

Assessment of dronabinol and its stereo-isomers^{1,2}

1. Substance Identification

- A. International Nonproprietary Name (INN): dronabinol³
- B. Chemical Abstract Service (CAS) Registry Number: 1972-08-3
- C. Other Names: Δ^9 -tetrahydrocannabinol; Δ^9 -THC; *delta-9*-THC⁴; THC⁵
- D. Trade Names: Marinol®; Elevat®
- E. Identification Characteristics: Dronabinol is an optically active resinous substance, insoluble in water and extremely lipid soluble.
- F. WHO Review History: Dronabinol was included in Schedule I of the 1971 Convention on Psychotropic Substances at the time of its adoption as *Delta-9*-tetrahydrocannabinol together with several other isomers of tetrahydrocannabinol⁶. At its 26th meeting, ECDD recommended that dronabinol, which is the (-)-*trans* isomer of *delta-9*-tetrahydrocannabinol, be moved to Schedule II, while keeping the other stereoisomer in Schedule I. This proposal was rejected by the Commission on Narcotic Drugs and ECDD reviewed the question again at its 27th meeting in 1990, which recommended that all the stereochemical variants of *delta-9*-tetrahydrocannabinol be rescheduled to Schedule II. This recommendation was adopted by CND.

At the 32nd meeting, ECDD pre-reviewed dronabinol and recommended its critical review on the grounds that the rate of abuse of dronabinol was extremely low.

Dronabinol was critically reviewed by the 33rd ECDD in September 2002. On the basis of the available data the Committee considered that dronabinol should be rescheduled to Schedule IV of the 1971 Convention. However, the procedure was not finished and the Committee's advice was not sent to the CND at that time. For this reason the existing critical review report is updated, including the numerous new scientific publications of the last few years, in order to enable the ECDD to finalize the process of critical review.

¹ This title refers to the substances included by the description "delta-9-tetrahydrocannabinol and its stereochemical variants", as scheduled at present in Schedule II of the 1971 Convention. However, the International Nonproprietary Name (INN) should be used, as it is the preferred name.

² It should be remarked that "delta-9-tetrahydrocannabinol and its stereochemical variants" defines the same substances as "dronabinol and its stereo-isomers", but the latter description should be preferred for scientific reasons as well as for reasons of nomenclature.

³ Dronabinol refers to the (-)-*trans*-stereo-isomer.

⁴ delta-9-tetrahydrocannabinol refers to the four stereo-isomers described under 2.c.

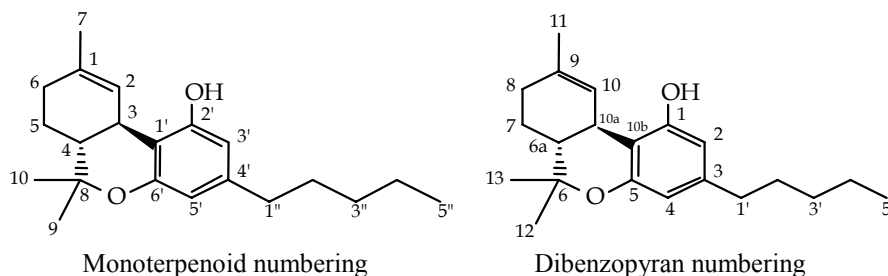
⁵ THC or tetrahydrocannabinol refers to the constitutional isomers and the stereo-isomers as well, and hence, is a wider definition than currently under review (see also footnote 5)

⁶ Today the other constitutional isomers are still in Schedule I

2. Chemistry

- A. Chemical Name: (6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol

B. Chemical Structure:



Chemical Formula: C₂₁H₃₀O₂

Molecular Weight: 314.5

C. Stereoisomers:

(-)-*trans*- Δ^9 -tetrahydrocannabinol and (+)-*trans*- Δ^9 -tetrahydrocannabinol,
 (-)-*cis*- Δ^9 -tetrahydrocannabinol and (+)-*cis*- Δ^9 -tetrahydrocannabinol

3. General Pharmacology

The primary psychoactive compound in botanical cannabis (*Cannabis sativa* L.) is dronabinol ((-)-*trans*- Δ^9 -tetrahydrocannabinol, Δ^9 -THC) (Gaoni and Mechoulam, 1964; ElSohly, 2002). Other cannabinoids present in the cannabis plant modulate the pharmacological effects of dronabinol.

Based on an alternate monoterpenoid numbering system, Δ^9 -THC is also known as Δ^1 -THC (see: chemical structure above). The pharmacological activity of Δ^9 -THC is stereospecific; the (-)-*trans* isomer (dronabinol) is 6-100 times more potent than the (+)-*trans* isomer depending on the assay (Dewey *et al.*, 1984). Preparations of dronabinol can be administered by mouth (oral, sublingual or buccal), as rectal suppositories, pulmonary (smoked, inhaled with a vaporizer, aerosolized or nebulized), intravenously, topically (ophthalmic application), or with transdermal delivery systems (Grotenhermen, 2004).

Receptor binding: To date two cannabinoid receptors have been identified, the CB₁ (cloned in 1990) (Matsuda *et al.*, 1990), and the CB₂ receptor (cloned in 1993) (Munro *et al.*, 1993), exhibiting 48% amino acid sequence identity. Besides their difference in amino acid sequence,

they differ in signaling mechanisms, tissue distribution, and sensitivity to certain agonists and antagonists that may show marked selectivity for one or the other receptor type (Howlett, 2002).

Activation of the CB₁ receptor produces effects on circulation and psychotropic effects common to cannabis ingestion, while activation of the CB₂ receptor does not. Dronabinol displays similar affinity for CB₁ and CB₂ receptors but behaves as a weak agonist for CB₂ receptors.

CB₁ receptors are mainly found on neurons in the brain, spinal cord and peripheral nervous system, but are also present in many peripheral organs and tissues (Pertwee, 1997). In the central nervous system the CB₁ receptor is the most abundant G-protein coupled receptor. CB₁ receptors are highly expressed in the cerebral cortex, basal ganglia (substantia nigra pars reticulata, globus pallidus, nucleus caudatus and putamen) cerebellum, hippocampus, periaqueductal grey, rostral ventromedial medulla, certain nuclei of the thalamus and amygdala, and dorsal primary afferent spinal cord regions, which reflect the importance of the cannabinoid system in motor control, memory processing and pain modulation.

CB₂ receptors occur principally in immune cells, among them leukocytes, spleen and tonsils (Pertwee, 2002). Immune cells also express both CB receptors but there is markedly more mRNA for CB₂ than CB₁ receptors in the immune system. One of the functions of CB receptors in the immune system is modulation of cytokine release.

Stimulation of both types of cannabinoid receptors by dronabinol activates a number of signal transduction pathways (Pertwee, 1997; Pertwee, 2002). Both are coupled through inhibiting G-proteins (G_{i/o} proteins), negatively to adenylate cyclase and positively to mitogen-activated protein kinase. Inhibition of adenylate cyclase results in the inhibition of the conversion of ATP to cyclic AMP (cAMP). CB₁ but not CB₂ receptors are also coupled to several ion channels through G_{i/o} proteins, negatively to N-type and P/Q-type calcium channels and D-type potassium channels, positively to A-type and inwardly rectifying potassium channels. CB₁ receptors may also mobilize arachidonic acid, close 5-HT₃ receptors ion channels, modulate nitric oxide production and mobilize arachidonic acid and intracellular calcium stores (Pertwee, 2004). CB₁ receptor activation can also initiate ceramide production through a non-G protein mediated mechanism, and under certain conditions CB₁ receptors may also activate adenylate cyclase and/or reduce outward potassium current through stimulating G proteins (G_s proteins) (Pertwee, 2004).

In vitro experiments have demonstrated that CB₁ receptors can mediate inhibition of the neuronal release of a multitude of neurotransmitters and neuromodulators, including acetylcholine, dopamine, gamma-aminobutyric acid (GABA), histamine, serotonin (5-hydroxytryptamine), glutamate, cholecystokinin, D-aspartate, glycine and noradrenaline (norepinephrine) in several brain regions and outside the brain. Inhibition of neurotransmitters by CB₁ receptor activation in the central nervous system is caused by presynaptic inhibition of neurotransmitter release from axon terminals (Pfitzer, 2005). In some experiments CB₁ receptor agonists have been reported not to inhibit but to enhance the release of certain neurotransmitters. However, it is possible that these effects also result from a CB receptor-mediated inhibitory effect on neurotransmitter release resulting in a stimulatory effect on neurotransmitter release at some point downstream of the side of the initial inhibitory effect (Pertwee, 2004).

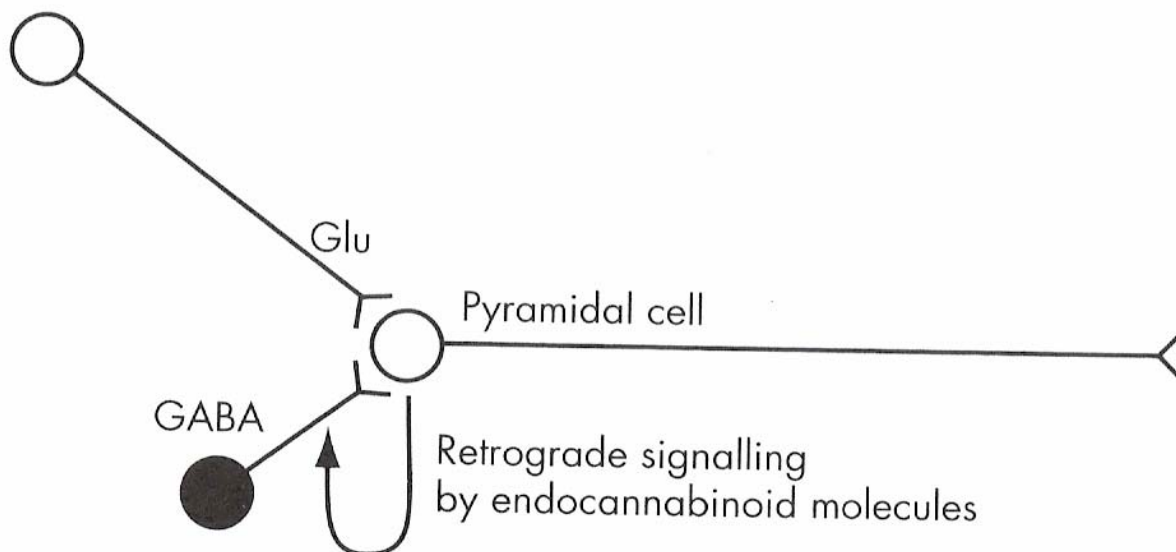


Figure 1: Schematic diagram illustrating endocannabinoid mediated feedback inhibition in the hippocampus (from: Pertwee, R. In : Guy GW, Whittle B, Robson P, eds. *The Medicinal Uses of Cannabis and Cannabinoids.*)

Interaction of dronabinol effects with other neurotransmitters is supported by the fact that antagonists of these neurotransmitters blocked specific dronabinol effects. The memory disruptive effects of dronabinol were completely reversed by the GABA antagonist bicuculline, while other dronabinol effects were unaffected (Varvel *et al.*, 2005). Opioid receptor antagonists blocked several behavioral effects of CB₁ agonists (Braida *et al.*, 2001a; Tanda *et al.*, 1997). A number of pharmacological effects can be explained (at least in part) on the basis of interactions with other neurotransmitters. Cross-talks between the CB₁ receptor and other receptors in the brain has been reported for the dopamine-2 receptor (D₂ receptor) (Kearn *et al.*, 2005), the corticotropin releasing hormone receptor type 1 (CRHR₁) (Hermann and Lutz, 2005) and for the μ -opioid receptor (Salio *et al.*, 2001).

Some non-cannabinoid receptor mediated effects of dronabinol have also been described, e.g. some effects on the immune system (Bueb *et al.*, 2001) and some neuroprotective effects (Hampson, 2002). There is increasing evidence for the existence of additional cannabinoid receptor subtypes in the brain and periphery (Di Marzo *et al.*, 2000b; Fride *et al.*, 2003; Wiley and Martin, 2002). It is possible that several effects previously thought to be non-receptor mediated are mediated by cannabinoid receptor subtypes that have not yet been identified.

The identification of cannabinoid receptors was followed by the detection of endogenous ligands for these receptors, which are called endogenous cannabinoids or endocannabinoids (Devane *et al.*, 1992; Giuffrida *et al.*, 2001; Sugiura *et al.* 1995). All endocannabinoids are derivatives of arachidonic acid, thus differing in chemical structure from phytocannabinoids of the cannabis plant. To date five endocannabinoids have been identified. These are *N*-arachidonoyl

ethanolamide (AEA, anandamide) (Devane *et al.*, 1992), 2-arachidonoyl glycerol (2-AG) (Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995), 2-arachidonoyl glyceryl ether (noladin ether) (Hanus *et al.*, 2001), *O*-arachidonoyl ethanolamine (virodhamine) (Porter *et al.*, 2002), and *N*-arachidonoyl-dopamine (NADA) (Huang *et al.*, 2002).

The first two discovered endocannabinoids, anandamide and 2-AG, are best studied. They are synthesized in neuronal cells, including cortical and striatal neurons, but not astrocytes, and their synthesis is increased in response to membrane depolarization. Specific membrane depolarization-induced release is characteristic of classical neurotransmitters. However, in contrast to classical neurotransmitters that are being synthesized and stored in intraneural vesicles, endocannabinoids are produced “on demand” by cleavage of membrane lipid precursors and released immediately from cells into the synapse in a stimulus-dependent manner (Giuffrida *et al.*, 2001). After release, endocannabinoids are rapidly deactivated by uptake into cells and metabolized. Metabolism of anandamide and 2-AG occurs by enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (Di Marzo, 1998, Giuffrida *et al.*, 2001).

In addition to phytocannabinoids of the cannabis plant a vast number of exogenous modulators of the endocannabinoid system have been synthesized. They comprise cannabinoid receptor agonists, CB receptor antagonists and inhibitors of degradation and re-uptake of endocannabinoids that promote accumulation of endocannabinoids *in situ*. Antagonists allowed a detailed investigation of mechanisms of cannabinoid actions. Both antagonists and agonists are under clinical investigation for a broad number of indications.

In conclusion, progress in cannabinoid pharmacology, including the characterization of the cannabinoid receptors, isolation of endogenous cannabinoid ligands, synthesis of agonists and antagonists with diverse degree of affinity and selectivity for cannabinoid receptors, have provided the foundation for the elucidation of the specific effects mediated by cannabinoids and their roles in memory, cognitive functions, stress and anxiety disorders, movement disorders, neuroprotection, analgesia, appetite control, gastrointestinal motility, antiemesis, antineoplastic activity, hormonal processes, fertility, intraocular and systemic blood pressure modulation, broncodilation, and inflammation.

Animal Studies:

Dronabinol in general produces a reduction in spontaneous locomotor activity, hypothermia, catalepsy in mice, dog ataxia and unique effects on the behaviour of a wide variety of animal species (Martin *et al.*, 1984; Compton *et al.*, 1991). These effects are characterized at low doses as depressant and stimulatory effects, and at higher doses as predominantly central nervous system depression. In mice the mixture of depressant and stimulatory effects causes the so-called "pop corn" effect: A group of mice remains in a sedated state until a stimulus causes one of them to jump (hyperreflexia). This mouse then falls on another, causing that one to jump as well. This process continues until all the mice are sedated again, when a later phase of hyperreflexive jumping may be initiated.

In rhesus monkeys at low doses (0.05 mg/kg, i.v.), dronabinol causes tranquility, drowsiness,

decreased motor activity, occasional partial ptosis, occasional head drop; at higher doses (0.1-0.25 mg/kg) the drug causes stupor, ataxia, suppression of motor activity, full ptosis, typical crouched posture (thinker position) kept for up to 3 h. At doses above 0.5 mg/kg, dronabinol causes severe stupor and ataxia, full ptosis, immobility, crouched posture lasting for more than 3 h, and absence of reaction to external stimuli. In general, a compound is not considered to be cannabimimetic if at 5 mg/kg i.v., it fails to induce the above characteristic syndromes (Martin *et al.*, 1981).

Studies in Humans:

Much available data in humans is not available for pure dronabinol but for whole cannabis plant preparations. Dronabinol is present with concentrations in a range between 2 and 30% in the flowering tops and upper leaves of the female cannabis plant. Given alone dronabinol produced similar psychological and physiologic effects as whole plant drug cannabis in healthy volunteers (Hart *et al.*, 2002, Wachtel *et al.*, 2002) and patients (Abrams *et al.*, 2003, Zajicek *et al.*, 2003). The dronabinol main effects including medicinal properties may be modulated by other cannabinoids, mainly CBD, and other cannabis constituents (Russo and McPartland, 2003).

Psychological effects: The use of cannabis is usually described as a pleasant and relaxing experience. Occasionally there are unpleasant feelings such as anxiety that may escalate to panic. A sense of enhanced well-being may alternate with dysphoric phases. Acute dronabinol intoxication impairs learning and memory (Hampson and Deadwyler, 1999; Heyser *et al.*, 1993; Slikker *et al.*, 1992), and adversely affects psychomotor and cognitive performance (Solowij and Grenyer, 2002).

The most conspicuous psychological effects of dronabinol in humans can be divided into four groups: affective (euphoria and easy laughter), sensory (increased perception of external stimuli and of the person's own body), somatic (feeling of the body floating or sinking in the bed), and cognitive (distortion of time perception, memory lapses, difficulty in concentration) (Perez-Reyes, 1999). The quality of these psychological effects in healthy individuals did not differ according to the route of application (oral, inhalative, intravenous). Many physical effects are achieved below the threshold of psychological effects.

Hollister *et al.* (1968) reported that the clinical effects of dronabinol administered orally resembled those of other psychotomimetics e.g. LSD, but high doses are needed. Dronabinol differed from LSD in the following respects: sedation was prominent, euphoria was longer lasting, and dreamlike sequences were more pronounced. Sedative effects became evident early and grew with passage of time. After several hours, when testing procedures became less frequent, subjects spent most of their time sleeping. Although euphoria and uncontrollable laughter are frequently encountered early in the course of LSD intoxication, dronabinol's effect was usually brief and transient. Chait and Zacny (1992) compared the subjective effects of oral dronabinol (2.5, 5.0, or 10 mg) and smoked cannabis (pre-rolled cannabis cigarettes containing 0.0%, 2.3%, or 3.6% dronabinol) in two groups of regular cannabis users. The subjective effects elicited by smoked cannabis and oral dronabinol were qualitatively and quantitatively similar. On the Addiction Research Center Inventory (ARCI) scales, oral dronabinol produced significant

increases in the LSD (dysphoria), stimulant (A) and marijuana (M) scales. Similar increases were observed with smoked cannabis. Several participants did not experience psychological effects following oral dronabinol at these doses.

Psychological and psychomotor effects only appear if an individually variable threshold of dose is exceeded. During a study on the efficacy of dronabinol in 24 patients with Tourette's syndrome who received up to 10 mg dronabinol daily for 6 weeks no detrimental effects were seen on neuropsychological performance (learning, recall of word lists, visual memory, divided attention) (Müller-Vahl *et al.*, 2003).

Physiologic effects: Physiologic effects from dronabinol are quite different from those observed with other psychotomimetics. Pulse rate tends to rise, reduction of saliva production causes dry mouth, strength is impaired, and vasodilation in the eye results in reddening of the conjunctivae (Dewey, 1986). Sympathomimetic effects such as pupillary dilation or increased deep reflexes are absent. The iris constriction response of the eye is slowed (Kelly *et al.*, 1993). Dronabinol decreases intraocular pressure and causes bronchodilatation.

Cardiovascular and autonomic effects: Dronabinol can induce tachycardia (Perez-Reyes, 1999) and increase cardiac output with increased cardiac labor and oxygen demand (Tashkin *et al.*, 1977). It can also produce peripheral vasodilatation and orthostatic hypotension (Benowitz and Jones, 1975; Hollister, 1986). Data on cerebral blood flow effects are contradictory. Regional increases and decreases of blood flow with no mean change of flow were reported by one group (O'Leary *et al.*, 2002), while another report suggests that systolic velocity and the pulsatility index, a measure of cerebrovascular resistance, were significantly increased in cannabis users (Herning *et al.*, 2005). The latter effects on cerebral blood flow persisted in heavy users for more than one month of monitored abstinence and were regarded as a partial explanation for cognitive deficits in heavy cannabis users.

In young healthy subjects the heart is under control of the vagus that mediates bradycardia. Tachycardia by dronabinol may easily be explained by vagal inhibition (inhibited release of acetylcholine) through presynaptic CB₁ receptors (Szabo *et al.*, 2001), which can be attenuated by beta-blockers (Perez-Reyes, 1999) and blocked by the selective CB₁ antagonist SR141716A (Huestis *et al.*, 2001). Regular use can lead to bradycardia (Benowitz and Jones, 1975). Hypotension is mediated by central inhibition of the sympathetic nervous system, apparently by activation of CB₁ receptors since this effect can also be prevented by a CB₁ antagonist (Lake *et al.*, 1997). Vascular resistance in the coronaries and the brain is lowered primarily by direct activation of vascular cannabinoid CB₁ receptors (Wagner *et al.*, 2001).

Effects on the endocrine system and fertility: Dronabinol interacts with the hypothalamic-pituitary adrenal axis influencing numerous hormonal processes (Murphy, 2002). Minor changes in human hormone levels due to acute cannabis or dronabinol ingestion usually remain in the normal range (Hollister, 1986). Tolerance develops to these effects, however, and even regular cannabis users demonstrate normal hormone levels. Reductions in male fertility by cannabis are reversible and only seen in animals at concentrations higher than those found in chronic cannabis users. After several weeks of daily smoking 8-10 cannabis cigarettes a slight decrease in sperm count was observed in humans, without impairment of their function (Hembree *et al.*, 1978). In

animal studies high doses of cannabinoids inhibited the acrosome reaction (Chang *et al.*, 1993).

There are no conclusive indices to any dronabinol-associated influences on the menstrual cycle length, the number of cycles without ovulation or on the plasma concentrations of estrogens, progesterone, testosterone, prolactin, LH or FSH in female cannabis users (Mendelson *et al.*, 1984, Block *et al.*, 1991, Mendelson *et al.*, 1986). A transient dronabinol-induced suppression of prolactin and LH levels was observed if the drug was inhaled during the luteal phase of the menstrual cycle (Mendelson *et al.*, 1985).

Effects on the immune system: Animal and cell experiments have demonstrated that dronabinol exerts complex effects on cellular and humoral immunity (Cabral, 2002; Melamede, 2002). Dronabinol was shown to modulate the immune response of T lymphocytes (Yuan *et al.*, 2002). It suppressed the proliferation of T cells and changed the balance of T helper 1 (Th₁) and T helper 2 (Th₂) cytokines. It decreased the pro-inflammatory Th₁ reaction (e.g. the production of interferon-gamma) and increased the Th₂ reaction. This may explain why dronabinol is effective against inflammation with a strong Th₁ reaction, e.g. in multiple sclerosis, Crohn's disease and arthritis. The regulation of the activation and balance of human Th₁/Th₂ cells seems to be mediated by a CB₂ receptor-dependent pathway (Yuan *et al.*, 2002).

In a three week clinical study the effects of cannabis cigarettes and oral dronabinol (3x2.5 mg daily) were investigated on immunological functioning in 62 AIDS patients who were taking protease inhibitors (Abrams *et al.*, 2003). There were no changes in HIV RNA levels compared to placebo, demonstrating no short-term adverse virologic effects from using cannabinoids. Neither CD4+ nor CD8+ cell counts were adversely affected by dronabinol or cannabis.

Medicinal uses: Dronabinol has been employed in the treatment of numerous diseases (Grotenhermen, 2005). It is approved in several countries for the medical use in refractory nausea and vomiting caused by antineoplastic drugs used for the treatment of cancer (for review see: Plasse, 2002) and for appetite loss in anorexia and cachexia of HIV/AIDS patients (Beal *et al.*, 1995, 1997, Plasse *et al.*, 1991). In a clinical setting 5-HT₃ antagonists are usually superior to dronabinol, but the cannabinoid has proven to be effective at least in some cases of intractable nausea and vomiting (Gonzalez-Rosales and Walsh, 1997, Zutt *et al.*, 2006). Animal research demonstrated that dronabinol reinforces the anti-emetic effects of ondansetron in vomiting produced by cisplatin (Kwiatkowska *et al.*, 2004), suggesting that a combination of both drugs may be meaningful in clinical practice. Dronabinol was also effective in cancer cachexia (Jatoi *et al.*, 2002).

Dronabinol was shown to reduce central pain in patients suffering from multiple sclerosis (Svendsen *et al.*, 2004). Analgesic effects were also obtained with a cannabis extract rich in dronabinol in central pain of MS patients (Rog *et al.*, 2005), in central neuropathic pain from brachial plexus avulsion (Berman *et al.*, 2004), and in pain due to rheumatoid arthritis (Blake *et al.*, 2006). A recent review by scientists of the Mayo Clinic concluded that cannabinoids provide a potential approach to pain management with a novel therapeutic target and mechanism (Burns and Ineck, 2006).

Dronabinol was recently shown to improve spasticity of MS patients according to the Ashworth Scale in a 52-week large-scale study (Zajicek *et al.*, 2005). Further suggested medicinal uses

include Tourette's syndrome (Müller-Vahl *et al.*, 2003), agitation in patients with Alzheimer's disease (Volicer *et al.*, 1997), glaucoma (Merritt *et al.*, 1981), and asthma (Tashkin *et al.*, 1974, Yoshihara *et al.*, 2004). The bronchodilator effects of 15 mg dronabinol approximately corresponded to those obtained with therapeutic doses of common bronchodilator drugs (salbutamol, isoprenaline).

4. Toxicology, including adverse reactions in humans

Adverse effects of the medical use of dronabinol are within the range of effects tolerated for other medications (House of Lords Select Committee on Science and Technology, 1998; Joy *et al.*, 1999). The median lethal dose (LD₅₀) of oral dronabinol in rats was 800-1900 mg/kg depending on sex and strain (Thompson *et al.*, 1973). There were no cases of death due to toxicity following the maximum oral dronabinol dose in dogs (up to 3000 mg/kg dronabinol) and monkeys (up to 9000 mg/kg dronabinol) (Thompson *et al.*, 1973). Acute fatal cases in humans have not been substantiated. Acute serious unwanted effects of dronabinol are mainly related to its effects on psyche and psychomotor performance as well to its effects on circulation.

Serious cardiovascular effects of smoked or oral cannabis have not been shown to produce any health problems in healthy and relatively young users. However, cannabis smoking by older patients, particularly those with some degree of coronary artery or cerebrovascular disease, is postulated to pose greater risks, because of the resulting increased cardiac work, increased catecholamines, and postural hypotension (Benowitz and Jones, 1981). Mittleman *et al.* (2001) studied 3882 patients with recent myocardial infarction, of whom 124 (3.2%) reported smoking cannabis in the prior year, 37 within 24 hours and 9 within 1 hour of myocardial infarction symptoms. The risk of myocardial infarction onset was elevated 4.8 times over baseline in the 60 minutes after cannabis use. Authors concluded that the use of cannabis is a rare trigger of acute myocardial infarction.

Impairment of psychomotor performance may decrease the ability to drive a car and to operate machinery, which may result in an increased risk to cause a traffic accident (Ramaekers *et al.*, 2004).

The mental effects of dronabinol can vary widely among individuals, the most serious acute unwanted effect being toxic psychosis, which is caused directly by high-dose intoxication with cannabis. Figures on this consequence of cannabis use vary. While Hall and Degenhardt (2000) concluded from their review of the literature that true cannabis psychosis must be very rare, others reported that a high percentage of cannabis users (15%) had at some time experienced psychotic symptoms after use (Thomas, 1996). The difference between these conclusions certainly rest on different definitions of acute toxic psychosis. Paranoia, panic attacks and dysphoria are rather common after the ingestion of high dronabinol doses, whereas delusions and hallucinations are rare even at high doses. Cannabis has been reported to precipitate schizophrenia (Zammit *et al.*, 2002), to adversely affect the clinical course of an existing schizophrenia (van Os *et al.*, 2002), and to increase the risk for depression and personality disorders (Patton, 2002). However, results from different studies are somewhat inconclusive (Kalant, 2004). A study with dizygotic and monozygotic twins suggests that the association

between cannabis use and depression may not be causal and that genetic vulnerabilities make substantial contributions since the association was higher in dizygotic than in identical twins (Lynskey *et al.*, 2004).

It is controversial whether heavy regular consumption may have a long-term negative impact on cognition (Pope *et al.*, 2001; Pope, 2002; Solowij *et al.*, 2002), but this impairment seems to be minimal if it exists (Lyketsos *et al.*, 1999; Pope *et al.*, 2001). Early users who started their use before the age of 17 presented with poorer cognitive performance, especially verbal IQ compared to users who started later or non-users (Pope *et al.*, 2003). In a twin study cannabis-using twins significantly differed from their non-using co-twins in general intelligence (Lyons *et al.*, 2004). However, this difference was minimal and authors concluded that these results indicate an absence of marked long-term residual effects of cannabis use on cognitive abilities.

Adverse drug events for dronabinol (Marinol®) observed in controlled clinical studies are presented in Table 1. These trials were conducted in AIDS and cancer patients. Studies of AIDS-related weight loss included 157 patients receiving dronabinol at a dose of 2.5 mg twice daily and 67 receiving placebo. Studies of different durations were combined by considering the first occurrence of events during the first 28 days. Studies of nausea and vomiting related to cancer chemotherapy included 317 patients receiving dronabinol and 68 receiving placebo. In the studies with cancer patients dronabinol dosages ranged from 2.5 mg/day to 40 mg/day, administered in equally divided doses every four to six hours (four times daily). Dosages above 7 mg/m² increased the frequency of adverse experiences, with no additional antiemetic benefit.

A dronabinol dose-related high (easy laughing, elation and heightened awareness) has been reported in both the antiemetic (24%) and the lower dose appetite stimulant clinical trials (8%). The most frequently reported side effects in patients with AIDS during placebo-controlled clinical trials involved the central nervous system (CNS) and were reported by 33% of patients receiving the drug. About 25% of patients reported a minor CNS-related adverse drug event during the first 2 weeks and about 4% reported such an event each week for the next 6 weeks thereafter.

The WHO Uppsala Monitoring Centre (UMC) reported of world wide PMS-data 2 cases of death, out of 279 reported adverse effects (0.7%). No adverse effects related to drug dependency were reported. (unpublished, communication to WHO, 2005).

Table 1. Summary of adverse reactions in clinical trials. (Source: Product information for Marinol®, Unimed Pharmaceuticals, Inc.)

Incidence greater than 1%. Rates derived from clinical trials in AIDS-related anorexia (N = 157) and chemotherapy-related nausea (N = 317). Rates were generally higher in the anti-emetic use (given in parentheses).
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<i>Body as a whole:</i> Asthenia.

<i>Cardiovascular:</i> Palpitations, tachycardia, vasodilation/ facial flush.

<i>Digestive:</i> Abdominal pain*, nausea*, vomiting*.
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<i>Nervous system:</i> (Amnesia), anxiety/nervousness, (ataxia), confusion, depersonalization, dizziness*,
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euphoria*, (hallucination), paranoid reaction*, somnolence*, thinking abnormal*. * Incidence of events 3% to 10%.
Incidence less than 1%. Event rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N = 317).
<i>Cardiovascular:</i> Conjunctivitis*, hypotension*. <i>Digestive:</i> Diarrhea*, fecal incontinence. <i>Musculoskeletal:</i> Myalgias. <i>Nervous system:</i> Depression, nightmares, speech difficulties, tinnitus. <i>Skin and Appendages:</i> Flushing*. <i>Special senses:</i> Vision difficulties. *Incidence of events 0.3% to 1%.
Incidence less than 1%. The clinical significance of the association of these events with Marinol® treatment is unknown, but they are reported as alerting information for the clinician.
<i>Body as a whole:</i> Chills, headache, malaise. <i>Digestive:</i> Anorexia, hepatic enzyme elevation. <i>Respiratory:</i> Cough, rhinitis, sinusitis. <i>Skin and Appendages:</i> Sweating.

5. Pharmacokinetics

Absorption, metabolism, and pharmacokinetic profile of dronabinol vary with route of administration and formulation (Adams and Martin, 1996; Agurell *et al.*, 1984, 1986; Grotenhermen, 2003). Dronabinol is commonly either taken orally as dronabinol capsules or inhaled by smoking a cannabis cigarette. Various other routes of administration and delivery forms have been tested for therapeutic purposes (Grotenhermen, 2004). Sublingual administration is used with dronabinol in a cannabis extract (Sativex®), which has a conditional marketing authorisation in Canada since 2005. The rectal route with suppositories has been applied in some patients (Brenneisen *et al.*, 1996), dermal administration (Stinchcomb *et al.*, 2004) is under investigation. Other methods include eye drops to decrease intraocular pressure (Merritt *et al.*, 1981), as well as aerosols and inhalation with vaporizers to avoid the harm associated with smoking (Lichtman *et al.*, 2000; Williams *et al.*, 1976).

On inhalation of the smoke of a cannabis cigarette, dronabinol is detectable in plasma only seconds after the first puff (Huestis *et al.*, 1992) with peak plasma concentrations being measured 3 to 10 min after onset of smoking (Huestis *et al.*, 1992; Ohlsson *et al.*, 1980; Perez-Reyes *et al.*, 1982). Systemic bioavailability generally ranges between about 10 and 35%, and regular users are more efficient (Lindgren *et al.*, 1981). Bioavailability varies according to depth of inhalation, puff duration and breathhold.

With oral use, absorption is slow and erratic, resulting in maximal plasma concentrations usually after 60-120 min (Ohlsson *et al.*, 1980; Timpone *et al.*, 1997). In several studies, maximal plasma levels were observed as late as 4 h (Law and Moffat, 1985) and even 6 hours in some cases (Ohlsson *et al.*, 1980; Sporkert *et al.*, 2001). Dronabinol is expected to be degraded by the acid of the stomach and in the gut (Garrett and Hunt, 1974). It has been suggested that a somewhat higher bioavailability is obtained in an oil formulation (Harvey, 1991). However, absorption seems to be nearly complete in different vehicles. 95% of total radioactivity of radiolabeled dronabinol was absorbed from the gastrointestinal tract in an oil vehicle (Wall *et al.*, 1983) and 90-95% if taken in a cherry syrup vehicle (Lemberger *et al.*, 1972), but it is unclear from these data how much of this radioactivity belongs to unchanged dronabinol and how much to breakdown products. An extensive first pass liver metabolism further reduces oral bioavailability of dronabinol, i.e. much of the dronabinol is initially metabolised in the liver before it reaches the sites of action. Ingestion of 20 mg dronabinol in a chocolate cookie (Ohlsson *et al.*, 1980) and administration of 10 mg dronabinol (Sporkert *et al.*, 2001) resulted in a very low systemic bioavailability of $6 \pm 3\%$ (range: 4-12%) (Ohlsson *et al.*, 1980) or $7 \pm 3\%$ (range: 2-14%) (Sporkert *et al.*, 2001), respectively, with a high interindividual variation. The pharmacokinetics following sublingual administration is much similar to that with oral administration. Dronabinol plasma concentrations of up to 14 ng/ml were noted after sublingual use (Notcutt *et al.*, 2002).

Tissue distribution of dronabinol and its metabolites is assumed to be governed only by their physicochemical properties with no specific transport processes or barriers affecting the concentration of the drug in the tissues (Leuschner *et al.*, 1986). About 90% of dronabinol in the blood is distributed to the plasma, another 10% to red blood cells (Widman *et al.*, 1974). 95-99% of plasma dronabinol is bound to plasma proteins, mainly to lipoproteins and less to albumin (Fehr and Kalant, 1974; Widman *et al.*, 1974).

The apparent (initial) volume of distribution of dronabinol is small for a lipophilic drug, equivalent to the plasma volume of about 2.5-3 l, reflecting high protein binding that complicates initial disposition. The steady state volume of distribution has been estimated to be more than 100 times larger, in the range of about 10 l/kg (Lemberger *et al.*, 1971; Wall *et al.*, 1983). These early data have been questioned because of the possible inaccuracy of the quantification methods used. Based on pharmacokinetic data of two studies that used gas chromatography/mass spectrometry (GC/MS) for analysis of dronabinol concentration an average volume of distribution of 236 l or 3.4 l/kg (assuming a 70kg body weight) has been calculated (Sticht and Käferstein, 1998).

The lipophilicity of dronabinol with high binding to tissue and in particular to fat causes a change of distribution pattern over time (Ryrfeldt *et al.*, 1973). Dronabinol rapidly penetrates highly vascularized tissues, among them liver, heart, fat, lung, jejunum, kidney, spleen, mammary gland, placenta, adrenal cortex, muscle, thyroid, and pituitary gland, resulting in a rapid decrease in

plasma concentration (Ho *et al.*, 1970). Only about 1% of dronabinol administered i.v. is found in the brain at the time of peak psychoactivity (Gill and Jones, 1972). The relatively low concentration in the brain is probably due to a high perfusion rate of the brain moving dronabinol in and out of the brain rapidly (Chiang and Rapaka, 1987). Subsequently intensive accumulation occurs in less vascularized tissues and finally in body fat, the major long-term storage site.

Metabolism of dronabinol occurs mainly in the liver by microsomal hydroxylation and oxidation catalysed by enzymes of the cytochrome P-450 complex (Matsunaga *et al.*, 1995; Narimatsu *et al.*, 1992). In rats more than 80% of intravenous dronabinol was metabolized within 5 min (Alozie *et al.*, 1980). Major metabolites are monohydroxylated compounds. In man and many other species, C-11 is the major site attacked (Wall, 1971; Widman *et al.*, 1978). Hydroxylation results in 11-hydroxy-THC (11-OH-THC) and further oxidation in 11-nor-9-carboxy-THC (THC-COOH) that may be glucuronated to 11-nor-9-carboxy-THC glucuronide.

Average plasma clearance rates have been reported to be 197 ± 50 ml/min for females and 248 ± 62 ml/min for males (Wall *et al.*, 1983), while others determined higher mean clearance rates of about 600 ml/min for naive dronabinol users and about 1000 ml/min for chronic users (Hunt and Jones, 1980). The latter values are similar to the volume of hepatic blood flow (Hunt and Jones, 1980), indicating that the limiting step of the metabolic rate is controlled by hepatic blood flow.

Smoking a single cannabis cigarette containing about 16 or 34 mg dronabinol caused average peak plasma levels of 84.3 ng/ml (range: 50.0-129.0 ng/ml) for the lower dose and 162.2 ng/ml (range: 76.0-267.0 ng/ml) for the higher dose, then rapidly decreased to low levels of about 1-4 ng/ml within 3-4 h (Huestis *et al.*, 1992). The maximal dronabinol plasma level after smoking a cannabis cigarette (3.55% dronabinol) was reported to exceed the maximal THC-COOH level by threefold and 11-OH-THC by twentyfold (Huestis *et al.*, 1992). However dronabinol/11-OH-THC ratios declined and reached a ratio of about 2:1 after 2-3 h (Huestis *et al.*, 1992). Peak concentrations for dronabinol were observed 8 min (range: 6-10) after onset of smoking, while 11-OH-THC peaked at 15 min (range: 9-23) and THC-COOH at 81 min (range: 32-133) (Huestis *et al.*, 1992).

After oral application the dronabinol plasma concentration shows a flat course with peaks ranging from 4.4-11 ng/ml following 20 mg dronabinol (Ohlsson *et al.*, 1980), from 2.7-6.3 ng/ml with 15 mg dronabinol (Galiègue *et al.*, 1995), and from 0.58-12.48 ng/ml with 2.5 mg dronabinol (Timpone *et al.*, 1997). Much higher amounts of 11-OH-THC are formed than with inhalative or intravenous administration.

After smoking a low dose cannabis cigarette (about 16 mg dronabinol) the detection limit of 0.5 ng/ml dronabinol in plasma was reached after 7.2 h (range: 3-12 h) and following a high dose cigarette (about 34 mg dronabinol) a plasma concentration of 0.5 ng/ml dronabinol was reached within 12.5 h (range: 6-27 h) (Huestis *et al.*, 1992). THC-COOH was detectable for a considerably longer time, for 3,5 days (range: 2-7 d) after the low dose and for 6,3 days (range 3-7 days) after smoking the high dose cigarette (Huestis *et al.*, 1992). The major reason for the slow elimination of dronabinol from the plasma is the slow rediffusion of dronabinol from body fat and other tissues into the blood (Leuschner *et al.*, 1986). The true elimination half-life of dronabinol from the plasma is difficult to calculate, as the concentration equilibrium ratio

plasma/fatty tissue is only slowly reached, resulting in very low plasma levels that are difficult to analyse. In a study by Wall *et al.* (1983) who followed the plasma concentration for 72 h the half life of the terminal phase $t_{1/2\beta}$ ranged from 25-36 h for dronabinol, from 12-36 h for 11-OH-THC and from 25-55 h for THC-COOH after oral or intravenous dosing in men and women. Longer half lives of dronabinol plasma elimination have been determined after higher doses and longer periods of measurement, up to 12.6 days with four weeks of observation (Johansson *et al.*, 1989).

Dronabinol is excreted within days and weeks, mainly as acid metabolites, about 20-35% in urine and 65-80% in faeces, less than 5% of an oral dose as unchanged drug in the faeces (Hunt and Jones, 1980; Wall *et al.*, 1983). After three days overall excretion rates were about 65% following oral and about 45% with intravenous administration. A single dose of dronabinol may result in detectable metabolites in urine for up to 12 days, usually for 3-5 days (Schwartz *et al.*, 1985). The average time to the first negative result in urine screening for dronabinol metabolites (enzyme immunoassay with a cut-off calibration of 20 ng/ml) was 8.5 days (range: 3-18 d) for infrequent users and 19.1 days (range: 3-46 d) for regular users (Ellis *et al.*, 1985). Excretion is delayed by an extensive entero-hepatic recirculation of metabolites (Wall *et al.*, 1983). Due to this marked entero-hepatic recirculation and the high protein binding of cannabinoids, they are predominantly excreted with the faeces.

These pharmacokinetic characteristics significantly affect the abuse potential of dronabinol. For example, one study has correlated rapidly rising dronabinol plasma levels to episodes of euphoria. Subjects reported multiple episodes of intense good effects or euphoria during the first 15 min after inhaling cannabis (Lukas *et al.*, 1995). Most psychoactive drugs exert their maximum subjective effects when blood levels of the drug are rapidly increased. Smokable drugs enter the blood stream rapidly, and inhalation can produce a sharp increase in arterial blood concentration delivering the drug directly to the brain.

The intense psychoactive drug effect which can be rapidly achieved by smoking is often called a "rush" and generally is considered to be the effect desired by the abuser. This effect may be useful in explaining why abusers prefer to administer certain drugs by the inhalation, intravenous or intranasal routes, rather than by the oral route.

6. Dependence potential

Animal Studies:

Basic research demonstrates, that like other substances with dependence potential dronabinol activates the reward system of the brain and is reinforcing, produces conditioned place preference (CPP), a behavioural model of incentive motivation, and is self-administered. Dronabinol produces tolerance to most of its effects and withdrawal is observed after cessation of long-term administration.

The reinforcing properties of a number of commonly abused drugs such as amphetamine, cocaine, alcohol, morphine and nicotine, have been explained by the effects of these drugs in the activation of dopaminergic pathways in certain areas of the brain (Koob, 1992). Reinforcement and reward are two major determinants of a substance's abuse potential (Justinova *et al.*, 2005).

The brain's reward circuitry consists of a circuit of dopaminergic neurons in the ventral tegmental area (VTA), nucleus accumbens, and that portion of the medial forebrain bundle which links the VTA and the nucleus accumbens and closely-related structures ventral to the nucleus accumbens (Gardner, 2005). Dronabinol activates these brain reward processes and reward-related behaviours, but the exact sites and substrates of dronabinol action in the reward circuitry of the brain are as yet unclear (Gardner, 2005).

Self-administration: Older studies usually demonstrated that animals will not typically self-administer dronabinol when they must choose between saline and the cannabinoid (e.g. Harris *et al.*, 1974; Carney *et al.*, 1977). However, recent studies demonstrated that intravenous dronabinol is self-administered by squirrel monkeys (Tanda *et al.*, 2000; Justinova *et al.*, 2003). In the first study the animals were first trained to self-administer intravenous cocaine and continued to bar-press at the same rate when dronabinol was substituted for cocaine, at doses that were comparable to those used by humans who smoke cannabis (Tanda *et al.*, 2000). This effect was blocked by the CB₁ receptor antagonist, SR 141716. In the second study by the same group, monkeys with no history of exposure to other drugs learned to press a lever for intravenous injections of dronabinol (Justinova *et al.*, 2003). Doses of dronabinol were varied from 1 to 16 µg/kg per injection with vehicle extinction following each dose of dronabinol. Dronabinol maintained significantly higher numbers of self-administered injections per session and higher rates of responding than vehicle at doses of 2, 4 and 8 µg/kg per injection, with maximal rates of responding at 4 µg/kg per injection. Response rates, injections per session and total dronabinol intake per session were two- to three-fold greater in monkeys with no history of exposure to other drugs compared to the previous findings in monkeys with a history of cocaine self-administration.

These data demonstrate that under specific treatment conditions, an animal model of reinforcement by dronabinol now exists. Additionally, animals have been reported to self-administer the synthetic cannabinoid receptor agonists WIN 55,212-2 (Martellotta *et al.*, 1998; Ledent *et al.*, 1999) and CP-55940 (Braida *et al.*, 2001b). As with dronabinol these effects were blocked by SR 141716. Scientists had to learn the conditions under which dronabinol is self-administered by animals. High doses of dronabinol or other cannabinoid receptor agonists cause aversive effects in animals. There is a parallel to humans, where high doses of dronabinol can cause anxiety and other unwanted effects, while low doses are well tolerated with both stimulating and sedating effects.

A dependency from dose and/or potency of the cannabinoid was observed, since aversive effects, rather than reinforcing effects, have been described in rats with even low doses of the potent CB receptor agonist WIN 55,212-2 (Chaperon *et al.*, 1998) as well as with high doses of dronabinol (Sanudo-Pena *et al.*, 1997). The cannabinoid antagonist, SR 141716, counteracted these aversive effects. Mansbach *et al.* (1994) used higher dronabinol doses (17-100 µg/kg/injection) in rhesus monkeys than Tanda *et al.* (2000) and Justinova *et al.* (2003) in their studies presented above. Using a fixed-interval of reinforcement followed by a two hour time-out, three rhesus monkeys were trained to self-administer phencyclidine at a dose of 100 µg/kg/injection. The primates were allowed a maximum of 3 injections per day under this schedule contingency. Once self-administration behavior was reliably maintained by phencyclidine, dronabinol at this

comparatively high dose was substituted for phencyclidine. Positive reinforcement by dronabinol was not demonstrated, as response rates were not greater than those of training drug.

Drug discrimination: Animals, including monkeys and rats (Gold *et al.*, 1992) as well as humans (Chait *et al.*, 1988) can discriminate cannabinoids from other drugs or placebo. The drug discrimination technique is one of the most widely used behavioral approaches in psychopharmacology. It adds to knowledge of the effects, modes of action and abuse liability of psychoactive drugs.

Dronabinol produces discriminative stimulus effects in several species in a variety of drug discrimination paradigms. Jarbe and Henriksson (1974) reported that dronabinol is capable of attaining stimulus control of learned response in a T-shaped water maze, such that rats learn to enter one arm of the T-maze in the presence of dronabinol and enter the opposite arm following the administration of vehicle. The ability of dronabinol to serve as a discriminative stimulus in primates was first reported by Ferraro *et al.* (1974). Acquisition of the drug discrimination was relatively slow; monkeys learned the procedure within 55-89 days. Despite a slow initial acquisition, all primates reliably learned to discriminate dronabinol from vehicle in this complex drug discrimination task above the criterion level.

Discriminative stimulus effects of dronabinol are pharmacologically specific for cannabinoid receptor agonists (Barrett *et al.*, 1995; Browne and Weissman, 1981; Wiley *et al.*, 1995). Cannabinoid receptor agonists, including the dronabinol-metabolite 11-OH-THC, the synthetic THC-derivative nabilone (Browne and Weissman, 1981), the natural cannabinoid *delta*-8-THC, the synthetic cannabinoid receptor agonist WIN 55,212-2 (Wiley *et al.*, 1995), and many others (Browne and Weissman, 1981) fully substituted for dronabinol. The discriminative stimulus effects of the cannabinoid group appear to provide unique effects because stimulants, hallucinogens, opioids, benzodiazepines, barbiturates, NMDA antagonists and antipsychotics have not been shown to substitute for dronabinol (Browne and Weissman, 1981; Barrett *et al.*, 1995; Jarbe and Henriksson, 1974).

Conditioned place preference: The conditioned place preference (CPP) test is another widely used predictor of reinforcing effects. CPP is the learned approach to a previously neutral set of environmental stimuli, which have been paired with administration of a rewarding treatment. As with self-administration the cannabinoid dose is crucial, since animals show CPP to cannabinoids only at mid-dose levels. Other important factors are timing and potency of the cannabinoid (Gardner, 2005).

Lepore *et al.* (1995) found CPP or conditioned place aversion (CPA) depending on dose and time intervals. When the CPP pairing interval was 24 h 2.0 and 4.0 mg/kg dronabinol produced a reliable shift in preference for the dronabinol-paired compartment, while 1.0 mg/kg did not produce CPP. The dronabinol place preference observed at 2.0 and 4.0 mg/kg was nearly equivalent to that produced by low doses of cocaine (5.0 mg/kg), morphine (4.0 mg/kg), and food in non food-deprived animals. When the CPP pairing interval was 48 h a dronabinol place preference could be obtained with 1.0 mg/kg, while 2.0 or 4.0 mg/kg produced CPA. A possible explanation of these observations is that at the shorter pairing interval the post-cannabinoid

rebound dysphoria due to withdrawal attenuated the rewarding effect of the low dose (1.0 mg/kg) and lowered the higher doses into the rewarding range. At the longer interval, withdrawal and dysphoric rebound had passed allowing the low dose to become rewarding and pushing the high doses into an aversive dose range. A later study confirmed that if a long conditioning period was used and care taken to avoid dysphoric rebound from previous dronabinol administration, the cannabinoid produced a robust CPP (Valjent and Maldonado, 2000). In this study CPA was observed with 5 mg/kg dronabinol using a standard protocol. However, mice receiving a priming dronabinol injection and conditioned 24 h later showed CPP with 1 mg/kg dronabinol and no effect with 5 mg/kg dronabinol. Authors emphasized that it is important to avoid the possible dysphoric consequences of the first drug exposure.

Tolerance: Tolerance occurs when a larger dose of a drug is required to achieve a given effect, or when a dose that normally achieves an effect is no longer sufficient to produce it. The repeated use of many drugs leads to the normal physiological adaptations of tolerance and is not a phenomenon unique to drugs of abuse. Tolerance develops to most of the dronabinol effects (Romero *et al.*, 1997), among them the cardiovascular, psychological and skin hypothermic effects (Jones *et al.*, 1976; Stefanis, 1978), analgesia (Bass and Martin, 2000), immunosuppression (Luthra *et al.*, 1980), corticosteroid release (Miczek and Dixit, 1980), and disruption of the hypothalamo-hypophyseal axis (Smith *et al.*, 1983), causing alterations in endocannabinoid formation and contents in the brain (Di Marzo *et al.*, 2000a).

Tolerance can mainly be attributed to pharmacodynamic changes, presumably based on receptor downregulation and/or receptor desensitisation (Di Marzo *et al.*, 2000a; Rubino *et al.*, 2000a). Rate and duration of tolerance varies with different effects. Rats receiving dronabinol over a period of five days exhibited a decreased specific binding ranging from 20 to 60% in different receptor sites of the brain compared to controls (Romero *et al.*, 1997). However, in another study no significant alteration in receptor binding was observed after chronic administration of dronabinol resulting in twenty-sevenfold behavioral tolerance (Abood *et al.*, 1993). Chronic administration of anandamide as well resulted in behavioral tolerance without receptor downregulation (Rubino *et al.*, 2000b), and it was proposed that desensitisation of the CB₁ receptor might account for this observation (Rubino *et al.*, 2000b). Electrophysiological data showed that the ability of dronabinol to increase neuronal firing in the ventral tegmental area (VTA) was not reduced following chronic administration of the drug to animals, whereas dopamine neurons of the substantia nigra pars compacta were significantly less responsive to dronabinol (Wu and French, 2000). Authors suggest that this observation may be of relevance to differences in development of tolerance to different pharmacological effects of dronabinol.

Tolerance has been observed to occur together with modified biotransformation activities with regard to mitochondrial oxygen consumption, monooxygenase activities, and the content of liver microsomal cytochrome P450 (Costa *et al.*, 1996). However, only a small proportion of tolerance can be attributed to changes in metabolism (Hunt and Jones, 1980).

Withdrawal: Prior to the development of cannabinoid receptor antagonists, researchers precipitated withdrawal in animals that had been chronically maintained on dronabinol by either abruptly ceasing dronabinol administration or by administering the opioid antagonist naloxone. An abstinence or withdrawal syndrome was not consistently elicited, although many studies

reported abstinence symptoms (Compton *et al.*, 1990). An abstinence syndrome has been reported following long-term administration of dronabinol in primates and rats. Rhesus monkeys receiving gradually increasing doses of dronabinol (to 1 mg/kg/day) for 36 days displayed an abstinence syndrome 12 days after dronabinol was discontinued, which persisted for five days (Kaymakcalan, 1972). The behavioral signs associated with this syndrome included: aggressiveness, hyperirritability, tremors, yawning, photophobia, hallucinatory behavior and anorexia. Kaymakcalan also reported that an abstinence syndrome (scratching, licking, arched back and ptosis) occurs in rats abruptly withdrawn from chronic administration of dronabinol.

With the availability of the cannabinoid antagonist SR 141716A, it has been shown that a withdrawal syndrome can occur with modest usage of dronabinol (Aceto *et al.*, 1996). The major withdrawal signs in rats consisted of scratching, rubbing face with paws, licking, wet-dog shakes, arched back and ptosis (at least 50% closure of eyelids). These signs were evident approximately 10 min after administration of SR 141716A and subsided within one hour. Some of the rats in the high dose group also exhibited biting, tongue rolling, retropulsion, head shakes, extended limbs or high stepping, ataxia, myoclonic spasms and front paw treading.

Human Studies:

Results from animal studies can not fully transferred to the use of dronabinol and cannabis by humans since dose conditions may not be comparable (Maldonado, 2002). In addition, the abuse potential of a substance can not be derived from brain reward behaviour of animals alone (Berger, 2000). However, reinforcing effects of dronabinol, tolerance and withdrawal have also been observed in humans.

Tolerance can develop in humans to cannabis-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, mood and certain behavioral changes (Jones *et al.*, 1981). In a number of studies Jones and Benowitz (1976, 1981) administered daily doses of 210 mg oral dronabinol to about 120 volunteers for 11-21 days. Participants developed tolerance to cognitive and psychomotor impairment and to the psychological high by the end of the studies (Jones *et al.*, 1976). After a few days an increased heart rate was replaced by a normal or a slowed heart rate. Tolerance develops also to cannabinoid-induced orthostatic hypotension (Benowitz and Jones, 1975).

Clinical long-term studies with dronabinol in patients suffering from multiple sclerosis (Zajicek *et al.*, 2004; Robson *et al.*, 2005), spasticity and pain (Maurer *et al.*, 1990) and AIDS (Beal *et al.*, 1997) did not find tolerance to the medicinal effects of moderate doses of dronabinol (usually 5-30 mg daily) within 6-12 months.

As with tolerance, withdrawal symptoms are dose-dependend (Budney *et al.*, 2004). In experimental studies comparatively high doses were administered to volunteers (80-120 mg and 210 mg daily, respectively) (Haney *et al.*, 1999; Jones and Benowitz, 1976, 1981). In the study by Haney *et al.* (1999) abstinence from dronabinol increased ratings of "anxious," "depressed," and "irritable," decreased the reported quantity and quality of sleep, and decreased food intake. In the studies by Jones and Benowitz most of the participants (55-89%) experienced irritability, restlessness, insomnia, anorexia, nausea, sweating, salivation, increased body temperature,

altered sleep and altered waking EEG, tremor, and weight loss after discontinuation of dronabinol administration (Jones and Benowitz, 1976, 1981). These withdrawal symptoms that were described as "mild and transient" started within 5-6 hours after intake of the last dose and disappeared within 4 days. Sleep disturbances were observed for several weeks after discontinuing therapy. Withdrawal symptoms were alleviated by the administration of a cannabis cigarette or oral dronabinol (Jones and Benowitz, 1976).

The U.S. National Comorbidity Study indicated that 9 per cent of lifetime cannabis users met DSM-R-III criteria for dependence at some time in their life, compared to 32 per cent of tobacco users, 23 per cent of opiate users and 15 per cent of alcohol users (Anthony *et al.*, 1994). In a representative sample of German adolescents (N = 1228), who were followed for 20 months the cumulative life-time incidence for DSM-IV cannabis abuse was 3.5% (Perkonigg *et al.*, 1999). Similar data were obtained from an Australian sample of 10.641 adults of whom 1.5% were dependent according to DSM-IV and 0.7% were diagnosed with cannabis abuse (Swift *et al.*, 2001). The natural course of cannabis use, abuse and dependence is rather variable (von Sydow *et al.*, 2001). Cumulative incidence and patterns of cannabis use and disorders were examined in a prospective longitudinal design (mean follow-up period=42 months) in a representative sample (N = 2446) aged 14-24 years at the outset of the study. Cannabis use was widespread in this sample, but the probability of developing cannabis abuse or dependence was relatively low (8%) and about half of all cannabis users stopped their use spontaneously in their twenties (von Sydow *et al.*, 2001).

7. Epidemiology of use and abuse, with an estimate of the abuse potential

In terms of abuse potential, there seems to be no big difference between oral dronabinol on the one side and marijuana and hashish, natural preparations of the cannabis plant, on the other side. In terms of abuse liability (likelihood of abuse), however, there is a huge difference between isolated dronabinol that is used medicinally and the whole plant cannabis preparations. While cannabis is the most widely abused illegal drug the abuse of dronabinol and its medicinal preparations is almost non-existent.

Unimed Pharmaceuticals, Inc. in the USA is manufacturing by far most of the dronabinol world wide and most of this dronabinol (Marinol®) is used medicinally in the USA. According to U.S. law enforcement sources cited by Calhoun *et al.* (1998) there is no evidence of any diversion of dronabinol for sale as a street drug. None of the published Drug Abuse Warning Network (DAWN) reports list dronabinol as a drug that was mentioned 200 or more times per year in emergency room visits. In the 1992 data, 135 drugs were listed as having more than 200 mentions. Between 1988 and 1994, there were no reports of dronabinol to emergency department facilities participating in the DAWN survey (Calhoun *et al.*, 1998).

Out of a global database of 279 reported adverse effects, covering a 2 year period, the UMC reported none of the following dependency related adverse effects: increased tolerance, withdrawal syndrome, withdrawal convulsions, withdrawal headache, drug abuse and drug dependence (unpublished, communication to WHO, 2005).

In 2002, of the 100 countries which responded to the WHO Questionnaire, only two indicated some abuse of this substance: Denmark reported some abuse of "cannabinol", clarifying that it meant the detection of δ^9 -THC in the exhibit, and USA mentioned 3 cases of δ^9 -THC abuse reported by the American Association of Poison Control Centres during the period 1992-1994.

Also in 2005, there are in general no or low levels of abuse reported, nor any illicit activity with the substance. Of the 66 countries that responded to the WHO Questionnaire

The US responded that, although its susceptibility for abuse can vary with the dosage form, the pharmaceutical product containing Marinol is associated with low levels of diversion and abuse. The US is not aware of any drug related deaths, drug dependence or addiction associated with Marinol. France reported not to have knowledge of any case of abuse, dependency or diversion.

8. Nature and magnitude of public health problems

Dependence and various, mostly psychological adverse effects may result following the use of high dronabinol doses. However, to date, there have only been a few reports of serious adverse effects. As of March 1996, there were a total of twelve adverse event reports involving Marinol® reported to the Spontaneous Reporting System of the U.S. Food and Drug Administration (FDA) (Calhoun *et al.*, 1998). Five of the subjects required hospitalization. While it is a voluntary reporting system, the small number of reports suggests that the medicinal use of dronabinol is not associated with many adverse effects. From 2000-2005 the US forensic laboratory reported 1 to 4 cases annually (16 in total).

Most psychoactive drugs exert their maximum subjective effects when blood levels of the drug are rapidly increased. Inhalation of drugs permits a rapid delivery and distribution of the drug to the brain. The intense psychoactive drug effect, which can be rapidly achieved by smoking is considered to be the effect desired by the abuser. This explains why cannabis abusers prefer the inhalation route rather than the oral route of administration. Routes that allow a rapid increase in blood levels, including inhalation, intravenous and intranasal administration, are also preferred by drug abusers for other substances, such as cocaine, opium, heroin, phencyclidine, and methamphetamine (Wesson and Washburn, 1990).

Oral administration of dronabinol has the slowest onset of action due to the time required for digestion and absorption, and results in lower levels of circulating dronabinol compared to smoking. In addition to the slow onset of action the long half-life of dronabinol is believed to have an effect on its relative abuse potential. Its long half-life may partly explain the comparatively weak withdrawal symptoms after cessation of use. While clinical studies of dronabinol show a pattern of CNS-related effects somewhat typical of those seen with cannabis, there is a dramatic difference between actual abuse and illicit trafficking of dronabinol and cannabis. Despite its availability in the United States for nearly twenty years, there have been no significant reports of abuse, diversion, or public health problems related to dronabinol.

9. National control

National controls were consistent with the requirements applicable to Schedule I psychotropic substances until 1991, when dronabinol was moved down to Schedule II. It is used for medical purposes in several countries (see next paragraph). In several countries dronabinol is only available for medicinal uses with a special permission from government authorities. Since the medical use of dronabinol increased in recent years in countries where it is more easily available (USA, Germany, Austria) it seems likely that the current control status of dronabinol constitutes a relevant obstacle to its therapeutic use in at least some countries.

10. Therapeutic and industrial use

The dronabinol preparation Marinol® is approved in the USA for the treatment of two conditions, (1) anorexia associated with weight loss in patients with AIDS and (2) nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. There is some off-label use of Marinol®. According to an U.S. Institute of Medicine Report of 1999 on the medical use of cannabis the manufacturer of Marinol®, Unimed Pharmaceuticals, Inc. estimated that about 80% of Marinol's patient population used it for HIV, 10% for cancer chemotherapy, and about 5-10% for other conditions (Joy *et al.*, 1999). Unimed cannot promote Marinol® for unlabeled indications, but physicians are free to prescribe it for other indications. The same report noted that Marinol® is developed or considered for development of five new indications: disturbed behaviour in Alzheimer's disease, nausea and vomiting in HIV patients who are receiving combination therapy, spasticity in multiple sclerosis, intractable pain, and anorexia in cancer and renal disease.

The product has a marketing authorization for the same indications in Canada.⁷ In Germany the substance is produced domestically for pharmacy compounding by two manufacturers and also imported from the USA. According to one German manufacturer of dronabinol, THC Pharm, in Germany dronabinol is mainly used against chronic pain, neurological disorders and appetite loss in cachexia.

In the Netherlands, France, Denmark and Australia, it is available on a special import license. In the Netherlands it is mainly used for the same indications as are official in the USA. This is also the case in Israel, where it is produced locally. In Israel dronabinol may be administered by physicians of the Hadassah University Hospital on a special request.

In Spain it is used against the side effects of chemotherapy. In Switzerland it is also available for medical purposes after permission of the Ministry of Health. In Italy, dronabinol may be

⁷ In Canada, also Sativex, a sublingual spray containing dronabinol and cannabidiol in a ratio of 52:48, is available. This preparation is approved for the symptomatic relief of neuropathic pain in adults with MS. As it is produced by extracting cannabis, this preparation is controlled according to the provisions of the Single Convention on Narcotic Drugs (1961).

prescribed with a special permission from the ministry of the interior. In 2002 the Northern Mariana Islands and Saudi Arabia reported the availability of dronabinol for medical use. It is not known if this is still the case.

In France patients can get a special approval in case of the following indications:

- treatment of pain refractory to usual pain treatment
- treatment of vomiting induced by chemotherapy if other anti-emetic treatments fails
- anorexia associated with weight loss in patients with AIDS
- syndrome of Gilles de la Tourette
- dystonia refractory to usual treatment
- treatment of paroxysmal pain
- treatment of M. Unverricht-Lundborg.

Dronabinol is used as an analytical standard in forensic laboratories for the analysis of marijuana and hashish. Thailand, Switzerland Australia and the Czech Republic reported such use, but it can be assumed that such use of the substance is made in many more countries.

11. Production, consumption and international trade

As evidenced by manufacturing quota data, prescription usage data and estimates of medical need, availability of dronabinol is very low, especially in comparison to the widespread availability of illegal cannabis products (marijuana and hashish). Dronabinol is produced in 6 countries: the United States of America, Israel, Germany, the Netherlands, South Africa (under the brand name Elevat) and the United Kingdom.

The United States reported legitimate production figures of 135.0 kg (2003), 180.0 kg (2004) and 312.5 kg (2005), and exported amounts of 4.307 grams (2003), 3.287 grams (2004) and 2.557 grams (2005). This means that the production of the United States is used almost totally domestically.

Germany reported manufacture of 7 kgs annual average for the past five years) and the United Kingdom reported 2 kgs on an average. Several countries reported imports of the substance in 2004, the most significant quantities being reported by Canada (1,953 g), followed by the United Kingdom (971 g), Denmark (901 g), Belgium (315 g), Germany (310 g) and Austria (122 g).

12. Illicit manufacture and illicit traffic, and related information

As indicated in section 7, reports on illicit activities involving dronabinol are practically non-existent.

13. Current international controls in place and their impact

Dronabinol (Δ^9 -THC) is currently controlled as a Schedule II psychotropic substance.

14. References

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