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4906 *Current Pharmaceutical Design,* 2012, *18,* 4906-4914

# Cannabis in the Arm: What Can we Learn from Intravenous Cannabinoid Studies?

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**Abstract:** Cannabis is widely used recreationally and for symptomatic relief in a number of ailments. However, cannabis has been implicated as a risk factor for the development of psychotic illness. For forty years researchers have utilised intravenous preparations of $\Delta^9$-THC, as well as several other phytocannabinoids, in a laboratory setting. The intravenous route has the most reliable pharmacokinetics, reducing inter-individual variation in bioavailability and is well suited for the delivery of synthetic compounds containing a sole pharmacological moiety. Given the association between cannabinoids and psychotic illness, there has been a resurgence of interest in experimental studies of cannabinoids in humans, and the intravenous route has been employed. Here in a critical review, we appraise the major findings from recent intravenous cannabinoid studies in humans and trace the historical roots of this work back to the 1970's.

**Keywords:** Cannabis, Intravenous, delta-9-tetrahydrocannabinol, delta-9-tetrahydrocannabivarin, cannabidiol, THC.

## INTRODUCTION

Cannabis is the world's most popular recreational drug, behind only alcohol and tobacco. The most recent figures estimate that between 125 - 203 million people around the world (4 million in the UK) used cannabis at least once in 2009 [1], and out of all first-time users around 10% become dependent [2]. Chronic cannabis use can be detrimental to memory and other cognitive functions [3], but these effects are largely reversible upon discontinuation of use [4].

Cannabis use has been associated with an increased risk of developing psychosis [5, 6], and worsening of symptoms for people with a pre-existing psychotic illness [7]. Patients who smoke cannabis have been found to relapse more frequently and have a poorer outcome [8]. Furthermore, with the growing popularity of strains of cannabis that have stronger psychoactive effects, such as "skunk" [9], the relevance of cannabis use to psychotic illness may be increasing. These stronger strains of cannabis have been hypothesised to carry a greater risk for psychosis [10] and to be more addictive [11].

Although the above findings are of concern, there are also beneficial effects of cannabis. Cannabis has been used for thousands of years as a treatment for various physical conditions as well as to 'improve' mood and appetite [12]. In medicine, cannabis preparations are used as anti-emetics for patients undergoing chemotherapy [13], appetite stimulants for people with HIV/AIDS, and to treat pain and spasticity in multiple sclerosis [14].

The cannabis plant is divided into three separate species, *Cannabis sativa*, *Cannabis indica*, and *Cannabis* [15]. The plant produces roughly 80 compounds referred to as phytocannabinoids [16, 17]. Among these cannabis compounds (cannabinoids), the most abundant, and largely responsible for the psychological effects of cannabis, is delta-9-tetrahydrocannabinol ($\Delta^9$-THC) [18]. Other cannabinoids, some of which have very weak or no psychological effect, such as $\Delta^8$-tetrahydrocannabinol ($\Delta^8$-THC), Cannabidiol (CBD), Cannabigerol (CBG), Cannabinol (CBN), Cannabichromene (CBC), Cannabivarin (CBV), and $\Delta^9$-tetrahydrocannabivarin ($\Delta^9$-THCV), are believed to modulate the effect of $\Delta^9$-THC depending on the concentration of the cannabinoid in the plant [18].

Cannabinoids exert their effect on the mind by interacting with the endocannabinoid system (ECS) [19]. The ECS refers to a set of endogenous ligands, their receptors, and the enzymes that synthesize and degrade them. Twenty years after the discovery of the structure of $\Delta^9$-THC [20] researchers identified cannabinoid-specific receptors: cannabinoid receptor type-1 ($CB_1R$) [19], shortly followed by cannabinoid receptor type-2 ($CB_2R$) [21]. The cannabinoid receptors belong to the super-family of G-protein coupled receptors with densities about 10 to 50 times that of classical neurotransmitters, such as opioid or dopamine receptors [22]. The $CB_1R$ is predominantly found in the central nervous system with the highest concentrations in the neocortex, basal ganglia, hippocampus, cerebellum, and anterior olfactory nucleus [23]. Moderate concentrations of $CB_1R$ are also present in the hypothalamus, basolateral amygdala, and the periaqueductal gray matter in the midbrain. The $CB_2R$ was initially thought to be localized only in immune cells in the periphery [24], but have more recently also been found in the cerebellum and brain stem [25].

To date, several endogenous cannabinoid receptor ligands have been found, although the most well known are arachidonoylethanolamide (Anandamide, AEA) [26] and 2-arachidonoylglycerol (2-AG) [27]. These are biosynthesized postsynaptically in an activity-dependant manner [28]. $CB_1Rs$ are predominantly pre-synaptic, occurring at high density on the terminals of GABA-ergic neurons, and at lower density, on the terminals of glutamate-ergic terminals. Activation of $CB_1Rs$ leads to a decrease of pre-synaptic neurotransmitter release. Endocannabinoids regulate GABA-ergic and glutametergic terminals over short and long-term durations by adjusting synaptic weights (Synaptic plasticity) [29]. Clearance of AEA and 2-AG is by a re-uptake mechanism and enzymatic hydrolysis, fatty acid amide hydrolase (FAAH) for AEA and monoacylglyceride lipase (MAGL) for 2-AG [30].

Endocannabinoid transmission is finely-tuned, with precise mechanisms for local synthesis and degradation. Administration of exogenous $CB_1$ agonists is unlikely to capture the subtleties of endocannabinoid signalling. Rather, disruption of endogenous cannabinoid dependent processes is more likely to occur. Also prolonged activation of $CB_1Rs$ by $\Delta^9$-THC can lead to desensitisation and downregulation of the $CB_1R$. The effects of exogenous cannabinoids are critically dependent upon the dose. This has been demonstrated in rodents, where low doses of $\Delta^9$-THC exerted anxiolytic effects, while high doses produced anxiety [31]. Bidirectional effects have also been demonstrated in man [32]. These dose-dependent effects are also dependent on factors such as environment and previous exposure to the drug.

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1873-4286/12 $58.00+.00 

## ROUTE OF ADMINISTRATION

Cannabis is most commonly smoked as cigarettes or ingested orally. Naturalistic studies exploring the effects of recreational cannabis use on various outcomes benefit from allowing the participant to smoke or ingest the drug in a manner as similar to real life as possible [33]. One drawback however is that there are significant inter-individual differences in drug absorption from both oral and smoked routes of administration. For smoked cannabis, factors such as duration of smoking, puff duration, volume inhaled, smoking-skill, lung capacity, and loss of side-stream smoke may affect bloodstream cannabinoid concentrations [34, 35]. Orally consumed cannabinoids (either via capsules or food items) suffer from poor and irregular absorption [36], and are pharmacologically the least reliable. It is estimated that about 50% of the cannabinoids are lost due to stomach acids [37]. Intravenous (i.v.) administration on the other hand provides the most reliable delivery of synthetically prepared cannabinoids, with low inter-individual variability in drug plasma concentrations [38]. The plasma profile following an intravenous dose approximates that from the inhalational route [38]. Concentrations fall rapidly due to redistribution. Further reductions, attributable to drug metabolism, progress at a slower rate. Table **1** provides an overview of i.v. cannabinoid studies from the early 1970s to the present day.

## INTRAVENOUS $\Delta^9$-THC STUDIES

As $\Delta^9$-THC is the main psychoactive component of cannabis, it is the molecule which has been most commonly used in i.v. studies.

$\Delta^9$-THC is a partial agonist at the $CB_1R$ and $CB_2R$ with comparable affinity as the endocannabinoids anandamide and 2-AG, although with less efficacy [66]. The main psychological effects of cannabis use have been attributed to the activation of the $CB_1R$ by $\Delta^9$-THC [66, 67]. Work in the 1970s focussed on the pharmacokinetic and pharmacodynamic effects of i.v. administered $\Delta^9$-THC [39, 40, 42, 43, 45]. In one of the first studies, Lemberger and colleagues [39] studied the clearance of a 0.5mg i.v. dose of $\Delta^9$-THC. Hollister and colleagues [42] administered incremental doses (1-6mg) of i.v. $\Delta^9$-THC to 4 healthy volunteers. After a return to baseline, each subsequent stepped dose was administered only to those participants who were able to tolerate the lower doses. The reported psychological effects on the participants were dose-dependent with increasing doses causing more intense experiences. Some of the milder symptoms were ”feeling happy, dizzy, relaxed, visual perceptual changes, hunger, and sensitivity to sound”; while higher doses brought about “difficulty in concentration, poor memory, tension, flight of ideas, spontaneous laughter, and mental confusion”. The authors concluded that 6mg approached the limit of tolerability.

The Yale THC Study Group, have carried out a series of studies using i.v. $\Delta^9$-THC, making use of validated clinical assessment tools to measure psychological changes, and neurocognitive test batteries to follow changes in cognitive performance. They showed that i.v. administered $\Delta^9$-THC can elicit transient schizophrenia-like positive psychotic symptoms and schizophrenia-like cognitive impairments in a proportion of healthy volunteers [54]. $\Delta^9$-THC impaired cognitive performance in the domains of immediate and delayed recall, and in working memory [54]. Pre-treatment of healthy volunteers with Haloperidol (a dopamine D2 antagonist) did not protect against the psychotomimetic effects of $\Delta^9$-THC and cognitive impairments were exacerbated [57]. The Yale group also studied the effects of i.v. $\Delta^9$-THC in a sample of clinically stable schizophrenic patients. $\Delta^9$-THC was shown to elicit transient psychotic symptoms and impair cognition [55], with no apparent benefits on mood.

Our group have used a similar approach in healthy volunteers and found that $\Delta^9$-THC increased psychotic symptoms and cognitive impairments [59,60, 61, 62, 63, 64, 65]. Participant-rated and investigator-rated positive symptoms were correlated and positive symptoms were not explained by anxiety [59]. Self-rated negative symptoms were also elicited by i.v $\Delta^9$-THC [65]. In a subsequent study, we explored the co-administration of i.v. $\Delta^9$-THC and CBD and found preliminary evidence that CBD protected against THC-elicited psychotic symptoms in 6 healthy volunteers [60]. We have also investigated the involvement of striatal dopamine release in $\Delta^9$-THC induced psychotic symptoms using [123I]IBZM single photon emission tomography (SPET). We found that although $\Delta^9$-THC increased positive psychotic symptoms, this was not accompanied by increased dopamine release as measured by single photon emission tomography (SPET) [61]. This is in agreement with a recent positron emission tomography (PET) study, where THC was administered orally [68].

In animal studies, $CB_1$ agonists impair neural oscillations, particularly in the theta (4-8Hz) and gamma (≥40Hz) band [69,70, 71, 72]. We found that, in agreement with the animal work, the administration of 1.25mg i.v THC resulted in a reduction of theta power. In addition, coherence within the theta band between bi-frontal electrodes was significantly reduced. The latter EEG phenomenon was highly predictive of the degree of elicited positive psychotic symptoms [63]. Further analysis of this sample revealed yet another measure of neural synchrony, inter-trial-coherence (ITC), to be inversely correlated with measures of salience and identity disturbance [64].

Although there have been several fMRI studies using orally administered cannabinoids, there is to our knowledge, no fMRI work using the i.v. route.

## OTHER CANNABINOIDS ADMINISTERED INTRAVENOUSLY

One of the first i.v. studies using cannabinoids other than $\Delta^9$-THC gave three healthy male volunteers the hydroxylated metabolite of $\Delta^9$-THC, 11-OH-$\Delta^9$-THC [41]. This metabolite is also a $CB_1$ agonist, and it is said to be more potent than $\Delta^9$-THC [48]. Two out of the three participants described the effects as very intense and were rated as unpleasant; although half an hour post-injection the "high" took on a more pleasurable quality. At the end of the study, the "high" had been described as being greater in intensity than they had previously experienced from cannabis.

In another study [43], participants were slowly infused with i.v. 11-OH-$\Delta^9$-THC and told to ask for the termination of the drug as soon as they had reached the desired level of "high". The same procedure was used for $\Delta^9$-THC which required a significantly higher dose to produce the same "high".

With the exception of $\Delta^9$-THC, CBD is the cannabinoid that has been given intravenously most frequently. The receptor pharmacology of CBD has not yet been fully elucidated, but CBD has been shown to block some of the pharmacological effects of CB1 agonists [66]. CBD has been given i.v. in increasing doses to healthy participants. Neither 20mg [44], 30mg [45], nor 40mg [47] brought about any overt psychological changes in the participants tested, and no side effects were reported.

CBN is found to be a weak $CB_1R$ partial agonist, with roughly 10% the potency of $\Delta^9$-THC [66]. In one study [44], participants were slowly infused with increasing doses of CBN and were instructed to terminate the infusion when they reached the maximum tolerated "high". All participants who were given CBN tolerated it well and none asked to have the infusion stopped; they reported very mild and pleasant cannabis effects.

$\Delta^9$-THCV is a $CB_1R$ partial agonist which antagonises the receptor at low doses, but stimulates the receptor at higher doses[66]. The only study that explored i.v. $\Delta^9$-THCV in healthy volunteers found it produced mild to moderate $\Delta^9$-THC-effects for some, while others did not feel any change [48]. The authors concluded that 7mg of $\Delta^9$-THCV was approximately 25% as potent as $\Delta^9$-THC.

**Table 1. List of Intravenous Cannabinoid Studies with Cannabinoid Used, Dose, Duration of Infusion, and Outcome**

| Year | Author | Participants | Cannabinoid given | Dose | Duration of infusion | Psychotic symptoms | Cognitive impairment | Observations |
|---|---|---|---|---|---|---|---|---|
| 1970 | Lemberger *et al.* [39] | 3 healthy volunteers | Δ9-THC | 0.5mg | Not reported | Not reported | Not reported | N/A |
| 1972 | Lemberger *et al.* [40] | 12 long-term users | Δ9-THC | 0.5mg | Not reported | Not reported | Not reported | N/A |
| 1972 | Lemberger *et al.* [41] | 3 infrequent users | 11-OH-Δ9-THC | 1mg | Not reported | Not reported | Not reported | Participants reported greater "high" than they had experienced from smoking |
| 1972 | Hollister and Gillespie [42] | 4 healthy volunteers | Δ9-THC | 1-6mg | Not reported | Visual perception changes, mental confusion, "in-and-out" feeling. | Poor memory and difficulty concentrating (3mg and over) | Δ8-THC is slightly less potent than Δ9-THC |
| | | 3 healthy volunteers | Δ8-THC | 1-9mg | Not reported | Similar to Δ9-THC | Similar to Δ9-THC | |
| 1973 | Perez-Reyes *et* . [43] | 6 healthy volunteers | Δ9-THC | 3.10±0.9mg | 15-25 min | Not reported | Not reported | Δ9-THC produced a |
| | | 6 healthy volunteers | 11-OH-Δ9-THC | 2.27±0.8mg | 15-25 min | Not reported | Not reported | longer lasting and more intense 'high' than its metabolite |
| 1973 | Perez-Reyes *et* . [44] | 21 healthy volunteers | Δ9-THC | ~ 4mg | 15-25 min | Not reported | Not reported | Participants reported never have been so "high" from smoking cannabis after IV Δ9-THC |
| | | 6 healthy volunteers | CBN | ~ 20mg | 15-25 min | Not reported | Not reported | CBN produced a mild "high" at the higest dose. |
| | | 6 healthy volunteers | CBD | ~ 20mg | 15-25 min | Not reported | Not reported | CBD did not produce any psychological effect at any dose |
| 1973 | Hollister [45] | 4 healthy volunteers | CBD | 5-30mg | Not reported | Not reported | Not reported | CBD did not produce any psychological effect at any dose |
| 1974 | Perez-Reyes *et al.* [46] | 30 frequent and infrequent users | Δ9-THC | 53-68 μg/kg (3.71-4.76mg for 70kg) | 15-25 min | Not reported | Not reported | N/A |
| 1974 | Perez-Reyes and Wingfield [47] | One epileptic patient | CBD | 40mg | ~ 16 min | Not reported | Not reported | N/A |

**(Table 1) Contd....**

| Year | Author | Participants | Cannabinoid given | Dose | Duration of infusion | Psychotic symptoms | Cognitive impairment | Observations |
|---|---|---|---|---|---|---|---|---|
| 1974 | Hollister [48] | 6 healthy volunteers | Δ9-THCV | 7mg | Not reported | Not reported | Not reported | Mild to moderate side effects, similar to Δ9-THC reported |
| 1977 | Raft *et* . [49] | 10 healthy volunteers | Δ9-THC | 0.022-0.044 mg/kg (1.54-3.08mg for 70kg) | Not reported | Increased anxiety | Not reported | N/A |
| 1980 | Hunt and Jones [50] | 6 healthy volunteers | Δ9-THC | 2mg | 15 min | Not reported | Not reported | N/A |
| 1980 | Ohlsson *et* . [38] | 11 healthy volunteers | Δ9-THC | 5mg | 2 min | Not reported | Not reported | N/A |
| 1981 | Lindgren *et* . [34] | 18 light and heavy users | Δ9-THC | 5mg | 2 min | Not reported | Not reported | Light users were more intoxicated by IV Δ9-THC than heavy users |
| 1983 | Wall *et* . [51] | 12 healthy volunteers | Δ9-THC | 2.2-4mg | 15-25 min | Not reported | Not reported | N/A |
| 1991 | Volkow *et* . [52] | 8 occasional users | Δ9-THC | 2mg | Not reported | Anxiety and paraoia in 2 participants | Not reported | 3 out of 8 rated the experience as unpleasant |
| 2004 | Naef *et* . [53] | 8 cannabis naïve subjects | Δ9-THC | 0.053mg/KG (3.71mg for 70kg) | 2 min | Anxiety, hallucinations, perceptual change, strange ideas/mood | Not reported | No observed analgesic effect of Δ9-THC |
| 2004 | D'Souza *et* . [54] | 22 infrequent users | Δ9-THC | 2.5 and 5mg | 2 min | Paranoia, grandiose delusions, conceptual disorganisation, illusions, depersonalisation, slowing of time, blunted affect, emotional withdrawal, lack of spontaneity | Immediate, delayed recall and learning. Working memory for 'easy' task. | Verbal fluency and working memory for 'hard' task remained intact. |
| 2005 | D'Souza *et* . [55] | 13 stable (medicated) schizophrenic patients | Δ9-THC | 2.5 and 5mg | 2 min | Worsening in positive, negative, and general psychotic symptoms (PANSS). Increased perceptual alterations (CADSS). | Immediate/delayed recall, learning and vigilance | Worsening of anti-psychotic side effects |
| 2008 | D'Souza *et* . [56] | 30 frequent users | Δ9-THC | 2.5 and 5mg | 2 min | Perceptual alterations and psychotomimetic effects. | Immediate, delayed recall and learning. | Although Δ9-THC produced psychotic symptoms and cognitive impairments, this was significantly less compared to controls |

**(Table 1) Contd....**

| Year | Author | Participants | Cannabinoid given | Dose | Duration of infusion | Psychotic symptoms | Cognitive impairment | Observations |
|---|---|---|---|---|---|---|---|---|
| 2008 | D'Souza *et* . [57] | 28 frequent and infrequent users | Δ9-THC (Haoperidol pretreatment) | 0.0286mg/kg (2mg for 70kg) | 20 min | Perceptual alterations and psychotomimetic effects. | Immediate, delayed recall and learning. | Pretreatment with Haloperidol worsened cognitive performance under Δ9-THC condition |
| 2009 | Zuurman *et* . [58] | 21 infrequent users | Org 28611 (potent CB1 agonist) | 0.3-10μg/kg (0.021-0.7mg for 70kg) | 1 or 25 min (bolus or slow infusion) | Delusional perception, derealisation, confusional state, hallucinations | Attention | No adverese effects were experienced from bolus dose of 3μg/kg and less |
| 2009 | Morrison *et* . [59] | 22 healthy volunteers | Δ9-THC | 2.5mg | 5 min | Positive symptoms (PANSS, CAPE), anxiety | Working memory, executive function | Psychotic symptoms were not related to levels of cognitive impairment or anxiety |
| 2010 | Bhattacharyya *et* . [60] | 6 healthy volunteers | Δ9-THC, with CBD or placebo pretreatment | 1.25mg (Δ9-THC) 5mg (CBD) | 5 min 5 min | Positive symptoms (PANSS) | Not reported | Pretreatment with CBD protected against psychotomimetic effects of Δ9-THC |
| 2010 | Barkus *et* . [61] | 10 healthy volunteers | Δ9-THC | 2.5mg | 5 min | Positive and general symptoms (PANSS) | Not reported | No significant dopamine release in the striatum following Δ9-THC |
| 2010 | Stone *et* . [62] | 16 healthy volunteers | Δ9-THC | 1.25mg | Not reported | Not reported | Subjective impairments to attention and concentration | Impaired time perception and estimation |
| 2010 | Morrison *et* . [63] | 16 healthy volunteers | Δ9-THC | 1.25mg | 5 min | Positive, negative and general symptoms (PANSS) | Reduced accuracy on the hardest working memory task | Neural synchronicity (Theta-coherence) associated with psychotic symptoms |
| 2011 | Stone *et* . [64] | 16 healthy volunteers | Δ9-THC | 1.25mg | 5 min | Paranoid ideations, anxiety, salience, identity disturbance, perceptual abnormalities | Not reported | Neural synchronicity (Inter-trial-coherence) associated with salience and identity disturbance |
| 2011 | Morrison *et* [65] | 22 healthy volunteers | Δ9-THC | 2.5mg | 5 min | Negatice psychotic symptoms (PANSS, CAPE-state) | Not reported | Negative symptoms were not associated with sedation |

Org 28611 is a synthetically derived, potent, $CB_1R$ agonist [73]. Zuurman and colleagues [58] investigated Org 28611 for its potential sedative properties, and administered it i.v. to 21 infrequent cannabis users. They explored doses ranging from 0.3-10μg/kg (0,021-0,7mg for a 70kg individual) in either a slow 25 minute infusion, or a bolus infusion of 1 minute. Due to the adverse effects for the higher doses, 6-10μg/kg given as a slow infusion, these doses were not tested using bolus infusion. Participants reported symptoms such as delusional perception, derealisation, confusion, and hallucinations. The highest dose that was administered via bolus infusion was 3μg/kg (0,21mg for a 70kg individual), and was well tolerated by all participants.

## DOSES AND PHARMACOKINETICS

Recreational cannabis use can be defined as self-titration of cannabis until desired level of intoxication has been reached. However, this level may easily be exceeded for reasons such as peer-pressure, alcohol use, and varying $\Delta^9$-THC content of the cannabis used.

In one of the first i.v. $\Delta^9$-THC studies [44], participants were given $\Delta^9$-THC over 25min and asked to first mention when they felt when they had reached the desired level of "high" and then encouraged to receive the largest amount they could tolerate. The dose required for the desired level of "high" ranged between 11.26μg/kg to 26.28μg/kg (0.79mg to 1.84mg for a 70kg individual), while the maximum tolerated was between 36.98μg/kg to 69.3μg/kg (2.59mg to 4.85mg for a 70kg individual). After receiving the maximum tolerated dose, participants invariably reported never have been so "high" previously from cannabis. The more recent i.v. $\Delta^9$-THC studies have used doses of 1.25mg, 2.5mg, and 5mg [54, 63]. These doses have been found to be psychotomimetic, anxiogenic, dysphoric and cognitively impairing. It may therefore be possible that doses which are considered by participants to be the strongest they have experienced reflect an over-intoxication, which in turn results in such symptoms.

Plasma concentrations of $\Delta^9$-THC following i.v. administration are characterised by a steep increase in concentration followed by a rapid fall due to redistribution (Fig. **1**). Studies exploring the pharmacokinetics of different routes of administration have found i.v. and smoked routed to be very similar, both in terms of plasma concentrations as well as onset and offset of psychological effects [34, 38].

Table **2** provides a list of studies exploring plasma levels after inhaled and i.v. $\Delta^9$-THC. The inhalation studies included in Table **2** were chosen as the amount of $\Delta^9$-THC smoked was known, and participants either stopped when desired level of "high" was achieved [34, 38] or no increase in anxiety was reported [53, 74].

In a study by Lindgren and colleagues [34], heavy and light users were asked to smoke a cigarette containing 19mg $\Delta^9$-THC and stop when they reached their desired level of "high". On a later occasion they were given an i.v. dose of 5mg $\Delta^9$-THC. The following analysis of the plasma levels found $\Delta^9$-THC concentrations to be approximately 67-98 ng/ml 3 minutes after smoking, and 288-302 ng/ml 3 minutes after i.v. injection. Subjective rating of "high" was significantly greater for the i.v. dose compared to when participants chose their own level of intoxication by smoking.

A more recent study gave participants half the above mentioned dose (2.5 mg) of i.v. $\Delta^9$-THC. The participants had a mean (SD) plasma level of 68.0 (14.1) ng/ml 5 minutes after the injection; accompanied by psychotic symptoms, increased anxiety and dysphoria [59].

In contrast, Brenneisen and colleagues [74] asked participants to smoke a cannabis cigarette containing 70mg $\Delta^9$-THC, 25mg of which was estimated to have been inhaled. Mean plasma (SD) $\Delta^9$-THC 5 minutes post inhalation was 20.9 (16.9) ng/ml. No psychotic symptoms, anxiety or dysphoria were reported by the authors.

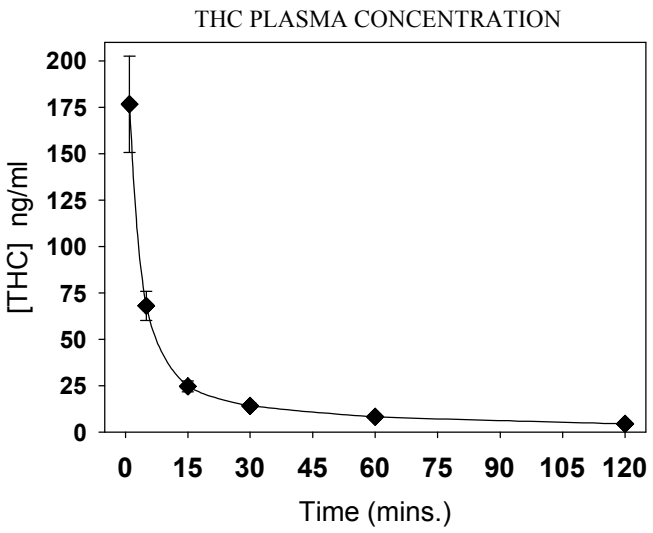


**Fig. (1).** Mean plasma concentrations following the intravenous administration of $\Delta^9$-THC (2.5mg). Error bars show ± 95% CI [59].

Although results of plasma $\Delta^9$-THC levels post administration are highly variable, due to factors such as drug preparation, time of sampling, type of assay used, etc., conclusions regarding the dose may still be drawn. In spite of some studies reporting plasma levels after i.v. $\Delta^9$-THC being similar to inhaled $\Delta^9$-THC, it is a relatively consistent finding that i.v. plasma levels are 2-3 times that of inhaled $\Delta^9$-THC. This is especially true if participants self-titrate until they have reach their desired level of "high" [34, 38], or in studies where unpleasant reactions such as anxiety or dysphoria are not reported [74].

## INDIVIDUAL DIFFERENCES

As expected, there is wide variation and individual reactions to i.v. $\Delta^9$-THC. This is illustrated by i.v. studies administering high doses of $\Delta^9$-THC to healthy volunteers, and observing psychotic symptoms, anxiety, and dysphoria. Volkow and colleagues [53] administered a 2mg i.v. dose of $\Delta^9$-THC to 8 healthy volunteers, of whom two became anxious and one became paranoid.

In a study by Morrison and colleagues [60], 50% of their participants experience increased positive psychotic symptoms following a 2.5mg i.v. $\Delta^9$-THC dose. D'Souza and colleagues [56] administered 2.5 mg and 5mg i.v. $\Delta^9$-THC to both healthy volunteers and clinically stable schizophrenic patients. They observed 35% of the controls and 80% of patients displayed psychotic symptoms following 2.5 mg, while 50% of controls and 75% of patients did so after 5mg. Jointly, these observations suggest that about 35-50% of the psychiatrically healthy general population are susceptible to psychotomimetic effects and anxiety experienced from high doses of $\Delta^9$-THC. Conversely, this means about half the general population are in some way resilient towards these effects. One possible hypothesis to this may be that these individuals have a naturally higher level of endocannabinoid activity.

## CONCLUSION

There has been four decades of intravenous cannabinoid studies. Researchers have been able to investigate the actions of individual cannabinoid molecules, as opposed to smoked cannabis where the concentrations of a range of other components may be unknown. Intravenous administration also circumvents the problem of inter-individual variation in bioavailability. Most i.v. studies have focussed on $\Delta^9$-THC. However there remains a need for more detailed information on i.v. $\Delta^9$-THC dose-response relationships,

**Table 2. List of studies reporting plasma $\Delta^9$-THC levels using various routes of administration**

| Study | Route of administration | Dose | Mean plasma level ng/ml (SD) [Range] | Time of sample (post administration) |
|---|---|---|---|---|
| Ohlsson et al. [38] | i.v. | 5mg | 219 [161 - 316] | 3 min |
| | | | 62 | 10 min |
| | inhaled | 13mg (range: 11.6-15.6) | 77 [33 - 118] | 3 min |
| Lindgren et al. [34] | inhaled | | | |
| | heavy users | 12.7±1.3 mg | 98 (44) | 3 min |
| | | | 64 (36) | 6 min |
| | light users | 13.4±1.6 mg | 67 (38) | 3 min |
| | | | 46 (23) | 6 min |
| | i.v. | | | |
| | heavy users | 5mg | 288 (119) | 3 min |
| | | | 128 (48) | 6 min |
| | light users | 5mg | 302 (95) | 3 min |
| | | | 148 (42) | 6 min |
| Volkow et al. [52] | i.v. | 2mg | 17 (12) | 20 min |
| Naef et al. [53] | inhaled | 0.053mg/kg | 18.7 (7.4) | 10 min |
| | i.v. | 0.053mg/kg | 271.5 (61.1) | 5 min |
| Morrison et al. [59] | i.v. | 2.5mg | 68.0 (14.1) | 5min |
| Barkus et al. [61] | i.v. | 2.5mg | ~60 (~5) | 5 min |
| Brenneisen et al. [74] | inhaled | 25mg | 20.9 (16.9) | 5min |

especially for the lower dose range. There has also been a re-awakening of interest in other plant-derived cannabinoids, many of which were given by the i.v. route in the 1970s. In the intervening years it has become clear that the other cannabinoids also have a receptor pharmacology and central effects (albeit, more subtle than $\Delta^9$-THC). Future work will hopefully shed light on the central properties of the other cannabinoids, as well as explaining individual differences to these compounds; taking advantage of the i.v. route.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

## ACKNOWLEDGEMENT

None declared.

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**Received: March 30, 2012** **Accepted: April 9, 2012**