Abuse and dependence potential of Cannabis sativa and nabiximols

Professor Jason White
Professor of Pharmacology and Head,
School of Pharmacy and Medical Sciences,
Division of Health Sciences,
University of South Australia, Australia

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Contents

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SUMMARY

A number of studies in animals and humans, using a variety of methodologies, have assessed the abuse and dependence potential of cannabis, its main active component THC and nabiximols (Sativex), the THC/cannabidiol mixture derived from the cannabis plant. The evidence from animal studies (that have mainly used THC) indicates that it should be considered a drug of dependence, but that it does not seem as strong a reinforcer as some other drugs, such as cocaine and morphine: the increase in dopamine in the nucleus accumbens is not as great and it is not as reliable at lowering self-stimulation threshold, inducing and maintaining self-administration and inducing conditioned place preference. Furthermore, the degree of physical dependence is not as pronounced.

Human studies demonstrate that cannabis has significant potential for abuse and dependence: it has recognisable subjective effects that are mostly considered positive and it is self-administered. In interpreting these data it should be noted that human experimental studies may not reflect the range of responses to cannabis in the community as the participants are almost always cannabis users. Epidemiological evidence supports the potential for abuse of and dependence on cannabis, but the rates of dependence appear to be lower than for some other drugs. Cannabis can induce physical dependence among those using the drug frequently, but the withdrawal syndrome is not considered to be severe.

When THC and cannabidiol are combined as nabiximols, there is little evidence of abuse or dependence and it seems that there is relatively little potential for either to develop. However, trials to date have used mainly therapeutic doses and it is possible that supratherapeutic doses may have some potential for abuse and/or dependence.

1 INTRODUCTION

1.1 Cannabis sativa

The cannabis plant contains a number of different psychoactive cannabinoids. The primary psychoactive component of cannabis, Δ^9-tetrahydrocannabinol (THC), was first identified in the 1960s. THC is a partial agonist of both cannabinoid-type receptors: CB1 and CB2. CB1 receptors are expressed at the highest concentrations in the basal ganglia, cerebellum, hippocampus, and cerebral cortex, while CB2 receptors are expressed primarily in the immune system. It is thought that the psychoactive properties of THC arise from its agonist activity at the CB1 subtype.

1.2 Coverage of the present review

Cannabis, its extracts and tinctures are scheduled (as Schedule I) under the 1961 Convention. The present review covers cannabis and extracts of cannabis. Currently, there are no commercially available tinctures of cannabis. One approved medicinal product, nabiximols (brand name Sativex Oromucosal Spray), is an extract of cannabis. The product is an oromucosal spray that combines two cannabinoids, THC and cannabidiol, in an approximate 50:50 mixture. Both cannabinoids are present in pure form, but are obtained by a process of extraction from cannabis leaf and flower. Other constituents of cannabis may also be present in very small concentrations. In contrast to nabiximols, other products have used synthesized THC and therefore are not covered under the wording in the 1961 Convention and will not be included in this review.

This review focuses only on the abuse and dependence potential of cannabis and cannabis extract in the form of nabiximols. A second review (Amato et al. 2016) considers the medical uses of cannabis and cannabis extracts and a previous review (Madras 2015) included considerable detail on the adverse effects of cannabis. The first part of the review considers the evidence concerning cannabis and THC, from experimental studies on animals and humans and from epidemiological evidence. Animal studies almost all focus on THC, whereas human studies are concerned mainly with smoked cannabis. The second section focuses on nabiximols.

2 CANNABIS AND THC

2.1 Animal models of abuse and dependence

There are a number of animal models that have been used to assess the abuse and dependence potential of CNS active drugs. While each has its limitations, in general they have a high degree of predictive ability, particularly when used in combination. The advantage of animal models is the ability to separate inherent biological actions of the drug that predispose to the development of abuse and dependence from individual (including genetic) characteristics and social and other environmental factors that influence human drug use.

2.1.1 Mesolimbic dopamine

Activation of the mesolimbic dopamine system has been implicated as the key neural event that underlies drug reinforcement and the development of drug dependence. The mesolimibic dopamine system comprises a group of neurons with cell bodies in the ventral tegmental area (VTA) and axonal terminals in the nucleus accumbens (NAcc). Drugs that are commonly abused, such as opioids, ethanol, nicotine, amphetamine and cocaine increase extracellular dopamine concentrations in the NAcc, but especially in the shell of the NAcc (Di Chiara & Imperato 1988). In contrast, drugs without such action are not generally subject to abuse and dependence. The increase in dopamine can be due to activation of dopamine neurons in the VTA (e.g. nicotine), decreased inhibition of VTA neurons (e.g. opioids) or through direct synaptic action in the NAcc (e.g. cocaine, amphetamine).

Administration of THC to rats has been shown to result in a dose-dependent increase in the firing rate of VTA dopaminergic neurons (French, Dillon & Wu 1997), and increased levels of extracellular dopamine in the shell of the NAcc (Tanda, Pontieri & Di Chiara 1997). At the doses tested, this increase in dopamine was significant, but of lesser magnitude than the increase produced by heroin. The THC-induced increase was blocked by the CB1 antagonist rimonabant and at least partially blocked by the opioid receptor antagonist naloxone, suggesting an opioid influence on the mechanism of action. The increase in dopamine has also been shown to be associated with self-administered THC (Fadda et al. 2006).

While widespread in the brain, including the VTA and the NAcc, CB1 receptors are not found on dopaminergic neurons. However, there is evidence from a variety of studies suggesting that the increase in dopamine in the NAcc is due to reduction in the inhibitory

actions of GABAergic neurons, a mechanism similar to opioids (Pierce & Kumaresan 2006; Oleson & Cheer 2012).

2.1.2 Drug discrimination studies

Drug discrimination studies in animals are considered as a model for subjective drug effects in humans (Swedberg & Giarola 2015). In drug discrimination studies, animals are typically trained to respond in one manner when administered a drug and in a second manner when they have been administered vehicle or placebo. Correct responses are reinforced with food or some other reward. The discrimination between drug and placebo is assumed to be based upon the presence or absence of perceivable central nervous system effects of the drug. The characteristics of these effects can then be determined by administration of other substances either alone or in conjunction with the drug used for training. In general, drugs that have subjective effects in humans can be discriminated by animals, whereas those that do not have such effects cannot be discriminated, and drugs with similar subjective effects in humans are discriminated as similar by animals.

There are a number of studies of drug discrimination using THC in animals, using a variety of species, including rats, mice and rhesus monkeys. They show that animals can learn to reliably discriminate THC and that the THC discriminative stimulus shows a high degree of specificity (for example see Balster & Prescott 1992). While drugs from other pharmacological classes failed to substitute for THC, a number of synthetic and natural cannabinoids (e.g. levonantradol, nabilone, Δ^8-tetrahydrocannabinol) have been found to have THC-like discriminative stimulus effects (Barrett et al. 1995). The discriminative stimulus effects of THC can be blocked by the CB1 receptor antagonist rimonabant (Wiley et al. 1995; Vann et al. 2009), indicating that the THC discriminative stimulus is CB1 mediated.

2.1.3 Intracranial self stimulation

Intracranial self-stimulation (ICSS) refers to the reinforcing effects of currents administered to certain parts of the brain (so-called 'reward centres'). The threshold current required to produce such reinforcement is a measure of reward activity and can be used to assess and compare the abuse liability of drugs. Lowering of the ICSS threshold indicates a facilitation of brain stimulation reward, whereas elevation of the threshold reflects diminished reward value of the stimulation. Acute administration of most drugs of abuse (e.g. cocaine,

amphetamine, morphine) lowers the ICSS threshold, reflecting an increase in activity in the neural substrates of reward due to the action of the drug. In contrast, withdrawal from chronic administration of these compounds results in an elevation of ICSS threshold, reflecting the decrease in reward activity compared to the normal state. These actions are presumed to model the respective positive and negative affective states of drug intoxication and drug withdrawal in humans.

Using this model, the results to date with THC have been contradictory. In some studies, THC has been shown to lower the threshold for electrical stimulation. For example, significant reductions in self stimulation threshold were recorded in Lewis rats 15 and 30 minutes after administration of 1.5 mg/kg THC (Gardner et al. 1988). In contrast, a significant increase in the self-stimulation threshold was observed in Sprague Dawley rats administered 1 and 2 mg/kg THC intraperitoneally (Vlachou et al. 2007). The differences may be attributable to variations in results between strains, with Lewis rats showing decreases in threshold that have not been seen with other strains (Lepore et al. 1996; Vlachou & Panagis 2014). However, other aspects of the methodology used, such as dose, could also have played a role.

It appears that THC is not as effective at reliably reducing ICSS threshold compared to some other drugs of abuse. This could be indicative of lower abuse potential, although it also needs to be recognized that the number of studies in this area is small and that this methodology is not as effective at predicting abuse potential as some others.

2.1.4 Self-administration in animals

Drugs that are commonly abused by humans are also typically self-administered by laboratory animals under controlled experimental conditions. Self-administration in animal models is considered to be one of the most reliable predictors of abuse potential in humans. Self-administration studies allow animals to self-administer a drug by performing an operant response, such as pressing a lever. Measures recorded include the number of lever presses per minute (rate of responding), the number of self-administered doses and the frequency of doses delivered in the session, and the total drug intake during the session. The studies are often performed in animals that have previously learnt to self-administer a training drug (a recognized drug of abuse such as cocaine) and require a fixed number of responses to obtain

an injection of the drug ('reward'). The drug to be tested is then substituted for the training drug and assessed for its ability to produce equivalent or greater levels of responding than those maintained during training.

It is well established that laboratory animals will self-administer most drugs that are abused by humans. For example, cocaine is self-administered under a wide range of experimental conditions and in a number of different species (Kelleher & Goldberg 1977; Griffiths, Bradford & Brady 1979; Bergman et al. 1989). Animals will also reliably self-administer a range of opioids, including morphine, heroin, and codeine (Jones, BE & Prada 1977; Mello 1991). In contrast, early laboratory animal studies failed to clearly demonstrate persistent, dose-related, self-administration behaviour maintained by THC (for review see Justinova et al. 2005). There were some examples of self-administration, but these occurred under limited experimental conditions. For example, Takahashi and Singer (1979) demonstrated THC self-administration in drug naïve, diet restricted rats exposed to a schedule of intermittent food delivery that has been shown to produce a variety of 'excessive' behaviours. These animals, which were maintained at 80% body weight, self-administered low dose THC, but self-administration immediately returned to placebo levels when food restriction was discontinued.

THC self-administration has been established in squirrel monkeys in one laboratory (Tanda, Munzar & Goldberg 2000; Justinova et al. 2004; Justinova et al. 2003). Tanda, Munzar and Goldberg (2000) demonstrated persistent THC self-administration using doses of THC similar to those inhaled by human cannabis users. Squirrel monkeys were initially trained to press a lever for an i.v. injection of cocaine, with 10 lever presses resulting in a 30 μg/kg injection (fixed-ratio 10; FR10). A five-session washout period, where saline was substituted for cocaine, was implemented prior to testing THC. Responding increased following substitution of 2 μg/kg injections of THC for saline and stabilized within a week. Approximately 30 injections of THC were self-administered per session, a rate comparable to that maintained by cocaine under identical conditions (Tanda, Munzar & Goldberg 2000).

While early studies relied on first training animals to self-administer cocaine, THC self-administration has also been shown in drug-naïve squirrel monkeys using the same dosing schedule. THC was found to maintain significantly higher numbers of doses self-administered per session and higher rates of responding than vehicle at doses of 2, 4 and

8 µg/kg per injection (Justinova et al. 2003). The response rates maintained by the drug-naïve squirrel monkeys under the fixed-ratio were similar to or greater than peak responding rates maintained by i.v. cocaine (Spear et al. 1991), nicotine (Sannerud et al. 1994) and midazolam (Munzar et al. 2001). Pre-treatment with naltrexone was shown to reduce THC self-administration, but not to the level of placebo, suggesting a role of the opioid system in the rewarding effects of cannabis (Justinova et al. 2004).

It appears that self-administration of THC may be somewhat species-specific. Confirming earlier studies, a very recent report indicates that under optimal training conditions, THC is only a weak reinforcer in rats (Wakeford et al. 2016). In contrast, under the same conditions, cocaine produced reliable self-administration. While primates are a somewhat closer model to humans than rats, the lack of species generality may suggest that the reinforcing properties of THC are not as robust as some other drugs of abuse.

2.1.5 Conditioned place preference

The conditioned place preference (CPP) test is considered to measure the rewarding effects of a drug in a manner that is less affected by the direct behavioural effects of the drug (stimulation or sedation) than self-administration. CPP involves periods of exposure to a compartment on one side of an apparatus under the influence of the drug and exposure to the compartment on the other side after placebo. The two compartments are made physically distinctive. The animals are then given a choice between the sides and preference (CPP) is demonstrated if the animals are found to spend significantly more time in the drug-paired compartment compared to the non-drug (placebo or vehicle) compartment (Bardo, Horton & Yates 2015). Conditioned place aversion (CPA) is found if the animal spends significantly more time in the non-drug compartment than the drug compartment.

There are a number of studies of CPP/CPA in rats and mice using THC and the results have been somewhat inconsistent (for a summary see Vlachou & Panagis 2014). In many instances, THC induces CPA rather than CPP in rats and mice, particularly at high doses (e.g. 15-20 mg/kg) (Sañudo-Peña et al. 1997; Hutcheson et al. 1998; Schramm-Sapyta et al. 2007). Lepore et al. (1995) compared the rewarding properties of THC with cocaine and morphine in Long-Evans rats. Administration of 1 mg/kg THC resulted in neither CPA nor CPP, however higher doses of THC (2 and 4 mg/kg) produced a preference for the THC

compartment. The CPP observed at these doses was less than that produced by low dose cocaine and morphine. In the same study, changes in the timing of drug exposure resulted in CPA at the higher THC doses. CPP has been observed in Sprague-Dawley and Wistar rats at THC doses ranging from 0.075-0.75 mg/kg (Braida et al. 2004; Le Foll, Wiggins & Goldberg 2006).

Schramm-Sapyta et al. (2007) showed only CPA, which was stronger in adult compared to adolescent rats. In addition, they found that THC was anxiogenic in two rodent models of anxiety, the elevated plus maze and the light-dark test. In both models, the anxiogenic effects were stronger in adult compared to adolescent rats. They suggested that these anxiogenic effects may underlie the CPA they observed.

The evidence using the CPP/CPA procedure suggests that, like the results from the self-administration procedure, THC can have reinforcing effects, but they may not be as robust or strong as for some other drugs of abuse. There is also evidence of the ability of THC to produce aversion rather than rewarding effects.

2.2 Withdrawal in animals

Withdrawal studies involve chronic administration of the drug to animals followed by abrupt cessation or administration of an antagonist. The disruptive effects of withdrawal can be determined by measurement of changes in the animals' behavior, while the negative reward value can be measured using CPA and changes in ICSS threshold. Changes to dopaminergic activity in the NAcc can also be measured in withdrawal states.

A range of behavioural changes associated with THC withdrawal have been observed in laboratory animals. Aggressive behaviour, hyperirritability, tremors, photophobia, anorexia, and apparent hallucinations have been reported in rhesus monkeys following cessation of long-term THC administration (Kaymakcalan 1972). A study by Aceto et al. (1996) found the most common withdrawal signs in rats were scratching, licking, arched back, and ptosis. Following cessation of high dose continuous infusions (12.5-50 mg/kg/24 hrs for 4 days), rats also displayed biting, tongue rolling, retropulsion, and ataxia. Administration of the CB1 antagonist rimonabant (SR141716A) following twice-daily THC administration in mice resulted in an increase in paw tremors and headshakes and a decrease in normal behaviour

such as grooming and scratching (Cook, Lowe & Martin 1998). Disruption of operant behavior during cessation of chronic THC administration indicative of dependence or by rimonabant-precipitated withdrawal has also been reported in rhesus monkeys (Beardsley et al., 1986) and in rats (Beardsley and Martin, 2000), respectively .

Using ICSS threshold, withdrawal from THC has been demonstrated in rats following a single 1 mg/kg dose of THC. Brain reward threshold was significantly increased in the period after cessation of THC effects, with the change lasting approximately 24 hours (Gardner & Vorel 1998). In rats repeatedly administered THC, dopaminergic neuronal activity in the VTA and dopamine release in the NAcc are reduced following abrupt THC discontinuation or administration of a selective CB1 antagonist (Diana et al. 1998; Tanda, Loddo & Di Chiara 1999). These changes in the mesolimbic pathway have also been observed in the early phase of withdrawal following chronic exposure to amphetamine, cocaine, and morphine (Rossetti, Hmaidan & Gessa 1992).

2.3 Conclusions from studies using animal models

In animal models, THC shows a number of the characteristics of a drug of dependence. In particular, it:

- has discriminative effects that are linked to its receptor action (although it is important to recognize that drugs that are not abused also have discriminative effects),
- increases dopamine concentration in the shell of the NAcc
- lowers ICSS threshold
- is self-administered, and
- induces CPP (at least under some experimental conditions)

In addition, cessation of administration of THC is associated with a withdrawal syndrome that is both behaviourally disruptive and aversive in nature.

It is reasonable to conclude from these studies that THC should be considered a drug of dependence in the same way as a range of opioids, stimulants, etc. Nevertheless, there is some evidence that it is not as strong a reinforcer as some other drugs, such as cocaine, heroin and morphine: the increase in NAcc dopamine is not as great as that occurring with some other drugs and it is not as reliable at lowering ICSS threshold, inducing and

maintaining self-administration and inducing CPP as at least some other drugs of dependence. It should be recognised, however, that the evidential basis for direct comparison of THC with other drugs is limited and therefore the conclusion is a cautious one.

2.4 Human studies of abuse potential

There are a range of methods that have been used to experimentally assess the abuse potential of drugs in humans. Some of these parallel the methods used in animals (e.g. self-administration), while others, such as the self-reporting of subjective effects, are different. Some techniques used in animals cannot be used in humans (e.g. ICSS thresholds). In addition, for ethical reasons, participants in human studies are normally limited only to those people who have prior experience of cannabis use; in many instances they are frequent cannabis users. This means that they are a self-selected population who may not reflect the range of responses to cannabis across the population.

2.4.1 Subjective and discriminative effects

Cannabis produces clear subjective reports of pleasurable effects and these are associated with motivational responses, including drug-seeking and drug-taking behaviour. Euphoria or a feeling of 'high' has been identified as a primary factor associated with cannabis use, however changes in perception, feelings of relaxation, appetite and occasionally dysphoria are also reported (Kleinloog et al. 2014; Green, Kavanagh & Young 2003). The dysphoric effects are mainly related to anxiety. From limited data, it appears that the strength of subjective effects is correlated, to at least some extent, with blood THC concentration (Hartman et al. 2015).

It is important to note that comparing the subjective effects of THC between studies can be difficult due to differences in smoking protocols between studies (i.e. varying cigarette THC content, paced smoking protocol where number of puffs, duration of puffs and smoking interval are controlled) as well as variation in smoking between participants within studies. However, research to date has shown no significant differences in smoking measures (i.e. number of puffs, duration of puffs, and smoking interval) between cigarettes containing different concentrations of THC (0.2, 0.4, and 0.8% THC, Cappell, Kuchar & Webster 1973; 1.32, 1.97, and 2.54% THC, Perez-Reyes et al. 1982).

The subjective effects produced by oral THC have been reported to be of a similar intensity to those described following smoked cannabis. For example, a study by Hart and colleagues (2002) reported that smoked cannabis (3.1% THC) and oral THC (20 mg) produced comparable increases in ratings of 'good effects', 'high', and 'liking' on a 50-item subjective-effects visual analog questionnaire. Adolescents with cannabis use disorders report increased ratings of 'good drug effect', 'high', and 'drug liking' following 10 mg oral THC (Gray et al. 2008).

A study by Chait and colleagues (1988) demonstrated that experienced cannabis users could reliably learn to discriminate cannabis from placebo cigarettes. Participants could correctly identify the training dose (2.7% THC cigarettes) within 90 seconds of commencing smoking. The effect was dose dependent, with lower THC cigarettes producing proportionally lower drug appropriate responses.

Lile et al. (2009) established a 25mg oral dose of THC as a discriminative stimulus in moderate cannabis users. The participants learned to identify the stimulus reliably and showed graded responses to lower doses of the drug. There was no overlap with other psychoactive drugs tested, but, in a subsequent study, the synthetic cannabinoid nabilone was shown to produce THC-like discriminative effects (Lile, Kelly & Hays 2010).

2.4.2 Choice and self-administration in humans

In humans, cigarettes with a higher concentration of THC are preferred over cigarettes with lower THC concentrations (Mendelson & Mello 1984; Kelly et al. 1997). For example, Chait and Burke (1994) allowed subjects to sample low-potency cannabis (0.63% THC) cigarettes and high potency cannabis (1.95% THC) cigarettes prior to a choice session. Subjects chose high-potency cannabis cigarettes on 21 of 24 occasions. In addition, when participants chose between a cannabis cigarette and an alternative reward such as food or money, cannabis was chosen over the alternative reward more often when the THC content was higher (e.g. Haney et al. 1997). These results suggest that the reinforcing strength of cannabis is related to THC content. However, the choice to self-administer THC can often be reduced when an alternative reinforcer (e.g. money) is concurrently available (Haney et al. 1997; Hart et al. 2002).

Human subjects will also choose oral THC over placebo. Chait and Zacny (1992) investigated the reinforcing and subjective effects of smoked cannabis and oral THC. All subjects chose smoked cannabis over placebo, and 10 out of 11 subjects chose oral THC over placebo.

2.5 Withdrawal in humans

The cannabis withdrawal syndrome has been well characterised. It has some elements in common with withdrawal from other drugs, but the overall withdrawal symptom profile is unique to cannabis (Vandrey et al. 2008; Vandrey et al. 2005). Following cessation of heavy cannabis use, patients experience craving, irritability, anger, depression, difficulty sleeping, and decreased appetite (Budney et al. 2008). Most symptoms begin within 24 to 48 hours of abstinence and peak within 4 to 6 days (Haney et al. 1999). Withdrawal symptoms can last from 1 to 3 weeks, although significant individual differences occur. Unlike opioid, amphetamine or alcohol withdrawal syndromes, cannabis withdrawal does not appear to include severe or life-threatening medical consequences or major psychiatric disturbances and is therefore considered mild (Carlson et al. 2012; McKeon, Frye & Delanty 2008; Ashton 2005).

The most common withdrawal symptoms observed in 49 dependent cannabis users during two weeks of abstinence were sleep disturbances (nightmares or strange dreams, 41%; trouble getting to sleep, 37%; waking up early, 33%; waking up sweating, 32%), mood changes (angry outburst, 27%; irritated, 30%; feeling tense, 27%) and gastrointestinal symptoms (loss of appetite, 27%; nausea, 19%; stomach ache, 19%) (Allsop et al. 2011). Lee et al. (2014) characterised the prevalence, duration, and intensity of withdrawal and craving effects in 30 male chronic, frequent cannabis smokers during abstinence on a closed research unit. The most frequently reported symptoms based on self-report using visual analogue scales (VAS) were craving cannabis (48%), irritability (37%), angry/aggressive (36%), depressed (31%), feeling anxious (29%), and restless (27%). Peak abstinence symptoms were observed on days 0-3, with most symptoms declining thereafter. In contrast, difficulty getting to sleep and strange dreams were found to increase over time, suggesting that chronic cannabis users may have intrinsic sleep problems that may have predisposed them to use cannabis.

The effectiveness of oral THC in suppressing cannabis withdrawal has been tested in cannabis users (Budney et al. 2007). Administration of doses of 10-30mg THC suppressed symptoms including craving, irritability, aggression and overall discomfort in a dose dependent manner. At the higher doses, symptoms were only a little above the level reported by participants prior to withdrawal. While other components of cannabis smoke may play some role in physical dependence, these findings highlight the central role of THC.

It has also been demonstrated that THC alone is able to induce physical dependence. Withdrawal symptoms have been reported following interruption of oral THC dosing: irritability, restlessness, sleep disturbances, and decreased appetite were observed in subjects following abrupt cessation of high dose oral THC (210 mg/kg for 10-20 days) (Jones, RT, Benowitz & Bachman 1976). Subsequent administration of THC was able to diminish the withdrawal symptoms.

2.6 Epidemiology

It is estimated that in 2014, 3.8% of the global population had recently (past 12 months) used cannabis (UNODC 2016). While estimates of cannabis use are generally well reported, the extent of cannabis abuse and dependence is not known. Degenhardt et al. (2011) conducted a systematic analysis of available data on the extent of global illicit drug use and dependence. The results show that only seven countries had reported estimates of cannabis dependence: four national estimates and three subnational estimates. Estimates of cannabis dependence ranged from 0.4% (Germany; estimate year 2006) to 9.4% (New Zealand; estimate year 2000).

Another epidemiological study estimated the population level of cannabis dependence across Western and Eastern Europe, America, Australia and Southeast Asia with figures ranging from 0.1-1.5% (Degenhardt & Hall 2012). A more recent epidemiological study estimated that there were 13.1 million cannabis dependent people globally in 2010 (Degenhardt et al. 2013). Prevalence of cannabis dependence was greater in people aged 20-24 years, and was higher in males than females.

Figures from the US show an increasing rate of cannabis use in the population between 2001-2 and 2012-3 (Hasin et al. 2015). The number of users with a cannabis disorder (defined as

cannabis abuse or dependence according to DSM-IV criteria) also increased, but the proportion did not significantly change. These authors estimated that in the US in 2012-3, approximately 27% of cannabis users had a cannabis disorder. This is higher than the figures above, but this also included cannabis abuse and therefore those who were not dependent but had experienced adverse effects from their cannabis use.

In order to assess the dependence potential of cannabis, estimates need to be made of dependence among users. Ideally, these would then be compared to the risk of dependence among users of other drugs. The only estimates of this nature have been made from US data in the 1990s (Anthony, Warner & Kessler 1994) and then approximately 10 years later (Wagner & Anthony 2002). The first estimates show that the rates of dependence among non-medical drug users were as follows: tobacco 32%, heroin 23%, cocaine 17%, alcohol 15%, cannabis 9%, anxiolytics and sedatives 9%. The subsequent estimates show a rate of dependence of 8% for cannabis compared to 12-13% for alcohol and 15-16% for cocaine. It should be recognised that these figures are particular to one country and a limited time period, and are likely to vary according to factors such as drug availability and prevailing social sanctions. Nevertheless, they show that while there is a significant rate of dependence among people who have used cannabis, it is somewhat lower than the rates for a number of other drugs.

2.7 Conclusions

The results from studies in humans indicate that cannabis has significant potential for abuse and dependence: it has recognisable subjective effects, it produces effects that are mostly considered positive and it is self-administered. As noted earlier, these results largely come from a self-selected population of cannabis users and it is possible that in a random group from the population the responses would be more diverse and include some people for whom cannabis was not reinforcing. Epidemiological evidence supports the potential for abuse of and dependence on cannabis. However, the rates of dependence may be lower than for some other drugs.

Cannabis can induce physical dependence, but the withdrawal syndrome is not considered to be severe and is certainly less pronounced than withdrawal from opioids and alcohol.

The evidence to date suggests that the abuse and dependence potential of cannabis are largely due to the actions of THC, although a role for other cannabinoids cannot be excluded.

3 NABIXIMOLS

While the abuse potential of cannabis has been widely studied, less is known regarding the abuse potential of nabiximols. Nabiximols is an approximate 1:1 ratio of THC and cannabidiol (CBD) with small concentrations of other cannabis constituents delivered as an oromucosal spray. It therefore differs from cannabis in the cannabinoid composition and in the route of administration. The abuse and dependence potential of THC has been presented above, therefore this section will consider the current information on the abuse and dependence potential of nabiximols (THC+CBD). CBD will be considered to the extent that it informs the likely actions and effects of nabiximols, particularly in studies using animal models.

Unlike THC, CBD appears to have no agonist activity at either CB1 or CB2 receptors, but may act as an antagonist at these sites (Petwee 2008). CBD interacts with many other non-endocannabinoid receptors, including the 5-HT_{1A} receptor and vanilloid receptor type 1 (Bisogno et al. 2001; Zuardi 2008). CBD may additionally affect cannabinoid systems by enhancing the action of the endogenous cannabinoid ligand anandamide. This results from blockade of anandamide reuptake and the inhibition of its enzymatic degradation (Bisogno et al. 2001; Mechoulam & Hanuš 2002).

3.1 Animal models of abuse and dependence

3.1.1 Intracranial self-stimulation

In male Sprague-Dawley rats, administration of low dose (5 mg/kg) CBD did not change the threshold frequency required for ICSS, however high dose (10 mg/kg and 20 mg/kg) CBD resulted in an elevation of the threshold (Katsidoni, Anagnostou & Panagis 2013).

3.1.2 Conditioned place preference

It appears that CBD given alone has little effect on place conditioning. For example, Long-Evans rats treated with 10 mg/kg CBD showed neither CPP nor CPA (Vann et al. 2008).

However, rats treated with increasing doses of CBD and THC (1, 3, and 10 mg/kg) exhibited a trend towards CPP not seen in those given THC alone (Klein et al. 2011). The authors attributed this to a pharmacokinetic interaction leading to higher THC concentrations rather than a change in receptor action.

3.1.3 Drug discrimination studies

CBD appears not to exhibit THC-like discriminative stimulus effects. For example, CBD did not produce the level of responses induced by THC in Long-Evans rats (Vann et al. 2008). CBD also failed to substitute for THC in pigeons trained to discriminate THC from vehicle (Jarbe, Henriksson & Ohlin 1977). Co-administration of THC and CBD at ratios similar to those in nabiximols did not result in changes in THC-lever responding, suggesting that CBD may not significantly alter the subjective effects of THC.

3.2 Human abuse potential

Only one study has had the primary aim of investigating the abuse potential of nabiximols using a randomized, double blind, crossover design. In the study by Schoedel et al. (2011), experienced cannabis smokers received, in random order, single administrations of placebo; nabiximols 4 sprays (equivalent to 10.8 mg THC, 10 mg CBD: low dose), 8 sprays (equivalent to 21.6 mg THC and 20 mg CBD: medium dose) and 16 sprays (equivalent to 43.2 mg THC and 40 mg CBD: high dose); and dronabinol (synthetic THC) 20 mg (medium dose) and 40 mg (high dose). Low dose nabiximols was found not to differ significantly from placebo on measures of 'drug liking', euphoria, or subjective drug value, while medium and high doses showed evidence of abuse potential in comparison with placebo. However, the effects with nabiximols were consistently lower on a dose-for-dose basis compared to dronabinol.

To date there have been no reports of misuse of nabiximols. In clinical trials, the incidence of intoxication and euphoria has been low (Robson 2011). For example, Wade et al. (2006) investigated the safety and efficacy of long-term term treatment with nabiximols. Patients entering the study had reported initial benefits from nabiximols treatment following a four-week open label, placebo control period. Median intoxication scores (measured daily by VAS) were <5 out of 100 at all time points, and only three (2%) patients withdrew due to

symptoms possibly associated with intoxication (confusion, light headedness, somnolence). Low levels of intoxication were also reported in a six week randomized, double blind study. Mean intoxication scores remained below 2 (measured on a numerical rating scale; 0, no intoxication; 10, extreme intoxication), and less than 4% of subjects receiving nabiximols reported euphoric mood (Collin et al. 2007).

Patients receiving nabiximols at a supratherapeutic dose (36 sprays per day) reported greater levels of events potentially associated with intoxication; these included somnolence (49%), euphoric mood (39%), and disorientation (15%) (Sellers et al. 2013). By comparison, euphoria was reported in 7% of subjects receiving placebo and 17% of subjects receiving therapeutic doses (8 sprays per day). This suggests that nabiximols has a dose-related euphoric effect that is relatively low at therapeutic dose levels.

Self-reported intoxication scores have been found to decrease following chronic use, consistent with the development of tolerance. Serpell, Notcutt and Collin (2013) reported intoxication scores following acute (initial dosing) and chronic (≥4 weeks) exposure. Intoxication scores (measured using 100 mm VAS) increased to 12.4±18.9 mm two hours after the first dose. Intoxication scores then decreased following chronic dosing, and at the last observed visit the mean was 3.1±8.3 mm. In addition, only 4.8% of patients receiving nabiximols reported euphoric mood.

3.3 Withdrawal in humans

To date there is limited evidence of a withdrawal syndrome associated with cessation of nabiximols treatment, and abrupt withdrawal from long-term use has produced only mild and temporary disturbance of sleep, mood and appetite in a small number of subjects (Robson 2011).

A study by Wade et al. (2006) investigated the effects of a planned, sudden two-week interruption of long-term nabiximols treatment (mean duration of study participation 434 days; range 21-814). No consistent withdrawal syndrome was observed, however 11 of the 25 (44%) subjects experienced symptoms potentially associated with withdrawal including: interrupted sleep (16%), hot and cold flushes (16%), tiredness (16%), low mood (12%), decreased appetite (8%), mood swings (4%), vivid dreams (4%), and intoxication (4%).

Notcutt et al. (2012) randomly allocated nabiximols maintained multiple sclerosis patients (average nabiximols treatment 3.6 years) to continue with nabiximols (n=18) or to change to placebo (n=18). No withdrawal syndrome was observed, however 2% of the group changing to placebo reported depressed mood.

3.4 Conclusions

It appears that cannabidiol itself has little or no potential for abuse. It may moderate some of the effects of THC, but the changes have been small and the direction inconsistent.

When THC and cannabidiol are combined as nabiximols, there is little evidence of abuse or dependence and relatively little potential for those to develop. However, trials to date have used mainly therapeutic doses and it is possible that supratherapeutic doses may have some potential for abuse and/or dependence. At this stage, while the evidence for the effects of such doses is limited, the extant evidence suggests that abuse potential of nabiximols may be lower than that of THC.

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