptoms since anxiety is a more common consequence of cannabis use among the general population. The most validated measures were selected first if using multiple scales to assess the same outcome. Therefore, among psychological outcomes, STAI was selected first, followed by VAS “anxiety”, PANSS and then PSI. When specifying outcomes to report on for measures of cognition, we selected items in a similar manner to psychological outcomes. Specifically, we selected outcomes that assessed concentration/attention first, followed by memory, and then psychomotor performance. Although all three of these cognitive realms are most impacted by cannabis use, concentration

and attention can severely impact daily functioning and potentially perpetuate CUD, therefore findings will be indicative of whether CBD can improve impaired focus. Among subjective outcomes, VAS ‘high’/ ‘stoned’/ ‘intoxicated’ was selected first, followed by VAS ‘liking’, ARCI (Marijuana Scale), followed by other VAS items and other measures of subjective intoxication. We selected subjective measures in this manner to highlight how subjective intoxication may change as a result of differing chemovar use. If one study examined both heart rate and blood pressure, we selected the heart rate data to represent physiological outcomes as it commonly is most affected by cannabis use.

To minimize unit-of-analysis error, a hierarchy was also determined by the authors for analyzing repeated measures of a specific outcome within a study. If possible, baseline measures were subtracted from post-dose outcome measures (i.e., change from baseline) at specific timepoints pertaining to peak pharmacokinetic effects relating to the ROA that the intervention and comparison were administered via. However, if data pertaining to change from baseline or specific-time point values were not available, peak values were selected, followed by drug x time data. Subsequently, the mean difference (MD) between groups was calculated. For instance, if treatments were administered orally, data was extracted from the first time point (or the peak mean value) that fell between 45 minutes to 3 hours. For smoking ROA, the timeframe for obtaining outcome data was between 15 minutes to 2 hours and for oromucosal spray we selected between 30 minutes to 2.5 hours. If baseline values were not provided, post-dose data were selected based on the same time points described above and used to calculate the MD. Change from baseline outcomes can be statistically combined with post-intervention measurements when utilizing the MD method, as is used in this review, but not when employing the standardized mean difference (SMD) method.

2.1.6 Risk of Bias and Quality Assessment

Two reviewers (LD and LB) independently assessed the quality of included RCTs using the Cochrane Collaboration’s risk of bias tool (Higgins et al., 2011). Cochrane’s risk of bias tool assesses the following domains for critical evaluation of bias in sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting (Higgins et al., 2011). Discrepancies that arose were either resolved on consensus or by

a third independent reviewer (TV). Risk of bias assessments for each study are located in Appendix 4.

2.2 Statistical Analysis

2.2.1 Investigating Sources of Heterogeneity

Heterogeneity can arise from clinical, methodological and statistical sources. Clinical differences between studies' populations not only include differences in demographic factors (i.e., age and gender) but also in cannabis history (i.e., previous cannabis-exposure, current cannabis use, dose consumed, frequency) and underlying conditions and symptoms. Additionally, settings vary in the number of sessions included, the length between sessions (including washout periods) and with some studies requiring participants to remain as in-patients throughout the duration of the study, and others allowing participants to return home between sessions. Further, some studies may pretreat participants with one cannabinoid before administering the next, but the timeframe may vary even among these studies. ROAs differ widely between studies as well as the use of different preparations and sources of cannabis. Methodological diversity in risk of bias and quality of methodology, as well as statistical differences among studies regarding sampling error also may contribute to the heterogeneity of this review.

2.2.2 Data Synthesis

Data was organized into a significance table according to the ROA used (oral, inhaled, combined). Studies within each sub-table were further divided based on the outcome(s) assessed (psychological, cognitive, subjective, physiological) and the Type 2 chemovar (Type 2a, 2b, 2c) utilized (see, 2.3 Secondary Analysis, below) including the dose of both Type 1 and 2 chemovars provided.

The mean difference (MD), as opposed to the standardized mean difference (SMD) was calculated to determine the effect size of the intervention, by subtracting Type 2 mean values from Type 1 means. SMD is used when assessing an outcome that has been measured in a variety of ways (e.g., using differing scales to measure anxiety) and is a method to standardize findings to a uniform scale. The SMD takes the difference in mean outcome between the intervention and comparator relative to the between-participant variability of that outcome. The MD, in contrast, measures the absolute difference between two group means, providing an

estimate of how much on average the intervention changes the effects of the comparator. MDs that were calculated were corrected by multiplying the result by –1 depending on the direction of the scale.

For parallel trials, standard deviation (SD) of the MD was obtained depending on the data provided by the study. If the standard error (SE) of both groups were provided, the following formula was used to calculate the difference in SD:

$$SD_{MD} = \sqrt{SE_1^2 + SE_2^2}$$

If the MD and associated SE were provided along with the sample size for each group, the SD was calculated using the following equation:

$$SD_{MD} = \frac{SE_{MD}}{\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

If a study provided SD and not SE values, SE was first calculated from individual group SD and sample size (n) and then those values were subsequently inputted into the formula above. If pooled SD was provided, the SD of the MD was calculated using the sample size (n) and SD of each group using the following formula:

$$SD_{MD} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}$$

Among studies that reported mean values but not variance (neither SD nor SE), SD was calculated either by using the mean and respective p-value, t-statistic or confidence interval for parallel trials only.

P-values were obtained directly from crossover studies, either from the text, extracted from graphs and/or tables, or provided after contacting the authors. If direct comparisons between Type 1 and Type 2 were not provided for an outcome measure within a crossover trial nor could not be provided by the original authors upon request, this information was considered ‘not available’ or N/A for the purposes of this review. Calculating the SE of the MD (SE_{MD}) for crossover trials using the same methods to meta-analyze parallel trials would provide an SE_{MD}

that is too large. A large SE_{MD} is due to the positive correlation that arises from using the same sample in both the treatment and control groups, which decreases MD variance.

Findings were recorded as significant if Type 2 produced a statistically significant improvement in effects compared to Type 1 ($p < 0.05$), signified as 'Yes' under the 'Overall Findings' column in Table 3–5. If Type 2 could not significantly ameliorate the deficits produced among a specific outcome by Type 1, but if either Type 1 or Type 1 and 2 independently produced significant impairments compared to placebo or baseline scores, then we classified this as 'No', having no effect over Type 1. Similarly, if Type 2 produced significantly more impairing outcomes compared to Type 1, the p-value was recorded in Table 3–5 with the description reflecting 'No', that Type 2 was unable to mitigate these deficits. However, if both Type 1 and Type 2 did not produce any significant effects for a specific outcome compared to either placebo or baseline, the term, 'non-significant' ('NS') was recorded to reflect these findings in the 'Overall Findings' column. As previously stated, crossover trials that did not report direct comparisons of Type 1 versus Type 2 were considered to have N/A statistical significance. Therefore, for these studies, we based the finding for the description column on what was either stated in the article text, graphs, figures or tables.

2.2.3 Secondary Analyses

Conceptualization of Categorical Chemovar Domains

For the secondary analysis of this review, we expanded on Small, Beckstead & Chan (1975) and MacCallum & Russo (2018)'s classification of Type 1 (THC-dominant), Type 2 (THC + CBD in ~1:1 ratio) and Type 3 (CBD-dominant) chemovars. Specifically, we wanted to determine whether a difference exists between Type 1 and Type 2 cannabis at a more granular level given CBD's inverted-U dose-response curve when administered alone. The definition of hemp differs across jurisdictions ranging from <1 % THC (Johnson, Hodgkin, & Harris, 2017; Meier et al., 2018) to stricter thresholds in Canada (<0.3% THC). However, considering low rates of adverse effects associated with THC and CBD when both are in concentrations of <1%, this threshold was used as a cut-off to distinguish Type 2 varieties from Type 1 (<1% CBD) and Type 3 (<1% THC) chemovars, as mentioned previously.

Type 2 cannabis can vary greatly in terms of the ratio of THC:CBD and there have been minimal distinctions afforded between differing ratios to date. We therefore subcategorized Type 2 chemovars into three classifications, Type 2a, Type 2b and Type 2c (see Appendix 1). Type 2a chemovars are THC predominant and reflect any proportion of THC and CBD that is equal to 2:1 or greater (e.g., 20:1 THC to CBD; 20% THC + 5% CBD; or 30 mg of THC + 1 mg CBD) as long as concentrations of CBD are > 1%. Type 2b represents an equivalent, or near-equivalent, ratio of THC:CBD. More specifically, Type 2b is any chemovar that is lower than a 2:1 ratio of THC:CBD while also not surpassing a 2:1 ratio of CBD:THC, (e.g., 10 mg THC + 8 mg CBD; or 10% THC + 12% CBD). Type 2c chemovars are CBD dominant, consisting of CBD to THC ratios that are 2:1 or greater (e.g., 15:1 CBD:THC; 10% CBD + 5% THC; or 600 mg CBD + 10 mg THC) but must contain a THC concentration > 1%. A simplified description of the three chemovars (Type 1–3) including the three Type 2-subcategories can be found in Figure 2 and below:

Type 1: THC-dominant (> 1%), < 1% CBD

Type 2a: Ratio of THC:CBD ≥ 2:1, with >1% CBD

Type 2b: Ratio of THC:CBD < 2:1 and > 1:2 of THC:CBD (i.e., ~1:1 of THC:CBD), with CBD and THC both > 1%

Type 2c: Ratio of CBD:THC ≥ 2:1, with >1% THC

Type 3: CBD-dominant (>1%), < 1% THC

Frequency of Use

A secondary analysis was also performed to assess the robustness of the findings and to determine whether differences emerged between infrequent and frequent cannabis users. Studies were divided into one of two groups based on whether participants were frequent or infrequent cannabis users to qualitatively analyze whether differences among outcomes between groups arose. Frequent users, for this review, are defined as consuming cannabis, in any variety and via any ROA, at least three or more times per week whereas infrequent users consist of those using cannabis two times, or less, per week. These recommendations were based largely from Newmeyer et al. (2016, 2017) and findings may differ had cutoffs been more liberal or

conservative regarding frequency of cannabis use. It should also be noted that the majority of users in the general population would be considered ‘infrequent users’ according to this classification.

3 Results

3.1 Included Studies

A total of 11,390 studies were identified on August 17, 2017 as a result of the literature search (Appendix 1), of which 7,130 duplicates were removed leaving 4,260 studies remaining to be screened (Figure 1). A subsequent literature search was performed on January 25, 2019 identifying an additional 2208 articles and after the removal of 1026 duplicates, 960 residual studies were left to screen. Following title and abstract screening, 131 papers remained for full-text review, of which 22 reports were included. Reasons for exclusion of the 112 articles were: non-RCT (n = 51), non-human participants (n = 6), the study did not measure at least one of the four broad outcomes (n = 18), and the study did not contain ≥ 1% CBD or THC in their 'Type 2' group (n = 31; see Appendix 2). For instance, Wachtel et al. (2002) was excluded for not having a CBD concentration ≥ 1% in what would be considered their Type 2 group, despite meeting all other criteria. Studies similar to Wachtel et al. (2002) were excluded if they utilized only one ratio of CBD:THC in differing doses (i.e. two groups using differing number of sprays of Sativex) and did not compare it to at least one THC-dominant chemovar (Type 1).

Three studies were excluded for assessing participants after being treated for two weeks with study medication, not while they were acutely intoxicated (Wade et al., 2003; Johnson et al., 2010) and for assessing participants the following morning, 10 hours post-administration of treatment (Nicholson et al., 2004). Bird et al. (1980) and Babalonis et al. (2017) were initially included, as both studies met all eligibility criteria for the review, however, both authors presented their data in a way that no Type 1 versus Type 2 comparisons could be made. Attempts to contact these authors for this data were unsuccessful. Babalonis et al. (2017) note that their primary results have been published in another paper, which has been included in this review (Haney et al., 2016). Similarly, despite meeting eligibility criteria, Berman, Symonds & Birch (2004) were excluded from the review based on not reporting on items of intoxication, as stated in their methodologies.

Dalton et al. (1975a;b) comprised of two independent trials, one of which administered both cannabinoids jointly (Dalton et al., 1975a), and the other which pretreated participants with CBD or placebo prior to THC administration (Dalton et al., 1975b), among two differing populations. Juckel et al. (2007), Roser et al. (2008) and Roser et al. (2009) are three reports of one study.

Similarly, Lawn et al. (2016) and Freeman et al. (2017b) are two reports of the same study, as well as are Hindocha et al. (2015) and Morgan et al., (2018). Therefore, for the purposes of this review, a total of 19 studies were included in the qualitative analysis.

3.1.1 Study Characteristics

Study characteristics and patient demographics of all 19 included studies are outlined in Table 1. Included studies were published from 1974 to 2019, with a cumulative total of 363 participants. The majority of trials were conducted in the United States (7), followed by the United Kingdom (4), Australia (2), Brazil (2), Germany (2), Canada (1) and Switzerland (1). A large proportion of included studies in this review (14 out of the 19) involved less than 25 participants, with over half of these (8 out of the 14) including less than 15 participants. Only five trials (26%) examined 30–48 individuals. Males predominated in the majority of included trials, with seven of the 19 studies comprising all males and no females, and an additional five studies who had males making up two-thirds, or higher, of their respective populations. The remaining seven studies had an even distribution between males and females. Ages ranged from 18–51 years old among the 363 participants, with the majority between 20–30 years old.

Seven trials examined effects among ‘frequent’ cannabis users (as defined by this review, see Section 2, Methods), 11 studies assessed outcomes in ‘healthy’ participants (nonusers of cannabis) and one study (Solowij et al., 2019) recruited both ‘healthy’ and ‘frequent’ cannabis using populations. Even among the eight trials investigating outcomes in cannabis consuming populations, study eligibility criteria as well as participant demographic information relating to the frequency and history of cannabis use varied greatly (Table 2). Most inclusion criteria for ‘healthy’ participants were vague, using terms such as “occasional use” or, “had experienced the effects of cannabis more than once” as well as, “previous exposure to cannabis in limited amounts” and also differed in eligibility regarding the time since participants last consumed cannabis prior to study entry. Regarding ‘frequent’ users, some studies assessed and quantified history of cannabis consumption by either the frequency of use (days/month) and onset of use (years) whereas other trials asked participants to estimate the number of ‘joints’ they consumed per month, or report use in terms of the number of overall times participants consumed cannabis throughout their lifespan (number of occasions they used cannabis), making it difficult to draw inferences based on prior cannabis consumption history.

The composition of Type 1 and Type 2 chemovars (including both the ratio of THC to CBD, and the dose/concentration of each cannabinoid individually) were inconsistent across studies. Eight of the 19 included studies used at least one synthetic and/or pharmaceutical preparation in their study (i.e. Sativex, dronabinol, synthetic THC and/or CBD preparations; Table 1). Bhattacharyya et al. (2010) do not describe whether the cannabinoid derivatives they administer are plant extractions or synthetic formulations. However, Englund et al. (2013) utilized a similar IV procedure to Bhattacharyya et al. (2010) and explicitly state the administration of synthetic cannabinoids to groups. Two trials in this group of eight mention the use of dronabinol as their Type 1 group (Schoedel et al., 2011; Eichler et al., 2012), while one uses nabilone as Type 1 (Leweke et al., 2000). Dalton et al. (1976a; 1976b) and Englund et al. (2013) just state the use of 'synthetic THC' as their Type 1 condition. Two of the eight use nabiximols spray as their Type 2 group (Schoedel et al., 2011; Karschner et al., 2011) and the remaining study used synthetic CBD, administered in capsules prior to smoked THC (Haney et al., 2016).

Six of the 19 studies dissolved cannabinoid extracts in ethanolic solutions and one dissolved extracts into sesame oil (Gong et al., 1983). The remaining four included studies (Hollister & Gillespie, 1975; Ilan et al., 2005; Lawn et al., 2016; Arkell et al., 2016) administered plant-derived cannabinoids to participants (or it was not clear whether they manipulated cannabis treatments in any way), but these derivatives also varied greatly in chemical composition (i.e., ratio of cannabinoids) including the dose (mg) administered to participants. Given that some ROAs are tailored specifically to their pharmaceutically developed preparations (i.e., oromucousal route for Sativex spray; oral route for dronabinol capsules), plant-derivatives were administered less frequently in the combined and oral (gastrointestinal) ROA compared to the smoked (alveolar) ROA. A detailed description of cannabis preparations and variances among studies, along with a description of sessions and broad outcomes that were assessed can be found in Table 1.

Of importance, timing of administration (of treatment administrations and outcome measurements) and number of sessions (i.e., treatment conditions for crossover trials), varied (Table 1). A few studies did not use the concomitant application of THC and CBD (administering both cannabinoids within the same chemovar) but instead pre-treated participants with placebo or CBD before administrating THC (3 of the 19 studies). However, the studies that pretreated participants with CBD (Bhattacharyya et al., 2010; Dalton et al., 1976b; Englund et

al., 2013) did so at different time points (administering the second cannabinoid at 5, 30 and 210 minutes post-first cannabinoid, respectively) and via differing ROAs (Table 1). Moreover, studies differed in the time that they would administer measurements and tests post-dose, even among similar ROAs (Table 1 – under the *'Duration'* column). To account for this heterogeneity, timepoints were selected for each outcome from individual studies based on pharmacokinetic data pertaining to the ROA used for each study (Tables 3–5). Additionally, studies differed in whether they required participants to fast or not prior to dose administration, or whether they were provided with a 'standardized' breakfast by researchers (Table 1, '*Extracts & Absorptivity Factors'*), which inherently can influence absorptivity and bioavailability of cannabis and therefore the overall effects on outcomes.

To decrease heterogeneity among included studies (given the known pharmacokinetic and bioavailability data of different ROAs), results were grouped based on how cannabinoids were administered to participants [i.e., oral administration (capsules, edibles; Table 3); inhaled administration (cannabis cigarettes, vaporizing; Table 4); and combined administration (i.e., studies that pretreated with one cannabinoid prior to administering the other; those that administered THC and CBD using differing ROA, e.g., intravenous THC + capsules containing CBD; Table 5). Data was analyzed based on each ROA for differential psychological, cognitive, abuse liability, and physiological outcomes between Type 1 and Type 2 chemovars. Tables 3–5 detail the specific treatment groups, dosages, various outcome measures assessed in each study and the associated mean difference (MD), standard error (SE) and p-value for the MD of Type 1 versus Type 2.

3.1.2 Risk of Bias Assessment

Included studies were assessed independently by two separate reviewers, LD and LB, using the Cochrane Risk of Bias Tool (Higgins et al., 2011), with Figure 2 and 3 depicting the Risk of Bias Graph and Risk of Bias Summary, respectively, for this review.

Almost half (47.8%) of the included papers were at low risk of selection bias, 46.9% had an unclear risk of bias and one study was considered high-risk for selection bias due to insufficient reporting of random sequence generation. Allocation concealment (selection bias) was considered to be low-risk in 78.3% of the papers with the remaining 21.7% having an unclear risk of bias in this regard due to insufficient reporting. Risk of bias for blinding of participants

and personnel was considered low-risk in 47.8% of the included papers and an unclear-risk for the remaining 52.2% for failing to report how blinding was achieved. The majority of the included papers (56.5%) were considered low risk for blinding of the outcome assessment and an unclear risk of this detection bias was shown in the remainder of the trials. There was a high risk of attrition bias among 26.0% of the papers as a result of incomplete outcome data due to high rates of participant drop-out, with Haney et al. (2016) losing 19 out of 50 participants prior to study completion. More than half of the studies (56.5%) were considered low risk for any reporting bias, however, over a third (34.8%) were considered high risk due to selective outcome reporting and failing to include data from measurements specified in their protocol. A number of papers (30.5%) were considered high risk for other biases, for reasons such as the recruitment of male medical students and / or doctors only, making it necessary interpret these results with caution when generalizing findings. The remaining 56.5% and 13.0% of trials were at unclear and low risk, respectively. Further details about bias and complete risk of bias tables for individual papers can be found in Appendix 3.

3.2 Oral Route of Administration

Seven of the 19 included studies administered chemovars to participants via the oral ROA, using either capsules or ‘edibles’ (cannabis-infused baked goods), to determine differing cannabinoid effects (Table 3). Four of these seven studies examined psychological phenomenon, four measured cognitive outcomes, four looked at abuse liability and subjective outcomes, and four of the trials investigated physiological effects.

3.2.1 Psychological Outcomes

Karinol et al. (1974), Zuardi et al. (1982), Leweke et al. (2000) and Eichler et al. (2012), all used various psychological measures to examine the effects of THC alone or in combination with CBD on anxiety, mood and psychosis. In two of these studies, CBD was able to mitigate THC-induced psychological reactions and anxiety, but only in higher-ratio-CBD chemovars. Specifically, Karinol and colleagues (1974) observed that participants who were allocated to the higher-CBD Type 2 groups did not experience strong psychological reactions (classified as grade 4, on a scale of 0-4) that were noted in the Type 1 group ($p < 0.05$) at 95 minutes post-dose. Participants in the Type 2 groups noted more ‘pleasurable’, anxiolytic effects, compared to those in the Type 1 condition who experienced strong ‘waves’ of anxiety sometimes reaching close to

a panic-state. Similarly, although Zuardi et al. (1982) noticed a significant increase in anxiety in their Type 2 group compared to baseline scores ($p < 0.05$) as measured by the STAI (A-state), scores were also significantly reduced in comparison to what was observed under Type 1 conditions ($p < 0.05$) at 120 minutes post-cannabis.

Leweke et al. (2000) and Eichler et al. (2012), however, did not observe any significant changes in anxiety nor in ratings of acute psychotic symptoms between any of their groups. Leweke et al. (2000) utilized the Adjective Mood Scale, a subjective mood-scale, to measure mood and the STAI-XI and a Self-Rating Anxiety Scale to assess alterations in anxiety, however, there were no significant differences between any of the groups, including in comparison to placebo. Eichler et al. (2012) examined the effects of heated vs. unheated cannabis extracts in comparison to synthetic THC (dronabinol) in ten healthy male volunteers, nine of whom completed the study and one who left post-administration of dronabinol due to intoxication. The authors used VAS scales to measure "anxiety", "illusion and derealization", "hallucination", and "changed emotions", among others. No significant differences between any of their groups for these measures emerged, despite a weak intensity of psychotropic effects being present amongst all conditions (Eichler et al., 2012). They noted Type 1 (dronabinol) produced slightly greater psychotropic outcomes, however they did not display nor discuss the data further.

3.2.2 Cognitive Outcomes

Four oral ROA studies measured some aspect of cognition including working memory, processing speed, visual perception, attention, psychomotor performance and coordination. CBD was able to significantly mitigate THC-induced impairments in working memory, reaction time and mental imagery in two out of the four studies (Karinol et al., 1974; Leweke et al., 2000).

For instance, Type 2 was able to block deficits in a time production task that were produced in the Type 1 group at 95 minutes post-dose (MD = -11.3 ± 2.58; 95% CI, -16.36, -6.24; $p = 0.002$; Karinol et al., 1974). This time production task, administered to capture the subjective 'internal clock' in relation to geophysical time, involved experimenters alternating provision of feedback to participants after their 60-second estimation, in two blocks of five (i.e., five estimations without feedback, five estimations with feedback such as 'correct', 'too short', 'too long'). Larger deviations were apparent when participants were not provided with feedback within the task. There were no significant differences observed between any of the Type 2 groups and

placebo when provided with feedback, despite slight impairments observed in the Type 1 group post-feedback, suggesting CBD may have a protective effect over working memory, however further evidence is needed to corroborate these findings.

Leweke and colleagues used the Binocular Depth Inversion test to examine whether visual perception is altered upon consuming cannabis, as is typically observed in psychosis, among nine infrequent male cannabis users. The authors administered nabilone as Type 1, which produced a significant reduction in the binocular depth inversion of the 'ordinary objects', 'flowers' and 'faces' classes compared to baseline, signifying a more pronounced depth inversion (all $p < 0.05$). The Type 2 condition, however, displayed a weak, non-significant, partial antagonistic effect, reducing the clinical experience of Type 1-induced intoxication in the early and late stages post-administration. Moreover, change from baseline scores at 120 minutes revealed that Type 2 was significantly able to modulate impairments in depth inversion among the 'faces' category ($MD = 0.09$; $p = 0.021$) with a trend in significance for 'ordinary' and 'flowers' classes as well (data not shown). Leweke and colleagues also utilized Betts Questionnaire Upon Mental Imagery (QMI) to assess the vividness of mental imagery under each treatment condition. Scores appear significantly reduced (signified by a higher score in QMI) in the Type 2 group in comparison to Type 1, when looking at the graph of the results. However, due to the nature of the study, being a crossover design, no precise p-value could be calculated. Interestingly, Type 1 (nabilone) had no effect on vividness of mental imagery whereas Type 2 indicated a reduction in this vividness, the opposite of what one would expect cannabis to produce. The authors note strong conceptual and methodological criticisms directed at the QMI, providing one potential explanation as to why Type 1 cannabis did not influence mental imagery, and another being due to the fact the authors used nabilone, a synthetic analogue of THC. All participants also noted that the intensity of impairments in concentration were greater under all experimental conditions.

In contrast to Karinol et al. (1974) and Leweke et al. (2000), two papers from the same study did not find CBD to have a significant influence on THC-induced impairments in cognition, specifically on measures of attention, working memory, psychomotor coordination, and reaction times (Roser et al., 2008; 2009). Roser et al. (2008), investigated the effects of placebo, Type 1 and Type 2 cannabis on auditory-evoked P300 amplitudes recorded during a choice reaction task that tested aspects of decision-making, attention, motor coordination and reaction speed. Reduced P300 amplitudes in midline central and parietal electrode regions represent a robust

finding in schizophrenia as well as neurodegenerative (i.e., Alzheimer's disease) and depressive conditions (bipolar disorder and unipolar depression), signifying deficits in attentional functioning and working memory (Roser et al., 2008). The Type 1 condition produced significant reductions in P300 at frontal, central and parietal electrodes in comparison to placebo. Type 2 was unable to mitigate these THC-induced impairments, producing a statistically significant reduction in P300 amplitudes at central ($p = 0.005$) and parietal electrodes ($p = 0.016$), with a trend at frontal electrodes ($p = 0.064$), in comparison to placebo. Reaction times under Type 1 and Type 2 conditions did not significantly differ from placebo or each other. However, plasma concentrations of THC, 11-OH-THC and THC-COOH for Type 1, and of THC, CBD and THC-COOH for Type 2 groups did not correlate with their respective P300 amplitudes. It is important to note that three of the seven total participants who did not complete the experiment were excluded as a result of experiencing panic attacks, two of whom were female in the Type 2 condition and one female in the Type 1 condition.

In a following study, Roser et al. (2009), assessed psychomotor performance using a finger tapping test series (Finger Tapping Asymmetry; FTA; Sessions A-D, Appendix 1), known to be a highly reliable test for assessing motor impairments (Lezak, 1995) with lower values representing greater disturbance. The authors also used Intermanual Coordination (IMC; alternate tapping – Session E; see Appendix 1) as an indicator of interhemispheric transfer, with higher values corresponding to increased cognitive disturbances (Gorynia & Egenter, 2000). It should be highlighted that only right-handed participants with a laterality quotient between 60-100 were included in the study and that the finger tapping test was executed 120-minutes post-dose. Surprisingly, Type 2 revealed a greater reduction of right-hand tapping frequencies compared to placebo (Sessions A-D, $p < 0.01$), similar to what is seen in patients with schizophrenia, that was not seen in the Type 1 condition except for Session D ($p = 0.014$). However, despite these impairments for individual hand tapping, there were no significant differences between the Type 1 and Type 2 condition for IMC or FTA compared to placebo. Interestingly, left-hand tapping frequencies and FTA were negatively correlated with plasma concentrations of 11-OH-THC ($r = 0.421$, $p = 0.041$) under the Type 1 condition. Although this present review did not examine gender differences, it is worth noting that cannabinoid concentrations produced differing effects dependent on gender, with males showing quicker left-hand tapping compared to females, under the Type 1 condition (Sessions A-D, $p < 0.04$),

suggesting male tolerance compared to females for THC-induced psychomotor impairments. Additionally, the standard deviation of right-hand tapping frequencies for females were significantly higher in the Type 1 versus placebo group ($p = 0.015$) but not in the Type 2 condition. Importantly to note, this deviation was not observed in male participants, whom experienced no differences in right-hand tapping frequency standard deviation. There were also no gender differences observed in the placebo group. Left hand tapping was faster among males under the Type 2 as well (sessions A-C, $p < 0.05$) compared to females. Disturbances observed in left-hand tapping for female participants suggests a potential gender sensitivity to the acute psychomotor effects of cannabis through greater functional instability of female participants' dominant hand, and that CBD may be protective for this subgroup specifically. Limitations of this study include the exclusion of left-handed individuals and those without 'normal hearing'. The participants were also required to fast at least eight hours prior to cannabinoid dosing and for four hours post-dose, unlike other studies using the oral ROA that provided individuals with a light standardized breakfast (Karinol et al., 1974; Leweke et al., 2000). Given that the treatments were administered orally, this can reduce the uptake of the cannabinoids into the bloodstream whereas high-fat foods can increase absorption.

Eichler et al. (2012) used VAS scales to measure aspects of cognition including "concentration" and "disorientation". However, the authors did not report on any of this data and categorized these two VAS measurements as 'psychotropic effects', stating that although Type 1 (dronabinol) produced slightly increased effects compared to the other conditions, no statistically significant differences were found between groups. Comparably to Roser et al. (2008; 2009), participants were obliged to fast for 12 hours prior to receiving study medication and may be a reason as to why both studies observed no significant differences among their Type 1 and Type 2 groups compared to placebo for cognitive outcomes.

3.2.3 Abuse Liability Outcomes

Abuse liability measures were assessed by four of the seven included gastrointestinal ROA studies. Three of these four studies determined that Type 2 was unable to ameliorate Type 1-induced intoxication or 'high'. Hollister & Gillespie (1975) assessed propensity to dependence using the card-sort version of the Addiction Research Centre Inventory (ARCI; see Appendix 1), specifically the 'Hallucinogen' and 'Marihuana' scales at 120 minutes post-administration.

ARCI-Hallucinogen scores, or participants' subjective intensity of intoxication, were slightly higher but had a slower onset of effects in the Type 2 condition compared to Type 1 (mean intensity ratings: 6.6 vs. 6.0, respectively). The authors did not provide measures of variance or significance and therefore the MD and its associated p-value could not be calculated.

Gong et al. (1983), used a VAS scale to depict subjective 'high' ratings and found that both Type 1 and Type 2 significantly increased intoxication scores in comparison to placebo ($p < 0.05$), but not between each other, suggesting CBD was ineffective in mitigating perceived intoxication.

Similarly, Juckel et al. (2007) assessed level of intoxication through the Analogue Intoxication Rating scale (AIR-Scale; see Appendix 1), which is comparable to VAS 'high' or 'stoned' scales as both the VAS and AIR use a 0–10-point scale to assess intoxication. Type 1 and Type 2 conditions produced significantly greater scores than placebo (both $p < 0.001$) but did not differ among each other ($p > 0.05$). Moreover, mean Type 2 intoxication scores were slightly higher than Type 1 [4.16(2.32) and 3.57(2.25), respectively]. The authors examined their AIR-Scale findings based on gender in a following paper of the same study (Roser et al., 2009), where differences were observed. Female participant AIR-scale scores were very similar in both Type 1 and Type 2 conditions [4.58(2.57) vs. 4.92(2.82)], however, they experienced significantly higher intoxication scores ($p = 0.064$) and increased levels of 11-OH-THC ($p = 0.008$) and THC-COOH ($p = 0.012$) under the Type 1 but not Type 2 condition in comparison to males. In contrast, males were less intoxicated under the Type 1 versus the Type 2 condition [2.88(1.52) vs. 4.75(2.49)]. AIR-scale scores were also significantly and dose-dependently correlated with IMC in the Type 2 condition but not Type 1, showing an inverted-U relationship ($r_2 = 0.375$, $p = 0.007$) with the peak AIR-scale score around 3.5 (Roser et al., 2009).

Divergent from these previous three studies, Zuardi et al. (1982), using the ARCI 'Marijuana' scale, found that Type 2 cannabis diminished subjective intoxication induced by the Type 1 condition. Although Type 2 ARCI-Marijuana values were significantly higher compared to baseline (Difference = 9.643, $p < 0.05$) they were much lower than post-administration of Type 1 scores compared to baseline values ($p < 0.05$; Zuardi et al., 1982). The authors noted STAI A-state and ARCI-Marijuana ratings, which were assessed by two separate independent observers, were significantly correlated, alluding to participants' accuracy in self-rating.

3.2.4 Physiological Outcomes

Four of the seven studies examined cannabinoid effects of Type 2 versus Type 1 on heart rate. CBD was unable to mitigate THC-induced increases in pulse rate 120 minutes post-dose in three of these studies (Hollister & Gillespie 1975; Zuardi et al., 1982; Gong et al., 1983). Moreover, Gong et al. (1983) observed that the Type 2 group had a 30% increase in pulse rate at 120 minutes post-administration compared to baseline, whereas the Type 1 group experienced only a 22% increase. Blood pressure was not examined (Hollister & Gillespie, 1975; Zuardi et al., 1982) or produced non-significant findings (Gong et al., 1983) among these three studies.

In contrast, Karinol et al. (1974) observed a significant decrease of Type 1-induced elevated heart rate in the Type 2 condition at 90 minutes post-dose (MD = -24.8 ± 10.28; 95% CI 4.65, 44.95; p = 0.042). Importantly, Karinol et al. (1974) restricted eligibility to include those without allergy, cardiac disease or psychotic episodes.

3.3 Smoked / Inhaled Route of Administration

A total of six studies (eight papers) utilized the intrapulmonary route of absorption to investigate differing cannabinoid effects (Dalton et al., 1975a; Ilan et al., 2005; Hindocha et al., 2015 + Morgan et al., 2018; Lawn et al., 2016 + Freeman et al., 2017b; Solowij et al., 2019; Arkell et al., 2019). Four of the six studies investigated psychological phenomenon, three assessed aspects of cognition, five examined abuse liability, and three measured physiological outcomes. Of importance, two of the six studies used cannabis rolled into ‘cannabis cigarettes’ or ‘joints’ while the remaining four administered cannabis to participants via vaporization, three using the Volcano Medic Vaporizer (Sotrz & Bickel, Tuttlingen, Germany; Table 1) and Arkell et al. (2019) utilizing the Mighty Medic Vaporizer (Mighty Medic, Storz & Bickel, Tuttlingen, Germany). Dalton et al. (1975a), Hindocha et al. (2015), and Solowij et al. (2019) dissolved extracted cannabinoids into ethanol as part of the cannabis preparation.

3.3.1 Psychological Outcomes

Ilan et al. (2005), Hindocha et al. (2015), Morgan et al. (2018), Solowij et al. (2019) and Arkell et al. (2019) investigated psychological outcomes, specifically, anxiety among Ilan et al. (2005), Hindocha et al. (2015) and Arkell et al. (2019). Type 2 was unable to mitigate Type 1-increases in anxiety among two of the studies (Ilan et al., 2005; Arkell et al., 2019), whereas neither Type

1 nor Type 2 groups produced significant findings compared to placebo among Hindocha et al. (2015).

Type 1 (3.6% THC) produced significant increases in anxiety compared to placebo ($p < 0.05$) that were not observed in the Type 2 group (Ilan et al., 2005). According to Ilan and colleagues, ratings of anxiety in the Type 2 condition may have relied on the THC concentration and ratio of THC to CBD. Participants reported more anxiety after receiving the Type 1-high dose compared to Type 1-low dose, with the addition of CBD decreasing this anxiety in the Type 1-high but not -low group. However, the MD between Type 2 and Type 1-high regarding anxiety did not reach levels of significance at 20 minutes post-administration minus baseline. The authors cite insufficient concentrations of CBD as a limitation of their study, as they used only 1.0% CBD in their Type 2 group. Similarly, Arkell et al. (2019) assessed anxiety via a VAS 'anxious' scale as well as using the STAI. Type 1 significantly increased VAS ratings of "anxious" and scores on the STAI at 60 minutes post-dose compared to placebo (both $p < 0.05$; Arkell et al., 2019). Although Type 2 was not significantly different from placebo at this timepoint for either measure of anxiety, Type 2 was unsuccessful in mitigating the anxiety produced by Type 1 as both measures of anxiety revealed insignificant findings ($p = 0.139$ and $p = 1.000$, respectively). Conversely, no interactions emerged between drug and time nor were there any within-subject effects after correction for multiple comparisons for VAS 'anxiety' among participants in Hindocha et al. (2015)'s study.

Morgan et al. (2018) and Solowij et al. (2019) utilized the Psychomimetic States Inventory (PSI) to assess acute schizotypal symptoms and changes in psychological phenomenon (paranoia, perceptual and cognitive disorganizations, mania and delusions), as well as the Brief Psychiatric Rating Scale (BPRS) to assess positive and negative symptomatology in Morgan et al. (2018) only. There was a significant linear contrast for Type 1 and both Type 2 ratios administered (Linear contrast: 8 mg THC + 4 mg CBD > 8 mg THC > 12 mg THC + 400 mg CBD) on PSI subscales of 'Mania' ($p = 0.016$) and 'Perceptual Distortion' ($p = 0.004$) compared to placebo, although no significant differences emerged between Type 1 and Type 2 (Solowij et al., 2019). Similarly, PSI total overall scores were significantly greater for Type 1 ($p = 0.014$) and Type 2 ($p = 0.022$) compared to placebo in Morgan et al. (2018). Specifically, significant effects for Type 1 and Type 2 compared to placebo also emerged for 'Perceptual Distortion' ($p = 0.006$ and $p = 0.005$, respectively) and 'Cognitive Disorganization' subscales ($p = 0.008$ and $p = 0.004$

respectively), although this may have been driven by the high-schizotypy group who experienced increased scores on ‘Cognitive Disorganization’ compared to the low-schizotypy group ($p = 0.001$). However, no significant differences emerged between Type 1 and Type 2 for these two measures or the total PSI score. Both Type 1 and Type 2 additionally produced significant increases in negative symptomatology on the BPRS compared to placebo ($p = 0.025$ and $p = 0.008$, respectively) with no significant differences apparent between Type 1 and 2 (Morgan et al., 2018). BPRS positive symptomatology scores were not significant across all groups.

Solowij et al. (2019) additionally used the Clinician Administered Dissociative States Scale (CADSS; Bremner et al., 1998; Appendix 1) to assess objective intoxication in addition to subjective intoxication (PSI). Results were similar to PSI findings, with the total score and majority of subscale data being non-significant between Type 1 and Type 2.

3.3.2 Cognitive Outcomes

Four of the six studies using the inhaled ROA investigated some aspect of cognition including: memory, performance accuracy, reaction times, coordination, and emotional processing. Although Ilan et al. (2005) examined working and episodic memory among participants, along with utilizing electroencephalographic (EEG) and event-related potential (ERP) measures (providing a sensitive index to coincide with the findings on participant task performance), the authors combined Type 1 and 2 data and compared it to placebo only. Therefore, the data from Ilan et al. (2005) cannot be interpreted here. All active treatments, however, produced a decrease in accuracy, an increase in reaction time and impaired the recognition of ‘new’ words compared to placebo ($p < 0.001$). Accuracy was slightly less altered in the recognition of ‘old’ words ($p < 0.05$), compared to placebo (Ilan et al., 2005). The remaining two studies provide heterogenous findings for cognitive parameters.

Dalton et al. (1975a) used an instrument known as the “Wobble Board” to assess standing stability, a modified “Pursuit Meter” to measure attentive motor performance, a “Delayed Auditory Feedback” system to assess mental performance, and a pegboard with 16 holes and 16 different coloured pegs to evaluate manual coordination. Type 2 cannabis did not ameliorate deficits in standing steadiness, manual dexterity or hand-eye coordination observed in the Type 1 group, however, Type 2 scores were consistently lower for all three cognitive outcomes compared to Type 1. Verbal output and mental performance (Delayed Auditory Feedback) were

significantly altered by both Type 1 and Type 2 compared to placebo with no significant differences emerging between the two conditions.

Hindocha et al. (2015) investigated the effect Type 1 and 2 would have on an individual's ability to interpret ambiguous faces with differing emotions (emotional facial affect recognition), by administering an Emotional Processing Task. Each face differed in the degree of intensity of the emotion it displayed from 0% (neutral) to 100% (intense) and were combined into 20% increments (20%, 40%, 60%, 80%, 100%). Using a 4-way crossover trial, they divided participants based on low or high schizotypy and low or high cannabis use into the four categorical groups to assess recognition accuracy. Although for the purposes of this review, both frequent and infrequent participants were considered frequent cannabis users. Participants' performance accuracy was significantly worse following Type 1 cannabis compared to both the Type 2 and placebo groups. CBD was able to mitigate the impairment produced by THC in the recognition of emotional facial affect, being equivalent across both high and low frequency of cannabis use and schizotypy. The Type 1 group experienced a significant decline in the recognition of ambiguous faces at 40% emotional intensity, while the Type 2 condition did not produce any impairment at this intensity. Therefore, accuracy was significantly improved at 40% in the Type 2 group compared to Type 1 (MD = 3.77; $p = 0.024$). Accuracy at 40% intensity for the Type 1 condition was 5.2% less than that for placebo and was not associated with schizotypy nor frequency of cannabis use. To put this into perspective, Kohler et al. (2003) determined that healthy controls perform only 4% better than patients with schizophrenia upon recognizing faces of mild intensity. Interestingly, at 60% intensity, participants in the Type 3 condition were significantly more accurate than after placebo, producing an effect size (partial eta squared=0.137) in the moderate range of 0.10-0.30 (Hindocha et al., 2015). These results imply the influence of cannabis at intermediate emotional intensity, in which participants reach an accuracy threshold of responses above 60% and demonstrate that Type 1 coupled with uncertainty (at 40% intensity) can impair performance. The authors also noted a drug-intensity interaction ($p = 0.001$) and an emotion-schizotypy interaction ($p = 0.02$). A major limitation of the Hindocha et al., 2015 study is that the authors did not conduct urine screens nor recorded measures of plasma cannabinoid metabolites, which would have aiding in interpreting the findings of this study and in assessing confounders. However, the authors suggest plasma levels would be similar to those in the study by Bossong et al. (2009) who had a similar timeline to

their study and used the same concentration of THC and the same ROA. Bossong et al. (2009) discovered that 84.5–95.9% of cognitive effects were still present 45–85 minutes post-dose.

Morgan et al. (2018) investigated episodic memory, verbal memory (using immediate and delayed prose recall), spatial working memory (using discriminability, reaction time, and processing speed tasks) and semantic fluency (using the Reitaan's trailmaking test; Appendix 1). Type 1 and 2 significantly impaired prose recall ($p = 0.031$ and $p = 0.024$, respectively) and discriminability ($p = 0.012$ and $p = 0.020$, respectively) compared to placebo, however they were not significantly different from one another for these parameters. Reduced scores for delayed recall compared to immediate recall was a main effect of drug ($p < 0.001$). Surprisingly, Type 2 was the only condition to produce increases in the number of correct exemplars generated compared to placebo (Morgan et al., 2018), implying potentially increased semantic fluency as a result of using chemovars containing CBD. No significant differences emerged, however, between Type 1 and Type 2. As mentioned, a major limitation of this trial is the lack of cannabinoid metabolites quantified in plasma and/or urine.

Arkell et al. (2019) assessed the effects of Type 1 and 2 on the Digit Symbol Substitution Task (DSST), including the number correctly identified and accuracy, although no significant differences arose for either measure between the two chemovars. No significant differences between Type 1 and 2 were evident among a Paced Auditory Serial Addition Task for response time (ms) or the number correctly identified, although they were significantly altered compared to placebo (both $p < 0.004$). The authors also employed a Divided Attention Task [DAT; Appendix 1; tracking error, response time (ms) and the number correctly identified] which revealed that Type 2 was actually more impairing than Type 1 and placebo for tracking error ($p = 0.042$ and $p < 0.001$, respectively) at 20 minutes minus baseline.

3.3.3 Abuse Liability Outcomes

CBD's role in mitigating certain abuse liability factors for high-potency strains did not prove to be strong for the intrapulmonary ROA. Four of the five studies examining subjective outcomes determined Type 2 cannabis produced similar intoxication ratings to those of Type 1, whereas Dalton et al. (1975a) found Type 2 to mitigate the euphoria and intoxication experienced by Type 1 cannabis.

Dalton et al. (1975a) utilized a modified “Cornell Medical Index” to evaluate subjective responses (Manno et al., 1970; Evans et al., 1973). Type 2 significantly mitigated the impairments produced at 35 minutes post-dose minus baseline by Type 1 for CMI ‘total questions’ ($p < 0.05$) and with a trend for CMI ‘responses’ ($p < 0.10$). Participants were asked to quantify their ratings of psychologic ‘high’ on a scale of 0 to 10, with 10 being the maximum and 0 being the minimum ‘high’ experienced, similar to VAS ‘high’ scales. Although Type 2 did not significantly decrease the maximum ‘high’ experienced among participants 35 minutes post-dose of Type 1, a trend was observed ($p < 0.10$).

Type 1 and Type 2 conditions produced similar intoxication ratings to one another at 30 minutes post-dose in Hindocha et al.’s (2015) study. Specifically, both chemovars significantly increased VAS ‘stoned’ ratings across all time points throughout the study compared to placebo, unaltered by the accompaniment of CBD. After Bonferroni-corrected paired t-tests between treatment conditions across time points were conducted, increased ‘stoned’ ratings for Type 1 vs. placebo and Type 2 vs. placebo (all $p < 0.001$) emerged. Differences between Type 1 and 2, however, were non-significant. Comparably, in Ilan et al. (2005)’s assessment of abuse liability, VAS ‘high’ ratings were larger for all treatments compared to placebo from 0:20–2:20 hr post-dose ($p < 0.001$). These ratings were also not affected by the addition of CBD.

Lawn et al. (2016) utilized VAS ‘stoned’ ratings, the Temporal Experiences of Pleasure Scale (Gard et al., 2006), the Snaith Hamilton Pleasure Scale (Snaith et al., 1995) and an Effort Expenditure for Rewards Task (EEfRT) (Treadway et al., 2009; see Appendix 1) to assess abuse liability among cannabis users with a mean Severity of Dependence Score (rated between 0 and 4) of 1.13(1.26). The EEfRT measured effort-related decision-making and required participants to make a series of choices between a low-effort option (to win 50p) and a high-effort option (winning between 80p and £2.00) which involved pressing a spacebar 30 times in 7s for the low-effort option and 100 times in 21s for the high-effort choice. The probability of winning varied, as well as the magnitude of the amount to be won in the high-effort condition. Therefore, expected value was produced by multiplying the probability times the magnitude (i.e., the chance of winning each trial if completed multiplied by the amount of money available to be won on a high-effort choice). Type 1 significantly reduced motivation for making a high-effort choice for a monetary reward on the EEfRT compared to placebo ($p = 0.029$) and there was no evidence suggesting Type 2 was able to mitigate the overall amotivational effects of Type 1. However,

compared to both placebo and Type 2, Type 1 significantly increased the sensitivity to the expected value, or how good a choice was and how much it was worth ($p = 0.014$ and $p = 0.006$, respectively). This increase in sensitivity results from the increase in sensitivity to magnitude at low probability in Type 1 compared to Type 2 ($\beta = 0.412 \pm 0.156$; 95% CI 1.113, 2.048; OR = 1.51; $p = 0.008$). The authors note changes they made to the original version of the EEfRT including less trials and using the less dominant finger for the "easy" decision-making option. Moreover, both Type 1 and Type 2 groups had significantly greater ratings of 'stoned' than placebo at 90 minutes minus baseline ($p < 0.001$) although they did not differ from each other (Lawn et al., 2016). No significant differences between Type 1 and Type 2 were present for additional VAS items of 'feel drug effect', 'like drug effect', and 'want more drug effect' despite both chemovars being significantly different from placebo for the two former VAS items (both $p < 0.001$; Freeman et al., 2017b). Interestingly, neither treatment group altered VAS measure of "Want More Drug", insinuating that participants enjoyed the drug without necessarily craving more.

In line with these findings, Type 2 cannabis was unable to significantly mitigate the increased VAS intoxication ratings produced by Type 1 in both Solowij et al. (2019) and Arkell et al. (2019)'s studies. Furthermore, similar to Freeman et al. (2017b), no significant differences between Type 1 and 2 emerged for VAS items of "liking of effect" and "strength of the effect" at 15 minutes post-dose, although both chemovars produced significantly increased ratings compared to placebo (all $p < 0.001$; Arkell et al., 2019). Limitations of Arkell et al. (2019) include basing their sample size calculation from a previous study administering dronabinol (i.e., oral administration instead of a vaporized ROA). Additionally, all 14 participants correctly guessed which condition was placebo by noting less vapor produced, indicating insufficient blinding of participants. The authors also note their small sample size as a limitation, explaining that recruitment was limited by "expiration of the study drug" (Arkell et al., 2019).

3.3.4 Physiological Outcomes

CBD proves to be unsuccessful in attenuating THC-induced physiological outcomes. Four of the six studies utilizing the intrapulmonary ROA examined heart rate, with Freeman et al. (2017b), and Solowij et al. (2019) additionally measuring systolic and diastolic blood pressure. Type 2 chemovars were unable to attenuate the significant increases in heart rate produced by Type 1 in

two of the three studies, at 35 minutes post-dose minus baseline (Dalton et al.,1975a) and at 1-hour post-dose minus baseline (Freeman et al., 2017b).

Type 1 and Type 2 treatments produced increases in heart rate greater than placebo which was largest 20-minutes post-consumption (all $p < 0.01$; Ilan et al., 2005) but did not differ among each other (data not shown because it was not provided in text and we were unable to obtain it from the authors). However, the bioavailability of THC in active treatments did not reflect administered doses, and therefore, the results should be interpreted with caution. For instance, participants in the Type 1-low group had larger carbon monoxide levels compared to the Type 1-high group, meaning the amount of THC delivered to participants in the Type 1-high condition may have been less than double than what was received in the Type 1-low group. Assays of THC levels in the cannabis cigarettes administered to the Type 1-high group confirmed this assumption and were less than the stated 3.6% concentration.

In contrast, Solowij et al. (2019) found Type 2 to significantly mitigate THC-provoked increases in heart rate with higher ratios of CBD to THC. It should be noted that Solowij et al. (2019) excluded participants based on cardiovascular disease, asthma, neurological conditions and significant head injuries. Further, plasma THC concentrations, along with its associated metabolites, did not correlate with the estimated dose of THC administered in each condition (all $p > 0.10$; Solowij et al., 2019). Like Freeman et al. (2017b), Solowij et al. (2019) did not observe any significant differences between any of the conditions for either systolic or diastolic blood pressure. Compared to placebo, Type 1 and 2 also increased systolic blood pressure ($p = 0.006$ and $p = 0.030$, respectively) but did not differ between each other ($p = 0.860$; Freeman et al., 2017b).

3.4 Combined Routes of Administration

Six of the 19 studies utilized a combined approach to cannabinoid and placebo dosing, delivering THC via one route of administration and CBD in another. Dalton et al. (1975b) administered either a placebo- or CBD-containing ‘cigarette’ 30 minutes ahead of providing participants with a THC-containing ‘cigarette’. Bhattacharyya et al. (2010) used the pretreatment of IV placebo or CBD five minutes ahead of IV administration of THC. Haney et al. (2016) and Englund et al. (2013) pretreated participants with either placebo or CBD capsules, 90- and 210-minutes ahead, respectively, of THC. Englund et al. (2013) administered synthetic THC intravenously (IV)

whereas Haney et al. (2016) delivered THC via a ‘cannabis cigarette’. Both Schoedel et al. (2011) and Karschner et al. (2011) administered either placebo or THC capsules (Dronabinol in Schoedel’s study) to participants who subsequently were then provided with Sativex and/or placebo-Sativex actuations in the form of oromucosal spray.

3.4.1 Psychological Outcomes

Englund et al. (2013) and Bhattacharyya et al. (2010) both compared the effects of Type 2 and Type 1 cannabis on psychotic symptoms using the Positive and Negative Symptom Scale (PANSS). CBD administered intravenously 5-minutes prior to intravenous THC, led to the attenuation of THC-induced psychotic symptoms among the three of six participants experiencing this phenomenon under the Type 1 condition ($p < 0.05$; Bhattacharyya et al., 2010).

Similarly, Englund and colleagues found Type 2 cannabis significantly reduced the odds of developing an acute clinical psychotic reaction (a priori definition of ≥ 3 points) that was observed in the Type 1 condition (OR = 0.22; $p < 0.05$). Although numerically lower, the PANSS scores in the Type 2 group did not reach statistical significance when compared to those from the Type 1 condition. Paranoia, assessed using the participant-rated State Social Paranoia Scale (SSPS), was significantly reduced by CBD in the Type 2 condition compared to Type 1 (MD = 0.94 ± 0.441; 95% CI 0.07, 1.81; $p < 0.05$). Interestingly, higher trait paranoia was observed prior to the start of the study in the Type 2 group, implying these participants may have had increased paranoia at baseline. Both studies used similar doses of THC, namely 1.25 mg for Bhattacharyya and 1.5 mg for Englund, despite using vastly different concentrations of CBD, 5 mg and 600 mg, respectively.

Karschner et al. (2011) utilized two concentrations of both Type 1 (synthetic) and Type 2 (pharmaceutical) chemovars to investigate their effects on anxiety using the STAI. All active treatments, except Type 2-low, produced significantly higher ‘state’ anxiety ratings (steadily up to a maximum at 5.5 hours post-cannabinoid dose) compared to the placebo condition (all $p < 0.05$), although they did not differ significantly among each other. There was a dose-dependent effect on anxiety such that the Type 2-high condition produced significantly greater ‘state’ and VAS anxiety scores compared to Type 2-low. This finding was positively correlated with plasma THC concentrations ($r \leq 0.23$).

3.4.2 Cognitive Outcomes

Haney et al. (2016) and Schoedel et al. (2011) did not find significant differences between any of the active treatment and placebo conditions (data not shown). Haney et al. (2016) describe administering a Digit Symbol Substitution Task (DSST), an assessment of cognitive function and accuracy, and a Continuous Performance Task (CPT), a measure of attention and psychomotor speed, in their methods, however, no specific data is provided on these outcomes other than their mention of non-significant findings. The authors attribute these findings to tolerance since participants consisted of "cannabis smokers".

Schoedel and colleagues (2011) used neurocognitive measures including a Choice Reaction Time (CRT) test, a measure of psychomotor speed and accuracy, a Divided Attention Test (DAT), investigating sustained and divided attention, and the Sternberg Short-Term Memory (STM) test, which assesses working memory and short-term storage capacity. Despite non-significant findings across these neurocognitive measures for active treatments, the authors highlighted that Type 1-high (40 mg of dronabinol) did have a significantly greater STM reaction time in comparison to placebo but not to Type 2.

Englund et al. (2013), used three out of the four tasks comprising the MATRICS Consensus Cognitive Battery, which included the Hopkins Verbal Learning Task Revised (HVLT-R), measuring memory and verbal learning; Symbol Coding, assessing processing speed; and the Digit-Span Forward and Reverse, a test of working memory. When pretreated with placebo, participants in the Type 1 condition had overall decreased delayed recall scores (episodic memory), evidenced by the HVLT-R, compared to Type 2 ($MD = 10.2 \pm 4.24$; $p = 0.027$). Impairments produced in immediate recall (working memory) by Type 1, however, were not restored by Type 2. Deficits in delayed recall were associated with PANSS-positive symptoms at the level of a trend (Spearman's $rho = 0.3$; $p = 0.09$). These findings were significantly correlated with SSPS ratings (Spearman's $rho = 0.5$; $p < 0.05$), suggesting that THC-induced alterations in delayed recall and paranoia may load onto a common factor.

3.4.3 Abuse Liability Outcomes

Four of the six studies investigated abuse liability outcomes using VAS measures to capture participant self-rated experiences of 'drug liking' or level of 'high' and/or subjective drug value

and ARCI measures. Both Type 1 and Type 2 increased 'high' ratings in a similar fashion in Dalton et al. (1975b)'s second study, involving the pretreatment of CBD 30-minutes prior to THC administration. Similarly, Type 2 produced comparable values to Type 1 for measures of Street Value Rating and on VAS items of 'liking' and 'strength' (Haney et al., 2016). Participants were permitted to purchase up to three additional 5-second inhales or 'puffs' of a cannabis cigarette 150 minutes post-initial dose administration at $0.50/puff to determine the reinforcing effects of each chemovar (Haney et al., 2016). The difference in percentage of individuals purchasing additional puffs between the Type 1 and 2 conditions was not significant.

VAS ratings for "Good Drug Effects" were significantly greater for Type 1-high and Type 2-high groups compared to placebo ($p < 0.001$ and $p = 0.022$, respectively), although there were no significant differences between the two chemovars (Karschner et al., 2011). These ratings were significantly higher among Type 2-low compared to Type 1-low ($p = 0.044$; Karschner et al., 2011). VAS 'high' ratings were also significantly increased among Type 1-high compared to placebo ($p = 0.019$). Although neither Type 2-low nor -high conditions produced any significant feelings of intoxication or 'high' compared to placebo, no significant differences emerged between Type 1 and 2 (Karschner et al., 2011). Paradoxically, ARCI-Marijuana scores were significantly greater for all active treatments compared to placebo and were also significantly higher for Type 2-low compared to Type 1-low ($p < 0.001$) in line with results from VAS "Good Drug Effects". Plasma THC concentrations and VAS "Good Drug Effect" and "High" ratings were positively correlated for Type 1-high ($r \leq 0.35$) and Type 2-high ($r \leq 0.32$). ARCI-Marijuana scale scores were positively correlated with plasma THC concentrations for Type 2-high ($r \leq 0.32$) only.

Schoedel et al. (2011) investigated the abuse liability of nabiximols (Sativex® Product Monograph, 2010) in a population of recreational cannabis users. Participants were administered sprays within a smaller timeframe to achieve increased concentrations and faster effects than what a patient would typically be prescribed. Similar to Karschner et al. (2011), both Type 1 doses (low and high) as well as Type 2-high similarly produced significantly greater scores on ARCI-Marijuana measures and subjective abuse liability outcomes including VAS 'Liking', 'Good Effects', and 'High', among others, compared to placebo. Type 2-low was significantly lower on most measures than both Type 1 doses. Values for Type 1-low vs. Type 2-med and Type 1-high vs. Type 2-high were greater for the Type 1 conditions, despite not being

statistically significant on most measures. However, for the purposes of this review we focused on the Type 1-low and Type 2-medium doses as they best matched Karschner et al. (2011)'s Type 1 and 2 high doses. Significantly greater reinforcing effects on ARCI-Marijuana and VAS measures of 'High', 'Stoned' and 'Overall Drug Liking' were produced by Type 1-low compared to Type 2-medium (all $p < 0.05$), suggesting lower abuse-related effects with the addition of CBD. However, Type 2-medium was the only condition to produce significantly greater scores on VAS 'Liking' and Subjective Drug Value (an estimate of the cost of the chemovar provided), compared to placebo but not Type 1.

3.4.4 Physiological Outcomes

Only three of the six combined ROA studies investigated physiological outcomes, including HR and BP (Dalton et al., 1975b; Karschner et al., 2011; Haney et al., 2016). CBD was unable to attenuate THC-induced increases in HR observed in all three studies. However, Karschner et al. (2011) observed a dose-dependent effect where Type 1-high and Type 2-high produced significant increases in HR compared to both placebo and their low-dose conditions, although they considered these increases clinically insignificant. Diastolic BP was significantly lowered in all active treatments except the Type 1-low condition 4–8 hours post-dose, returning to baseline levels 10.5 hours after administration only in the Type 1-low group. Type 2-low significantly reduced diastolic BP when compared to Type 1-low ($p < 0.003$). Diastolic BP was significantly increased among both Type 1-high and Type 2-high compared to placebo (both $p < 0.001$) but did not differ significantly between one another. Type 1-high diastolic and systolic BP scores had weak but significantly positive correlations to plasma THC concentrations ($r \leq 0.23$). The authors noted that the Type 1 and Type 2 (Sativex) preparations delivered in this study, produced clinically insignificant rises in anxiety and 'Good Drug Effects', in addition to HR, and produced fewer adverse events in comparison to the smoked methods of delivery.

Dalton et al. (1975) and Haney et al. (2016) did not observe any significant changes to blood pressure from any of the active treatments compared to placebo. There were varying individual plasma CBD concentrations, (C_{max} ranging from 1.6 – 271.9 ng/ml; mean = 77.9 ng/ml) and the time it took to reach peak levels (T_{max} 120 – 360 min.; mean = 180 min.; Haney et al., 2016).

It should be noted that one of the eight subjects in Schoedel's study withdrew based on mild tachycardia and moderate paranoia post-dose of Type 1-high and another participant due to mild

tachycardia after receiving Type 2-low. Plasma CBD concentrations were consistently lower than THC concentrations and mean peak THC concentrations associated with Type 1 were significantly increased and produced a more immediate onset of effects compared to those in the Type 2 conditions (1–3 hours post-dose vs. 3–4 hours post-dose). Caution should be taken when interpreting the evidence pertaining to the mitigating effects of CBD over THC as data is conflicting especially across ROAs.

3.5 Secondary Analysis Findings

3.5.1 Type 2 Subcategories

A qualitative analysis of the effects of the three categorizations of Type 2 chemovars (Type 2a, Type 2b, Type 2c; see Section 2 Methods) was undertaken to determine whether certain ratios of THC:CBD are less impairing than others compared to Type 1. A few studies (Karinol et al., 1974; Haney et al., 2016; Solowij et al., 2019) utilized more than one Type 2 ratio in their respective trials while other studies (Karschner et al., 2011; Schoedel et al., 2011) utilized more than one dose of the same Type 2 ratio. Therefore, there are more chemovars than studies (27 Type 2 chemovars in total across all 19 studies; Table 6). There was an unequal distribution of Type 2-subcategories among the included 19 studies, with a greater proportion of Type 2c varieties examined overall (Type 2a = 5/27; Type 2b = 10/27; Type 2c = 12/27; Table 6). However, when assessing chemovars based on ROA, the Combined route had a greater proportion of Type 2b chemovars compared to Type 2a or 2c which was a result of Karschner et al. (2011) and Schoedel et al. (2011) utilizing two and three Type 2b doses, respectively.

Chemovar classification into Type 2 subcategories was most consistent for Type 2b, with seven of the total 10 Type 2b chemovars assessed consisting of an exact 1:1 ratio of THC:CBD and the remaining three chemovars in the 1:1.25-1.5 range for THC:CBD. Out of the five Type 2a chemovars, four contained an exact 2:1 ratio of THC:CBD, and one with a ratio of 3.6:1 of THC:CBD (Ilan et al., 2005). Five out of the 12 Type 2c chemovars used high levels of CBD, with ratios ranging from 1:33–400 of THC:CBD, whereas four chemovars contained a precise 1:2 ratio of THC:CBD and three in the range of 1:4-6. Haney et al. (2016) utilized the same THC dose, with three differing CBD concentrations. The authors provided the amount of CBD in mg and THC as a percent, stating the amount of dried flower provided as 800 mg. Given that participants were instructed to smoke only half of the cigarette, this would roughly equate to 5.3-

5.8% THC within 400 mg of dried flower. Therefore, we categorized Haney et al. (2016)'s treatments based on this assumption, with their 'low' CBD dose coinciding with Type 2a, medium with Type 2b and high with Type 2c.

Two of the four oral studies examining psychological reactions and anxiety noticed significant reductions only in the higher CBD:THC ratios (i.e., Type 2b and 2c) compared to Type 1 ($p<0.05$) (Karinol et al., 1974; Zuardi et al., 1982) but not among Type 2a versus Type 1 (Karinol et al., 1974). The other two of four studies investigated Type 2b (Eichler et al., 2012) and Type 2c (Leweke et al., 2000) chemovars against Type 1 but none of their active treatments produced any significant findings compared to placebo.

Higher ratios of CBD:THC were also more protective over cognitive phenomenon among two of the four studies within the oral ROA. Specifically, reaction times (Karinol et al., 1974) as well as depth inversion and visual perception (Leweke et al., 2000) were improved among Type 2b and Type 2c compared to Type 1. Reaction times and psychomotor coordination scores were not significantly different when THC concentrations were greater than CBD, i.e., Type 2a (Roser et al., 2008; Roser et al., 2009).

No Type 2 ratio (a, b, c) appears protective over the intoxicating or physiological effects of Type 1 chemovars. Type 2c was unable to mitigate THC-induced increased in heart rate at 120 minutes post-dose among three of the four oral studies investigating physiological parameters (Hollister & Gillespie, 1975; Zuardi et al., 1982; Gong et al., 1983). Karinol et al. (1974) noted that participants in the Type 2a group had greater increases in heart rate compared to Type 1 at 50 minutes post-dose (change in baseline levels: 53% and 35% increase, respectively). However, CBD was able to mitigate THC-induced increases in heart rate only at higher combination ratios, specifically, Type 2c, which only produced a 6.2% increase from baseline (Karinol et al., 1974).

Higher CBD:THC ratios appear less protective among smoked ROAs than oral ROAs. A significant effect of active treatments compared to placebo on PSI subscales of 'Mania' ($p = 0.016$) and 'Perceptual Distortion' ($p = 0.004$) emerged with the highest scores obtained in Type 2a, followed by Type 1 and then Type 2c (Solowij et al., 2019). Similarly, Morgan et al. (2018) did not observe any significant differences between their Type 1 and Type 2c groups for PSI overall total scores and subscales of 'Perceptual Distortion' and 'Cognitive Disorganization'. However, Type 2c scores for these measures were typically lower than Type 1 (Table 4).

All three studies in the smoked ROA examining cognition administered either Type 2b (Arkell et al., 2019) or Type 2c (Dalton et al., 1975a; Hindocha et al., 2015 + Morgan et al., 2018) chemovars. Type 2c was able to mitigate deficits produced in the emotional processing task (Hindocha et al., 2015), and also significantly improved semantic fluency compared to placebo, although not compared to Type 1 (Morgan et al., 2018; Table 4).

In line with the oral ROA, no Type 2 chemovar (a, b, c) significantly altered the subjective or physiological impairments produced by Type 1 chemovars among the smoked ROA. Only one study examined the effects of Type 2a compared to Type 1 (Solowij et al., 2019). Overall, Type 2a produced higher scores in intoxication, followed by Type 1 and then Type 2c (Solowij et al., 2019). However, the authors note that Type 2a 'enhanced' while Type 2c 'reduced' the subjective impairing effects of Type 1. Upon further analysis, Solowij et al. (2019) discovered that the estimated THC dose delivered to participants differed between Type 2c and Type 1 conditions ($p < 0.001$), but not among Type 2a and Type 1 ($p = 0.29$). The authors repeated their analyses on a subsample ($n = 16$) who did not differ in the concentration of THC delivered between the two chemovars to confirm effects. The authors also observed greater increases in heart rate for both Type 1 and Type 2a compared to Type 2c ($p = 0.006$; Solowij et al., 2019) which was also not observed for Type 2c compared to Type 1 in Dalton et al. (1975a) or Type 2b versus Type 1 in Freeman et al. (2017b).

Among the combined ROA, both Bhattacharyya et al. (2010) and Englund et al. (2013) investigated psychosis-related symptomology via PANSS and SSPS (Englund et al., 2013). Type 2c significantly reduced PANSS scores (Bhattacharyya et al., 2010) and paranoia (Englund et al., 2013) compared to Type 1. Although both studies were classified as using Type 2c chemovars, they had vastly different concentrations of CBD, namely, 5 mg (Bhattacharyya et al., 2010) and 600 mg (Englund et al., 2013). Type 2b was unsuccessful in reducing THC-provoked anxiety (Karschner et al., 2011).

Subjective and physiological outcomes were not reduced by Type 2 chemovars among any of the ROAs, including the combined route. Although not significantly different from Type 1, scores were numerically higher for Type 2a, followed by 2b and then 2c, for subjective measures of VAS 'high' and the percentage of participants the purchased additional 'puffs' of cannabis (Haney et al., 2016). However, the opposite trend appeared, whereby Type 2c had the highest

scores followed by Type 2b then 2a for indices of ‘liking’ and ‘strength’ of the chemovar (Haney et al., 2016; Table 3). Only the Type 2b-low dose and medium doses used by Schoedel et al. (2011) significantly reduced the ‘high’, ‘overall drug liking’ and increased ARCI-Marijuana scores produced by Type 1. However, the authors concluded that the low Type 2b dose (10.8 mg THC + 10 mg CBD) has the lowest potential for abuse. Type 2b and 2c could not reduce the intoxication produced by Type 1 in the two remaining studies (Karschner et al., 2011; Dalton et al., 1975a, respectively). No Type 2 chemovar was able to mitigate Type 1-increases in heart rate among the combined ROA.

3.5.2 Infrequent vs. Frequent Cannabis Users

To assess whether current frequency of cannabis use has an impact on findings, a qualitative analysis was conducted by dividing the 19 included studies based on the number of times their respective populations consumed cannabis per week (Table 2). Frequency of use, for the purposes of this review, is defined as using cannabis greater than or equal to three times per week. Eight of the 19 studies were classified as having frequent users with the remaining eleven considered as infrequent samples. Solowij et al. (2019) included both frequent and infrequent users, as defined by our review, and findings were analyzed according to these groups. Similarly, Hindocha et al. (2015) and Morgan et al. (2018) recruited both infrequent and frequent users, however, infrequent users within their study were using cannabis on average 12 days per month (~3 times per week) and therefore were classified as frequent users in this review.

Psychological findings seem to be the most impacted by frequency of use. Among studies investigating psychological phenomenon, seven consisted of infrequent users whereas four studies comprised frequent users. Four of the seven ‘infrequent user’ studies found that Type 2 was able to mitigate Type 1-induced impairments, specifically anxiety and paranoia. Two of the studies produced insignificant findings for both chemovars compared to placebo. Importantly, the only study where Type 2 was not protective among this subpopulation was via the smoking ROA (Arkell et al., 2019). However, it is important to highlight that participants in Arkell et al. (2019), although not meeting criteria to be considered ‘frequent users’, were using cannabis 4.5(4.8) times per month, or at least once a week, which could be considered frequent in other jurisdictions and may explain why CBD was not protective. In contrast to these findings among ‘infrequent user’ studies, Type 2 could not reduce increases in anxiety or symptoms of psychosis

produced by Type 1 across all four studies examining psychological effects among frequent users.

Infrequent users displayed opposing findings to frequent users on the PSI subscale of ‘amnesia’, scoring highest following Type 2a, then Type 1 and lowest for Type 2c, whereas frequent users had increased scores following Type 2c, with Type 2a producing the lowest scores (interaction with group, $p = 0.046$; Solowij et al., 2019). Solowij et al. (2019) and Morgan et al. (2018) also examined the effects of CBD on its own (i.e., Type 3) among frequent and infrequent users. Frequent users for both studies had higher PSI scores post-Type 3 dosing compared to infrequent users, with infrequent users experiencing significantly less schizotypal symptoms than frequent users ($p = 0.015$) in Morgan et al. (2018). Despite the classification of Morgan et al. (2018)’s entire population as frequent users in this review, a lengthier history of cannabis use correlated with reduced antipsychotic effects of CBD ($r = 0.434$, $p = 0.034$). It is interesting to note, however, that similar to Solowij et al. (2019), PSI scores were reduced in ‘light’ ($p = 0.015$) but not heavy ($p = 0.104$) users in this study compared to Type 1 (Morgan et al., 2018).

There were no overall trends that emerged between frequent and infrequent users for cognitive items. Type 2 may be able to mitigate impairments in accuracy relating to emotional processing as well as enhance semantic fluency among frequent users (Hindocha et al., 2015, Morgan et al., 2018). However, attention (DAT, DSST), psychomotor speed and accuracy (CPT, CRT), and short-term memory (STM task) were unaltered compared to placebo among frequent users (Schoedel et al., 2011; Haney et al., 2016), suggesting tolerance from cannabis for certain cognitive items. However, a major limitation of Haney et al. (2019) was the loss of 19 out of 50 participants who did not complete the study, which could have impacted the findings.

Cognitive results appeared to be more heterogenous across studies examining infrequent users. Three of the seven studies examining cognitive phenomenon among infrequent users found Type 2 to reduce cognitive deficits produced by Type 1, specifically regarding time production (Karinol et al., 1974), visual perception (Leweke et al., 2000) and episodic memory (Englund et al., 2013). In contrast, two studies observed insignificant findings between Type 1 and Type 2 for attention, psychomotor speed and stability (Dalton et al., 1976a; Arkell et al., 2019). Findings from the remaining two studies of infrequent users were not significant for measures of

concentration and disorientation (Eichler et al., 2012) as well as reaction time and coordination (Roser et al., 2008, Roser et al., 2009).

It is uncertain whether frequency of use appears to have an impact on subjective intoxication outcomes for Type 1 versus Type 2 chemovars. Two of five studies assessing subjective intoxication among infrequent users observed Type 2 to significantly mitigate Type 1-increases in abuse liability measured via the CMI and ARCI (Dalton et al., 1976a; Zuardi et al., 1982, respectively). The remaining three studies found no significant differences between Type 1 and Type 2 (Hollister & Gillespie, 1975; Juckel et al., 2007; Arkell et al., 2019). Six studies examined abuse liability among frequent users, with five concluding Type 2 is just as impairing as Type 1 regarding VAS measures of intoxication (Gong et al., 1983; Karchner et al., 2011; Hindocha et al., 2015; Haney et al., 2016; Freeman et al., 2017b). In contrast, Schoedel et al. (2011) observed a significant difference between Type 1 and Type 2 across their sample of frequent users, specifically for Type 2-medium compared to Type 1-low. However, this difference was not observed when comparing Type 1-high to Type 2-high. This is in line with findings of a blunted effect of CBD among frequent users from the other five studies. Solowij et al. (2019) examined abuse liability between infrequent and frequent cannabis users. Divergent from the above findings, infrequent users were significantly more intoxicated than frequent users in all Type 1 ($p < 0.0001$) and Type 2a and 2c (both $p = 0.012$) conditions (Solowij et al., 2019).

Solowij et al. (2019) also observed greater changes in heart rate for Type 1 and 2a conditions compared to Type 2c among infrequent compared to frequent users ($p = 0.075$). Besides Solowij et al. (2019), however, no notable distinctions were made between studies classified as infrequent versus frequent users for physiological outcomes.

4 Discussion

4.1 Efficacy of CBD in Mitigating THC-induced Harms

This systematic review examined the efficacy of CBD in attenuating THC-induced adverse effects on four classes of outcomes, including psychological, cognitive, abuse liability and physiological outcomes. Our review identified 22 articles reporting on 19 randomized controlled studies that included a comparison between THC-dominant cannabis versus cannabis containing different ratios of THC and CBD. Given the substantial heterogeneity in study populations, cannabis products and doses, measures and outcomes, we were unable to pool the results in a meta-analysis. We decided instead to conduct a narrative synthesis of the included studies by grouping studies based on the route of administration and the classes of outcome reported.

Our review suggests that CBD may exert its effects differently across varying THC-induced outcomes. It also suggests that CBD may have a differential effect depending on the route of administration. These findings should be interpreted with caution given the limited number of studies informing each route of administration and outcome reported. However, we believe that grouping studies based on the route of administration and different classes of outcomes provide a more nuanced view of the current state of this emerging literature. As secondary analyses, we were also interested in taking a preliminary look at whether different compositions of THC:CBD within cannabis as well as if frequency of use had a differential effect in mitigating THC-induced adverse effects.

The presence of CBD in cannabis containing THC may afford protection over THC-induced psychological outcomes and over some cognitive outcomes but it does not appear to significantly mitigate measures of abuse liability or physiological impairments. It is likely that CBD potentiates THC's effects through differing mechanisms of action and does not cause a 'general block' on the effects produced by THC (Zuardi et al., 1982), which would explain why CBD seems to show a protective effect over some outcomes and not others. CBD has a known poor bioavailability of less than 20% (Mechoulam et al., 2002) and most of its mechanisms of action still need to be elucidated. It may be that CBD is exerting some of its THC-modulating effects via its low affinity to the CB_1 receptor orthosteric site and other effects via different interactions with non-cannabinoid receptors, enzymes and pathways. Neuroimaging studies suggest CBD may predominantly alter emotional/psychological reactions in comparison to cognitive

phenomenon, as it activates the ventral putamen but not the dorsal caudate (Grimm et al., 2018), providing some support for the findings of this review, whereby CBD more consistently attenuated psychological impairments.

Findings from this review suggest THC:CBD chemovar effects for psychological phenomenon may be dependent on the route of administration. Our findings imply that chemovars with THC:CBD may exert these protective effects over THC-dominant varieties to a greater degree among the oral route, followed by combined routes and finally, via inhalation. This is in contrast to evidence suggesting that oral administration produces more harmful consequences compared to smoking, particularly for psychological outcomes such as acute psychosis and paranoia as well as intoxication (Kim & Monte 2016; Borodovsky et al., 2017; Russell et al., 2018; Spindle, Bonn-Miller, & Vandrey, 2019). These studies reflect epidemiological findings, resulting from self-administration of cannabis edible products that are not always labelled with the correct concentration of cannabinoids contained in the actual product consumed (Vandrey et al., 2015). It may be that the greater proportion of psychiatric experiences resulting from edible consumption is driven by high THC-potency and a lack of CBD within products. In contrast, RCTs typically administer lower doses than what individuals would consume recreationally on their own and provide doses from reliable sources in a controlled environment. Even among these regimented settings, a few participants had to be excluded from several studies based on adverse reactions including intoxication and panic attacks across all routes of administration.

Included studies provided mixed findings on the protective effects of chemovars containing CBD on cognitive outcomes. Similar to the psychological findings, cannabis comprised of CBD with THC decreased THC-induced cognitive impairments among the oral and combined routes to a greater degree than among smoked administrations. Measures of psychomotor performance, such as reaction times and coordination, do not appear to be reliably improved by the addition of CBD, as well as deficits in concentration. CBD may reduce some impairments in cognitive flexibility produced by THC. Impairments in visual information processing, including depth inversion and processing of emotional faces, as well as verbal memory deficits produced by THC were rescued by CBD among oral and combined routes of administration. However, when cannabinoids were administered through intrapulmonary routes via smoking, impairments in prose recall (immediate and delayed recall) nor deficits in psychomotor speed produced by THC were mitigated by CBD. Surprisingly for the inhaled route, however, when CBD was combined

with THC it was the only condition to produce increases in the number of correct exemplars generated (Morgan et al., 2018), implying potentially increased semantic fluency as a result of using chemovars containing CBD.

This review did not find differences among routes of administration regarding the ability of CBD to reduce the subjective intoxication produced by THC. Chemovars with CBD were typically not associated with reductions in abuse liability produced by THC-dominant varieties such as the 'liking' and the experience of a 'high'. However, these scores were consistently lower than THC-only, especially among chemovars with higher proportions of CBD, either approaching ratios of 1:1 of CBD:THC or higher. Others have argued that CBD may modulate the 'wanting' and 'liking' of cannabis without mitigating the overall euphoria or 'high' produced (Niesink & Van Laar, 2013), however, our results cannot support this conclusion as CBD did not consistently mitigate these more prominent measures of concern for dependence items across studies. Importantly, however, 400 mg of Type 3 cannabis (CBD-only) induced subjective intoxication (depersonalization and derealization) irrespective of frequency of use (Solowij et al., 2019), which has been replicated by more recent studies showing that CBD may produce impairing effects on its own with concentrations of THC less than 1% (Meier et al., 2018; Hundal et al., 2018; Schoedel et al., 2018; He et al., 2019). Considering CBD may be impairing on its own, this may provide additional insight as to why the addition of CBD with THC produced impairing subjective effects among the abuse liability outcome category.

In addition, CBD did not have a strong effect over THC-induced increases in physiological parameters, specifically, heart rate. Included studies that examined alterations in blood pressure had heterogenous findings, with some studies observing no mitigation of blood pressure, whereas changes in diastolic blood pressure may (Freeman et al., 2017b) or may not (Karschner et al., 2011) be attenuated by CBD.

4.1.1 Type 2 Subcategory Findings

One potential explanation for these equivocal findings may be related to the potential effects of CBD on endocannabinoid disruption. If CBD only produces its protective effects when the endocannabinoid tone is disrupted, it may be that levels of THC administered were not high enough to elicit this response among some of the trials (Leweke et al., 2000). Morgan et al. (2018) note that they used a "relatively low dose of THC (8 mg) compared to doses estimated in

naturalistic studies (~35 mg in the UK [Freeman et al., 2014]; ~32 mg in the Netherlands [Gruenewald & Lockhead, 1980])". Since the majority of studies included in this review administered levels of THC under 30 mg, this could explain why we failed to find more consistent protective effects of CBD-containing products, especially among regular users (i.e., although Type 2 scores were consistently lower than Type 1 scores, they were not statistically significant). Conversely, other studies cite using too-low of a CBD dose (especially when investigating Type 2a chemovars) as a limitation in the lack of findings pertaining to CBD's mitigating effect over THC. CBD, when present in low concentrations relative to THC (i.e., Type 2a), was potentiating in some studies, producing scores that were numerically higher than those reported for Type 1 products. The discussion of dosing should be central when examining the effects of cannabis which has been limited in the recreational and psychiatric literature over the past 30 years. Although ratios greater than 1:1 of CBD:THC typically reduced the psychological and cognitive deficits produced by THC-dominant preparations, these results may be driven by ratios that are closer to a 1:1–2:1 ratio of CBD:THC. Especially high ratios of CBD to THC in Type 2 chemovars (e.g., 400:1; Englund et al., 2013) could not significantly reduce psychotic symptom scores, but produced clinically significant reductions in psychotic symptomatology, suggesting that there may be an optimal range of CBD to THC with greater protective effects. For instance, a 4:1 ratio of CBD:THC was sufficient to significantly decrease PANSS scores (Bhattacharrya et al., 2010). Alternatively, this lack of statistical significance, despite evidence for clinical significance, could suggest CBD exerts its acute effects over THC more chronically, overtime (Morgan & Curran, 2008; Morgan et al., 2010a; Morgan et al., 2010b; Morgan et al., 2012).

Regarding the potential protective effects of CBD and relative doses, it is worth noting that a number of studies that met all other eligibility criteria were excluded if they examined THC:CBD chemovars (with or without varying doses across groups) compared to placebo only (Wade et al., 2004; Portenoy et al., 2012; Stott et al., 2012; Sellers et al., 2013; & Cooper et al., 2017). Interestingly, some of these studies noted increased serious psychiatric adverse events including dizziness and disorientation, as well as physiological abnormalities (e.g., tachycardia) in high-dose groups (typically 11 sprays or higher) compared to low-dose groups. Higher doses such as 11–16 sprays (Portenoy et al., 2012) as well as 24 and 36 sprays (equivalent to 64.8 mg THC + 60 mg CBD and 97.2 mg THC + 90 mg CBD, respectively; Sellers et al., 2013) dose-

dependently increased these adverse effects compared to 1–10 sprays/day in both studies. These results support the general findings from this review whereby Type 2 groups classified as a 'low' dose produced greater protective effects compared to higher dose counterparts of the same ratio (Karschner et al., 2011; Schoedel et al., 2011). Significantly greater abuse liability and increased adverse events occurred with 16 sprays of a 1:1 ratio, compared to the other two groups receiving 4 and 8 sprays of the nabiximols (Schoedel et al., 2011). Wade et al. (2004) also compared titrated doses of Type 2b to placebo and observed impairments in attention, increased intoxication and disorientation with an average titrated dose of 15 sprays/day. Likewise, Trigo et al. (2016) assessed fixed or self-titrated doses of Sativex compared to placebo and "smoking as usual" (SAU) conditions, meaning sessions where participants with CUD smoked their own cannabis. Since there is no quantification of the concentration of THC or CBD in the SAU conditions, the only comparison groups involved differing doses of Type 2b compared to placebo, which excluded them from this review. Interestingly and in line with the previously stated findings, participants preferred lower doses of Type 2b and typically titrated ~10 fewer sprays of Sativex compared to what was administered in fixed sessions (30 sprays versus 40 respectively; Trigo et al., 2016).

4.1.2 Frequent vs. Infrequent User Findings

This review suggests Type 2 chemovars may be more protective than Type 1 chemovars among infrequent users compared to frequent users, particularly for psychological and cognitive outcomes and potentially for abuse liability outcomes. Solowij et al. (2019) and Morgan et al. (2018) found a trend whereby CBD's protective effects were blunted among frequent users but not among infrequent users, as previously shown in cross-sectional investigations (Morgan et al., 2012). Frequent users had the greatest experiences of mania, perceptual distortion and cognitive disorganization when they were administered Type 2c compared to infrequent users (Morgan et al., 2018; Solowij et al., 2019). Moreover, infrequent users experienced an opposing trend, with Type 2a producing the most intense psychological effects followed by Type 1 and then Type 2c (Solowij et al., 2019). Importantly, tolerance was not observed by frequent users to THC-only (Type 1), which has been replicated in other RCTs (Colizzi et al., 2018), but tolerance was apparent when CBD was combined with THC (Morgan et al., 2018). Schoedel et al. (2011)'s study lends support to this tolerance finding due to the lack of neurocognitive impairment produced by any active treatment among their population of heavy cannabis consumers,

especially taking into consideration the high-dosing procedure applied. Both dose and duration of regular use are associated with neuroanatomic alterations in the hippocampus and prefrontal cortex (two regions with high CB_1 density) in frequent cannabis users using chemovars high in THC and untraceable amounts of CBD (Lorenzetti, Solowij, & Yücel, 2016). In contrast, frequent users using CBD with THC display no hippocampal volume abnormalities compared to controls (Lorenzetti, Solowij, & Yücel, 2016). Decreased levels of CB_1 receptors are thought to underlie tolerance and dependence to cannabis (Ceccarini et al., 2015) and it may be that frequent users included in this review were using high potency cannabis (with minimal or no CBD). Frequent users also typically exhibit decreased levels of AEA (Gruenewald & Lockhead, 1980) accompanied by reduced CB_1 receptor expression, which normalizes upon abstinence (Curran et al., 2016) suggesting a mechanism for why frequent users develop a 'tolerance' to certain cannabis-induced effects. Part of the differential outcomes observed as a result of cannabis use is also explained in varying endocannabinoid tones, metabolisms and absorbability.

Although gender differences were not investigated in this review, it is worth noting that CBD may produce protective effects for females, while potentiating effects in males (Roser et al., 2009; Cooper & Haney, 2014) although the evidence is inconsistent (Penetar et al., 2005; Haney, 2007). This finding may be an artifact of the association between gender and patterns of use given that males on average consume cannabis more frequently than females do and are more likely to meet CUD criteria (Khan et al., 2013). Therefore, males using cannabis may be more blunted to CBD's protective effects due to greater frequent use. Given that the majority of studies included in this review were predominantly male, this may further explain the heterogeneity of the findings. For instance, almost three-quarters of this review's population consisted of males-only (264 of the 363 total participants), with almost half consisting of frequent users, potentially impacting the results.

4.2 Strengths

Systematic reviews of RCTs are considered the 'gold standard' of evidence-based medicine as they provide a synthesis of the literature following a rigorous methodology that minimizes potential biases. In addition, RCTs are considered superior to observational studies as they control for observed and unobserved potential confounders, thereby increasing internal validity of the studies by investigating whether a true effect exists between the intervention and control

groups. This was the first systematic review of RCTs that the authors are aware of that examined the effects of Type 2 compared to Type 1 on psychological, cognitive, abuse liability and physiological outcomes according to the route of administration, Type 2 chemovar subtypes, and participants' frequency of use.

Analyzing studies based on the route of administration may provide insight into how outcomes may differ based on the varying bioavailability and pharmacokinetic-specific interactions pertaining to where cannabinoids were absorbed. Although multiple factors can inherently influence cannabis-related outcomes, analyzing findings based on pharmacokinetic and bioavailability estimations relating to the route of administration is a strength of this review.

Another major strength of this study was that 48 Type 2 chemovars were assessed and compared to 21 Type 1 varieties, providing a range of data not yet examined in a systematic review. This review expanded on the work from Small, Beckstead, & Chan (1975) and MacCallum and Russo (2018) by subdividing Type 2 chemovars further into three categories, allowing for the examination of CBD's potential protective effect at differing doses. With inconsistent findings in the literature regarding CBD's capability to mitigate THC-induced harms, this approach was important in exploring whether certain ratios could produce more favourable outcomes and may set the stage for future meta-analytical investigations once additional papers are published in this area. This review also took into account frequency of use when analyzing findings. Since the amount and frequency in which an individual consumes cannabis can affect their response when acutely intoxicated, this consideration was an important strength of this review although additional studies are needed to reach more definitive findings.

4.3 Considerations

4.3.1 Intra- and Inter-study Participant Variations

The exclusion of certain populations and participants among the studies included in this review should be considered when interpreting our findings. The majority of the primary studies in this review, for ethical reasons, exclude participants with regular 'negative' experiences when using cannabis and/or a personal or family history of mental health or dependence-related issues. These exclusions did not allow us to consider the possibility that certain THC:CBD ratios may produce alternate effects in these vulnerable populations. Other studies only screened for personal and

familial histories of psychosis, but not any other mental health problems. CBD has been shown to be anxiolytic in people with social anxiety disorders (Bergamaschi et al., 2011a; Crippa et al., 2011), being most ‘effective’ in a state of hyperarousal, suggesting that CBD may produce a greater protective effect in those with underlying mental health conditions. It remains to be studied if a greater reduction in anxiety may be observed in individuals suffering from anxiety disorders.

Inconsistent eligibility criteria for past and current frequency of cannabis use among individual studies varied greatly in both the ‘infrequent’ and ‘frequent’ groups defined by this review. Studies additionally differed in whether participants were allowed to continue using cannabis and how long prior to the start of the experiment they were required to abstain from use. This ranged from 1 month prior to the start of the experiment to 12 hours before. It has been suggested that the cognitive dysfunction stemming from acute cannabis use may be a result of withdrawal or residual effects from prior use (Scott et al., 2018). It is important to note that the use of cannabis in these studies, despite 12 hours' worth of clearance time from the plasma, may have interfered with their respective findings. Even with 23 days of abstinence, previous users can remain impaired cognitively, specifically regarding attentional processing and conflict resolution compared to nonusers (Bosker et al., 2013) and psychomotor impairments may remain for 23–25 days upon abstinence (Broyd et al., 2016). This may explain why CBD was unable to attenuate psychomotor and concentration cognitive realms within this review. Moreover, despite impairments in executive functioning, performance on other tasks involving cognition remains intact, complicating the interpretation of findings (Broyd et al., 2016).

4.3.2 Inconsistencies in Cannabis Preparations and Doses

There were large inconsistencies between studies regarding dose and cannabinoid preparations, which should also be taken into consideration when interpreting the evidence. Cannabinoid preparations were obtained globally, from five different countries. Certain governments and regulations made it impermissible or extremely difficult, especially in earlier studies, to obtain either cannabis and/or pure isolates of CBD (Juckel et al., 2007; Roser et al., 2008; Roser et al., 2009). Therefore, authors studied cannabis containing CBD along with other cannabinoids. The potential for intra-cannabinoid and -terpenoid effects and differing concentrations of these unmeasured cannabinoids cannot be ignored when examining the results of these studies.

A further consideration is that cannabinoid preparations, including methods of freezing, storing and extracting differed among included studies. Cannabis can be subject to degradation via temperature and light. These methods of cannabis preparation are in contrast to the manner in which recreational and medicinal users' products are produced. Only one study (Ilan et al., 2005) actually re-tested the true concentration of cannabinoids in the samples directly provided to participants, whereas other studies simply relied on cannabinoid information provided by the source. This study revealed that the labelled concentration of cannabinoids did not entirely match its stated concentration from the provider when re-analyzed by this research group. For instance, the cannabis they obtained from the National Institute on Drug Abuse (NIDA; Ilan et al., 2005) stated that THC concentrations for low and high doses administered were 1.8% and 3.6%, respectively, whereas the actual concentration of THC in the 'high' dose ranged from 2.86–3.09%. NIDA has been the sole producer of legal cannabis for research in the United States, however, NIDA contains only 27% of the THC levels and between 11–23 times the CBN concentration found within cannabis chemovars produced in medically legalized states (Vergara et al., 2017), which may provide an alternate explanation to the discrepancies observed. Moreover, NIDA not only contains the lowest THC and CBD levels (5.15 ± 2.60% and 6.16 ± 2.43%, respectively) compared to four different US cities, but it also contains the lowest variability among these concentrations (Vergara et al., 2017). Future RCTs would benefit from assaying a sample of the exact cannabis they will administer to participants, after it has been prepared and treated, and in using chemovars that are representative of what participants are likely to use outside of the study. This is one benefit to naturalistic studies such as Morgan et al. (2012).

Dosing was also inconsistent across studies. Some studies based the dose administered to participants according to their body weight (Dalton et al., 1975a;b; Zuardi et al., 1982) whereas other studies provided the same dose across participants. Some included studies also administered top-up doses to participants (Solowij et al., 2019) or allowed participants to purchase additional cannabis to consume (Haney et al., 2016).

4.3.3 Route of Administration Variability

There were several inconsistencies even within the same ROA category in this review. Studies administering cannabinoids via intrapulmonary absorption employed differing inhalation

procedures that tried to control the rate, depth and frequency of inhalations. Recreational and medicinal users rarely tend to consume in this regimented manner and results need to be interpreted with caution. Further, some (typically older) studies utilized cannabis cigarettes or 'joints' versus others that used the Volcano Vaporizer or Mighty Medic Vaporizer (Storz & Bickel, Tuttlingen, Germany) to administer cannabinoids to participants.

Differing inhalation procedures were applied across studies using the inhaled route of administration (Ilan et al., 2005; Hindocha et al., 2015; Haney et al., 2016; Lawn et al., 2016; Arkell et al., 2019; Solowij et al. 2019) without any objective measures of depth of inhalations, save one study. Group variation was evidenced by increased CO levels in the study by Ilan et al. (2005), suggesting that the Type 1-high dose group received less than double the concentration of THC than the lower group, which was later confirmed through assays of THC concentration. Even the proportion of inhaled cannabis administered via the Volcano Vaporizer differed among groups of the same study, which was reflected in plasma concentrations, showing a significant difference in the proportion inhaled between THC and THC+CBD groups (Solowij et al., 2019). Only ~150 mg (instead of 400 mg) of CBD was delivered to participants because only ~40% of the CBD loaded would be vaporized, as a result of the sticky resin accumulated in the process, and due to the fact that it also induced heavy coughing and throat irritation among participants (Solowij et al., 2019).

Compared to intrapulmonary absorption, gastrointestinal absorption through the oral route of administration affords greater interindividual variability due to digestion in the stomach and metabolism in the liver (Grotenhermen, 2003). Many studies observed discrepancies between plasma THC metabolite concentrations and observed effects for Type 1 and Type 2 groups. One explanation for this could be a result of CBD's pharmacokinetics, where high CBD doses inhibit the cytochrome P450 oxidative system in vitro, therefore inhibiting THC liver metabolism and increasing plasma levels of THC (Bornheim and Grillo, 1998). Karschner et al. (2011) and Schoedel et al. (2011) provide evidence to the contrary, stating that this relationship is not clinically relevant in humans because it would require much higher concentrations of CBD to inhibit this metabolism.

Among studies using the combination ROA there was variance in the different routes of administration for each cannabinoid (e.g., oral CBD capsules ahead of intravenous THC vs. oral

THC capsules ahead of oromucosal spray). Although this provides valuable insight into potential cannabinoid administration for optimal efficiency, this does not reflect an accurate representation of a typical recreational or medicinal cannabis consumer's past and current cannabis regime. Moreover, inconsistencies not only resulting from the relative timing of separate CBD and THC administration, but also dependent on whether CBD and THC were administered using different routes of administration. Studies that administered cannabinoids via the intravenous route of administration did so differently as well, particularly regarding the time between one cannabinoid administration to the next. Since the full cannabinoid and terpenoid profiles are typically not provided, the presence of other cannabinoids in preparations administered to participants may have a different influence on outcomes depending on the route of administration. For example, CBN produces psychoactive effects when administered intravenously, but not orally (Perez-Reyes et al., 1973).

Further inconsistencies in bioavailability arise due to provision of food prior to cannabis administration whereas other studies restrict food by requiring a fasting state of up to eight hours. Dietary constituents of food inevitably affect the absorption of different medications, vitamins and minerals, and this is also true with cannabis. Lipophilic drugs such as cannabis in the presence of fats can increase absorption in the blood. Fats may affect cannabinoids first-pass metabolism in the liver, as fats are typically packaged into chylomicrons, which bypass the liver and are transported directly into the systemic circulation via the mesenteric lymphatic system (Zgair et al., 2016).

4.3.4 Measurement and Outcome Discrepancies

The timing of assessments varied in terms of the time between measurement intervals, the total number of assessments, and in the time taken to record the first measurement post-dose, within each and across all routes of administration. Although this review tried to account for this heterogeneity by selecting consistent timepoints within each routes of administration, variability was still present. For instance, although two studies using the oral route of administration administered Type 2c, Leweke et al. (2000) measured psychological outcomes (STAI, SAS, QMI, Bf-S) only at baseline, 3 hours post- and 24 hours post-treatment whereas Karinol et al. (1974) examined psychological phenomenon at baseline, 30 minutes post-dose and every 20-minutes after that for 3 hours. Roser et al. (2008) recorded ERPs three hours after administration

and took blood samples for THC, 11-OH-THC, THC-COOH and CBD 15 minutes later, which may not have been a sufficient time interval to capture peaks or potential fluctuations in findings, especially since no audiometry was performed before ERP recordings. Although pharmacokinetic parameters were not fully examined in this review, various studies mention plasma cannabinoid levels being inconsistent with the timing of various outcome findings.

Studies were heterogenous in measurement scales used to assess psychological phenomenon, even among capturing the same specific outcomes such as psychotic symptoms (PANSS, SSPS, PSI, BPRS) and anxiety (STAI, VAS 'anxiety', anxiety symptom grading). There was great variability especially in the cognitive outcome domain given the numerous aspects of cognition being measured and the large number of scales, tests and procedures available to assess these domains. A lack of sensitivity among specific outcome measurements may explain some of the negative findings. For instance, Karschner and colleagues (2011) observed similar scores (using a 5-point Likert scale for cognitive items such as, "difficulty concentrating" and "altered sense of time") across all treatments, including placebo, suggesting it may not be sensitive enough to detect subtle changes produced by THC. A similar limitation to Likert and VAS scales is their differential individual interpretation, including the way participants feel about scale markers (i.e., "strongly agree" to "strongly disagree"). Likewise, scales such as the Adjective Mood Scale, do not allow for differentiation of qualities of subjective experience outside of general wellbeing.

The sensitivity and specificity of subjective scales may be particularly problematic, especially to capture aspects of propensity to cannabis dependence such as VAS measures of "Good Drug Effects" versus "Liking", or terms like "High" versus "Intoxication" or "Stoned". This is partly evidenced by inconsistent or nonexistent dose-response effects with some of the cannabinoid metabolites mentioned. The majority of included trials in this review did not measure important metabolites such as 11-OH-THC and THC. Both THC and 11-OH-THC are significantly related to "Good Drug Effects" among a sample of occasional users, whereas "High" ratings were significantly associated with THC metabolite levels only (Newmeyer et al., 2017).

4.4 Limitations of This Review

Although considered a strength for systematic reviews, the restriction of eligibility to RCTs-only also has some limitations. RCTs do not resemble real-world use in terms of dosing procedures, cannabis composition and often recruit only a few highly-selected participants. The majority of

included studies contained small samples of participants which may overestimate treatment effects, although some stated being sufficiently powered to detect differences. Another limitation of this review regards the short nature of treatment and assessment periods among the included RCTs. This impedes a long-term observation of how acute cannabis consumption, specifically regarding Type 1 versus Type 2, may change over time. The majority of the included studies utilized one day per session to observe the acute effects of cannabis on cognition, dependence and psychological phenomenon, however, it is known that individual experiences of cannabis' psychoactive and cognitive effects, especially in novel consumers, may diminish over time. It may also be that CBD does not protect against the acute, impairing effects of THC while intoxicated, but rather reduces psychiatric and cognitive impairments after extended use (Lorenzetti, Solowij, & Yücel, 2016).

Another limitation of this review includes our decisions to extract data among repeated measures. By selecting outcomes based on consistent timepoints across each route of administration pertaining to pharmacokinetic estimations, significant data that occurred at different timepoints was not considered in this review. Had this review selected timepoints based on peak outcome data, alternative findings may have been observed, but we decided against this approach as we felt it incorporated additional sources of heterogeneity.

A major limitation of this review is that we were unable to conduct meta-analyses given the heterogeneity of populations, interventions, outcomes and routes of administration. An additional issue impeding the undertaking of a meta-analysis is that the majority of included studies (17/19) were crossover trials. A lack of first-period data from individual study groups precluded quantitative analysis. Quantitatively assessing crossover data after all study periods and using the entire sample size would provide an overestimation of SE. Alternatively, employing a specific calculation may resolve this issue, however, it was not appropriate for this review (Appendix 5). This review was further limited by the inability to calculate p-values from crossover data that did not make direct comparisons between Type 1 and 2. A few studies failed to report or display data that was stated to be obtained in their method sections, particularly if it was not the primary outcome of interest; this excluded valuable data for our analyses. Several attempts were made to contact authors for this data however, we were unable to reach them.

The way in which chemovars were classified into Type 2 subcategories for the secondary analysis poses as an additional limitation. Combination of plant extracts with synthetic formulations (namely, synthetic THC such as dronabinol and nabilone) were used among some included studies, making classification difficult due to differing pharmacokinetics and strength of synthetic varieties. However, when looking at the majority of the studies, we do not feel that this limitation is a fatal flaw. For instance, Leweke et al. (2000) administered 1 mg of nabilone with 200 mg of CBD to participants. Although nabilone is said to be five times as potent as THC, this would roughly equate to 5 mg of THC and is still way below the 2:1 cutoff point for the Type 2c category. Another limitation of this review is that each Type 2 category (a, b, c) varied greatly in terms of their respective cannabinoid concentrations of THC to CBD. For instance, Leweke et al. (2000), Gong et al. (1983) and Hollister & Gillespie (1975) all utilized chemovars classified as 'Type 2c' and they all administered treatments orally, however, they consisted of 200 mg CBD + 1 mg Nabilone; 400 mg CBD + 5 mg THC; and 40 mg CBD + 20 mg THC, respectively.

4.5 Future Directions

There is very little empirical evidence into the acute and chronic effects of cannabis in differing ratios of THC and CBD on critical neuropsychiatric and cognitive aspects such as motivation, dependence, anxiety, memory, attention and more. Future studies should investigate varying ratios and doses of CBD and THC based on large randomized trials, as this literature should become less reliant on preclinical trials or pilot studies. In addition to properly conducted RCTs, long-term observational studies should be implemented to monitor the effects of extended dosing over multiple days, months, and years and to observe the long-term effects of cannabis. Various cannabis-related factors need to be captured in a consistent way across studies, such as: (1) current frequency of use and past history of use; (2) the amount used on average and possibly on each occasion; (3) the type of product used, including the route of administration; (4) cannabinoid and terpenoid composition of ingested chemovars (including concentration/potency); and (5) corresponding symptoms experienced or alleviated (this would need to be monitored over time to determine long-term risks and benefits of chronic recreational and medicinal use and how they affect problematic cannabis use). The use of standardized units for quantifying THC and CBD in future studies would also be helpful to inform knowledge translation efforts (Orens et al., 2015). Obtaining measures of motivation, dependence (increasing the dose or frequency of use and associated impacts on activities of daily life) and

mental health (worsening or development of anxiety, depression, symptoms of psychosis), which are influenced by these factors, will be important in expanding the knowledge in this field.

It would be important for future studies to analyze subjective findings in relation to objective markers of intoxication, such as plasma levels of metabolites, and to gain a sense of cutoff points when measuring metabolites in plasma depending on frequency of use. More liberal plasma cutoff points in frequent smokers (e.g., 5 g/L) result in reduced detection windows post-smoking (between 12–26 hours) compared to more conservative cutoffs such as 1–2g/L being detected up to 72 hours (Newmeyer et al., 2016). Occasional smokers, in contrast, have shorter detection windows for the same 1–2g/L cutoff (3.5–5 hours post-smoking). The measurement of metabolites can be highly variable if not taking into consideration patterns of use.

The use of open-label, longitudinal and/or case-control studies, as well as data obtained from registries, are recommended for future investigations to allow for the determination of outcomes across a wide range of doses and cannabinoid ratios and to characterize effects on populations who have been so far excluded from randomized controlled trials. Two prominent patient registries in Canada, include the Quebec Cannabis Registry (Lough, 2015; Ubelacker, 2015) and DATAbase for CANNabinoid Consumption and Study (DATACANN; Zacharias et al., 2018), which collect a wide range of longitudinal data from patients using medicinal cannabis. Future investigations should aim to explore different ratios of Type 2 chemovars in comparison to those currently legally available for purchase, especially those with a ratio of 1:1 or greater of CBD:THC, and to examine how they differ between frequent, infrequent and novice users. For example, an investigation into differing Type 2 ratios, comparing a 1:9 ratio of THC:CBD with a 1:1 ratio through oral administration among individuals living with HIV to detect psychological and cognitive outcomes is currently underway in Montreal (Costiniuk et al., 2019). Future research should also investigate how outcomes differ depending on underlying genetic factors and based on gender (Hindocha et al., 2019). An exploration into how these findings vary based on route of administration, including among oromucosal preparations, is also needed. These studies will help to further elucidate associations between cannabis use and worsening mental health, including dependence.

There is a need for the development of more appropriate and sensitive evaluation criteria and measures for problematic cannabis use, including the measurement of Cannabis Use Disorder, as

currently the most relied upon scales may not capture the entire picture. The DSM-5, Cannabis Abuse Screening Test (CAS), Severity of Dependence Scale (SDS), Problematic Use of Marijuana (PUM) and Cannabis Use Disorders Identification Test (CUDIT) have been the most utilized scales for assessing dependence, however, alternate measures such as the adapted Alcohol Smoking and Substance Involvement Screening Test (ASSIST) for cannabis use have been administered among Canadian adults with important findings (Leos-Toro, Rynard & Hammond, 2017). This data reveals that users may underreport criteria such as strong desire to use again (19.7%) or failing to control their use (10.8%), despite acknowledging that their relatives and friends express strong concern about their use (25.5%; Leos-Toro, Rynard & Hammond, 2017). High urinary THC-COOH/creatinine levels in urine in conjunction with self-report measures on the amount of time since an individual last used cannabis can be useful indicators of increased dependence for healthcare professionals to utilize in the future (Curran et al., 2018).

Future research should utilize Ecological Momentary Assessments or Experience Sampling Methods (EMA/ESM), which are web-based interventions that have proven successful among patients with mental health disorders and are showing promise for cannabis use and dependence. Using an online, personalized feedback tool called, ‘Marijuana eCHECKUP TO GO’, among a sample of 298 heavy-using college students, Riggs et al. (2018) highlighted the tools’ ability to alter normative attitudes and reduce frequency and prevalence of use. Given that adolescents and young adults utilize mobile devices and apps frequently throughout the day, EMA/ESM provides promise in that it can send notifications and reminders, enhancing motivation to reduce use or remain abstinent.

4.6 Conclusion

The findings pertaining to CBD’s ability to mitigate THC-induced impairments remain inconclusive. Several reviews have looked at the interacting effects of CBD and THC on psychological and/or cognitive impairments, however, no review to date has aimed to quantify psychological, cognitive, subjective and physiological outcomes according to route of administration and to explore different ratios of THC to CBD in comparison to THC-dominant chemovars.

The findings of this review echo some of the recommendations in the Lower Risk Guidelines (Fischer et al., 2011; 2017), for instance, that higher THC products produce more acute adverse effects. This study additionally demonstrates that controlled oral methods of administration (e.g., oils, capsules) appear to contain superior adverse risk and tolerability profiles, when dosed appropriately, compared to smoked methods. The results of this review add to the literature by providing some evidence to suggest a protective effect of CBD over THC, specifically regarding anxiety and acute symptoms of psychosis as well as potentially improving impairments in acute memory as well as in emotional and visual information processing. It is unclear whether this protection extends to attention, reaction times or psychomotor coordination. CBD does not seem to impact the subjective reinforcing effects nor the increases in heart rate and blood pressure produced by THC, but further studies are needed. It should be noted that many measures used to capture 'abuse liability' obtained ratings of intoxication, indicating that the Type 2 chemovars produce similar euphoria as Type 1 chemovars. In this light, Type 2 chemovars may have potential in minimizing risk (especially among vulnerable populations susceptible to dependence, worsening mental health trajectories and cognitive impairments) by producing the same intoxicating effects users seek, with reduced psychological and cognitive impairments. Future research should focus on examining the effects of THC with CBD dependent on route of administration and dose. Additionally, future studies should determine whether Type 2 chemovars reduce the frequency and pattern of use as well as associated symptomatology among cannabis users, particularly among those with Cannabis Use Disorders and who experience mental health conditions.

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Tables

Table 1: Study Characteristics

Study	*Design*	*Study Description*	*Participants/Groups*	*ROA*	*Extracts & Absorptivity Factors*	*Duration*	*Outcomes*
Karinol 1974	Double-blind Parallel RCT	Healthy males recruited and randomized to 1 of 8 treatments	**Healthy** 100% M 22 – 34 yo 8 groups (n = 5/group)	**Gastro-intestinal** [Edible (juice)]	Placebo: 0.9 ml ethanol + 200 ml OJ THC alcoholic solution + (placebo) CBD alcoholic solution + (placebo). Participants instructed to have a light breakfast on the day of the experiment (coffee, milk and one toast).	1 session/day. (PS) recorded 55, 95 , 155 and 185 min post-ingestion; (C) tests 45, 95 and 180 min post-ingestion; (PH) taken in 20 min intervals for 180 mins	PS C PH
Zuardi 1982	Double-blind, placebo-controlled crossover	Whether CBD blocks THC-induced anxiety in 'normal' volunteers and how	**Healthy** 75% M; 25% F 20 – 30 yo 5 groups	**Gastro-intestinal** [Edible (juice)]	THC & CBD stored in alcohol solution (100 mg/ml). 1.5 ml taken from that with 200 ml artificial lemon juice. Diazepam tablets crushed and put into opaque capsule, placebo was 10 mg lactose in opaque capsule.	5 sessions separated by 1 week (min.) each. (PS) and (A) measurements self-evaluated at 65 and 125 mins post-ingestion. (PS) taken by interviewers recorded at 30, 60, 120 and 180 mins post-dose. (PH) recorded at 70 and 130 mins post-dose.	PS S PH
Gong 1983	Double-blind, crossover RCT	Effects of cannabinoids on bronchodilation and studying the dose-response and interactive relationships and tolerability	**Cannabis Consumers** 100% M 21-32 yo 6 groups	**Gastro-intestinal** (Capsules)	Cannabinoids obtained from the National Institute on Drug Abuse, dissolved in sesame oil and put into gelatin capsules. Given in a fasted state.	6 sessions separated by 24- to 48-hr intervals. (A) and (PH) measurements taken at 2, 4 and 6 hours post-dose.	S PH
Leweke 2000	Single-blind RCT	Clinical interaction of cannabinoid effects on binocular depth inversion, a measure of visual perception that is impaired in schizophrenia	**Healthy** 100% M 26-35 yo 3 groups	**Gastro-intestinal** (Capsules)	CBD (natural), nabilone (CESAMET™), placebo capsule (matched nabilone capsule). Participants received a 'standardized' breakfast 1 hour prior to dose.	3 sessions with an 8-day interval. (PS) recorded at 3 and 24 hours post-administration. (C) measured at 1, 2, 3, 5, 6 and 24 hr post-dose.	PS C

1. Juckel 2007 **2.** Roser 2008 **3.** Roser 2009	Prospective, double-blind, placebo-controlled crossover	**1.** Effects of cannabis on auditory evoked mismatch negativity amplitude (information processing & working memory) **2.** Acute effects of cannabis on auditory evoked P300 amplitude at midline, frontal, central & parietal electrodes (attention & working memory) **3.** Acute effects of cannabis on psychomotor performance in healthy volunteers	**Healthy** 50% M; 50% F 3 groups **1.** 28 ± 6 yo **2.** 28.2 ± 3.1 yo **3.** 27.9 ± 2.9 yo	**Gastro-intestinal** (Capsules)	Liquid extract from *C. Sativa* (solvent 96% ethanol) and plant-isolated THC. Placebo: mix of mono-, di- and triglycerides and glycerol). Soft gelatin capsules. Doses given in an 8-hour fasted state.	3 sessions in 3 consecutive weeks. **1.** (C) recorded 2.5 hours post-administration and (A) was taken 3 hours post-dose. **2.** (C) recorded 3 hours post-administration and (A) was taken 3 hours and 15 minutes post-dose. **3.** (C) and (A) were recorded 2 hours post -dose.	C S
Eichler 2012	Double-blind, single-centre, three-period crossover RCT	Examining the pharmacokinetic and metabolic profiles of *C. Sativa* (CBD/THC ratio > 1) heated (140 °C for 12 min), unheated & synthetic THC.	**Healthy** 100% M 21-45 yo 3 groups	**Gastro-intestinal** (Capsules)	Dronabinol (Marinol, Unimed Pharmaceuticals). Cannabis extracts from Switzerland (Cannapharm AG) prepared by ethanol 70% m/m (DER 4.5). Doses given in a 12-hour fasted state.	3 sessions with at least 2 weeks washout between each. (PS) and (C) measures taken at 2, 4, 8, 12, and 24 hours post-treatment.	PS C
Dalton 1975a	Double-blind, placebo-controlled RCT	Investigating the interaction between CBD and THC on subjective experiences, psychomotor and mental performance in healthy medical students.	**Healthy** 100% M 21 – 24 yo 4 groups	**Intra-pulmonary** Smoked cannabis cigarette.	Cannabinoids extracted from cannabis used and then added to ethanolic solution with either synthetic THC or CBD, mixed until ethanol evaporated and dried at room temperature	1 session. (C) taken at 5, 25, 45, 65, and 85 mins post-dose. (A) and (PH) taken at 15, 35, 55, 75, and 95 minutes post-dose.	C S PH
Dalton 1975b	Double-blind, placebo-controlled RCT	Investigating whether the pretreatment of CBD prior to THC affects the subjective and physiological experiences in healthy medical students.	**Healthy** 100% M 21 – 24 yo 4 groups	**Intra-pulmonary** Pretreats with placebo or CBD cannabis cigarette prior to a placebo or THC cigarette.	Cannabinoids extracted from cannabis used and then added to ethanolic solution with either synthetic THC or CBD, mixed until ethanol evaporated and dried at room temperature	1 session. Unsure of timing.	S PH

Ilan 2005	Double-blind, placebo-controlled, mixed between- and within-subject RCT	Whether differing concentrations of cannabinoids can alter subjective, behavioural or neurophysiological effects of cannabis	**Cannabis Consumers** 50% M; 50% F 21 – 45 yo High THC group use 17±12.6 joints/mo Low THC group use 15.2±16.6 joints/mo 4 groups	**Intra-pulmonary** (Smoked cannabis cigarette)	Active and placebo cannabis provided by National Institute on Drug Abuse. Cannabis cigarettes were covered with coloured cigarette paper	4 sessions separated by min. 1 week each. All measurements taken 20, 80, and 140 minutes post-administration.	PS C S PH
1. Hindocha 2015 **2.** Morgan 2018	Double-blind, placebo-controlled, 4-way crossover trial	1. Determine the effects of CBD and THC both alone and combination on emotional recognition and how this differs among frequency of cannabis use and schizotypy traits **2.** Investigating the effects of placebo, THC, CBD, and THC+CBD on memory and psychotic symptoms	**Cannabis Consumers** *Recruited from their previous study of >400 cannabis users. Participants scored based on high or low schizotypy and 'light' or 'heavy' cannabis use (4 groups). 71% M; 29% F Mean(SD) age range across groups = 21 (2.13) to 22.9 (2.02)	**Intra-pulmonary** (Inhaled via Volcano Medic Vaporizer)	Placebo was ethanol vehicle. Cannabinoid doses based on prior research using Volcano device. THC and CBD both dissolved in ethanol solution and purchased from STI Pharmaceuticals (Brentwood, Essex, UK). Treatments were administered on a 10-s inhalation cycle.	4 sessions separated by 1 week washout each. **1.** (C) recorded 10 minutes post-dose. (PS) and (A) measurements taken 2, 30, 60, 90, and 120 minutes post-dose. **2.** Baseline assessments were taken before and then starting 10 minutes post-administration, which took 1.5 hours to complete the full assessment.	PS C S
1. Lawn 2016 **2.** Freeman 2017b	Repeated measures, double-blind, placebo-controlled, crossover RCT	**1.** Determining whether CBD can shield THC-induced reward processing impairments. Specifically assessing whether THC can reduce motivation and if that is less pronounced in cannabis with CBD. **2.** To determine the interactive effects of cannabis with music using neuroimaging as well as emotional and reward processing paradigms.	**Cannabis Consumers** **1.** 44% M; 56% F Mean age: 26.18(7.13) 3 groups Smoke cannabis ≤3x/wk but at least >4x in the last year. Avg: 8.06(5.48) days/mo, taking 25.88(33.73) days to smoke 3.5 g **2.** 50% M; 50% F Mean age: 26.25(7.35)	**Intra-pulmonary** (Inhaled via Volcano Medic Vaporizer)	Bedrocan cannabis (Veebdan, the Netherlands). Strains named 'Bedrobinol', 'Bediol' and placebo derived from the strain 'Bedrocan'. Drugs were kept at –20ºC in foiled-sealed pouches and brought back to room temperature pre-dosing. Cannabis and placebo contained terpenoids, creating a "distinctive" cannabis smell and was used within the 6 months of purchase.	3 sessions separated by ≥7-day washout period. Participants given a top-up dose 90-mins post-first dose during every session. 1. (A) recordings taken at 5 and 90 minutes post-first-dose, and then at 95 and 180 minutes following second administration. 2. Physiological ratings were recorded at 0, 5, and 90 mins post-dose whereas abuse liability scores were taken only at 5 and 90 mins post-dose (not at baseline)	S PH
Solowij 2019	Double-blind, placebo-controlled crossover RCT	Investigating the effects of vaporized THC, CBD, placebo and two differing ratios of CBD:THC on subjective and objective measures of intoxication among current cannabis users and non-naïve nonusers.	**Cannabis Users/ Non-naïve Nonusers** 2 groups: Nonusers = 94% M; 6% F; median age of 21.8; range 21-44. Users = 78% M; 22% F; median age of 20.5; range 18-51)	**Intra-pulmonary** (Inhaled via Volcano Medic Vaporizer)	Cannabis was obtained from STI Pharmaceuticals (Essex, UK) and cannabinoids were dissolved in ethanol solution which was blown off at a lower temperature via vaporization prior to vaporizing cannabis. Placebo was ethanol + vehicle. Participants were provided with a standard light breakfast prior to session commencement.	5 sessions separated by a 1-week washout. Participants given two top up doses – the first, 65 mins post main dose, and the second, 120 minutes post-main dose. All measurements taken at baseline, some at ~1 min post-inhalation, ~5 min prior to first top up, ~1, 15 and 45 min post 1st top up, and ~1 and 60 mins post 2nd top-up.	PS S PH

Arkell 2019	Double-blind, within-subjects crossover RCT	Examining and comparing the effects of THC-only compared to a 1:1 ratio of THC:CBD on simulated driving and cognitive tasks	**Healthy** 'Occasional' users 78.6% M; 21.4% F Age: 27.5 (4.5) 3 groups	**Intra-pulmonary** (Inhaled via the Mighty Medic vaporizer)	Cannabis was obtained from Tilray, British Columbia, Canada. No other details of cannabis preparation were provided.	3 sessions separated by at least 1 week where participants received treatments in a randomized, counterbalanced fashion. Measurements taken at baseline (cognitive, subjective, anxiety) and again 20-, 60-, 120-, 180-, 210- and 240- minutes post-dose.	PS C S
Bhattacharyya 2010	Double-blind, placebo-controlled, repeated measures, crossover fMRI RCT	Determining whether pretreatment with CBD can prevent THC-induced psychotic symptoms in healthy participants	**Healthy** 50% M; 50% F 25.6 ± 8.2 yo Lifetime use: 150 times 2 groups	**Intravenous**	Pretreatment with CBD or Placebo administered intravenously (IV) over 5 minutes before IV THC. Participants given a 'light standardized breakfast' 2 hours prior to treatment.	2 sessions, separated by min. 2 weeks each. (PS) measured at 30 and 90 minutes post-THC administration.	PS
Karschner 2011	Double-blind, double-dummy, crossover RCT	Whether CBD mitigation of THC-induced effects is due to pharmacokinetic and/or pharmacodynamic interaction	**Cannabis Consumers** 67% M; 33 % F 19 – 43 yo Cannabis use ranging from 1x/mo to 30x/wk 5 groups	**Gastro-intestinal** [Capsules (Placebo, THC)] + **Sublingual and Buccal** (Sativex)	Placebo THC capsules contained only lactose. Placebo Sativex contained propylene glycol, ethanol and peppermint oil. Participants took capsules first, and then were administered spray.	5 sessions with at least 5 days between each. Tests completed 90 mins post-dose. (PH) recordings at 0.3, 0.8, 1.3, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9 and 10.5 hours post-dose. (A) taken at 0.3, 0.5, 1, 1.5, 2.3, 3, 3.7, 4.5, 5.5, 7.5, 9.5 and 10.5 post-dose. (PS) at 1, 3, 4.5, and 5.5 post-dose.	PS S PH
Schoedel 2011	Double-blind, placebo-controlled, crossover RCT	Exploring the abuse potential of nabiximols at three doses on subjective abuse potential measures with placebo and dronabinol	**Cannabis Consumers** 83% M; 17% F 28.9 ± 7.48 yo Cannabis use: min. 2x/wk in 3 mo + >5x/wk one time 6 groups	**Oromucosal** (Nabiximols; Placebo) **Gastro-intestinal** [Capsules (Dronabinol; Placebo)]	Spray + placebo capsules; Capsules + placebo spray. Placebo capsules contained flour. Nabiximols contain minor amounts of other cannabinoids, terpenes, ethanol solution, propylene gycol & peppermint oil. Dronabinol capsules were over-capsulated. Nabiximol/placebo sprays self-administered (4 sprays left, 4 sprays right), waited for 2 min., then self-administered another 4 on each side	6 sessions separated by 21 days. each Sessions included inpatient stay (2 nights) before dosing and for 24 hrs after. (C) and some (A) measurements (Visual Analogue Scale and ARCI) were taken at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-administration whereas other (A) measures were taken at 6, 12 and 24 hours post-dose.	C S
Englund 2013	Placebo-controlled, between-subjects, 2x3 mixed RCT	Examining the effect pretreatment with CBD has on THC-induced positive psychotic symptoms and cognitive impairments	**Healthy** 54% M; 46% F 26 ± 4 yo (placebo) 59% M; 41% F 25 ± 3 yo (CBD) 2 groups	**Gastro-intestinal** [Capsules (CBD; Placebo)] **Intravenous** (THC)	CBD and Placebo provided by STI Pharmaceuticals UK. Synthetic THC supplied by Pharm GmbH (Frankfurt am Main, Germany), prepared as 1 mg/mL vials by Bicshel Laboratories (Interlaken, Switzerland).THC preparation diluted in normal saline and contained 1.5% (v/v) ethanol absolute. THC administered in 1 ml/min pulses over 10 mins. Capsules administered 210 min before IV	2 groups, assessed at 3 separate time points (baseline, post-capsule, post-THC). (C) measures taken from 140 – 180 minutes and 180 – 270 minutes post-capsule. (PS) taken 180 – 190 minutes and 300 – 330 minutes post-capsule.	PS C

Haney 2016	Double-blind, placebo-controlled, multisite, crossover, out-patient RCT	Investigating the effects of differing CBD doses on the reinforcing, subjective, cognitive and physiological THC-induced outcomes	**Cannabis Consumers** 55% M; 45% F 29.1 ± 1.7 yo Cannabis use: 6.5±0.2 days/wk; lifetime use: 9.3±1.2 years 8 groups	**Gastro-intestinal** Capsules (CBD; Placebo) **Intra-pulmonary** (Smoked THC-cigarette)	Oral CBD capsules (pure synthetic (-) – CBD (STI Pharmaceuticals)) administered 90 mins before smoking Cannabis (cigarettes) provided by the National Institute on Drug Abuse. Inhalation cycle 15s. Smoked 1 puff/min with a 40-s interval between puffs until smoked 50%. Administered in a 9 hour fasted state.	8 sessions (7.5 hour) separated by 1-week washout each. (C) taken 30 and 90 minutes post-dose. (A) and (PH) taken 15, 30, 60, 90, 120, 190, 229, 250 and 310 minutes post-administration.	C S PH

Table 1: Study Characteristics. Studies fell into one of four main categories based on study route of administration (ROA): 1) **gastrointestinal** absorption (oral preparations / formulations); 2) **alveolar** absorption (through inhalation of cannabis cigarettes or 'vaporizing' dried flower); 3) **oromucosal** / **sublingual** absorption (administered in the form of spray / pump actuations) and a **combination** of ROA (one or more methods of the aforementioned ROA including intravenous delivery). Studies are classified according to the types of participants they recruited: 'healthy' participants, or cannabis consumers. Studies are further classified according to the outcomes investigated, with, PS = psychological measures; C = cognitive measures; S = subjective abuse liability measures; and PH = physiological measures.

Table 2: Cannabis Consumption Among Participants in Included Studies

STUDY	INCLUSION / EXCLUSION CRITERIA	ACTUAL USE
Cannabis Consumers / Frequent Users		
Gong 1983	"Smoked habitually for more than 2 yr"	Does not provide data.
Ilan 2005	Reported using cannabis at least 10x in their lifetime.	High THC group: 17 ± 12.6 joints/mo. Low THC group: 15.2 ± 16.6 joints/mo.
Karschner 2011	Smoked cannabis ≥ 1x but < daily within 3 months prior to study entry.	From 1x/mo to 30x/wk, 1-10 years of use.
Schoedel 2011	≥ 1x / wk in the 3 months prior to screening + ≥ 4x / wk at least one time sin the 3 months prior to screening.	Average: 2x / wk in past 3 months + ≥ 5x / wk at least one time.
Haney 2016	Smoke ≥ ½ a cannabis cigarette ≥ 4x /wk for the 4 weeks before study screening.	6.5 ± 0.2 days/wk, using for 9.3 ± 1.2 years.
Hindocha 2015 Morgan 2018	Light users: 1-24 days/month; Heavy users: 25+ days/month.	Cannabis used in light users (low schizotypy) = 5.88(3.48) years and 11.92(6.84) days/month; Cannabis used in light users (high schizotypy) = 6.91(3.00) years and 11.71(10.24) days/month; Cannabis used in heavy users (low schizotypy) = 5.92 (2.15) years and 24.38(9.06) days/month; Cannabis used in heavy users (high schizotypy) = 5.33(2.39) years and 26.00(5.64) days/month;
Lawn 2016 Freeman 2017b	Self-reported cannabis use ≥4 times in the past year and ≤3 times/week, including the ability to 'smoke a whole joint to oneself'.	Days of cannabis use per month = 8.06(5.48) Years of cannabis use = 8.94(7.02) Days since last cannabis use = 19.25(45.28) Days to smoke 3.5 grams of cannabis = 25.88(33.73) Scored 1.13 (1.26) on the Severity of Dependence Scale (SDS).

Solowij 2019	Current cannabis users must use cannabis ≥ 1 time/month in the past 2 years. Non-naïve nonusers required to have 5-10 lifetime uses with at least one use in the past 2 years	Frequent users = 133 to ~8000 lifetime uses, using cannabis 10 days/month (median) with a range of 2-28, at least 1x/month over 3 years (median). Infrequent users = 6 to 123 lifetime uses, using cannabis 0 days/month (median) with a range of 2-5, and a median of 0 years of monthly use.
'Healthy' Participants / Infrequent Users		
Karinol 1974	No description of inclusion/exclusion criteria or past use. However, they were told they were participating in a marijuana experiment.	Does not provide data.
Hollister 1975	"Had previous exposure to marihuana in limited amounts".	Does not provide data.
Dalton 1975a;b	"Smoked" cannabis at least once previously.	Does not provide data.
Zuardi 1982	Cannot have consumed cannabis 15 days prior to the start of the trial.	5/8 participants had smoked previously.
Leweke 2000	Exclusion criteria: consuming cannabis > 10x in lifetime.	Does not provide data.
Juckel 2007 Roser 2008 Roser 2009	Occasional use in the past but must be drug free for one month before study entry.	Does not provide data.
Bhattacharyya 2010	Does not provide data.	Mean lifetime use of 150 times.
Eichler 2012	No inclusion/exclusion criteria except exclusions based on a 'known' hypersensitivity to cannabinoids and other drugs.	Does not provide data.
Englund 2013	Previous cannabis use history ≥ 1x.	Mean past use ranged from 118(218) to 137(234) times.
Arkell 2019	"Self-reported cannabis consumption ≤ 2x/wk in the previous 3 months and ≥ 10 lifetime exposures"	Age of first cannabis use = 15.9 (2.6); Number of days cannabis was used in the last 28 days = 4.5 (4.8); Number of days cannabis was used in the last 3 months = 11.2 (8.0).

Table 2. Cannabis Consumption Among Included Participants. Cannabis consumption varied widely among studies in both inclusion/exclusion criteria (i.e., whether an individual consumed or did not consume a certain amount of cannabis in order to be eligible for study entry) and in actual use of included individuals.

Table 3: Oral Route of Administration / Gastrointestinal Absorption Study Outcomes

Study (Sample size)	Treatment Arms & Doses	Timepoints	Outcome Domains & Measures	Type 1 values [Mean ± SE or Mean (SD)]	Type 2 values [Mean ± SE or Mean (SD)]	Mean Difference ± SE	Statistical Significance (P-value)	Overall Findings
Karinol et al., 1974 N = 20/20 (n =5/group) For MD: N = 10/10 (n =5/group)	**Type 1:** 30 mg THC **Type 2a:** 30 mg THC + 15 mg CBD **Type 2b:** 30 mg THC + 30 mg CBD **Type 2c:** 30 mg THC + 60 mg CBD	(PS): 95 mins post-dose	**(P):** Psychological effects	*Median values for PS only:* 4	*Median values for PS only:* T2a: 2 **T2b: 1** T2c: 2	*T1 vs. 2b:* 3	p < 0.05*	**PS** = Yes
		(C): 95 mins post-dose	**(C):** Time production task (sec)	39.6 ± 2.1	T2a: 54.4 ± 2.7 **T2b: 50.9 ± 1.5** T2c: 54.7 ± 1.5	*T1 vs. 2b:* -11.3 ± 2.581	p = 0.002**	**C** = Yes
		(PH): 90 mins	**(PH):** Heart Rate (bpm)	130.2 ± 8.2	T2a: 142.6 ± 17.5 **T2b: 105.4 ± 6.2** T2c: 100.0 ± 4.2	*T1 vs. 2b:* 24.8 ± 10.280	p = 0.042*	**PH** = Yes
Hollister & Gillespie, 1975 (n = 15/15)	**Type 1:** Placebo + 20 mg THC **Type 2c:** 40 mg CBD + 20 mg THC	(S): 2-hr post-dose	**(S):** Addiction Research Centre Inventory (ARCI): - Hallucinogen - Marihuana	 6.0 7.3	 6.6 7.3	 -0.6 0	 N/A N/A	**S** = No
			(S): Intensity ratings	6.7	7.0	-0.3	N/A	
		(PH): Change from baseline	**(PH):** Heart Rate (bpm)	13	13	0	N/A	**PH**= No
Zuardi et al., 1982 (n = 8/8)	**Type 1:** 0.5 mg/kg THC **Type 2c:** 1 mg/kg CBD + 0.5 mg/kg THC	Change in ratings from baseline at 2-hr post-dose	**(PS):** State Trait Anxiety Inventory (STAI)	15.938	8.813	7.13	p < 0.05*	**PS**=Yes
			(S): ARCI-Marijuana	18.357	9.643	8.714	p < 0.05*	**S** = Yes
			(PH): Heart Rate (bpm)	-2.238	-2.238	0	NS	**PH**= No
Gong et al., 1983 (n = 12/12)	**Type 1:** 10 mg THC **Type 2c:** 5 mg THC + 400 mg CBD	(S): Peak values taken	**(S):** VAS Intoxication/ 'High'	2.31 ± 0.05	2.22 ± 0.60	0.09	NS	**S** = No
		(PH): % change from baseline at 2-hr	**(PH)**: Heart Rate (% change - bpm)	19.28 ± 3.63	14.63 ± 1.59	4.65	NS	**PH**= No
Leweke et al., 2000 (n = 9/9)	Day 2: **Type 2c:** 200 mg CBD + 1 mg Nabilone	(PS): Change from baseline at 3-hr	**(PS):** State Trait Anxiety Inventory (STAI)	-3.35 ± 1.5	1.39 ± 2.4	-4.74	NS†‡	**PS**= NS
			(PS): Adjective Mood Scale	7.7422 ± 2.25	9.5815 ± 3.16	-1.8393	NS	

	Day 3: **Type 1:** 1 mg Nabilone + Placebo	(C): Change from baseline at 2-hr (BDI) (C): Change from baseline at 3-hr (QMI)	**(C):** Binocular Depth Inversion (BDI): - Ordinary - Flowers - Faces	 0.13 ± 0.04 0.14 ± 0.02 0.12 ± 0.03	 0.02 ± 0.04 0.05 ± 0.03 0.04 ± 0.03	 0.11 0.09 0.09	 NS NS p = 0.0209*	**C**= Yes
			(C): Bett's Questionnaire upon Mental Imagery	4.2639 ± 3.62	24.3 ± 4.63	-20.04	N/A	
Juckel et al., 2007 (n = 22/27) **Roser et al., 2008** (n = 20/27) **Roser et al., 2009** (n = 24/27)	**Type 1:** 10 mg THC **Type 2:** 10 mg THC + 5.4 mg CBD	Assessed 2-3.5 hours post-dose	**(C):** Reaction Time (ms)	466.9 (49.8)	472.9 (65.2)	-6.0	NS†‡	**C**= NS
			(C): Finger Tapping Asymmetry	-12.322 (10.116)	-9.973 (10.577)	-2.349	NS†‡	
			(C): Intermanual Coordination	44.754 (19.340)	46.088 (27.956)	-1.334	NS†‡	
			(S): Analogue Intoxication Rating (AIR) Scales	3.57 (2.25)	4.16 (2.32)	-0.59	NS	**S** = No
Eichler et al., 2012 (n = 9/10)	**Type 1:** 20 mg Dronabinol **Type 2b:** 2 capsules containing *heated* cannabis (1.4 CBD/THC)	N/A	**(PS):** VAS 'Psychosis'	N/A	N/A	N/A	NS†‡	**PS** = NS
			(C): VAS 'Cognition'	N/A	N/A	N/A	NS†‡	**C** = NS

Table 3: Oral Route of Administration / Gastrointestinal Absorption Study Outcomes. This table details included studies that delivered treatments orally (i.e., capsules, 'edibles', oils) to participants. The sample size, concentration and dose of Type 1 and Type 2 chemovars administered, as well as time points used to assess outcomes post-dose are recorded in the first three columns. Data was extracted from individual studies and used to calculate the associated mean difference (MD) and standard error (SE) and the related p-value for parallel trials using an independent t-test. Studies that did not provide any of these measures (means, variance) were delineated 'not available' or 'N/A' and therefore their respective MD, SE and p-value could not be calculated. Among crossover trials, statistical significance was obtained from the original paper and not calculated by the authors of this review. Therefore, 'N/A' within the statistical significance column indicates the p-value was not available. Bolded Type 1 and Type 2 values indicate which specific treatment was used to calculate the MD in this review if multiple treatments were administered. Asterisks beside p-values indicate significant differences: * $p < 0.05$, ** $p < 0.01$. Findings greater than $p > 0.05$ were considered non-significant or 'NS'. $NS_{\dagger}$ and $NS_{\ddagger}$ represents non-significant findings between Type 1 compared to placebo or baseline and Type 2 compared to placebo or baseline, respectively. The 'Overall Findings' column provides a dichotomous outcome (yes/no) of whether or not Type 2 was able to significantly mitigate Type 1-induced impairments. However, if both Type 1 and Type 2 did not significantly alter an outcome either compared to placebo or baseline (if there was no placebo group) then this was considered as NS for the purposes of the description and overall finding. **PS** = psychological outcomes; **C** = cognitive outcomes; **S** = subjective outcomes; **PH** = physiological outcomes; **T1** = Type 1 chemovar; **T2** = Type 2 chemovar; **T2a,b,c** = Type 2a, Type 2b and Type 2c, respectively.

Table 4: Inhaled Route of Administration / Alveolar Absorption Study Outcomes

Study (Sample Size)	**Treatment Arms & Doses**	**Timepoints**	**Outcome Domains & Measures**	**Type 1 values** [Mean ± SE or Mean (SD)]	**Type 2 values** [Mean ± SE or Mean (SD)]	**Mean Difference ± SE**	**Statistical Significance (P-value)**	**Overall Findings**
Dalton et al., 1975a (N =15/16)	**Type 1:** Placebo + 25 µg/kg THC **Type 2c:** 25 µg/kg THC + 150 µg/kg CBD	(C): 45 mins post-dose	**(C):** Wobble Board	1424.8 (229.2)	1383.3 (229.2)	41.5	NS	**C** = No
			(C): Pursuit Meter	29,312.6 (5,547.0)	26,196.5 (5,547.0)	3116.1	NS	
			(C): Delayed Auditory Feedback: - *Output* - *Error*	 55.2 (5.1) 1.27 (1.11)	 57.2 (5.1) 0.87 (1.11)	 2.0 -0.4	 NS NS	
			(C): Pegs - Any colour - R-W-B	 23.5 (1.8) 24.3 (1.6)	 22.3 (1.8) 24.2 (1.6)	 1.2 0.1	 NS NS	
		(S): 35 mins post-dose	**(S):** Psychologic 'high'	5.1 (1.8)	3.9 (1.8)	1.2	$p < 0.10$	**S** = Yes
			(S): Cornell Medical Index (CMI): - *Questions* - *Responses*	 13.7 (4.8) 22.7 (12.0)	 10.3 (4.8) 13.3 (12.0)	 3.4 9.4	 $p < 0.05$* $p < 0.10$	
		(PH): 35 mins post-dose minus baseline	**(PH):** Heart Rate	12.8 (8.0)	8.3 (8.0)	4.5	NS	**PH**= No
Ilan et al., 2005 (N = 12)	**Type 1:** 3.6% THC + 0.1% CBC + 0.2% CBD **Type 2a:** 3.6% THC + 0.1% CBC + 1.0% CBD	(PH): Change from baseline at 20 mins post-dose	**(PS):** VAS 'Anxious'	25.33 ± 10.45	7.19 ± 11.68	18.14	NS	**PS =** No
Hindocha et al., 2015 **Morgan et al., 2018** (N = 48)	**Type 1:** 8 mg THC **Type 2c:** 8 mg THC + 16 mg THC	(PS): Full battery took 1.5 hours to complete	**(PS):** Psychotomimetic States Inventory (PSI) - Total - Delusory Thinking - Perceptual Distortion - Cognitive Disorganization - Anhedonia - Mania - Paranoia	 20.41 (14.44) 1.05 ± 0.23 1.8 ± 0.31 7.06 ± 0.78 5.06 ± 0.44 4.18 ± 0.35 1.32 ± 0.33	 19.66 (13.24) 0.98 ± 0.21 1.54 ± 0.35 7.11 ± 0.81 4.81 ± 0.5 3.93 ± 0.41 1.13 ± 0.35	 0.75 0.07 0.26 -0.05 0.25 0.25 0.19	 NS NS †‡ NS NS NS †‡ NS †‡ NS †‡	**PS =** No
			(PS): Brief Psychiatric Rating Scale (BPRS): - Positive Symptoms	 6.67 ± 0.15	 6.31 ± 0.08	 0.36	 N/A	

			- Negative Symptoms	4.69 ± 0.23	4.87 ± 0.3	-0.18	NS	
		(C): Full battery took 1.5 hours to complete	**(C):** Prose Recall: - Immediate - Delayed	 8.08 ± 0.53 7.63 ± 0.56	 8.37 ± 0.57 7.59 ± 0.57	 0.29 -0.04	 NS NS	**C** = Yes
			(C): Working Memory: - N-back (1-back) Discriminability - N-back (2-back) Discriminability - N-back (1-back) Reaction Time (ms) - N-back (2-back) Reaction Time (ms)	 2.27 ± 0.17 1.82 ± 0.20 788.26 ± 97.39 1135.22 ± 127.82	 2.35 ± 0.12 1.91 ± 0.17 736.52 ± 85.22 1013.48 ± 109.56	 0.08 0.09 51.74 121.74	 NS NS NS NS	
			(C): Semantic Fluency	17.2 ± 0.68	19.0 ± 0.55	-1.8	NS†	
			(C): Emotional Processing Task (% accuracy): - 40% Intensity	 39.75 (4.51)	 43.52 (10.9)	 3.77	 p = 0.024*	
		(S): 30 mins post-dose	**(S):** VAS 'Stoned'	4.2 (0.32)	4.13 (0.39)	0.07	NS	**S** = No
Lawn et al., 2016 **Freeman et al., 2018** (N = 16/17)	**Type 1:** 12% THC used to load 8 mg dose **Type 2b:** 6% THC + 7.5% CBD used to load 8 mg THC + 10 mg CBD	(S) Assessed 0-90 mins post-dose. An average of 21 trials (~15 s each per session) for EEfRT.	**(S):** Effort Expenditure for Rewards Task (EEfRT): - Model 1 - Model 2 (drug x magnitude) - Model 3 (drug x probability) - Model 4 (drug x expected value)	 N/A N/A N/A N/A	 N/A N/A N/A N/A	*Beta values ± SE for EEfRT only* -0.001 ± 0.028 -0.039 ± 0.039 -0.036 ± 0.019 -0.093 ± 0.034	 NS NS p = 0.073 p = 0.006**	**S** = No
		(S) 1 hr minus baseline (all VAS) except VAS 'stoned' taken at 90 mins post-dose	**(S):** VAS - 'Stoned' - 'Feel Drug Effect' - 'Like Drug Effect' - 'Want More Drug'	 5.28 ± 0.67 7.94 ± 0.71 7.30 ± 0.47 2.74 ± 0.71	 5.37 ± 0.40 7.74 ± 0.44 7.40 ± 0.52 3.22 ± 0.79	 -0.09 0.20 -0.10 -0.48	 NS NS NS NS †‡	
		(PH): 1 hr minus baseline	**(PH):** Heart Rate (bpm)	23.4 (5.0)	24.92 (5.23)	-1.52	NS	**PH** = No
			(PH): Diastolic Blood Pressure (mmHg)	7.52 (3.11)	3.87 (3.60)	3.65	NS	
			(PH): Systolic Blood Pressure (mmHg)	4.46 (4.80)	5.77 (5.59)	-1.32	NS	
Solowij et al., 2019) (N = 36)	**Type 1:** 8 mg THC **Type 2a:** 8 mg THC + 4 mg CBD	(PS): 15 mins post-second dose (~75 mins post-first dose) minus baseline	**(PS):** Clinician Administered Dissociative States Scale (CADSS) - Total Score - Amnesia	 6.76 ± 1.17 1.22 ± 0.19	 *T2a:* 7.19 ± 1.46 ***T2c:* 4.36 ± 0.90** *T2a:* 1.17 ± 0.21 ***T2c:* 0.97 ± 0.23**	 *T1 vs. T2c:* 2.4 ± 1.476 *T1 vs. T2c:* 0.25 ± 0.298	 N/A N/A	**PS** = No

	Type 2c: 12 mg THC + 400 mg CBD + two top-up drug administrations at ~55 and 120 mins post main dose.		- Depersonalization	1.52 ± 2.37	*T2a:* 1.25 ± 0.35 ***T2c:* 0.81 ± 1.43**	*T1 vs. T2c:* 0.71 ± 2.768	N/A	
			- Derealization	4.01 ± 0.73	*T2a:* 4.75 ± 0.99 ***T2c:* 2.58 ± 0.56**	*T1 vs. T2c:* 1.43 ± 0.920	N/A	
			- Observation	1.85 ± 0.36	*T2a:* 2.22 ± 3.72 ***T2c:* 0.83 ± 0.21**	*T1 vs. T2c:* 1.02 ± 0.417	N/A	
			(PS): Psychotomimetic States Inventory (PSI)					
			- Delusional Thinking	0.306 ± 0.45	*T2a:* 0.08 ± 0.5 ***T2c:* 0.17 ± 0.61**	*T1 vs. T2c:* 0.136 ± 0.758	N/A	
			- Perceptual Distortion	2.306 ± 0.50	*T2a:* 2.74 ± 0.58 ***T2c:* 1.83 ± 0.48**	*T1 vs. T2c:* 0.476 ± 0.693	N/A	
			- Cognitive Disturbance	6.333 ± 1.14	*T2a:* 7.00 ± 1.23 ***T2c:* 5.17 ± 1.10**	*T1 vs. T2c:* 1.163 ± 1.584	N/A	
			- Anhedonia	1.694 ± 0.57	*T2a:* 1.31 ± 0.7 ***T2c:* 1.44 ± 0.61**	*T1 vs. T2c:* 0.254 ± 0.835	N/A	
			- Mania	1.639 ± 0.52	*T2a:* 1.83 ± 0.52 ***T2c:* 1.03 ± 0.53**	*T1 vs. T2c:* 0.609 ± 0.743	N/A	
			- Paranoia	0.028 ± 0.44	*T2a:* 0.11 ± 0.58 ***T2c:* 0.19 ± 0.58**	*T1 vs. T2c:* -0.162 ± 0.728	N/A	
		(S) = 55 mins post-first dose	**(S):** VAS - Intoxication	5.375 ± 0.42	*T2a:* 5.68 ± 0.38 ***T2c:* 5.25 ± 0.32**	*T1 vs. T2c:* 0.125 ± 0.531	N/A	**S** = No
		(PH) = 55 mins post-first dose minus baseline	**(PH):** Heart Rate	38.88 ± 4.94	*T2a:* 39.75 ± 4.88 **T2c: 25.97 ± 4.07**	*T1 vs. T2c:* 12.91 ± 1.509	N/A	**PH** = Yes
			(PH): Systolic Blood Pressure	-4.3888 ± 4.46	*T2a:* -4.167 ± 3.6 ***T2c:* -1.528 ± 3.6**	*T1 vs. T2c:* -2.861 ± 5.732	N/A	
			(PH): Diastolic Blood Pressure	3.4444 (2.32)	*T2a:* 5.278 (2.28) ***T2c:* 4.75 (2.82)**	*T1 vs. T2c:* -1.306 ± 0.609	N/A	
Arkell et al., 2019 (N = 14/14)	**Type 1:** 11% THC + <1% CBD **Type 2b:** 11% THC + 11% CBD	(PS): 60 mins post-dose	**(PS):** VAS - Anxious	N/A	N/A	0.876 ± 0.435	p = 0.139	**PS** = No
			(PS): State Trait Anxiety Inventory (STAI)	N/A	N/A	0.964 ± 1.507	p = 1.000	
		(C): 20 mins post-dose minus baseline	**(C):** Digit Symbol Substitution Task (DSST)					**C** = No
			- Number correct	-3.07 (3.07)	-1.78 (2.98)	1.29	NS	
			- Accuracy (%)	-3.18 (2.08)	-1.93 (2.51)	1.25	NS	
			(C): Divided Attention Task (DAT)					
			- Tracking error	2.72 (1.34)	4.86 (2.12)	-2.14 ± 0.670	p < 0.05*	
			- Response time (ms)	8.09 (113.04)	115.78 (81.86)	-107.69 ± 37.301	NS	
			- Number correct	-0.36 (0.71)	-0.21 (0.60)	0.15 ± 0.248	NS	
			(C): Paced Auditory Serial Addition Task (PASAT)					
			- Number correct	-1.43 (4.84)	-3.93 (5.58)	-2.5 ± 1.974	NS	

		- Respones time (ms)	122.31 (53.54)	119.78 (57.97)	2.53 ± 21.090	NS
(S): 15 mins post-dose	**(S):** VAS					**S** = No
		- Stoned	N/A	N/A	1.04 ± 0.534	p = 0.163
		- Strength of effect	N/A	N/A	0.74 ± 0.553	p = 0.546
		- Liking of effect	N/A	N/A	1.07 ± 0.679	p = 0.349

Table 4: Inhaled Route of Administration / Alveolar Absorption Study Outcomes. This table details included studies that required to participants to smoke (i.e., a cannabis cigarette) or vaporize cannabis. The sample size, concentration and dose of Type 1 and Type 2 chemovars administered, as well as time points used to assess outcomes post-dose are recorded in the first three columns. Data was extracted from individual studies and used to calculate the associated mean difference (MD) and standard error (SE) and the related p-value for parallel trials using an independent t-test. Studies that did not provide any of these measures (means, variance) were delineated 'not available' or 'N/A' and therefore their respective MD, SE and p-value could not be calculated. Among crossover trials, statistical significance was obtained from the original paper and not calculated by the authors of this review. Therefore, 'N/A' within the statistical significance column indicates the p-value was not available. Solowij et al. (2019) provided mean, SE, SD and 95% CI values for each group and outcome, however, they were unable to provide associated p-values and therefore is considered N/A. The authors made judgements pertaining to the 'description' column based on findings stated in their paper. Arkell et al. (2019) provided the authors of this review with their own calculated MD, SE, 95% CI and p-value for STAI outcomes between Type 1 and Type 2. Bolded Type 1 and Type 2 values indicate which specific treatment was used to calculate the MD in this review if multiple treatments were administered. Asterisks beside p-values indicate significant differences: * $p < 0.05$, ** $p < 0.01$. Findings greater than $p > 0.05$ were considered non-significant or 'NS'. $NS_{\dagger}$ and $NS_{\ddagger}$ represents non-significant findings between Type 1 compared to placebo or baseline and Type 2 compared to placebo or baseline, respectively. The 'Overall Findings' column provides a dichotomous outcome (yes/no) of whether or not Type 2 was able to significantly mitigate Type 1-induced impairments. However, if both Type 1 and Type 2 did not significantly alter an outcome either compared to placebo or baseline (if there was no placebo group) then this was considered as NS for the purposes of the description and overall finding. **PS** = psychological outcomes; **C** = cognitive outcomes; **S** = subjective outcomes; **PH** = physiological outcomes; **T1** = Type 1 chemovar; **T2** = Type 2 chemovar; **T2a,b,c** = Type 2a, Type 2b and Type 2c, respectively.

Table 5: Combination Route of Administration / Absorption Study Outcomes

Study (Sample Size)	**Treatment Arms & Doses**	**Timepoints**	**Outcome Domains & Measures**	**Type 1 Values** [Mean ± SE or Mean (SD)]	**Type 2 Values** [Mean ± SE or Mean (SD)]	**Mean Difference ± SE**	**P-value**	**Overall Findings**
Dalton et al., 1975b (n = 8)	**Type 1:** Placebo 30 min. before 25 µg/kg THC **Type 2c:** 150 µg/kg CBD 30 min. before 25 µg/kg THC	(S): Change from baseline	**(S):** Cornell Medical Index (modified)	5.8	5.9	0.1	NS	**S** = No
		(PH): Change from baseline	**(PH):** Heart Rate (bpm)	26.0	29.0	-3.0	NS	**PH**= No
Bhattacharyya et al., 2010 (n = 6)	**Type 1:** Placebo 5 min. before 1.25 mg THC **Type 2c:** 5 mg CBD 5 min. before 1.25 mg THC	(PS): 30 mins post-dose	**(PS):** Positive and Negative Symptom Scale (PANSS)	13.0 (5.8)	9.0 (2.2)	4.0	$p < 0.05$*	**PS**= Yes
Karschner et al., 2011 (n = 9)	**Type 1 (low):** 5 mg synthetic THC **Type 1 (high):** 15 mg synthetic THC **Type 2b (low):** 5.4 mg THC +5 mg CBD **Type 2b (high):** 16.2 mg THC +15 mg CBD	Mean Average Difference from baseline ± SE at 90 mins	**(PS):** State Trait Anxiety Inventory (STAI)	*T1 (low):* 1.9 ± 2.68 ***T1 (high):*** **4.63 ± 1.5**	*T2 (low):* 1.05 ± 1.98 ***T2 (high):*** **3.52 ± 1.91**	*T1 (high) vs. T2 (high):* 1.11 ± 2.429	NS	**PS**= No
			(PS): VAS - 'Anxiety'	*T1 (low):* 6.78 ± 3.03 ***T1 (high):*** **6.33 ± 3.48**	*T2 (low):* 5.22 ± 2.93 ***T2 (high):*** **5.13 ± 3.3**	*T1 (high) vs. T2 (high):* 1.2 ± 4.796	NS	
			(S): VAS - 'Good Drug Effects'	*T1 (low):* 6.24 ± 5.93 ***T1 (high):*** **8.03 ± 4.97**	*T2 (low):* 1.69 ± 4.55 ***T2 (high):*** **6.38 ± 5.79**	*T1 (high) vs. T2 (high):* 1.65 ± 7.631	NS	**S** = No
			- 'High'	*T1 (low):* 0.86 ± 2.75 ***T1 (high):*** **1.03 ± 1.55**	*T2 (low):* 3.78 ± 4.21 ***T2 (high):*** **2.32 ± 2.92**	*T1 (high) vs. T2 (high):* -1.29 ± 3.036	NS	
			(S): Addiction Research Centre Inventory (ARCI): - Marijuana Scale	*T1 (low):* -0.81 ± 0.67 ***T1 (high):*** **-0.59 ± 0.6**	*T2 (low):* 0.42 ± 0.6 ***T2 (high):*** **-0.47 ± 0.56**	*T1 (high) vs. T2 (high):* 0.12 ± 0.821	NS	
			(PH): Heart Rate (bpm)	*T1 (low):* -0.37 ± 3.21 ***T1 (high):*** **4.04 ± 2.15**	*T2 (low):* -4.40 ± 5.6 ***T2 (high):*** **3.80 ± 2.17**	*T1 (high) vs. T2 (high):* 0.24 ± 3.055	NS	**PH**= No

			(PH): Systolic Blood Pressure (mmHg)	*T1 (low):* 4.22 ± 3.27 *T1 (high):* **7.83 ± 3.00**	*T2 (low):* 0.83 ± 3.69 *T2 (high):* **5.22 ± 3.38**	*T1 (high) vs. T2 (high):* 2.61 ± 4.519	NS	
			(PH): Diastolic Blood Pressure (mmHg)	*T1 (low):* 5.27 ± 2.26 *T1 (high):* **-3.89 ± 2.62**	*T2 (low):* -3.50 ± 2.53 *T2 (high):* **-4.55 ± 2.18**	*T1 (high) vs. T2 (high):* -0.66 ± 3.408	NS	
Schoedel et al., 2011 (n = 23/30)	**Type 1 (low):** 20 mg Dronabinol **Type 1 (high):** 40 mg Dronabinol	*Least Squares Mean of Peak Values ± SE*	**(S):** VAS: - 'Overall drug liking'	***T1 (low):*** **6.50 ± 0.61** *T1 (high):* 6.63 ± 0.61	*T2 (low):* 4.32 ± 0.61 ***T2 (med):*** **4.63 ± 0.61** *T2 (high):* 6.71 ± 0.61	*T1 (low) vs. T2 (med):* 1.87	*T1 (low) vs. T2 (med):* p < 0.05*	**S** = Yes
	Type 2b (low): 10.8 mg THC + 10 mg CBD (Sativex - 4 sprays) **Type 2b (med.):** 21.6 mg THC + 20 mg CBD (Sativex - 8 sprays) **Type 2b (high):** 43.2 mg THC + 40 mg CBD (Sativex – 16 sprays)		- 'Drug Liking'	***T1 (low):*** **6.96 (6.0, 7.9)** *T1 (high):* 7.61 (6.7, 8.6)	*T2 (low):* 5.31 (4.4, 6.3) ***T2 (med):*** **6.05 (5.1, 7.0)** *T2 (high):* 7.28 (6.3, 8.2)	0.91	NS	
			- 'Take drug again'	***T1 (low):*** **5.46 ± 0.79** *T1 (high):* 7.01 ± 0.70	*T2 (low):* 3.90 ± 0.79 ***T2 (med):*** **4.44 ± 0.79** *T2 (high):* 6.37 ± 0.79	1.02	NS	
			- 'Good drug effects'	***T1 (low):*** **6.87 ± 0.69** *T1 (high):* 7.54 ± 0.69	*T2 (low):* 5.37 ± 0.69 ***T2 (med):*** **5.69 ± 0.69** *T2 (high):* 7.67 ± 0.69	1.18	NS	
			- 'High'	***T1 (low):*** **6.09 ± 0.74** *T1 (high):* 7.52 ± 0.74	*T2 (low):* 4.08 ± 0.74 ***T2 (med):*** **4.42 ± 0.74** *T2 (high):* 6.94 ± 0.74	1.67	p < 0.05*	
			- 'Pleasant mental state'	***T1 (low):*** **7.94 ± 0.38** *T1 (high):* 8.22 ± 0.38	*T2 (low):* 7.66 ± 0.38 ***T2 (med):*** **7.85 ± 0.38** *T2 (high):* 8.36 ± 0.38	0.09	NS	
			- 'Stoned'	***T1 (low):*** **5.58 ± 0.73** *T1 (high):* 7.51 ± 0.723	*T2 (low):* 3.45 ± 0.73 ***T2 (med):*** **3.85 ± 0.73**	1.73	p < 0.05*	

					T2 (high): 6.14 ± 0.73		
			(S): ARCI: - Morphine-Benzedrine Group	***T1 (low):*** **6.8 (5.1, 8.6)** *T1 (high):* 8.1 (6.3, 9.8)	*T2 (low):* 5.2 (3.4, 6.9) ***T2 (med):*** **5.9 (4.1, 7.6)** *T2 (high):* 7.1 (5.3, 8.9)	*T1(low) vs. T2(med):* 0.9	*T1(low) vs. T2(med):* NS†‡
			- Marijuana	***T1 (low):*** **1.6 ± 0.2** *T1 (high):* 1.6 ± 0.2	*T2 (low):* 1.0 ± 0.2 ***T2 (med):*** **1.0 ± 0.2** *T2 (high):* 1.3 ± 0.2	0.6	p < 0.05*
			- Pentobarbital-Chlorpro-mazine-	***T1 (low):*** **6.5 ± 0.6** *T1 (high):* 6.6 ± 0.6	*T2 (low):* 5.6 ± 0.6 ***T2 (med):*** **5.4 ± 0.6** *T2 (high):* 6.5 ± 0.6	1.1	NS
			- LSD	***T1 (low):*** **3.87** *T1 (high):* 3.98	*T2 (low):* 3.39 ***T2 (med):*** **3.49** *T2 (high):* 4.0	0.38	p = 0.020*
			(S): Subjective Drug Value ($)	***T1 (low):*** **10.34(5.9, 14.8)** *T1 (high):* 17.32(12.8, 21.8)	*T2 (low):* 5.68 (1.2, 10.7) ***T2 (med):*** **7.42 (3.0, 11.9)** *T2 (high):* 13.8 (9.3, 18.3)	*T1 (low) vs. T2 (med):* 2.92	*T1 (low) vs. T2 (med):* NS
Englund et al., 2013 [n = 45/48; 2 groups: (T1 = 26; T2 = 22)]	**Type 1:** Placebo 210 min. before 1.5 mg THC **Type 2c:** 600 mg CBD 210 min. before 1.5 mg THC	(PS): 75 mins post-THC minus baseline	**(PS):** PANSS Positive Psychotic Symptoms	2.4 (3.1)	1.2 (1.8)	1.2 ± 0.719	p = 0.15	**PS**= Yes
			(PS): State Social Paranoia Scale (SSPS)	11.11 ± 0.43	10.17 ± 0.10	0.94 ± 0.442	p < 0.05*	
		(C): 60 mins post-THC minus baseline	**(C):** HVLT-R - Immediate Recall - Delayed Recall (%)	 -3.6 (4.5) -10.6 (18.9)	 -2.9 (5.3) -0.4 (9.7)	 0.7 ± 1.434 10.2 ± 4.245	 NS p = 0.027*	**C**= Yes
			(C): Symbol Coding	5.2 ± 3.38	7.0 ± 4.09	-1.8 ± 1.095	NS	
			(C): Digit Span Forward	-0.9 ± 0.33	-0.3 ± 0.41	0.6 ± 0.526	NS	
			(C): Digit Span Reverse	-0.7 ± 0.38	-0.5 ± 0.42	0.2 ± 0.566	NS	

			(C): Neuropsychological Assessment Battery	21.8 ± 3.8	23.2 ± 2.8	-1.4 ± 4.720	NS	
Haney et al., 2016 (n = 31)	**Type 1:** 0 mg CBD + 5.3- 5.8% THC **Type 2a:** 200 mg CBD + 5.3-5.8% THC **Type 2b:** 400 mg CBD + 5.3-5.8% THC **Type 2c:** 800 mg CBD + 5.3-5.8% THC	(S): 30 mins post-THC (120 mins post-CBD)	**(S):** VAS - 'High'	4.67 ± 0.55	T2a: 4.56 ± 0.67 T2b: **4.22 ± 0.40** T2c: 3.64 ± 0.53	*T1 vs. T2b:* 0.45	NS	**S**= No
			(S): % Self-Administering (# of Puffs Purchased)	1.67 ± 0.26	T2a: 1.71 ± 0.26 T2b: **1.58 ± 0.25** T2c: 1.56 ± 0.25	*T1 vs. T2b:* 0.09	NS	
			(S): Street Value Rating ($)	6.88 ± 0.76	T2a: 6.94 ± 0.82 T2b: **8.31 ± 1.00** T2c: 8.51 ± 1.37	*T1 vs. T2b:* -1.43	NS	
			(S): Marijuana Rating Form: - 'Liking'	5.70 ± 0.43	T2a: 5.76 ± 0.48 T2b: **5.82 ± 0.30** T2c: 6.16 ± 0.46	*T1 vs. T2b:* -0.12	NS	
			- 'Strength'	5.57 ± 0.66	T2a: 5.46 ± 0.76 T2b: **5.55 ± 0.69** T2c: 5.76 ± 0.46	*T1 vs. T2b:* 0.02	NS	
		(PH): 30 mins post-THC	**(PH):** Heart Rate	5.34 ± 3.48	T2a: 5.85 ± 3.42 T2b: **6.1 ± 4.05** T2c: 6.53 ± 2.85	*T1 vs. T2b:* -0.76	NS	**PH**= No

Table 5: Combination Route of Administration / Absorption Study Outcomes. This table details included studies that used a combination approach to deliver treatments to participants. The sample size, concentration and dose of Type 1 and Type 2 chemovars administered, as well as time points used to assess outcomes post-dose are recorded in the first three columns. Data was extracted from individual studies and used to calculate the associated mean difference (MD) and standard error (SE) and the related p-value for parallel trials using an independent t-test. Studies that did not provide any of these measures (means, variance) were delineated 'not available' or 'N/A' and therefore their respective MD, SE and p-value could not be calculated. Among crossover trials, statistical significance was obtained from the original paper and not calculated by the authors of this review. Therefore, 'N/A' within the statistical significance column indicates the p-value was not available. Bolded Type 1 and Type 2 values indicate which specific treatment was used to calculate the MD in this review, if multiple treatments were administered. Asterisks beside p-values indicate significant differences: * $p < 0.05$, ** $p < 0.01$. Findings greater than $p > 0.05$ were considered non-significant or 'NS'. $NS_{\uparrow}$ and $NS_{\updownarrow}$ represents non-significant findings between Type 1 compared to placebo or baseline and Type 2 compared to placebo or baseline, respectively. The 'Overall Findings' column provides a dichotomous outcome (yes/no) of whether or not Type 2 was able to significantly mitigate Type 1-induced impairments. However, if both Type 1 and Type 2 did not significantly alter an outcome either compared to placebo or baseline (if there was no placebo group) then this was considered as NS for the purposes of the description and overall finding. **PS** = psychological outcomes; **C** = cognitive outcomes; **S** = subjective outcomes; **PH** = physiological outcomes; **T1** = Type 1 chemovar; **T2** = Type 2 chemovar; **T2a,b,c** = Type 2a, Type 2b and Type 2c, respectively.

Table 6: Chemovar Prevalence Across Studies

ROA (# of studies)	***Type 1 Chemovars***	***Type 2a Chemovars***	***Type 2b Chemovars***	***Type 2c Chemovars***	***Total***	***Type 2 Only Total***
Smoking (n=6)	6	2	2	3	**Type 1** = 46.2% **Type 2a** = 15.4% **Type 2b** = 15.4% **Type 2c** = 23.1%	**Type 2a** = 28.6% **Type 2b** = 28.6% **Type 2c** = 42.8%
Oral (n=7)	7	2	2	5	**Type 1** = 43.8% **Type 2a** = 12.5% **Type 2b** = 12.5% **Type 2c** = 31.2%	**Type 2a** = 22.2% **Type 2b** = 22.2% **Type 2c** = 55.6%
Combination (n=6)	8	1	6	4	**Type 1** = 42.1% **Type 2a** = 5.3% **Type 2b** = 31.6% **Type 2c** = 21.0%	**Type 2a** = 9.1% **Type 2b** = 54.5% **Type 2c** = 36.4%
Total	21 (43.8%)	5 (10.4%)	10 (20.8%)	12 (25.0%)	48 (100%)	
Type 2 Only Total		5/27 (18.6%)	10/27 (37.0%)	12/27 (44.4%)		27/48 (56.3%)

Table 6. Chemovar prevalence across studies. The total number chemovars for each individual study were divided into Type 1, Type 2-subcategories (Type 2a, Type 2b, Type 2c) and Type 3. Studies with more than one dose of the same ratio (i.e., Type 2b-high dose and Type 2b-low dose) were counted separately. Chemovar prevalence was calculated for each chemotype as well as for each route of administration (ROA).

Figures

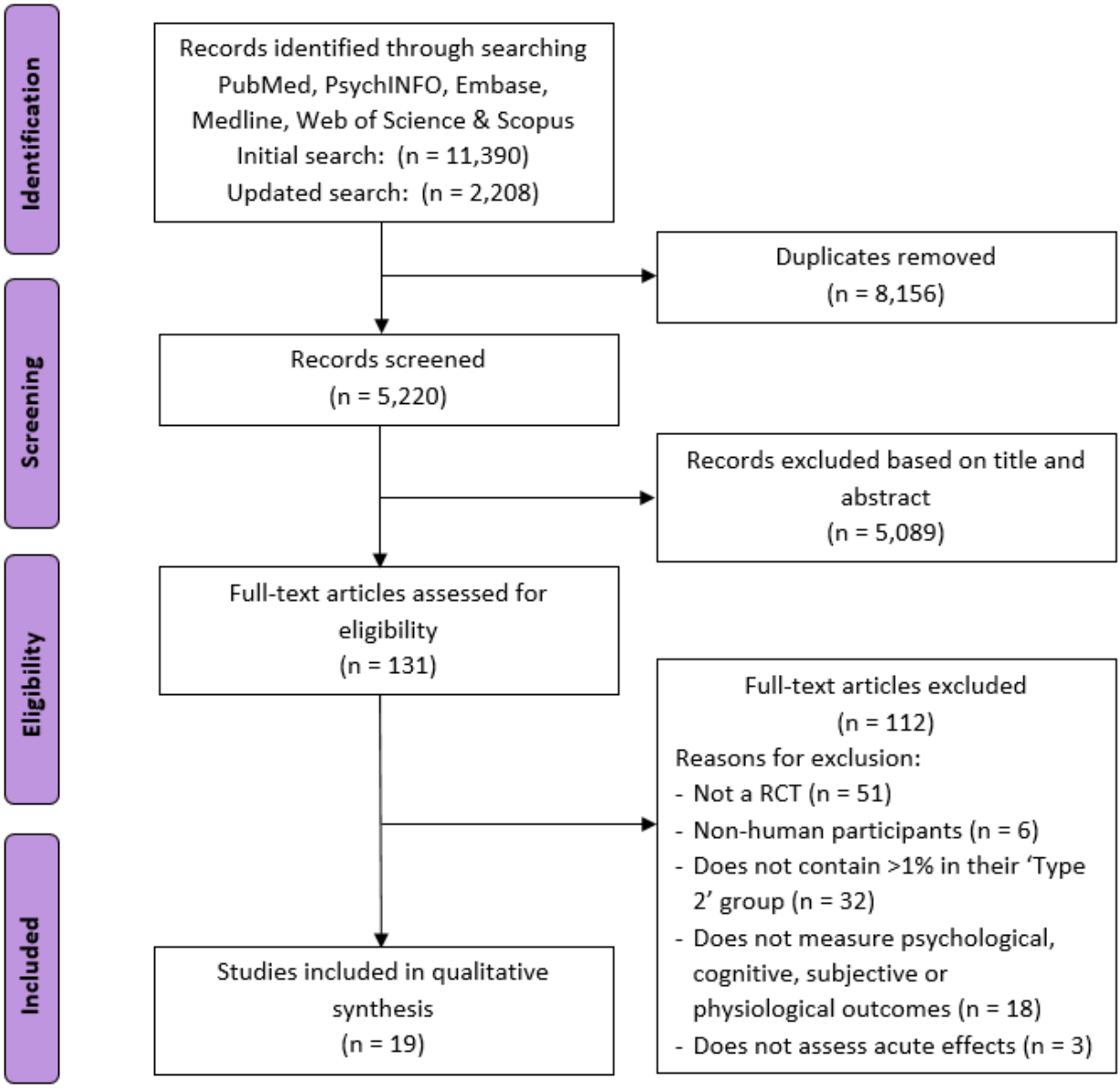

Figure 1: PRISMA Flow Diagram
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

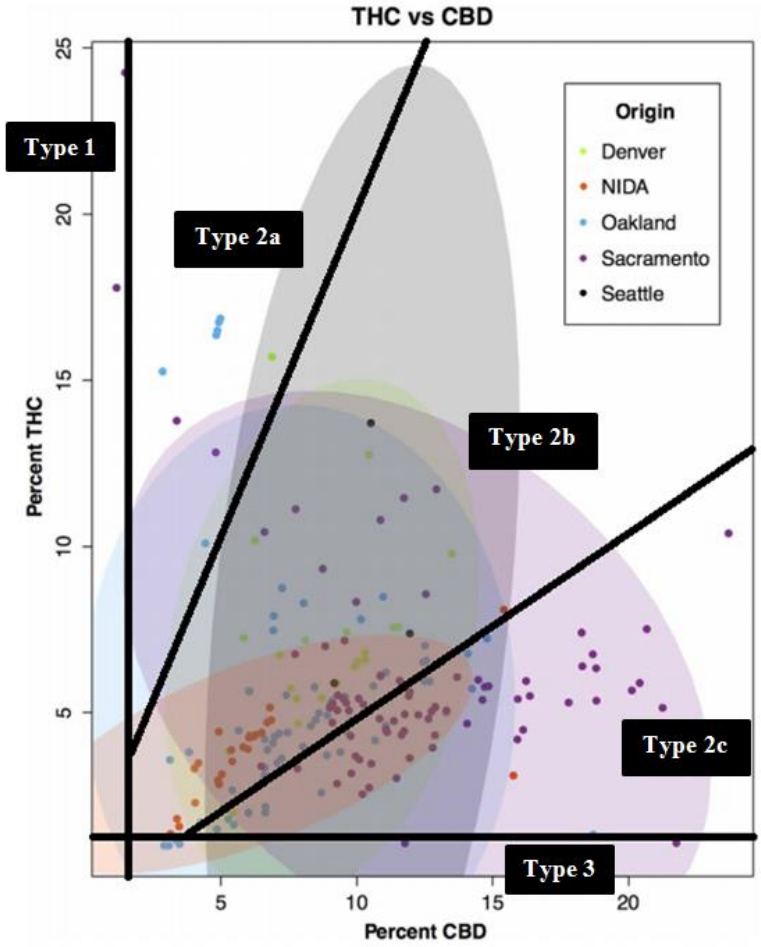

Figure 2: Chemovar Distinctions: This figure is adapted from Vergara et al. (2017) which depicts cannabis samples taken from the listed United States cities as well as National Institute on Drug Abuse (NIDA). The authors of this review demarcated the lines on the graph pertaining to chemovar classifications. Chemovars are illustrated via their respective cut-offs, with Type 1 representing any chemovar >1% THC with < 1% CBD, Type 2a is representative of chemovars ≥ 2:1 of THC to CBD, as long as CBD < 1%. Type 3 represents any chemovar with >1% CBD but < 1% THC and Type 2c consists of chemovars ≥ 2:1 of CBD to THC, as long as THC < 1%. Type 2b chemovars fall between Type 2a and 2c and are roughly equivalent to a 1:1 ratio of THC:CBD.

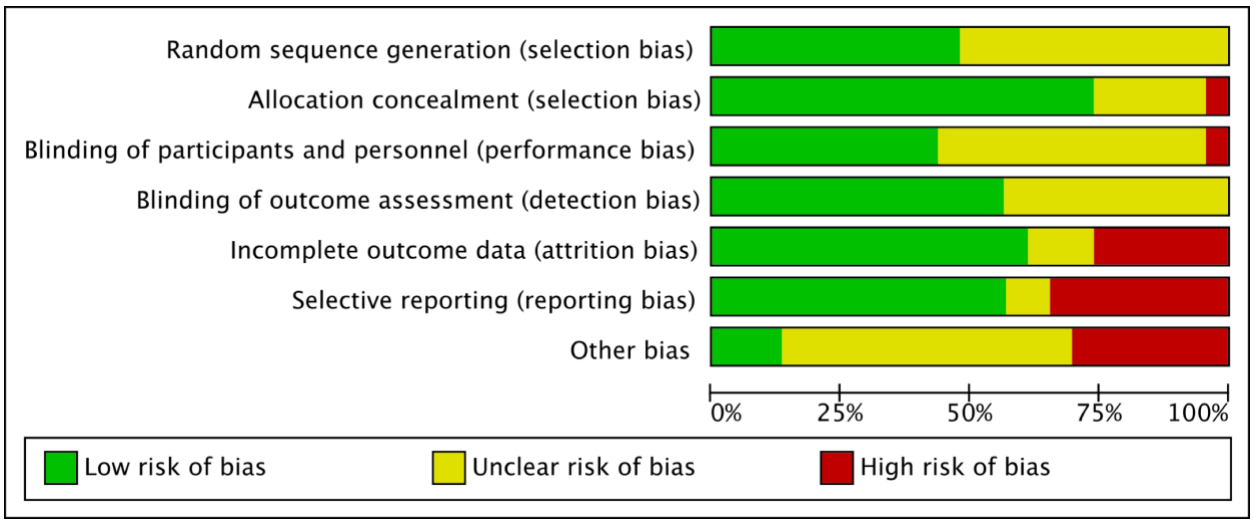

Figure 3: Risk of Bias Graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

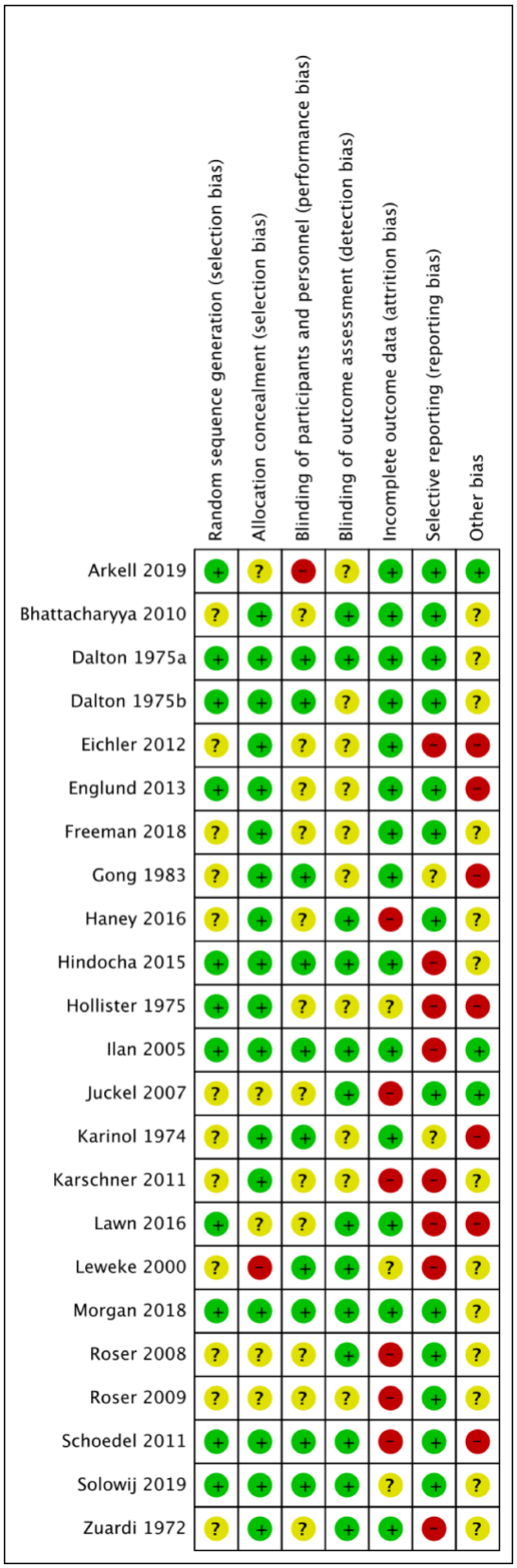

Figure 4: Risk of Bias Summary: review authors' judgments about each risk of bias item for each included study.

Appendices

Appendix 1: Definitions and Terms

Δ9 -THC: Delta-9-tetrahydrocannabinol; the predominant phytocannabinoid found in the plant *Cannabis* typically responsible for psychoactive effects experienced upon consuming cannabis.

11-OH-THC: 11-hydroxy-delta-9-tetrahydrocannabinol OR 11-hydroxy THC; THC's major active metabolite that is produced in vivo upon ingestion of decarboxylated cannabis.

2-AG: 2-arachidonoylglycerol; an endocannabinoid and agonist on CB_1 receptors and the primary ligand for CB_2 receptors.

AEA: Anandamide (*N*-arachidonoylethanolamine); an endocannabinoid and agonist at CB_1 and CB_2 receptors.

AIR-Scales: Analogue Intoxication Rating Scales; participants rate their level of intoxication on a 100 mm line, similar to VAS scales, with one end of the line marked "not intoxicated" and the other end marked "extremely intoxicated". The distance of the participant-drawn line is measure from the left end (Bond and Lader, 1974).

ARCI: Addiction Research Centre Inventory; A standardized self-reported questionnaire to assess the subjective experience of drug effects as well as some psychiatric characteristics (Haertzen et al., 1963). It includes various subscales such as, Marijuana (M), Hallucinogen, Amphetamine (A), Benzedrine Group (BG), Pentobarbital-Chlorpromazine Alcohol Group Scale (PCAG), and Lysergide Scale (LSD)

BDI: Binocular Depth; Stereoscopic pictures from 'Ordinary', 'Faces', and 'Flowers' categories are presented to participants in which depth information from the photos was altered. Using an operationalized description in conjunction with a 5-step rating scale, participants must describe their visual perception (Leweke et al., 1999).

BPRS: Brief Psychiatric Rating Scale; A clinician/research-administered scale that measures typically 18-24 symptoms including depression, anxiety, hallucinations, rating each symptom from 0 (not present) to 7 (extremely severe; Overall & Gorham, 1962). It consists of two subscales, one for positive and the other for negative symptoms.

CADSS Clinician Administered Dissociative States Scale; This is an objective quantification of intoxication, which requires a trained psychologists to rate participants on a scale of 0 (not at all) to 4 (extremely) pertaining to eight items, resulting in a total possible score of 32. Example items include: "Did the subject appear to be separated or detached from what is going on, as if not a part of the experience or not responding in a way that you would expect?"; "Did the subject say something bizarre or out of context, or not speak when you would have expected?" (Solowij et al., 2019).

CB_1 / CB_2: Cannabinoid receptor 1 & cannabinoid receptor 2. Although both are found throughout the central nervous system, CB_2 has a large role in immunologic function and inflammatory responses.

CBD: Cannabidiol; one of over 100 phytocannabinoids in the plant *Cannabis* particularly known for its anti-anxiety, neuroprotective and anti-inflammatory effects.

CBD-A: Cannabidiolic Acid; CBD's acid precursor which must undergo a process of decarboxylation to be transformed into the cannabinoid, CBD.

CBN: Cannabinol; a phytocannabinoid that must undergo a process of aging to be synthesized.

CBN-A: Cannabinolic Acid; CBN's precursor, derived from aging THC-A.

CMI: Cornell Medical Index; Clinician-rated instrument to measure medical and psychiatric data. Since July 2001 however, the CMI was no longer available to be used among human research as it was deemed outdated and not reliable (Samuel J. Wood Library, 2018).

CRT: Choice Reaction Time; A 2-choice reaction time test (with two possible stimuli and two potential responses) that assesses psychomotor speed and alertness. This test is typically performed on a computer with the participant pressing specific buttons depending on where the stimulus appears (Totterdell & Folkard, 1992)

DAF: Delayed Auditory Feedback; A task in which the time between speaking and auditory feedback are altered as a way of measuring mental performance via speech and auditory perception (Yates, 1963).

DAT Divided Attention Task; Participants are required to track a stimulus horizontally on screen with their computer mouse while at the same time using their peripheral vision to click on the left mouse button whenever one number presented in the corner screen matched to a number at the bottom of the screen. Mean distance of the mouse cursor from the intended target (tracking error) as well as the matched numbers correctly identified, out of 24, are the dependent variables (Kleykamp et al., 2010).

Dronabinol: Trade names, Marinol® and Syndros®. A synthetic form of THC administered orally in the form of capsules to treat weight loss in AIDS-related anorexia and used as an antiemetic. Although approved by Health Canada, it is no longer available for sale in Canada.

DSMT: Digit Span Memory Test (Forward & Reverse); A test of working memory requiring participants to repeat a sequence (either forward or backward) of numbers presented to them with increasingly longer sequences being presented at each trial (Schroeder et al., 2012).

DSST: Digit Symbol Substitution Test; A ‘paper and pencil’ test in which digit-symbol pairs are presented followed by a list of numbers. Participants must write the correct symbol pertaining to the specific number as quickly and precisely as possible. The number of correct transpositions over a 60-second trial is typically presented. This test is sensitive to neuropsychological damage (i.e., brain injury, dementia) and depression (McLeod et al., 1982).

ECS: Endocannabinoid system; The ECS is an inherent process in all mammals that is responsible for maintaining homeostasis among a wide range of psychological, cognitive and physiological processes. It is comprised of receptors, endogenous ligands and enzymes responsible for their facilitation and degradation.

EEfRT Effort Expenditure for Rewards Task; A measure of effort-related decision making which requires individuals to make either a low effort or high-effort choice for differing rewards. Making more high-effort choices is suggestive of impairments in the reward pathway (Treadway et al., 2009; 2012).

EPT Emotional Processing Task; A measure of emotional facial affect recognition via a computerized task in which participants have to correctly guess one of six basic emotions portrayed, with each emotional face varying in intensity from 0 to 100% (Hindocha et al., 2014)

ERP: Event-related potential; An electrophysiological response to a sensory, cognitive or motor stimulus, typically measured via electroencephalography (EEG; Luck, 2005).

FAAH: Fatty acid amide hydrolase; an enzyme responsible for the degradation of various biologically active amides. Specifically, FAAH hydrolyzes AEA to arachidonic acid and ethanolamine AEA.

FTA: Finger Tapping Asymmetry; Participants were instructed to press a button as quickly as possible using one finger on one hand. Certain sessions involved finger tapping in conjunction with other tasks such as reading a passage aloud and humming (Shimoyama, Ninchoji, & Uemura, 1990).

HVLT-R: Hopkins Verbal Learning Test-Revised; A test assessing verbal learning and memory in neuropsychiatric populations (Alzheimer's Disease, amnesia) and includes aspects such as total recall, delayed recall, retention and recognition discrimination index. It has proven to be highly reliable with construct, concurrent and discriminant validity well established (Brandt & Benedict, 2001)

IMC: Intermanual Coordination; Using alternating tapping from either hand . Defined as the percent frequency of alternating tapping in relation to the mean tapping frequency of both hands (Gorynia & Egenter, 2000; Roser et al., 2009).

K2 / "Spice": Synthetic cannabinoids. Other brand names include, 'Black Mamba', 'Bombay Blue', 'Genie', 'Krypton' and many more. These synthetic cannabinoids bind to cannabinoid receptors in the body similar to THC and are ingested through smoking or orally in a concentrated liquid form. These are different from synthetic therapeutic formulations (nabilone, dronabinol) as they are not standardized and may contain other additives and higher potencies, and their chronic use considered harmful.

MAGL: Monoacylglycerol lipase; the enzyme responsible for the degradation of 2-AG.

MMN: Mismatch Negativity paradigm; MMN is produced by any discernable change of a repetitive sound and is considered an objective, negative component of the brain's auditory ERP, allowing for the measure of auditory sensory memory functioning (Näätänen, 1995). Upon deviation of a tone stimulus in either frequency, intensity, duration and/or location from its previous continually repeated tone, MMN is automatically elicited with a 100 – 200 ms latency post-change. Deficits in MMN are a robust finding in chronic schizophrenia.

MRF: Marijuana Rating Form; A 5-item visual analogue scale measuring the subjective strength of the effect produced by cannabis, 'good' and 'bad' effects, liking, and willingness to smoke again (Haney et al., 2016).

N-Back: A measure of spatial working memory in the presence of an increased load. A smiley face is presented in one of six spatial locations on a computer screen with a fixation cross in the center. Upon the appearance of subsequent faces, participants have to indicate whether the smiley face is in the same location it was previously in (1-back) or whether it was in the same location two trials previous to the current (2-back). Individuals undergo, in random order, 25 "match" and 25 "no-match" trials (Morgan et al., 2018).

NAB: Neuropsychological Assessment Battery; A comprehensive clinician-administered battery focusing on attention, language, memory, spatial, executive functioning and screening modules (Stern & White, 2003).

Nabilone: Brand name, Cescamet®; a synthetic cannabinoid mimicking THC delivered orally in the form of capsules, with clinical uses in the treatment of nausea and neuropathic pain. In Canada, Cescamet® is used in chronic pain management as an adjunct therapy and in severe cancer chemotherapy-related nausea and vomiting.

Nabiximols: Trade name, Sativex®; plant-derived extracts, Tetranabinex® and Nabidiolex®, of THC and CBD delivered in an oromucosal (spray) 1:1 ratio developed by the UK company, GW Pharmaceuticals. Sativex® has been approved by Health Canada for the treatment neuropathic pain and spasticity symptoms, chiefly arising from multiple sclerosis.

P300 wave: A cognitive ERP component reflecting active working memory and attentional resource allocation (Polich, 1991). It is typically measured in accompaniment with an auditory 'oddball' experiment model requires participants perception of deviant ('oddball') targets.

PANSS: Positive and Negative Symptom Scale; A clinician-administered scale used to measure the severity of symptoms of schizophrenia that includes a positive (7-items), negative (7-items) and general psychopathological (16-items) scale that assesses positive, negative and general symptoms of the illness, respectively. Each item is given a score from 1 to 7, with a score of 30 being the lowest possible and 210 the highest (Kay, Fiszbein & Opler, 1987).

PASAT: Paced Auditory Serial Addition Task; Participants are instructed to watch numbers appear on screen and must add each number to the preceding one. They then must select the correct answer from a list of numbers provided. Response time on correct trials and the number of overall correct trials (out of 90) are the dependent variables (Herrmann et al., 2015).

PSI: Psychotomimetic States Inventory; An assessment of acute schizotypal symptoms with subscales measuring aspects of cognitive disorganization, perceptual distortions, mania, paranoia, delusional thinking and anhedonia with each item rated from 0 (not at all) to 3 (strongly; Mason et al., 2008)

QMI: Bett's Questionnaire upon Mental Imagery; A 150-item questionnaire to assess vividness of mental imagery across seven sensory modalities (visual, auditory, olfactory, gustatory, cutaneous, kinesthetic, and organic; Betts, 1909; Sheehan, 1967).

RTT: Reitaan's Trailmaking Test (TMT: 59); Consists of a Form A and B to measure processing speed. Participants are required to string 25 numbers in an ascending numerical sequence in Form A whereas Form B requires the connection of numbers (1-13) to letters (A-L) in ascending number to letter sequence. Time to complete the task as well as subtracting scores from Form A from Form B (psychomotor speed) are the two dependent variables (Morgan et al., 2018).

SDS: Severity of Dependence Scale; A 5-item self-rated questionnaire indicating the severity of dependence for a particular drug (Gossop et al., 1995). Items are rated from 0 to 3 with an increased score representing greater severity of dependence.

SDV: Subjective Drug Value; Requires participants to make multiple independent theoretical forced decisions between the treatment administered and monetary values (Griffiths et al., 1993; Schoedel et al., 2011)

SHPS: Snaith Hamilton Pleasure Scale; A 14-item scale that assesses anhedonia by measuring aspects of social interaction, appetite, sensory experiences and hobbies (Snaith et al., 1995). Each item is scored either "0" or "1" with a lowest potential score of 0 and highest of 14.

SOMC: Short Orientation Memory Concentration Test; A 6-item test that measures working memory, attention, executive functioning, reasoning and problem-solving (Katzman et al., 1983).

SPQ: Schizotypal Proneness Questionnaire; A 74-item self-reported scale that assesses criteria for schizotypal personality disorder containing subscales for all 9 schizotypal traits (Raine, 1991).

SSPS: State Social Paranoia Scale; A 20-item self-reported scale that assesses persecutory ideations and delusions with items ranked from 1 (do not agree) to 5 (totally agree; Freeman et al., 2007).

STAI: State Trait Anxiety Inventory; A 4-point self-administered Likert scale inventory that consists of 40 items, measuring either state (current or acute) and trait (chronic) anxiety (Spielberger et al., 1983).

STWT: Spot the Word Test; A measure of premorbid intellectual and cognitive functioning and estimate of robust verbal intelligence (Baddeley, 1993; Baddeley & Crawford, 2012) Participants are presented with a real word and non-word and they must select which word is the correct word.

SVR: Street Value Ratings; An estimate of the value of the cannabis treatment administered if it were sold in the black or grey market provided in USD ($).

TEPS: Temporal Experiences of Pleasure Scale; An 18-item scale to measure trait anhedonia with ratings ranging from 1 (very false for me) to 6 (very true for me) with two subscales, anticipatory anhedonia and consummatory anhedonia (Gard et al., 2006). Increased ratings indicate a greater ability to experience pleasure.

THC-A: Tetrahydrocannabinolic Acid; THC's precursor molecule that must undergo a process of decarboxylation in order to be transformed into the cannabinoid, THC.

THC-COOH: 11-nor-9-delta-9-tetrahydrocannabinol or 11-COOH-THC or 11-nor-9-carboxy-THC or THC-11-oic acid; THC's secondary metabolite produced in vivo via enzymatic oxidation of 11-OH-THC in the liver upon consumption of cannabis. Due to THC-COOH's long half-life, it is the main metabolite tested for in urine and blood assessments of cannabis consumption, however, high levels of its precursor, 11-OH-THC, found in the body signifies more recent consumption.

Type 1: Cannabis chemovar classification, predominant in THC with no, or negligible, CBD (<0.01%).

Type 2a: Cannabis chemovar sub-classification of "Type 2" or a mixture of THC and CBD within the same chemovar. Type 2a reflects chemovars with a THC:CBD ratio of 2:1, or higher, meaning a greater proportion of THC to CBD (e.g., a cannabis oil that contains 10 mg THC + 5 mg CBD).

Type 2b: Cannabis chemovar sub-classification of "Type 2" or a mixture of THC and CBD within the same chemovar. Type 2b reflects an equal or close to equal ratio of CBD:THC within the same chemovar. (I.e., CBD:THC of 2:1 ≦ Type 2b ≧ CBD:THC of 1:2). For example, a cannabis product containing 5.4 mg THC + 5 mg CBD.

Type 2c: Cannabis chemovar sub-classification of "Type 2" or a mixture of THC and CBD within the same chemovar. Type 2c reflects chemovars with a CBD:THC ratio of 2:1, or higher, meaning a greater proportion of CBD to THC. (e.g., dried flower that contains 4% THC and 15% CBD).

Type 3: Cannabis chemovar classification, predominant in CBD with no or negligible THC (<0.01%).

VAS: Visual Analogue Scales; typically presented as a 100 mm line in which a participant must rate (on the specified scale) from one extreme to the other. For example, the left side of one scale could represent 'strongly disagree', and the right would represent 'strongly agree' with 'neutral' being in the middle of the line.

Appendix 2: Search Strategies

EMBASE:

1. exp dronabinol/
2. exp tetrahydrocannabinol/
3. tetrahydrocannabinol$.mp.
4. marinol$.mp.
5. delta-9 tetrahydrocannabinol.mp.
6. THC.mp.
7. exp cannabidiol/
8. cannabidiol.mp.
9. CBD.mp.
10. or/1-6 [THC set]
11. or/7-9 [CBD set]
12. 10 and 11
13. limit 12 to embase
14. limit 12 to conference abstracts
15. 13 not 14

MEDLINE:

1. exp Dronabinol/
2. tetrahydrocannabinol$.mp.
3. delta-9-tetrahydrocannabinol.mp.
4. THC.mp.
5. marinol$.mp.

6. 1 or 2 or 3 or 4 or 5/

7. exp Cannabidiol/

8. cannabidiol.mp.

9. CBD.mp.

10. 7 or 8 or 9

11. 6 and 10

PsychINFO:

1. exp TETRAHYDROCANNABINOL/

2. tetrahydrocannabinol$.mp.

3. delta-9-tetrahydrocannabinol.mp.

4. THC.mp.

5. dronabinol.mp.

6. cannabinoids.mp or exp Cannabinoids/

7. 1 or 2 or 3 or 4 or 5 or 6

8. cannabidiol.mp.

9. CBD.mp.

10. 8 or 9

11. 7 and 10

PubMed:

(((((((THC) OR tetrahydrocannabinol) OR delta-9-tetrahydrocannabinol) OR marinol)) AND ((cannabidiol) OR CBD))) OR (("Dronabinol"[Mesh]) AND "Cannabidiol"[Mesh])

Scopus:

(thc OR tetrahydrocannabinol OR delta-9-tetrahydrocannabinol OR marinol) AND (cannabidiol OR cbd) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (SUBJAREA, "CENG"))

Web of Science:

#5	(#3 AND #4) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#4	(TS=(cannabidiol OR CBD)) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#3	(#1 OR #2) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#2	(TS=(delta-9-tetrahydrocannabinol OR marinol)) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#1	(TS=(THC OR tetrahydrocannabinol)) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*

Appendix 3: Screening Levels and Associated Questions

Question Text	Type	Question Header	Question Validation	Answer Text	Answer Header	Answer Validation
Is this study an RCT?	Radio	Is this study an RCT?		Yes	Yes	
				No	No	
				Can't Tell	Can't Tell	
Does this study involve humans only?	Radio	Does this study involve humans only?		Yes	Yes	
				No	No	
				Can't Tell	Can't Tell	
Does the intervention test one ratio of THC:CBD compared to different ratio(s) of THC:CBD and/or to THC-only chemovar(s)?	Radio	Does the intervention test one ratio of THC:CBD compared to different ratio(s) of THC:CBD and/or to THC-only chemovar(s)?		Yes	Yes	
				No	No	
				THC & CBD are administered in separate groups and not together-	THC & CBD are administered in separate groups and not together-	
				Can't Tell	Can't Tell	

Supplementary Table 1. First round of screening questions conducted in DistillerSR software.

Question Text	Type	Question Header	Question Validation	Answer Text	Answer Header	Answer Validation
Besides THC + CBD, what is the other intervention(s)?	Radio	Besides THC + CBD, what is the other intervention(s)?		THC, Placebo	THC, Placebo	
				THC only	THC only	
				Other ratio of THC + CBD	Other ratio of THC + CBD	
				Placebo only	Placebo only	
				CBD only	CBD only	
				Assesses CBD & THC independently	Assesses CBD & THC independently	
				Can't tell	Can't tell	
What outcome variable(s) does this study assess? (Select more than one if applicable)	Checkbox	What outcome variable(s) does this study assess? (Select more than one if applicable)		Psychological (positive psychotic symptoms, paranoia and/or anxiety)	Psychological (positive psychotic symptoms, paranoia and/or anxiety)	
				Cognitive (any aspect of cognition - memory, attention, neuroimaging etc.)	Cognitive (any aspect of cognition - memory, attention, neuroimaging etc.)	
				Subjective (abuse measures/scales, marijuana rating form, probability reward task, etc.)	Subjective (abuse measures/scales, marijuana rating form, probability reward task, etc.)	
				Physiological (heart rate, blood pressure)	Physiological (heart rate, blood pressure)	
				None of the above	None of the above	
				Can't tell	Can't tell	
Is this an RCT	Radio	Is this an RCT		Yes	Yes	
				No	No	

Supplementary Table 2. Second round of abstract screening questions conducted in DistillerSR software.

Question Text	Type	Question Header	Question Validation	Answer Text	Answer Header	Answer Validation
Is this study an RCT?	Radio	Is this study an RCT?		Yes	Yes	
				No	No	
Does this study involve humans only?	Radio	Does this study involve humans only?		Yes	Yes	
				No	No	
Is CBD + THC used in comparison to either THC only, THC + placebo, THC + a different ratio of CBD & THC, or differing ratios of CBD & THC?	Radio	Is CBD + THC used in comparison to either THC only, THC + placebo, THC + a different ratio of CBD & THC, or differing ratios of CBD & THC?		Yes	Yes	
				No	No	
What psychological outcomes are assessed? (N/A if not an outcome measure)	Text	What psychological outcomes are assessed? (N/A if not an outcome measure)	Free Text			
What cognitive outcomes are assessed? (N/A if not an outcome measure)	Text	What cognitive outcomes are assessed? (N/A if not an outcome measure)	Free Text			
What physiological outcomes are assessed? (N/A if not an outcome measure)	Text	What physiological outcomes are assessed? (N/A if not an outcome measure)	Free Text			
What abuse liability outcomes are assessed? (N/A if not an outcome measure)	Text	What abuse liability outcomes are assessed? (N/A if not an outcome measure)	Free Text			

Supplementary Table 3. Third round of full-text screening questions conducted in DistillerSR software.

Appendix 4: RISK OF BIAS DETAILED NOTES ON RATING

Arkell 2019:

Domain	Judgment	Notes on Rating
Random sequence generation	Low	"Participants received the three treatments (one per session) in a randomized and counterbalanced order. The randomization schedule was created by an independent researcher, and only the study pharmacist had access to it."
Allocation concealment	Unclear	Insufficient information to permit judgment.
Blinding of P&P	High	"The randomization schedule was created by an independent researcher, and only the study pharmacist had access to it." Blinding was assessed at the end (asked all participants to identify the cannabis they thought they received) and all 14 correctly identified placebo (commonly reported less vapor was produced in this session as well).
Blinding of outcome assessment	Unclear	Insufficient information to permit judgment.
Incomplete outcome data	Low	No missing outcome data or loss to follow-up <10%.
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Low	Insufficient reporting of attrition/exclusions to permit judgment.
Overall Assessment	**LOW RISK**	

Bhattacharyya 2010:

Domain	Judgment	Notes on Rating
Random sequence generation	Unclear	"Using a repeated measures, pseudorandomized, double-blind, within-subject design"
Allocation concealment	Low	"…'Pretreatments,' CBD (5 mg), or placebo were administered intravenously (IV) over 5 min immediately before IV delta-9-THC (1.25 mg), which was also administered over 5 min."
Blinding of P&P	Unclear	"Using a repeated measures, pseudorandomized, double-blind, within-subject design". Insufficient information provided to tell if blinding was successful.
Blinding of outcome assessment	Low	"Positive psychotic symptoms were assessed at baseline and at 30 and 90 min post-delta-9-THC, by an independent psychiatrist…"

Incomplete outcome data	Low	No missing outcome data or loss to follow-up <10%.
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Unclear	Insufficient reporting of attrition/exclusions to permit judgment.
Overall Assessment	**LOW RISK**	

Dalton 1976:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Low	"All treatments were administered in a double-blind manner to each subject according to a Latin-square design." 2 separate experiments, the first with 16 participants allocated and the second with 8 different participants allocated.
Allocation concealment	Low	"The marihuana used had been previously extracted to remove all natural cannabinoids and to this was added an ethanolic solution of either synthetic THC or CBD…The respective cannabinoid-coated plant materials were combined in predetermined proportions and administered in the form of a cigarette."
Blinding of P&P	Low	"All treatments were administered in a double-blind manner to each subject according to a Latin-square design."
Blinding of outcome assessment	Low	"Treatments were assigned in a manner which minimized the order and learning effects."
Incomplete outcome data	Low	"One subject withdrew from the study while in progress; the data therefore represent the performance of 15 subjects."
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Unclear	Insufficient reporting of attrition/exclusions to permit judgment. Sample consists of only male medical students.
Overall Assessment	**LOW RISK**	

Eichler 2012:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"A double-blind, randomized, three-period cross-over experiment was performed."

Allocation concealment	Low	"Cannabis extracts were prepared by ethanol 70% m/m (DER 4.5) and contained per capsule 10 mg THCTOT (THC + THCA-A) and 10-15 mg CBDTOT (CBD + CBDA). Galenical formulation of extracts was done by the Hospital Pharmacy, University C;inic Basel according to GMP regulations. The content of cannabinoids was controlled prior to the start of the study at Frutarom Ltd. By HPLC analysis using UV detection…"
Blinding of P&P	Unclear	"A double-blind, randomized, three-period cross-over experiment was performed. A wash-out phase between two consecutive treatments of at least 2 weeks was used".
Blinding of outcome assessment	Unclear	Insufficient information to permit judgment.
Incomplete outcome data	Low	9 out of 10 participants completed the study. "One subject after administration of dronabinol discontinued his participation due to mild paresthesia, warm feeling, conjunctional injection, vertigo, visual disturbances, abdominal discomfort, dry mouth, tremor, and paleness as well as moderate short-lasting anxiety. Since the symptoms were in the vast majority of mild severity, this subject was replaced."
Selective reporting	High	"There were psychotropic effects after administration of all treatments as assessed by VAS measurements. However, the intensity of these effects was weak, and no statistically significant difference between the treatments could be detected (data not shown)." One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
Other sources of bias	High	All males.
Overall Assessment	**HIGH RISK**	

Englund 2013:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Low	"In a 2x3 mixed design, participants were randomly allocated in a counterbalanced fashion to placebo or CBD groups. Placebo/CBD capsules were administered under double-blind conditions."
Allocation concealment	Low	"Cannabidiol (2 x 300 mg capsules) and matching placebo were obtained from STI Pharmaceuticals UK. Synthetic THC was supplied…and prepared as 1 mg/mL vials for IV injection."
Blinding of P&P	Unclear	"Placebo/CBD capsules were administered under double-blind conditions."
Blinding of outcome assessment	Unclear	Insufficient information to permit judgment.

Incomplete outcome data	Low	"In three subjects, failure of cannulation prevented the administration of THC, and data acquired up to that point were not used in any of the analyses."
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	High	Use synthetic THC with plant-derived CBD. "Capsules (placebo/CBD) were administered 3 h 30 min prior to IV THC challenge, based on the available (albeit limited) knowledge regarding the pharmacokinetics of CBD."
Overall Assessment	**UNCLEAR RISK**	

Freeman 2017b:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"A randomized, double-blind, crossover design…"
Allocation concealment	Low	"Each dose was vaporized using a Volcano Medic Vaporizer…in 2 sequentially administered balloons to minimize residual cannabinoids…placebo cannabis had a comparable terpene profile to the 2 active forms of cannabis, ensuring it was matched for smell."
Blinding of P&P	Unclear	Insufficient information to permit judgment.
Blinding of outcome assessment	Unclear	Insufficient information to permit judgment.
Incomplete outcome data	Low	"In three subjects, failure of cannulation prevented the administration of THC, and data acquired up to that point were not used in any of the analyses."
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Unclear	Insufficient information to permit judgment.
Overall Assessment	**UNCLEAR RISK**	

Gong 1983:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"Twelve…subjects received each of the…six drugs or drug combinations at 24- to 48-hr intervals in a randomized, double-blind crossover design"

Allocation concealment	Low	"Placebo (talc) and each dose of 9-THC, 8-THC, CBN and CBD were suspended in sesame oil and given in identical-appearing gelatin capsules."
Blinding of P&P	Low	"Twelve…subjects received each of the…six drugs or drug combinations at 24- to 48-hr intervals in a randomized, double-blind crossover design"
Blinding of outcome assessment	Unclear	Insufficient information to permit judgment.
Incomplete outcome data	Low	No missing outcome data or loss to follow-up <10%.
Selective reporting	Unclear	Insufficient information to permit judgment.
Other sources of bias	High	All males. "All 59 participants were asymptomatic men 21 to 32 years old who had smoked marijuana habitually for more than 2 yr…"
Overall Assessment	**UNCLEAR RISK**	

Haney 2016:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"The order of cannabis strength and CBD dose were completely randomized."
Allocation concealment	Low	"…capsules in size 00 opaque capsules…the cannabis was smoked through a cigarette holder and rolled at the end so that the cannabis was not visible…Participants also indicated whether they thought the cannabis was active or inactive…In addition, participants were asked to indicate whether they thought the capsule was placebo or active."
Blinding of P&P	Unclear	"…administered under double-blind conditions under observation of research staff 90 min prior to cannabis administration".
Blinding of outcome assessment	Low	"Participants were told that the study objective was to determine how CBD, an experimental compound not approved by the FDA, influences the effects of cannabis in cannabis smokers…Prior to the first laboratory session, participants completed one or two practice sessions during which they were familiarized with the study tasks and procedures (no cannabis or capsules were administered)."
Incomplete outcome data	High	"Nineteen additional participants started the study but did not complete it: one was discharged for pregnancy, and another was discharged for both ongoing gastrointestinal (GI) symptoms and inability to comply with the study requirements; the remaining 17 non-completers were unable to adhere to the protocol requirements."
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.

Other sources of bias	Unclear	"In the afternoon, participants were similarly guided through smoking up to three puffs of self-administered cannabis, depending on their choice."
Overall Assessment	**UNCLEAR RISK**	

Hindocha 2015:

Domain	Judgment	Notes on Rating
Random sequence generation	Low	"Participants were recruited as 24 light (1-24 days per month) and 24 heavy (25+ days per month) cannabis users following the criteria of Morgan et al. (2012). 50% of each of these groups scored high, and 50% scored low in schizotypy…and were selected from the bottom and top quartiles of our previous study large-scale study of over 400 cannabis users (Morgan et al., 2012)… Order of drug administration was randomized using a partial Latin square, resulting in 12 different combinations."
Allocation concealment	Low	"A single balloon was filled (as per guidelines from Hazekamp (2009)), covered with an opaque bag, and administered by an independent researcher to maintain blinding of the experimenter collecting behavioural data and participant."
Blinding of P&P	Low	"A randomized, double-blind, placebo controlled study was used…A single balloon was filled (as per guidelines from Hazekamp (2009)), covered with an opaque bag, and administered by an independent researcher to maintain blinding of the experimenter collecting behavioural data and participant."
Blinding of outcome assessment	Low	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data	Low	No missing outcome data or loss to follow-up <10%.
Selective reporting	High	One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
Other sources of bias	Unclear	Participants "were selected from the bottom and top quartiles of our previous study large-scale study of over 400 cannabis users".
Overall Assessment	**LOW RISK**	

Hollister 1975:

Domain	Judgment	Notes on Rating
Random sequence generation	Low	"…the treatments were administered in a Latin-square order."

Allocation concealment	Low	"Three treatments were given; the drugs were administered orally in the form of chocolate cookies to which the materials had been added…treatments were administered in a Latin-square order."
Blinding of P&P	Unclear	Insufficient information to permit judgment.
Blinding of outcome assessment	Unclear	Insufficient information to permit judgment.
Incomplete outcome data	Unclear	Insufficient reporting of attrition/exclusions to permit judgment.
Selective reporting	High	Do not report standard deviation and lack important details and transparency in statistical modelling.
Other sources of bias	High	All males. Insufficient reporting of attrition/exclusions to permit judgment.
Overall Assessment	**HIGH RISK**	

Ilan 2005:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Low	"A double-blind, placebo-controlled, mixed between- and within-subject design was employed. THC dose was manipulated between subjects, with each participant randomly assigned to receive either a low or high dose of THC in the three active marijuana sessions. CBC and CBD levels were manipulated within subject, with each participant receiving a combination of low and high levels of these constituents across the three active marijuana sessions."
Allocation concealment	Low	"…subjects smoked a placebo or active cigarette under double-blind conditions, according to a standardized smoking procedure…The cigarettes were covered with colored cigarette paper to mask any discoloration resulting from the added constituents."
Blinding of P&P	Low	"A double-blind, placebo-controlled, mixed between- and within-subject design was employed…Subjects were told that they might receive any of a number of different active or inactive ingredients normally found in the marijuana plant."
Blinding of outcome assessment	Low	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data	Low	"One subject [out of 24] was excluded for failure to understand and perform the tasks, and one subject was excluded from neurophysiological analyses because of abnormal epileptiform patterns throughout the EEG. Hence, $n = 22$ was used for all EEG and ERP analyses, and $n = 23$ was used for all other analyses"

Selective reporting	High	One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis
Other sources of bias	Low	The study appears to be free of other sources of bias.
Overall Assessment	**LOW RISK**	

Juckel 2007:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"The study was performed in a prospective, double-blind, placebo-controlled cross-over design".
Allocation concealment	Unclear	Soft gelatin capsules provided.
Blinding of P&P	Unclear	"The study was performed in a prospective, double-blind, placebo-controlled cross-over design".
Blinding of outcome assessment	Low	No blinding of outcome assessment, but in the reviewer's judgment the outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data	High	"Two male and three female subjects [out of 27] were excluded from analysis due to technical problems during the ERP recording or hypersensitivity towards the study medication in terms of panic attack."
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Low	The study appears to be free of other sources of bias.
Overall Assessment	**UNCLEAR RISK**	

Karinol 1974:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"They were distributed into the several groups, balanced for age and weight."
Allocation concealment	Low	"The drugs were previously dissolved in 0.9 ml of ethanol and added to 200 ml of orange juice. As placebo 0.9 ml of ethanol in 200 ml of orange juice was used."
Blinding of P&P	Low	"The volunteers were told that they were participating in a marihuana experiment, but that they could be receiving a small or large dose or even

		placebo. The experimenter administering the drug was also 'blind' to the drug he was giving."
Blinding of outcome assessment	Unclear	Insufficient information to permit judgment.
Incomplete outcome data	Low	No missing outcome data or loss to follow-up <10%.
Selective reporting	Unclear	Insufficient information to permit judgment.
Other sources of bias	High	"The 40 selected volunteers were 24 medical students and 16 medical doctors with ages and weights, varying from 21 to 34 years and from 50 to 91 kilograms." All males.
Overall Assessment	**UNCLEAR RISK**	

Karschner 2011:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"Double-blind, double-dummy, within-subject"
Allocation concealment	Low	"Each of the participants received two capsules and six sprays in each of the five sessions…Five different treatments were administered in random order".
Blinding of P&P	Unclear	"Double-blind, double-dummy, within-subject"
Blinding of outcome assessment	Unclear	"Double-blind, double-dummy, within-subject"
Incomplete outcome data	High	"Twenty-two subjects provided written informed consent to participate in the study. Seven were discharged prior to drug administration for various reasons…Six others were discharged after at least one drug administration. Of these, two could not be contacted, two experienced panic attacks in the fMRI scanner, one had inadequate venous access and one had orthostatic hypotension, dizziness, and nausea after the fMRI session."
Selective reporting	High	The study protocol is available however the authors only report a change in mean scores without providing baseline measurements and also do not include data from all measurements taken.
Other sources of bias	Unclear	Insufficient reporting of attrition/exclusions to permit judgment.
Overall Assessment	**HIGH RISK**	

Lawn 2016:

Domain	Judgment	Notes on Rating
Random sequence generation	Low	"A repeated measures, placebo-controlled, double-blind design… Participants were randomly allocated to one of three treatment order schedules, which were based on a Latin Square design."
Allocation concealment	Unclear	"A Volcano Medic Vaporizer (Storz and Bickel, Tuttlingen, Germany) was used to vaporize Bedrocan cannabis (Veendan, the Netherlands)." However, the authors do not mention whether the taste / smell of individual groups were adequately concealed.
Blinding of P&P	Unclear	"A repeated measures, placebo-controlled, double-blind design…"
Blinding of outcome assessment	Low	"Participants completed 21 trials in total, and the trial order was randomized. Participants kept the amounts of money won on two trials; these were randomly selected at the end of the task."
Incomplete outcome data	Low	No missing outcome data or loss to follow-up <10%.
Selective reporting	High	The study protocol is available however the authors do not provide data on certain outcome measures including the Snaith Hamilton Pleasure Scale or Beck Depression Inventory.
Other sources of bias	High	"It is important to note that the EEfRT used here (as described above) was slightly different to the original EEfRT (Treadway et al. 2009) in a number of ways…"
Overall Assessment	**UNCLEAR RISK**	

Leweke 2000:

Domain	Judgment	Notes on Rating
Random sequence generation	Unclear	Cross-over study. All volunteers followed the same schedule. "On the first day of the study, cannabidiol (200 mg) was given with an additional placebo capsule resembling the nabilone capsule. On the second day of the study, cannabidiol (200 mg) and nabilone (1 mg) were administered. Finally, on the third day nabilone (1 mg) was given together with another placebo capsule resembling the cannabidiol capsule".
Allocation concealment	High	Capsules were disguised to resemble each other. "Most of the volunteers were able to tell if they had received a psychoactive cannabinoid."
Blinding of P&P	Low	"The volunteers as well as the investigators were informed that two different cannabinoids were applied but were blind to the order of administration and pairing of the capsules."
Blinding of outcome assessment	Low	"The volunteers were instructed that depth perception of each object might vary or not."

Incomplete outcome data	Unclear	The authors did not report Self-Rating Anxiety (SAS) scores because there were no significant effects shown.
Selective reporting	High	One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
Other sources of bias	Unclear	Insufficient reporting of attrition/exclusions to permit judgment.
Overall Assessment	**UNCLEAR RISK**	

Morgan 2018:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Low	"Treatment order across the 4 sessions was determined by a balanced Latin square."
Allocation concealment	Low	"Participants were given a test balloon to familiarize themselves with the procedure before any drug administration occurred. The balloon was filled, covered with an opaque bag…"
Blinding of P&P	Low	"The balloon was filled, covered with an opaque bag, and administered by an independent researcher so that the experimenter collecting behavioural data and participant was blind to drug condition."
Blinding of outcome assessment	Low	"The balloon was filled, covered with an opaque bag, and administered by an independent researcher so that the experimenter collecting behavioural data and participant was blind to drug condition."
Incomplete outcome data	Low	The authors did not report Self-Rating Anxiety (SAS) scores because there were no significant effects shown.
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Unclear	Insufficient information to assess whether an important risk of bias exists.
Overall Assessment	**LOW RISK**	

Roser 2008:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"Twenty-seven healthy, right-handed, and normal hearing subjects were screened and randomized…"
Allocation concealment	Unclear	Liquid extracts prepared in the form of soft-gelatine capsules.

Blinding of P&P	Unclear	"The study was performed in a prospective, double-blind, placebo-controlled cross-over design"
Blinding of outcome assessment	Low	"…the subjects were presented with a pseudorandomized sequence of 2 x 30 tone stimuli of different frequencies…within a choice reaction task to elicit auditory evoked ERPs."
Incomplete outcome data	High	"…twenty (10 male, 10 female…) finished the study according to the protocol. Two male and five female subjects were excluded from the analysis due to technical problems during the ERP recording, insufficient quality of the recording (mainly due to a small number of artifact free sweeps…) or hypersensitivity towards the study medication in terms of panic attack…"
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Unclear	"…right-handed, and normal hearing subjects"
Overall Assessment	**UNCLEAR RISK**	

Roser 2009:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"Twenty-seven healthy right-handed subjects were screened and randomized…"
Allocation concealment	Unclear	Liquid extracts prepared in the form of soft-gelatine capsules.
Blinding of P&P	Unclear	"The study was performed in a prospective, double-blind, placebo-controlled cross-over design."
Blinding of outcome assessment	Unclear	Insufficient information to permit judgment.
Incomplete outcome data	High	"…24 (12 male, 12 female…) finished the study according to the protocol. Three female subjects suffering from panic attacks after administration of study medication were excluded from the study."
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Unclear	"In this study, only right-handed subjects with a laterality quotient of 60-100 were included."
Overall Assessment	**UNCLEAR RISK**	

Schoedel 2011:

Domain	Judgment	Notes on Rating
Random sequence generation	Low	"…single-dose, randomized, double-blind, balanced, placebo-cross over study with six treatment sessions…Eligible subjects were randomly assigned to a pre-determined randomized treatment sequence (William's square design)."
Allocation concealment	Low	"Dronabinol capsules…were over-capsulated to maintain blinding." Placebo and nabiximol sprays were blinded also.
Blinding of P&P	Low	"To maintain blinding, treatments were administered in a double-dummy manner, where all subjects received the same number of sprays (16) and capsules (four) at each period." Further details can be found in the article.
Blinding of outcome assessment	Low	"The training, practice and refresher sessions for neurocognitive measures were designed to include a sufficient number of practice cycles to minimize practice effects during the study".
Incomplete outcome data	High	"Twenty-three subjects (76.7%) completed all study sessions"
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	High	Frequent recreational users (at least 1x/week). "In order to qualify for the main study, the subjects were required to discriminate and show positive subjective effects of dronabinol 30 mg compared with placebo." To increase discrimination between drug "liking" when given orally rather than smoked.
Overall Assessment	**UNCLEAR RISK**	

Solowij 2019:

Domain	Judgment	Notes on Rating
Random sequence generation	Low	"… double-blind randomised placebo controlled trial…the order of drug conditions was pseudo-counterbalanced between groups and randomly assigned for each participant."
Allocation concealment	Low	"…administered via vaporization, with a 1 week washout…To ensure blinding to drug conditions, participants were administered two normal sized Volcano Easy Valve balloons to deliver the main dose and one balloon to deliver top-up doses at each session with the balloon covered by opaque fabric to prevent identification of vapour colour or density."
Blinding of P&P	Low	"Drug doses were discretely prepared and vaporized into the balloons by the principal investigator and handed to research staff with the opaque cover to administer to participants. In this way, the research staff responsible for data collection were blinded to the drug conditions."

Blinding of outcome assessment	Low	"The objective measures were obtained by independent observers blinded to drug condition and group, rating participants from 0 (not at all) to 4 (extremely) on the 8 observer items of the Clinician Administered Dissociative States Scale (CADSS)…The independent observers were trained psychologist members of the research team, assisting with daily project management but not involved in drug administration."
Incomplete outcome data	Unclear	Insufficient reporting of attrition/exclusions to permit judgement.
Selective reporting	Low	The study protocol is available and all of the study's pre-specified outcomes of interest have been reported in the pre-specified way.
Other sources of bias	Unclear	"It is likely that these dissociating effects were rapidly induced by vaporisation of this compound, delivering CBD with high bioavailability to the bloodstream and hence central nervous system, although this is likely also confounded by dose. While 400 mg was loaded into the vaporiser, we estimate that participants consumed slightly less—385 mg—by not inhaling all the balloons. Further, our preliminary studies for protocol development suggested that only about 40% of the CBD could be vaporised due to the sticky resin produced in the process, saturation and vaporisation inefficiency [60]. This may, therefore, have resulted in an actual dose delivered of ~ 150 mg."
Overall Assessment	**LOW RISK**	

Zuardi 1982:

Domain	**Judgment**	**Notes on Rating**
Random sequence generation	Unclear	"The treatments were administered in a different sequence to each volunteer, in such a way that each treatment followed each of the others."
Allocation concealment	Low	"The [drugs] were stored in alcohol solution (100 mg/ml). On the day of the experiment the necessary quantity was taken from the storage solution, made up to 1.5 ml with alcohol (ethanol - 99 %, Merck Co.) and then added to 200 ml of artificial lemon juice. The diazepam, commercially available in tablets containing 10 mg (Valium, Hoffmann-La Roche), was powdered and placed inside opaque gelatine capsules. The lemon juice placebo contained only 1.5 ml of alcohol, and the placebo capsule contained 10 mg of lactose. The lemon juice and the capsule with the drug or placebo, depending on the treatment, were swallowed simultaneously by the volunteers in each session over a period of 5 min."
Blinding of P&P	Unclear	"In each session the volunteers received orally, in a double-blind procedure, one of the [five]treatments".
Blinding of outcome assessment	Low	"In order to do this, a transcription of the forty recordings (five from each volunteer) was given to two independent observers, who awarded marks for anxiety on a scale of 0 to 3 (0 = no anxiety; 1 = slight anxiety (insecurity); 2 = moderate anxiety; 3 = intense anxiety or panic) and for the typical effects of C. sativa on a scale of 0 to 4 as described previously by Karniol and

		Carlini (1973). The results were compared to those obtained by self-evaluation."
Incomplete outcome data	Low	No missing outcome data or loss to follow-up <10%.
Selective reporting	High	"Table I presents the protocol for each experimental session, with the times in which the various measurements were taken." However, the authors do not report the standard deviations for any of their measures, preventing the inclusion of their data in the meta-analysis.
Other sources of bias	Unclear	Insufficient information to provide judgement.
Overall Assessment	**UNCLEAR RISK**	

Appendix 5: EQUATION FOR THE META-ANALYSIS OF CROSSOVER TRIALS

Quantitively assessing crossover data after all study periods and using the entire sample size using independent t-tests would provide an overestimation of SE. In order to quantitatively assess crossover trials via a meta-analysis, either data from individual groups after the first period must be extracted and calculated, or an equation must be employed to derive the SE of the MD. The following formula can be used to resolve the issue of overestimating SE in crossover designs, however, since none of the studies reported a correlation coefficient (*r*), it is recommended that a conservative *r* value of 0.5 be used (Fu et al., 2013).

$$SE_d = \sqrt{SE_T^2 + SE_C^2 - 2rSE_TSE_C}$$

SE$_T$ and *SE*$_C$ reflect the standard error of the treatment and control groups, respectively. Given the heterogeneity already present among this review, it would not be wise to pool data among crossover trials as the findings would not be considered a precise estimate of the results. Therefore, the above formula was not used to calculate variance among crossover trials and only the mean difference was calculated and reported among these studies, if not reported directly by the original authors. Since only two of the included trials consisted of a parallel design, a quantitative analysis, in the form of a meta-analysis, was not conducted. Taking into consideration the amount of heterogeneity present among studies, it would be unwise to pool data among crossover trials as it would produce an imprecise estimate of an effect. Although there was enough data to meta-analyze VAS 'high' and heart rate measures individually using a random effects model to account for the heterogeneity, it would not be appropriate to do so, especially considering random effects weights studies with fewer participants more heavily. The risk for a unit-of-analysis error may have been present if parallel and crossover trials data were combined in a meta-analysis.