Cannabis: an overview of its adverse acute and chronic effects and their implications.

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Abstract

In many communities, cannabis is perceived as a low-risk drug, leading to political lobbying to decriminalise its use. However, acute and chronic cannabis use has been shown to be harmful to several aspects of psychological and physical health, such as mood states, psychiatric outcomes, neurocognition, driving and general health. Furthermore, cannabis is highly addictive, and the adverse effects of withdrawal can lead to regular use. These in turn have adverse implications for public safety and health expenditure. Although the cannabinoid cannabidiol (CBD) has been shown to have positive health outcomes with its antioxidant, anticonvulsant, anti-inflammatory and neuroprotective properties, high-potency cannabis is particularly damaging due to its high tetrahydrocannabinol (THC), low CDB concentration. It is this high-potency substance that is readily available recreationally. While pharmaceutical initiatives continue to investigate the medical benefits of CDB, “medicinal cannabis” still contains damaging levels of THC. Altogether, we argue there is insufficient evidence to support the safety of cannabis and its subsequent legalisation for recreational use. Furthermore, its use for medicinal purposes should be done with care. We argue that the public conversation for the legalisation of cannabis must include scientific evidence for its adverse effects.

Key words: cannabis – cognition – psychosis – dependence – health – education

1. Introduction

The World Health Organisation (WHO)(World Health Organization, 2016), as well as the United Nations Office on Drugs and Crime (United Nations Office of Drugs and Crime, 2016), have recently handed down reports outlining the damaging effects of cannabis on humans, as well as the current recommendations as to the use and misuse of the psychoactive substance for recreational and medicinal purposes. It is noted that while the majority of participating United Nations countries are considered signatories to international treaties on the control of narcotic drugs (including cannabis), such as the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, several discrepancies between regions regarding the legal, personal and psychobiological implications of cannabis consumption remain, and individual countries have largely developed discrete control measures and guidelines for cannabis use. In recent years, well-funded campaigns to decriminalise recreational use of cannabis have portrayed cannabis as a relatively benign substance, thereby creating a degree of conflict between the recommendations set out by the treaties and those outlined by individual governances. This has led to the legalisation of cannabis consumption in a number of regions, including the Netherlands, several USA states and Uruguay. Furthermore, "medicinal cannabis" is increasingly accepted as an adjunct treatment for chronic pain, epilepsy and for the reduction of the adverse side effects of treatments such as chemotherapy (Iskedjian, Bereza, Gordon, Piwko, & Einarson, 2007; Machado Rocha, Stefano, De Cassia Haiek, Rosa Oliveira, & Da Silveira, 2008; Porter & Jacobson, 2013; Rog, Nurmikko, Friede, & Young, 2005). For those working in the field of drug dependency, this move to change legal policy around cannabis distribution and consumption is concerning, given the lack of scientific evidence regarding the specific adverse effects cannabis has on physical, psychological and neurocognitive health.

The drug cannabis is derived from the leaves and flowers of the *Cannabis Sativa* plant, and contain a class of compounds, called cannabinoids, that act upon cannabinoid receptors in the brain (CB1) and immune system (CB2). There are 13 main classes of cannabinoids, with the most extensively researched of these being tetrahydrocannabinol

(THC) and cannabidiol (CBD). THC is the primary psychoactive component of cannabis, while CBD is a non-psychotropic component with some positive therapeutic effects. Cannabis is typically consumed by combining species of the cannabis plant and smoking as a cigarette (often referred to as a joint). Modern joints typically contain 150mg to 300mg of THC, which is over 15 times the potency of joints in the 1960s and 70s (Ashton, 2001). When smoked, 50% of the THC is inhaled and absorbed through the lungs into the blood stream. When ingested orally, only 12-15% of the THC ingested reached the bloodstream (Ashton, 2001). The effects of as little as 2.5mg of THC can be felt within minutes after smoking, and with 30 minutes to 2 hours after ingesting (Ashton, 2001). The adverse effects and potential health benefits of cannabis and cannabidiol are summarised in Table 1 and Table 2, respectively, and are discussed in detail in this review.

This review provides an overview of the current evidence regarding some of the key adverse physical, psychological and neurological effects of cannabis consumption. In particular, we critique the widespread belief that consumption of cannabis may be beneficial overall. Although some of the adverse effects of cannabis are well recognised, there is a lack of awareness regarding cannabis dependency and withdrawal, and the effect of cannabis on mood states, psychiatric outcomes, neurocognition, driving and general health. We also review the literature regarding the possible health benefits of cannabis.

2. Acute effects of cannabis

Cannabis use can engender a range of positive mood effects which make it attractive for users. Acute effects often include feeling of happiness, relaxation and calmness, contemplativeness, creative thoughts, humorousness, social disinhibition and sociability (Green, Kavanagh, & Young, 2003; Titus, Godley, & White, 2007; Wachtel, ElSohly, Ross, Ambre, & de Wit, 2002). The acute effects of cannabis may last for a couple of hours, and are often extended by further usage, thus heavy dependent users spend much of their time each day in this drug-replete state. Cannabis can, however, also generate a

range of negative mood states, including feelings of anxiety, tension, agitation with a racing heart, mental confusion, forgetfulness, unsteadiness, suspiciousness and paranoia (Hall, 2015; Volkow, Baler, Compton, & Weiss, 2014). These effects can be present even with infrequent cannabis use (Hall & Pacula, 2003). A study of over 3,000 students found that of those who had consumed cannabis at least once, only 17% had experienced at least one negative outcome, while 76% experienced at least one positive outcome (Le Strat et al., 2009). The study also found that those reacting positively in their early experience with cannabis are more likely to become regular users, up to 28.7 times more likely than those who do not experience any positive outcomes (Le Strat et al., 2009). Hence, the nature of the effects of cannabis allows it to be highly susceptible to cannabis dependence (Coffey, Carlin, Lynskey, Li, & Patton, 2003; Le Strat et al., 2009), which may lead to subsequent addiction (Coffey et al., 2003).

3. Cannabis withdrawal

The period of post-drug recovery is a crucial time for any psychoactive substance, since the on-drug mood gains are typically followed by a period of negative moods (Parrott, Morinan, & Moss, 2008). This pattern is readily demonstrated by tobacco smokers, since their moods vacillate over time – becoming positive on smoke-inhalation, then worsening as time lapses between cigarettes (Parrott, 1994). Vandrey, Budney, Moore, and Hughes (2005) compared the mood effects of cannabis withdrawal and tobacco withdrawal, finding a similarity in the magnitude and time course of the withdrawal effects. The unpleasant mood effects of cannabis withdrawal for two to seven days often include reduced appetite, weight loss, difficulty sleeping, and increased anxiety, irritability, restlessness, physical agitation, anger, aggression, and depression (Allsop, Copeland, Lintzeris, & et al., 2014; Budney, Hughes, Moore, & Novy, 2001; Vandrey et al., 2005). These negative psychobiological sequelae can make it difficult for regular cannabis users to quit, however, more extended periods of cannabis withdrawal (up to 30 days) has been shown to normalise these characteristics to baseline levels (Vandrey et al., 2005). Nevertheless, the negative effects of cannabis withdrawal can lead to cannabis dependence.

4. Cannabis dependence

Cannabis use has been demonstrated as a relatively normative behaviour, particularly in young adults. However, when used regularly (i.e. weekly), the risk of cannabis dependence increased at a rate of 4.9:1. There are several factors that contribute to the progression from recreational cannabis user to cannabis dependence, including: avoiding withdrawal, unintentional use, persistent desire and increased tolerance to the effects of cannabis (Coffey et al., 2002; Coffey et al., 2003). Additional risk factors include regular cigarette smoking, antisocial behaviour and being male (Coffey et al., 2002; Coffey et al., 2003). The severity of smoking behaviour and presence of psychiatric ill-health in adolescence has been shown not to predict later cannabis dependence (Coffey et al., 2003). According to the DSM 5, substance use disorder includes a spectrum of behaviours ranging from substance abuse to substance dependence, whereby mental and physiological changes lead to increased tolerance and withdrawal symptoms. Substance addiction is a term used to represent the severity of substance use disorder symptoms; generally, an extreme degree of dependence that leads to a fixation on substance-seeking behaviour (DSM 5, 2013). For most recreational users, however, a substance use disorder does not eventuate (Coffey et al., 2003).

It has been estimated that over 300,000 and 69,000 individuals enter treatment for a cannabis use disorder each year in the United States of America and Europe, respectively (European Monitoring Centre for Drugs and Drug Addiction, 2016; Herrmann, Weerts, & Vandrey, 2015). Mood states experienced during withdrawal are often salient predictors of treatment success rates and rates of remission, with higher cannabis withdrawal symptom scores frequently associated with poorer treatment outcomes (Budney, Hughes, Moore, & Vandrey, 2004). These adverse mood effects on remission can lead to a strong dependency on the drug (Hall & Pacula, 2003); around one in ten people who report ever having used cannabis will go on to develop a clinically defined cannabis use disorder (Wagner & Anthony, 2002), and considerably more can be defined as subclinical.

There are estimated to be around 13.1 million cannabis dependent individuals globally, with peak prevalence among 20-24 year olds, and a general preponderance of males overall (Degenhardt et al., 2013). Young people tend to be more susceptible to cannabis dependence, particularly when use begins in early adolescence. A study found that cannabis use before the age of 17 years led individuals to be 18 times more likely to develop dependence by the age of 30 than those who began using later in adulthood (Silins et al., 2014). While adolescent cannabis use is a major challenge, those over the age of 50 were the fastest growing cannabis-using age group in the past two Australian population surveys (AIHW, 2014). Finally, dependency risk increases with frequency of use with as many as 65% of recreational cannabis users reporting some degree of cannabis dependence, which was more common for frequent cannabis users (2+ times per week) than by the occasional users (Terry, Wright, & Cochrane, 2007), and up to 50% of daily cannabis users have been reported to become dependent (Coffey et al., 2002). Living alone, self-medication and negative life events are additional predictors of cannabis dependence (van der Pol et al., 2013).

Cannabis dependence increases the risk of suffering from the negative side effects such as short-term memory impairment, mental health problems, and respiratory diseases (in the event of smoking). Dependence can also have negative financial, social, relationship (such as with family and friends), and employment implications (Coffey et al., 2003). Cannabis use disorder is commonly comorbid with other substance use disorders and mental health conditions, and should be assessed and treated concurrently in order to improve longer-term patient outcomes (Copeland, Clement, & Swift, 2014). Cannabis use disorder, both at a clinical and a subclinical level, often goes undetected or is detected indirectly through the presentation of comorbid conditions. Of the 65% of recreational cannabis users reporting some degree of cannabis dependence above, only 2.6% of the sample had sought clinical treatment (Terry et al., 2007).

Like other substance use disorders, continuous abstinence relapse rates are high among cannabis users, and many patients do not show a positive treatment response, indicating

that cannabis dependence is difficult to treat (McRae, Budney, & Brady, 2003). Evidence-based pharmacotherapies for cannabis use disorder are not currently available, despite recent studies indicating promising early results for agonist therapies (Allsop et al., 2014). Limited open-label studies have indicated clinical efficacy for drug therapies such as buspirone, dronabinol, fluoxetine, lithium, lofexedine, and rimonabant (Vandrey & Haney, 2009), however, comprehensive and systematic clinical trials assessing both their acute and long-term efficacy is currently lacking. A 2014 meta-analysis concluded that the evidence supporting the use of some pharmacotherapies such as selective serotonin reuptake inhibitor antidepressants, mixed action antidepressants, anticonvulsants and mood stabilisers for the treatment of cannabis dependence disorders is incomplete (Marshall, Gowing, Ali, & Le Foll, 2014).

Psychotherapeutic interventions are currently the most widely researched and utilised treatment approach to address cannabis dependence, particularly cognitive behavioural therapy (CBT) treatment. In fact, CBT treatment has been shown to be most effective for those wishing to reduce or abstain from cannabis, but not for polydrug users (Dutra et al., 2008). Predictors of an individual's success in treatment include inter-individual active coping strategies and distress tolerance (Copeland et al., 2014), as well as a desire to regain control over one's life, and to reduce associated cognitive and health consequences of cannabis use (Chauchard, Septfons, & Chabrol, 2013).

5. Psychiatric outcomes

The world's oldest pharmacopeia, attributed to Emperor Shen Nung in China, noted that although cannabis had some useful medicinal properties: "If taken in excess it will produce visions of devils" (Zuardi, 2006) p154. Modern research has empirically confirmed this. Acute and chronic cannabis use are associated with higher rates of psychiatric pathologies such as stress, anxiety, depression and psychosis (Volkow et al., 2014).

5.1. Acute outcomes

Acute adverse effects of cannabis consumption include disordered thoughts and cognitions (including paranoia), a sense of depersonalisation, fear of dying, and an impending feeling of panic (Ashton, 2001). D'Souza et al. (2004) administered the cannabinoid THC to recreational cannabis users without a prior psychiatric history, and reported significant increases in the positive and negative symptoms of schizophrenia as measured by the Positive and Negative Symptom Scale (PANSS). Some of the subjective experiences described by the participants are presented in D'Souza et al. (2004). Increased positive symptoms scores as measured by the PANSS following administration of THC are also related to increases in high frequency brain oscillations (Nottage et al., 2015). This increase in positive symptoms tends to reduce as the acute effects of cannabis wear off (D'Souza et al., 2004; Nottage et al., 2015), however, for regular users, these periods may be cumulatively damaging. Moreover, the cannabis use has been shown to increase schizophrenia and bipolar symptoms, while cannabis use is used by many to "self-medicate" against adverse symptoms and pharmaceutical side effects (N. Wilson & Cadet, 2009). Indeed, there is extensive clinical evidence for a heightened risk of developing schizophrenia in regular and/or chronic users (Andréasson, Engström, Allebeck, & Rydberg, 1987; Malone, Hill, & Rubino, 2010; Paparelli, Di Forti, Morrison, & Murray, 2011).

Although psychiatric conditions have been shown not to predict later cannabis use disorder, frequency of use was slightly increased for those with a clinical condition (Coffey et al., 2003). Furthermore, increased use of cannabis has been associated the presence of psychiatric and mood disorders such as anxiety and depression (Wittchen et al., 2007).

5.2. Chronic outcomes

Cannabis is one of several psychoactive drugs known to induce psychosis among heavy users and those sensitive to the psychoactive properties of cannabis (Paparelli et al., 2011), and the cannabinoid THC is thought to be responsible for the majority of the negative psychiatric and cognitive outcomes of chronic cannabis use (Crean, Crane, &

Mason, 2011; Volkow et al., 2014). The Swedish Conscript study was instrumental in first demonstrating an association between cannabis use and later development of schizophrenia (Andréasson et al., 1987). The study comprised 45,579 young armed-forces conscripts and found that those who consumed cannabis on more than 50 occasions were 6 times more likely to develop schizophrenia over a 15-year period than their non-using counterparts. Fergusson, Horwood, and Swain-Campbell (2003) followed a birth cohort of 1,265 children over 21 years, and found that those with cannabis dependence had an increased risk of psychotic symptoms. A seminal review conducted by Moore et al. (2007), investigated the relationship between cannabis use and the occurrence of psychotic or affective mental health outcomes reported in longitudinal studies. Overall, the risk of adverse psychiatric outcomes for former cannabis users was significantly higher than adverse affective outcomes. The review also demonstrated a dose-response association between cannabis use and psychiatric outcomes; these effects were more pronounced among regular users (Moore et al., 2007). Finally, Le Bec, Fatséas, Denis, Lavie, and Auriacombe (2009) reinforced the link between cannabis use and the emergence of psychosis or psychotic symptoms in their review.

Personality traits and psychiatric predispositions have been shown to modulate the relationship between cannabis use and psychiatric outcomes. Henquet et al. (2005) followed 2,437 young cannabis users who did or did not have a predisposition for psychosis and an increased risk of psychosis for both groups, but the increase was more pronounced for the predisposed group (23.8%) compared to the non-predisposed group (5.6%). In support of the previously reported studies, there was a significant effect of dosage; those who using cannabis less than monthly typically showed no increase in psychotic symptoms, while psychotic symptoms increased as frequency increased from one to two times per week to almost daily use.

Cannabis use is also associated with higher rates of other chronic mental health problems, such as stress, depression, and anxiety (Bovasso, 2014; O'Connor, Schwid, Herrmann, Markman, & Dworkin, 2008; Patton et al., 2002; Richardson, 2010; Van Laar, Van

Dorsselaer, Monshouwer, & De Graaf, 2007), and mania has been shown to increase more than two-fold in a non-clinical population (Henquet, Krabbendam, de Graaf, ten Have, & van Os, 2006; Richardson & Garavan, 2011). In several of these studies, dosage effects were again noted, with heavier users found to be most at risk of adverse psychiatric outcomes. Significant, albeit somewhat weaker association have also been noted between cannabis use and later development of hypomania symptomology among non-clinical samples of adolescents (Wittchen et al., 2007). It is important to note that research of this nature often involves complex interactions with a number of environmental and intra-individual factors such as personality traits and clinical predisposition factors, and thus definitive clinical characterisations of at-risk populations is often problematic (Richardson, 2010).

6. Neurocognitive effects

While cognition is acutely impaired after smoking cannabis, there is increasing evidence that such impairment can persist beyond the period of acute intoxication. Acute cognitive outcomes include disrupted immediate and delayed word recall, increased distractibility, poor verbal fluency, and poor working memory (D'Souza et al., 2004). Among chronic users, memory impairment is most consistently reported, particularly free recall, delayed recall and recognition (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003). Other affected cognitive functions include attention, inhibition, executive function, decision-making and psychomotor function (Jager, Block, Luijten, & Ramsey, 2010; Pope et al., 2001; Ramaekers, Kauert, Theunissen, Toennes, & Moeller, 2008). Cognitive dysfunction in long-term or heavy cannabis users has been shown to increase as a function of frequency of use, age of use initiation, and the urine/blood concentration of THC at the time of testing (Pope et al., 2001; Yücel et al., 2008), and a dose-response cognitive effect has been shown to exists among abstinent heavy users (Bolla, Brown, Eldreth, Tate, & Cadet, 2002). Evidence from animal and human studies suggests that the adolescent brain is more susceptible to the adverse effects of cannabis, leading to greater cognitive impairment. Even in abstinent users, marked deficits in memory performance are reported for frequently using versus non-using adolescents (Jager et al., 2010).

Cognitive dysfunction in long-term users tends to persist for at least one month following the cessation of cannabis use (Bolla et al., 2002); however, the extent of damage and time course of recovery over the lifespan has not yet been accurately mapped. While a number of studies suggest that some cognitive functions appear to recover within a few weeks (Hanson et al., 2010; Pope et al., 2001), other, more limited research, has demonstrated symptomatic persistence in some cognitive domains one month post-drug abstinence (or longer) (Bolla et al., 2002). Greater decline in IQ over 20-30 years has been reported among those who commenced using cannabis during adolescence, and persisted even among those who had ceased or greatly reduced their use later in adulthood, controlling for socioeconomic status (Meier et al., 2012).

Estimation of the degree of cognitive deficits beyond one month post-abstinence are currently unclear, as follow-up studies seldom track performance beyond a one- or two-month period, and a large variation in assessment sessions post-abstinence exist. To our knowledge, the longest follow-up protocol examined among longitudinal studies was that outlined by Meier et al. (2012), which employed a 38-year follow-up schedule. Often, age of initiation and total years of use are important predictors of residual cognitive effects associated with cannabis use, suggesting that cessation during critical developmental periods of adolescence may improve outcomes later in life (Meier et al., 2012). Clearly, longitudinal studies are needed to elucidate the long-term effects of cannabis use on cognitive functioning, while effectively controlling for potential confounding factors.

7. Neurological effects

Clinical research has suggested changes in brain morphology due to prolonged exposure to cannabis, and evaluation of these alterations in brain function following chronic cannabis use are often derived from neuroimaging studies. Abnormalities in brain regions with a high density of cannabinoid receptors, such as the prefrontal regions, hippocampus, amygdala and cerebellum, have been consistently shown, as well as overall reduced regional brain volume and increased grey matter (Lorenzetti, Solowij, & Yücel,

2016). Using magnetic resonance imaging (MRI) and positron emission tomography (PET) it was revealed that those commencing cannabis use prior to 17 years of age had reduced overall cortical size and percentage grey matter, and increased percentage of white matter volume compared to those who commence use later (W. Wilson et al., 2000). Structural neuroimaging studies have identified reduced grey matter in the medial-temporal, orbitofrontal, temporal pole, parahippocampal gyrus, insula and cerebellar regions (Batalla et al., 2013; Battistella et al., 2014; Lorenzetti, Solowij, Fornito, Ian Lubman, & Yucel, 2014), although, the evidence for significant differences between cannabis users and non-users is largely mixed (Lorenzetti et al., 2014). Reduced white matter density among regular users (Zalesky et al., 2012), dose-related reductions in hippocampal and amygdala volumes (Yücel et al., 2008), and shape alterations to the nucleus accumbens have also been reported (Gilman et al., 2014).

Further research into potential structural risk factors for young people requires further attention. To our knowledge, only one such study exists, which tracked adolescent brain structure from 12 to 16 years of age, and found that those who began smoking cannabis had significantly smaller orbitofrontal cortex volumes at 12 years of age. Such differences were not seen in the amygdala, hippocampus, and anterior cingulate cortex (Cheetham et al., 2012). These findings suggest that structural abnormalities in select brain regions may contribute to an increased risk for later cannabis use, however, considerably more longitudinal research is required before more definitive conclusions can be drawn regarding the strength of these associations.

8. Adverse health effects

Cannabis consumption has a damaging effect on several bodily functions, including the cardiovascular, respiratory, immune, endocrine and reproductive systems (Adams & Martin, 1996; Ashton, 2001; Volkow et al., 2014). Some adverse effects, such as those on the respiratory system, can be attributed to the mechanism of cannabis consumption (smoke inhalation) (Ashton, 2001), whereas others, such as damage to the immune system, are due more directly to the cannabinoids (Adams & Martin, 1996).

8.1. Pulmonary/respiratory pathology

When cannabis in smoked, carcinogens and other gaseous by-products are released, including vinyl chlorides, phenols, nitrosamines and reactive oxygen species (ROS), which are similar to those released by tobacco cigarette smoke (Ashton, 2001; Taylor & Hall, 2003; Taylor, Poulton, Moffitt, Ramankutty, & Sears, 2000). These have a comparable pro-inflammatory, histopathological and synergistic effects (Taylor & Hall, 2003; Zhang et al., 1999). Cannabis smoking is associated with inflammation of the airways and compromised lung function, thus users are susceptible to bronchial-related conditions (Tashkin, 2013) and chronic respiratory diseases, such as pneumonia (Tashkin, 2005). Meta-analyses support this assertion, noting consistently higher isolated respiratory complications among smokers, such as increased phlegm, wheezing and coughing (Tetrault et al., 2007).

8.2. Cancers

Several population-based case-control and cohort studies of cannabis smokers report increased rates of the various cancers that are often observed in tobacco smokers, such as oral (Llewellyn, Linklater, Bell, Johnson, & Warnakulasuriya, 2004), lung (Aldington et al., 2008) and head and neck cancer (Zhang et al., 1999); reduced pulmonary function is also reported (Aldington et al., 2007). The WHO report evidence for increased risk of upper digestive tract cancers, respiratory cancers and testicular cancer, as well as prostate and cervical cancer (World Health Organization, 2016). It is important to note that as cannabis is mixed with tobacco for smoking, it is difficult to differentiate the effect of cannabis from tobacco on respiratory health.

8.3. Cardiovascular pathology

Cardiovascular changes associated with low-moderate levels of cannabis include a dose-dependent elevation of resting heart rate (50-60% increase) and subsequent moderate increase in blood pressure (Menkes, Howard, Spears, & Cairns, 1991), and increased vascular constriction/constriction (Sidney, 2002). Higher doses of cannabis can lead to

orthostatic hypotension and bradycardia (Jones, 2002; Pratap & Korniyenko, 2012). These effects increase as THC plasma concentration peaks (typically 10-15 minutes), and can remain elevated for up to 3 hours post-ingestion (Sidney, 2002). Peripheral effects, such as reduced circulatory responses (Benowitz & Jones, 1975) and compromised middle cerebral artery blood velocity (CBV) (Mathew, Wilson, Humphreys, Lowe, & Wiethe, 1992), have also been reported. Cannabis use has been associated with more severe cardiovascular events, such as acute myocardial infarction among older (Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001) and some young users (Caldicott, Holmes, Roberts-Thomson, & Mahar, 2005), as well as ischemic stroke (Wolff et al., 2011) and cerebral infarction (Moussouttas, 2004).

Chronic cardiovascular complications resulting from cannabis use is likely attributed to lowered cardio-pulmonary thresholds as a direct result of drug use. Despite this, relative to the acute implication of cannabis use, there are considerably fewer studies systematically assessing long-term cardiovascular outcomes among chronic cannabis users, and inconsistencies regarding methodological approaches somewhat preclude accurate comparisons to be drawn among available clinical and epidemiological research. Observations of the chronic cardiovascular effects of cannabis use are often impeded by issues of tolerance, level of exposure and intra-individual differences. Indeed, the cardiovascular implications among frequent cannabis users are found to be somewhat attenuated as a function of exposure, with some degree of cardiac compensation observed following extended use (Renaud & Cormier, 1986). Meta analytic studies assessing the collective risk of cardiovascular dysfunction due to extended cannabis use are notably lacking, with much of the available reviews being largely descriptive in nature [for example see (Pratap & Korniyenko, 2012; Sidney, 2002)]. Thus, additional comprehensive systematic evaluations that effectively collate clinical and experimental findings are urgently required if these associations are to be confirmed, and if appropriate clinical and public health recommendations are to be made.

8.4. Pregnancy and childhood cancer

Trans-generational assessment of the effect of paternal and maternal cannabis use during the gestational period and preceding conception on the cancer rates of the child have indicated as much as an 11-fold increased risk of childhood acute nonlymphoblastic leukaemia (Robison et al., 1989), astrocytoma (Kuijten, Bunin, Nass, & Meadows, 1990) and childhood rhabdomyosarcoma (Grufferman, Schwartz, Ruymann, & Maurer, 1993). However, the data was generally acquired through hospital surveys, and concomitant tobacco use was often not assessed, and dose-response evaluations were often not included, thus preclude the ability to generalise the observed results (Hashibe et al., 2005; Mehra, Moore, Crothers, Tetrault, & Fiellin, 2006).

Cannabis consumption causes health burden across several bodily systems, and are not only limited to those discussed above. Compromised pulmonary/respiratory and cardiovascular functioning, and increased rates of cancer, account for significant health and economic burden among cannabis users. Clinical and experimental research has indicated significant acute and chronic health effects resulting from cannabis use, however, comprehensive assessments their magnitude are currently lacking. Furthermore, many experimental studies have marked methodological limitations. Increasing rates of cannabis consumption among the general population present a growing area of concern for acute and long-term healthcare, and may have significant implications for health providers, and public and private healthcare systems. Additional resources are therefore urgently needed to adequately describe and evaluate the scope of this potential health problem.

9. Adverse effects on cognitive-motor skills and implications for road safety

Cannabis produces dose and experience-dependent effects on a variety of neurobehavioural and performance indices of high clinical relevance to public health (Hart, van Gorp, Haney, Foltin, & Fischman, 2001; O'Leary et al., 2002; Ramaekers et al., 2008; Ramaekers et al., 2006). Studies indicate that cannabis use produces a measureable effect on several safety-sensitive cognitive-motor abilities, including (but not limited to) body sway and imbalance (Liguori, Gatto, & Robinson, 1998), behavioural execution,

and aspects of physical competences (Huestis, 2002). Accordingly, much of the data pertaining to the neurobehavioural consequences of cannabis intoxication refer to impairments associated with high-risk routine daily activities, such as driving a motor vehicle, that engender these skills. Driving is a complex neurobehavioural task that necessitates accurate perception, appropriate judgement, adequate response time and suitable physical capability. Survey studies indicate that between 10% (Mura et al., 2003) and 17% (Drummer et al., 2003; Lowenstein & Koziol-McLain, 2001) of drivers injured or killed in road-traffic accidents test positive for the presence of THC metabolites; this rate of detection is second only to those driving under the influence of alcohol (Mura et al., 2003). Indeed, cannabis is considered second only to alcohol for predictive value of car accidents resulting in death (Li et al., 2012). Of note, rates of drug driving under the influence of cannabis and consequential rates of injury and death are typically higher among cohorts of younger, male drivers (Marquet et al., 1998; Mura et al., 2006).

The potential safety impact of driving under the influence of cannabis has been demonstrated in numerous experimental (Rafaelsen, Bech, & Rafaelsen, 1973; Ronen et al., 2010; Ronen et al., 2008), on-road (Ramaekers, Robbe, & O'Hanlon, 2000; Robbe & O'Hanlon, 1999), meta-analytical (Berghaus, Scheer, & Schmidt, 1995) and review studies (Hartman & Huestis, 2013; Ramaekers, Berghaus, van Laar, & Drummer, 2004). These studies indicate highly compromised motor skills and subsequent reductions in driver safety under both low and high dose cannabis conditions. Specific simulation-based driving studies have demonstrated that low to moderate acute doses of THC (up to 200 µg/kg) result in notable deficits in reaction time (Ronen et al., 2008), visual tracking ability (Ménétrey et al., 2005), road tracking (weaving) and standard deviation of the lateral position (SDLP) (Ronen et al., 2008), speed maintenance (Ronen et al., 2010) and variability (Rafaelsen et al., 1973), and contribute to increased collision rates (Ronen et al., 2010; Ronen et al., 2008). Some studies, however, have failed to replicate this magnitude of effect (Anderson, Rizzo, Block, Pearlson, & O'Leary, 2010; Liguori et al., 1998). Several on-road, closed-course driving studies have similarly indicated marked deficits in driving performance following THC exposure. Specifically, increased SDLP

(Ramaekers, Robbe, et al., 2000; Robbe, 1998), time driven out of lane (Ramaekers, Robbe, et al., 2000), standard deviation of headway (Ramaekers, Robbe, et al., 2000), braking time (Klonoff, 1974), and reduced road tracking and car-following ability have been observed (Ramaekers, Lamers, Robbe, & O'Hanlon, 2000). Furthermore, research has indicated a significant dose-response curve under moderate to high THC conditions (Robbe, 1998), and these effects are considered reflective of measurable THC blood concentration over time (Papafotiou, Carter, & Stough, 2005). By comparison, the cognitive-motor effects of newer-generation cannabis-derivative products, such as medicinal cannabis or cannabis foodstuff, on these parameters are largely understudied and poorly defined, and thus the potential impact for road safety is unknown.

Evaluations pertaining to driver culpability (fault) of those involved in road trauma under the influence of THC are somewhat mixed, with some reporting no increase in culpability (Longo, Hunter, Lokan, White, & White, 2000; Lowenstein & Koziol-McLain, 2001; Movig et al., 2004) and others reporting a six-fold increase in the likelihood that THC-affected drivers would be responsible for an incident than THC-unaffected drivers (Drummer et al., 2004; Lauman, Gadegbeku, Martin, & Biercheler, 2006). Meta-analyses, however, have largely concluded that, on average, individuals under the influence of THC are 2.8 times more likely to be involved in road trauma compared to unaffected drivers. This increased risk is comparable for both fatal and non-fatal collisions (Asbridge, Hayden, & Cartwright, 2012; Li et al., 2012), as well as for damage to property resulting from a collision (Elvik, 2013). However, some caution must be made when inferring risk for crash involvement following cannabis use; due to the toxicological differences between acute cannabis intoxication and assessments made using the presence of traces of cannabinoids in samples of blood or urine (used as an indicator of previous use) (Gjerde & Mørland, 2016).

Cannabis use produces marked, dose-dependent effects on several safety-sensitive facets of neurobehavioural performance; which has direct implications for public health. Indeed, research suggests considerable impairments in numerous acute driving parameters

following THC administration (Ramaekers et al., 2006), and indicate that its use presents as a salient risk factor for increased crash-risk and rate of road-trauma involvement (Asbridge et al., 2012; Drummer et al., 2004; Lauman et al., 2006; Li et al., 2012). However, additional research investigating specific neuropharmacokinetic and pharmacodynamic profiles are urgently required to better characterise these associations and establish reliable models of impairment due to acute intoxication, and if appropriate multi-platform and targeted preventative strategies are to be employed. This is particularly important considering the rise in use of newer-generation cannabis products, including cannabis-based foodstuffs, synthetic cannabis products and medicinal cannabis.

10. Health benefits of cannabinoids

Despite the extensive adverse effects of cannabis as a whole product, and THC alone, cannabis is effectively administered for medicinal purposes. It is therefore important to discuss cannabis in terms of its potential clinical benefits in a therapeutic context. CBD (cannabidiol) is a non-psychoactive cannabinoid that has been extensively researched for its therapeutic potential as it has a range of antioxidant, anticonvulsant, anti-inflammatory and neuroprotective properties (Croxford, 2003; Hampson, Grimaldi, Axelrod, & Wink, 1998; Scuderi et al., 2009). Furthermore, CBD does not elicit any significant cognitive or psychoactive effect, it is well tolerated as noted in a number of pre-clinical studies, and it exhibits very low toxicity, even in higher doses (Scuderi et al., 2009).

The clinical data regarding potential health benefits of CBD are largely derived from research that evaluates alternative or adjunct treatments for chronic disease where the existing treatment regime is unsatisfactory or ineffective. Patients with chronic pain, neurological conditions, such as epilepsy (Devinsky et al., 2016), multiple sclerosis (Iskedjian et al., 2007), and psychiatric conditions, such as schizophrenia and bipolar disorder (N. Wilson & Cadet, 2009), have been shown to benefit from a cannabis intervention. The utility of cannabis as an intervention for chronic pain and epilepsy are discussed below.

10.1. Chronic pain

The clinical utility of CBD as a complementary or alternative mode of treatment for neurological disorders such as multiple sclerosis has been studied extensively, and the potential benefit of providing acute symptomatic relief for the chronic and disabling features of such disorders are widely founded (Iskedjian et al., 2007; Rog, Nurmikko, Friede, et al., 2005). Indeed, early open-label research assessing the efficacy of CBD products in treating neuropathic pain associated with advanced multiple sclerosis has indicated good control of symptoms as a function of treatment, with little tolerability issues (Rog, Nurmikko, & Young, 2005). These findings have been similarly replicated in double-blind placebo trials (Rog, Nurmikko, Friede, et al., 2005). Despite these promising clinical results, the efficacy of this compound to treat neuropathic pain in multiple sclerosis suffers has been largely inconclusive, which is partly attributable to the complex nature of the condition, as well as the notable lack of well-designed controlled studies currently available (Iskedjian et al., 2007; O'Connor et al., 2008). Thus, additional research is warranted in order to accurately characterise the natural history, mechanisms, and treatment of pain using CBD treatment in patients with multiple sclerosis, and similar conditions, in order to better clarify the possible therapeutic potential.

10.2. Epilepsy

CBD has been effective in the treatment of epilepsy due to the anticonvulsant features of the compound, the novel mechanisms of action, and the lack of side effects. Early animal research suggests the antiepileptic activity of CBD is due to its efficacy in reducing or blocking the motor manifestations of medically-induced convulsions in rats (Chiu, Olsen, Borys, Karler, & Turkanis, 1979; Karler, Cely, & Turkanis, 1973). Despite these promising pre-clinical animal studies, there are relatively few comparable human trials, which may be due to limited patient samples. An early clinical trial conducted by (Cunha et al., 1980) was perhaps the first controlled clinical trial to evaluate the anticonvulsive effect of CBD, employing patients who were suffering from treatment resistant secondary generalised epilepsy with temporal focus. Results indicated that half of those treated with CBD reported an absence of symptoms for the duration of the trial, and no significant

toxicity was reported as a result of the treatment. More recent preliminary survey research has similarly indicated the potential efficacy of CBD as a therapeutic tool for treatment-resistant paediatric epilepsy, with the administration of CBD reported to reduce the frequency of seizures (Porter & Jacobson, 2013). These findings, however, are derived from parental observations, thus treatment benefits may be inflated due to personal bias. Indeed, much of the evidence indicating the therapeutic benefits of CBD in paediatric populations are largely derived from anecdotal, parental reports or retrospective assessments, and thus, the true efficacy of the treatment approach remains unclear (Press, Knupp, & Chapman, 2015; Sirven, 2014). One recently published phase-II uncontrolled study examining whether the addition of CBD to an existing treatment regime would be beneficial, finding some evidence for the benefit of the treatment (Devinsky et al., 2016). It is essential that randomised, controlled clinical trials are conducted, however, before any real consideration can be given to using CBD as a front-line treatment in groups of children and adolescents. Concordantly, many governing bodies representing the interests of epilepsy communities and research, such as the American Epilepsy Society (AES), are currently opposed to its use until such evidence can be provided. The AES cites issues with treatment standardization and regulation, dosing requirements, possible long term adverse side effects and potential medication interactions for complex cases as current barriers to clinical acceptance and support (American Epilepsy Society, 2016).

Evidently, there are some positive outcomes associated with cannabis use, however, these may largely result from the efficacy of CBD. Furthermore, the reliability of clinical trials that investigate the medicinal efficacy of cannabis has come into question due to the highly prevalent placebo effect, which is accentuated by subjective symptom severity reporting measures, the positive reputation of cannabis and subsequent patient expectations, and the acute psychiatric effects of cannabis (Russo, 2016). Further research into the efficacy of cannabis and CBD is needed to ensure that the benefits of cannabis use do not outweigh the potential costs.

11. Synthetic ‘Spice’ cannabinoids

Products containing synthetic cannabinoids (also known as K2 or Spice, hereafter referred to as Spice) are high-potency, high-efficacy, CB1 cannabinoid-receptor agonists, and are often marketed under the pretence of being a benign substance, such as potpourri or incense (Spaderna, Addy, & D'Souza, 2013). Unlike organic forms of the *Cannabis Sativa* plant, synthetic cannabis does not contain cannabidiol, which exhibits both anxiolytic and antipsychotic properties (Croxford, 2003). Although the Spice is marketed as 'not for human consumption' in order to circumvent drug laws and regulation, it is generally purchased for the purpose of intoxication (Vardakou, Pistos, & Spiliopoulou, 2010). These products are generally inhaled (smoked), and can be ingested as a liquid (Vardakou et al., 2010). The use of these 'designer cannabinoid' products was first reported in Europe in the mid-2000's, then spread to the Americas and elsewhere (Spaderna et al., 2013). Consumption of Spice is considered to be increasing, which is likely driven by the ease of availability and novelty of the product among first-time users (Dargan, Hudson, Ramsey, & Wood, 2011; Schifano et al., 2010), as well as it delivering a relatively cheap 'legal high' and the inability of traditional urine drug screens to detect use (Seely, Lapoint, Moran, & Fattore, 2012).

Despite the general increase in the use of Spice, accurate descriptions regarding its adverse effects and toxicological profile are currently lacking. The acute effects of Spice are typically significantly stronger than for natural cannabis products (Kronstrand, Roman, Andersson, & Eklund, 2013), and sometimes lead to severe psychological and psychophysiological effects, including tachycardia/hypertension, visual/auditory hallucination, mydriasis, agitation/anxiety, tachypnea, nausea/vomiting, and seizures (Papanti, Orsolini, Francesconi, & Schifano, 2014). Indeed, the acute use of Spice has been reported to cause severe respiratory depression requiring intubation (Jinwala & Gupta, 2012), contributing to cases of myocardial dysfunction (Mir, Obafemi, Young, & Kane, 2011) and stroke (Hoyte et al., 2012), and has even been cited as a primary cause of death (Kronstrand et al., 2013). The adverse chronic effects of Spice are also similar to those of the natural plant product, including panic, anxiety, catatonia, psychosis, and a range of 'bizarre behaviours' and disordered cognition (Gurney, Scott, Kacinko, Presley,

& Logan, 2014; Vandrey, Dunn, Fry, & Girling, 2012). The psychosis associated with these synthetic cannabinoids has been colloquially termed ‘Spiceophrenia’ (Papanti et al., 2013), and the pathological profile is considered comparable to that observed in cases of drug-induced psychosis, involving symptoms of severe agitation, disorganised thoughts, paranoid delusions, and assaultive behaviour. One inherent and ongoing difficulty in effectively characterizing both the acute and long-term effects, as well as the toxicological profile, of commercially available Spice, is due the broad range of ingredients often included in the packets. Often, many of the included ingredients differ substantially in regard to the mechanistic profile and neurobiological actions of the compounds between products. These compounds used are frequently altered in response to local and federal legislative changes implemented to stop the legal purchase of these products. Thus, flexible and ongoing monitoring of available marketed products is necessary if appropriate policing efforts and current recommendations are to be implemented and adhered to.

12. Conclusions

Proponents for cannabis have largely focused on its acute effects as a relaxant and euphoriant. This narrow focus is misleading and often undermines the considerable literature base demonstrating the adverse effects of the substance. Both the acute and chronic effects should be considered when debating the overall efficacy of cannabis as a recreational and therapeutic substance. Indeed, if one focused on acute drug effects, psychoactive drugs in general would be misperceived as beneficial as the effect on-drug is typically more desirable than off-drug (Parrott et al., 2008). The same principal applies to caffeine, alcohol and nicotine. However, negative acute effects, such as disordered thoughts and cognitions, fear of dying, panic and increased PANSS symptoms, are reported (Ashton, 2001; Crean et al., 2011; D'Souza et al., 2004; Volkow et al., 2014). These negative effects are largely due to the high concentration of THC in recreational cannabis (Crean et al., 2011; United Nations Office of Drugs and Crime, 2016; Volkow et al., 2014). THC is also largely responsible for the detrimental effects of regular drug use (Crean et al., 2011; Volkow et al., 2014). One of the core paradoxes of recreational drug

usage is that while acute effects tend to be positive, chronic effects are largely negative; hence the well-documented adverse effects of regular alcohol, nicotine, cocaine and methamphetamine, and heroin consumption (Cadet, Krasnova, Jayanthi, & Lyles, 2007; Cruickshank & Dyer, 2009; Parrott, 1999, 2013; Parrott et al., 2008).

Weekly recreational use of cannabis progresses to substance dependence and chronic use in 17% of cases (Coffey et al., 2003). Risk factors for dependence include avoidance of withdrawal symptoms, compulsive use and tolerance (Coffey et al., 2002; Coffey et al., 2003), while mood and psychiatric conditions have been shown to increase likelihood of substance initiation (Coffey et al., 2003; N. Wilson & Cadet, 2009), and symptoms severity have been associated with increased use (Volkow et al., 2014; N. Wilson & Cadet, 2009; Wittchen et al., 2007).

Additional effects of chronic cannabis use include adverse neurocognitive (D'Souza et al., 2004; Grant et al., 2003; Jager et al., 2010; Pope et al., 2001; Ramaekers et al., 2008), neurological (Batalla et al., 2013; Battistella et al., 2014; Lorenzetti et al., 2014; Lorenzetti et al., 2016), respiratory and cardiovascular (Benowitz & Jones, 1975; Sidney, 2002; Wolff et al., 2011), cancer (Aldington et al., 2008; Llewellyn et al., 2004; Zhang et al., 1999) and pregnancy outcomes (Grufferman et al., 1993; Kuijten et al., 1990; Robison et al., 1989). Extensive evidence also suggests that smoking cannabis leads to similar cardiovascular and cancer outcomes as cigarette smoking (Aldington et al., 2008; Aldington et al., 2007; Ashton, 2001; Taylor & Hall, 2003). However, this may be due in part to a moderating effect of tobacco, as cannabis is often combined with tobacco to be smoked, which is seldom controlled for.

It is important to recognise that although consumption of cannabis has significant adverse health effects, specific cannabinoids, such as CBD, appear to have significant benefits due to its antioxidant, anticonvulsant, anti-inflammatory and neuroprotective properties (Croxford, 2003; Hampson et al., 1998; Scuderi et al., 2009). Although, clinical trials are at risk of demonstrating a placebo effect, due to the subjective nature of symptom

measures, the positive expectations of cannabis, and its acute psychiatric effects (Russo, 2016). Hence, we strongly support research into the potential benefits of specific cannabinoids.

With rapidly shifting social and legal policies in a number of jurisdictions across the world, the use of cannabis is likely to increase in some regions. Consequently, an increase in adverse health, psychobiological, educational, and psychosocial outcomes for individuals is inevitable (Volkow et al., 2014). These outcomes have roll on effects on the health, safety and welfare of the community, for example, in terms of road safety. Although there are many potential benefits for the legalisation and regulation of cannabis, educating the global community about the widespread adverse effects of cannabis consumption is important.

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