Chapter 1 Definition of terms and classification of dependence-producing drugs

1.1. Terminology

In 1967, the World Health Organization (WHO) raised several criteria for drug addiction. The terms used in this thesis are in accordance with the definitions given by the WHO as proposed in their 28th report (1992), which in its turn, is in accordance with the International Classification Diseases (ICD-10) of mental and behavioral disorders (Hoffman, 1983).

Drug dependence:

replaced the term "drug addiction" and is defined as "a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. A person may be dependent on more than one drug".

Harmful use:

replaced the term "abuse" and is defined as "a pattern of psycho-active drug use that causes damage to health, either mental or physical. Harmful use of drugs by an individual often has adverse effects on the drug user's family, community and society, in general".

The existence of a state of drug dependence is not necessarily harmful in itself, but may lead to the use of the drug(s) at dosage levels that produce deleterious physical or behavioral changes, constituting public health and social problems.
Chapter 1 Definition of terms and classification of dependence-producing drugs

Written by Suzanne Cappendijk
Sunday, 03 January 2010 00:00

Tolerance:

is defined as "a reduction in the sensitivity to a drug following its repeated administration, in which increased doses are required to produce the same magnitude of effect previously produced by a smaller dose. This increase in dose may be necessitated by changes in the metabolism of the drug, or a cellular, physiological or behavioral adaptation to the effects of the drug".

Sensitization ("reverse-tolerance"):

describes the situation in which a constant drug dose elicits increasing effects (Nestler et al., 1993). It differs from tolerance since less drug is required to reinstate the initial effect.

Withdrawal syndrome:

is described as "after the repeated administration of certain dependence-producing drugs, e.g. opioids, barbiturates and alcohol, abstinence can increase the intensity of drug-seeking behavior, because of the need to avoid or relieve withdrawal discomfort and/or produce physiological changes of sufficient severity to require medical treatment".

The withdrawal syndrome following cessation of hypnosedatives (Roelofs, 1985) or opioids (Martin and Eades, 1963) has a mainly excitatory character, which may culminate in an epileptic convulsion. In contrast, drug dependence induced by stimulants (Gawin and Kleber, 1986) or cannabinoids (Jones, 1983) give rise to a sedative withdrawal syndrome, which is less inconvenient and clinically less important.

Craving:

is defined as "the desire to experience the effect(s) of a previously used psycho-active substance". It has to be noted that not all drug craving is based on withdrawal, since craving
can often occur in the absence of withdrawal (Markou et al., 1993).

Stimulus:

is defined as "an environmental event that produces a change in the behavior of an organism".

Response:

is defined as "the behavioral consequence of presenting a stimulus to an organism".

Positive reinforcer:

is defined as "a stimulus that increases the frequency of behavior that leads to its presentation". For example, if a hungry rat, placed in a box, presses a bar and is then given food, the animal will have a "positive" experience. The probability of a particular response (the bar press) has been increased through the immediate delivery of the "positive reinforcer" (the food). Things such as food, water, sex, and the opportunity to explore are usually considered as positive reinforcers (Houston, 1986). Also many dependence-producing drugs, such as cocaine, morphine, phencyclidine (PCP), barbiturates, ethanol and some volatile solvents serve as a positive reinforcer (Stolerman, 1992).

Negative reinforcer:

is defined as "stimulus that increases the frequency of a behavior that prevents' or terminates its presentation". Generally speaking, noxious stimuli, such as shock are considered to be negative reinforcers.

Aversive stimulus:
is defined as "stimulus causing an organism to behave so as to minimize exposure to it (as in negative reinforcement or punishment procedures)".

Conditioning:

generally refers to relative simple learning situations, such as classical- and instrumental conditioning (Houston, 1986).

Classical/Pavlovian conditioning:

is defined as "procedures that present different stimuli in temporal proximity (contiguity), but where resulting responses have no reinforcing or aversive consequences". Well-known are the experiments performed by Pavlov, in which dogs were conditioned to salivate at the sound of a tone.

Instrumental/Operant conditioning:

is defined as "procedures where responses have reinforcing or aversive consequences and are instrumental (for example pressing a bar) in attainment of a goal (getting food or dependence-producing drugs)".

Reward:

is often defined similarly as reinforcement, but with some positive affective colouring, such as pleasure (Stolerman, 1992).
The most important animal models to study rewarding properties of drugs are:

Intracranial electrical self-stimulation in specific brain regions. In this model electrodes are implanted in brain regions, with physiologically active dopaminergic (DAergic) systems (Fibiger and Phillips, 1988). The role of the DA-ergic system in respect to reinforcement is discussed in more detail (see chapter 2 and chapter 8).

Place preference conditioning. The apparatus used in this model consists of two different compartments (differences could be of visual-, tactile- or odour origin). During conditioning sessions, animals are allowed to access to only one compartment at a time. One compartment is repeatedly paired with drug injections and the other compartment with vehicle injections. During test sessions, the animals have access to the whole apparatus and the amounts of time spent in each compartment are usually recorded by a system of light beams and photo cells.

Self-administration model. In this model a drug serves as a reinforcer of behaviour. The drugs are mostly obtained by an indwelling intravenously catheter (see technical details in chapter 9).

Dependence-producing drugs (with exception of lysergic acid diethylamide (LSD) and cannabinoids) can serve as positive reinforcers in the self administration model in rats and monkeys (Stolerman, 1992).

1.2. Dependence-producing drugs

ICD-10 recognizes the following psycho-active drugs or substances, which may produce drug-dependence: hypnosedatives • cannabinoids • hallucinogens • tobacco • volatile solvents • opioids

psychostimulants

In the following paragraphs of this chapter, recent experimental data relevant to the dependence-inducing properties of these drugs are briefly discussed.
1.2.1. Hypnosedatives

Drugs belonging to this group are ethanol (alcohol), benzodiazepines (BDZs) and barbiturates. In general, these compounds induce sleep and reduce anxiety.

A. Alcohol

Action on cellular level

There are indications that the binding place of alcohol is on the a-subunit section 6 ((c6) of GABAA (γ-amino butyric acid) receptor-complex (Korpi and Seeburg, 1993). However, no substance is known, which might interfere with the binding place of alcohol. The importance of this subunit in respect to alcohol drug dependence has to be revealed in future.

If labelled membranes from neurons are exposed to intoxicating concentrations of alcohol, an increased "motion" within the membrane was observed ("membrane fluidity theory": Goldstein, 1984). This disordering (fluidizing) effect of alcohol on the membrane may affect some receptors, such as the GABA or/and the NMDA (N-methyl-D-aspartate) receptors of the excitatory amino acid (EAA) glutamate. Accordingly, chronic alcohol treatments reduces GABA A function (Buck and Harris, 1991). GABA receptor systems (together with serotonin and noradrenaline) seemed to be involved in the decreased compulsivity of alcohol intake (Deitrich et al., 1989). During chronic alcohol use, there is an up-regulation of the NMDA receptors (probably due to NMDA receptor blockade) in the hippocampus, a brain area known to be associated with ethanol withdrawal seizure activity (Grant et al., 1990). Removal of alcohol induces a state of excessive EAA activation which may contribute to the alcohol withdrawal excitability (Grant et al., 1990; Michaelis et al., 1993). Alcohol use inhibits the production of nitric oxide (NO, Persson and Gustafsson, 1992), which could be a result of NMDA receptor blockade. However, further research is necessary to reveal whether chronic alcohol intake could alter NO production and bring some clarification in alcohol-related pathology.
Besides the GABA and EAA-NMDA receptor-complex, alcohol affects a variety of other neurotransmitter systems. Of particular importance is the fact that alcohol interferes with DA-ergic rewarding pathway, which is claimed to mediate positive reinforcement (Samson et al., 1990). It has been found that both systemic and locally-infused alcohol stimulate the release of dopamine (DA) in the nucleus accumbens (part of the mesocorticolimbic DA projection). Conversely, an alcohol withdrawal is associated with reduced release of DA in this pathway (Nutt and Peters, 1994). To some extent, it has been demonstrated that DA receptor antagonists are able to block the reinforcing actions of alcohol (Nutt and Peters, 1994).

Ethanol also interacts with the endogenous opioid system. Acute administration of ethanol increased plasma levels of 13-endorphin in humans (Barret et al., 1987) and metenkephalin in rat brain and pituitary (Seizinger et al., 1983). These findings might be of relevance, since opioid receptor antagonists tend to reduce alcohol consumption (Goldstein, 1984).

Tolerance

Repeated administration of alcohol results in tolerance for most of the effects of this drug (hypothermia, sedation, anxiolytic and motoric effects) in both humans (Tabakoff and Hoffman, 1988) and animals (Holloway et al., 1989). The acute tolerance for alcohol can be influenced by genetic selection, in a way that animals selected for higher ethanol preference demonstrate a greater acute tolerance than those selected for ethanol aversion (Waller et al., 1983).

Withdrawal syndrome

The physical abstinence syndrome in man, in severe form, develops after about 8 h. In the first stage, the main symptoms are tremor, nausea, sweating, fever and sometimes hallucinations. These symptoms last for about 24 h. This phase may be followed by tonicclonic convulsions. Over the next 48 h, “delirium tremens” could develop, in which the patient becomes confused, agitated and often aggressive, and may suffer from severe hallucinations. However, not all components of withdrawal need to be present. The alcohol withdrawal (similarly to the diazepam withdrawal) is associated with anxiety (Roelofs, 1985).
Different treatments have been proposed in order to prevent the subject for the intake of alcohol or to attenuate a withdrawal syndrome after cessation of the alcohol use. Besides compounds inducing an aversive reaction, such as disulfiram (Goldstein, 1994) and calciumcyanide (Nagasawa et al., 1990), the use of antagonists of opioid or NMDA receptors has been recently suggested.

• Opioid antagonists tended to reduce alcohol consumption (Goldstein, 1984). Administration of naltrexone to alcohol addicts during detoxification process reduced craving and prevented single drinks from triggering binges (Volpicelli et al., 1992). A binge is a period of several hours during which large amounts of drugs are being consumed. Generally, a binge is followed by emotional distress ("coming down" or "crashing, Jaffe, 1990).

• NMDA antagonists. Some alcoholics become magnesium depleted, which accentuates the excessive NMDA stimulation during alcohol withdrawal (Mg2+-ion is known to block the NMDA-receptor). Therefore, many features of withdrawal can be blocked by magnesium sulphate infusions (Becker and Hale, 1993).

B. Benzodiazepines (BDZs) Action on cellular level

BDZs facilitate the inhibitory GABA neurotransmission by increasing the permeability of a chloride ion channel in the CNS of animals (Young and Kuhar, 1979) and humans (Schoch et al., 1985). BDZs (like alcohol and barbiturates) interact with the GABAA receptor-complex. It is demonstrated that the a-subunit of the GABA A receptor is responsible for the binding of BDZs, in association with the y-subunit. The functional importance of the 8- and the e-subunits of the GABA A receptor-complex in respect to the mechanism of action of the BDZs, is still unclear.

(Giusti and Arban, 1993).
Tolerance

The clinical consequences of sedative effects of BDZs are partly counterbalanced by the development of tolerance to these effects. In clinical terms this means that patients frequently report diminution or disappearance of sedative effects despite continued use of the BDZ. Tolerance to the sedative effects is not accompanied by tolerance to the antianxiety effects of these drugs (Linnoila et al., 1983).

Withdrawal syndrome

Discontinuation of chronic use of BDZ could induce withdrawal signs in both animals and humans (Woods et al., 1987). The symptoms of the withdrawal syndrome in BDZ-dependent subjects are excessive sensitivity to light and sound, tremors, sweating, sleeplessness, abdominal discomfort, tachycardia, mild systolic hypertension and rarely seizures (Marks, 1978). After withdrawal, patients recover completely, but anxiety may occur (Shader and Greenblatt, 1993). The half-life of a BDZ is important in the expression and severity of the withdrawal syndrome. The abrupt cessation of various BDZs with short half-lives (Woods et al., 1992) is associated with rapid onset of withdrawal syndrome. Therefore, the BDZs with short half-lives should be stopped gradually rather than abruptly. It has been shown that the serotonin 5-HT, antagonist ondansetron attenuates the BDZ withdrawal in animals (Oakley et al., 1988; Goudie and Leathley, 1990). However, this subject is controversial (Costall et al., 1988).

C. Barbiturates Action on cellular level

Similar to alcohol and BDZs, the barbiturates have also binding site on the GABA A receptor-complex, which is claimed to be different from that of alcohol (Korpi and Seeburg, 1993) and BDZs (Haefely, 1980). Recently, it was demonstrated that a barbiturate binding site is also present on the nicotinic acetylcholinergic receptors (nAChRs, De Armendi et al., 1993).
Chapter 1 Definition of terms and classification of dependence-producing drugs

Written by Suzanne Cappendijk
Sunday, 03 January 2010 00:00

Tolerance

Tolerance to barbiturates develops to a marked degree and it is partly of a pharmacokinetic type. Repeated dosage of the drug is destroyed more rapidly (becomes somewhat less effective), because of the increased synthesis of hepatic cytochrome P450 and conjugating enzymes, which facilitate the biotransformation of barbiturates (Priest, 1980).

Withdrawal syndrome

A cessation of chronic use of barbiturates induces withdrawal syndromes sometimes accompanied with grand mal type convulsions or delirium tremens (Lockhart-Ewart and Priest, 1967). BDZs block the withdrawal seizures in subjects made dependent on barbiturates (Haefely, 1980).

1.2.2. Cannabinoids

(-)-A9-Tetrahydrocannabinol (A9-THC, also called delta-THC according to different ringnumbering system) has been recognized for a long time as the major psycho-active component of marijuana (Gaoni and Mechoulam, 1964). The mechanism by which cannabinoids exert their behavioral effects in humans and animals, has recently been partially clarified.

Action on cellular level
Cannabinoid receptor. The cloning of central (Matsuda et al., 1990) and peripheral (Munro et al., 1993) cannabinoid receptors was performed recently. Autoradiographic studies showed a heterogenous distribution of the cannabinoid receptor in brain of a variety of mammalian species, including humans. Most of the cannabinoid receptors are located in the basal ganglia, hippocampus and cerebellum, but also in cerebral cortex and striatum (Herkenham et al., 1990, 1991). It could be speculated that some of these anatomical sites correlate with observed pharmacological effects of marijuana, for example, cognitive impairment (hippocampus and cortex), ataxia (basal ganglia and cerebellum) and low toxicity (lack of receptors in brainstem) (Howlett et al., 1990; Martin et al., 1991). In the substantia nigra of humans, cannabinoid receptors are located on striatonigral terminals, which degenerate in Huntington's disease (Glass et al., 1993). These findings indicate that cannabinoids could be involved in locomotion and hyperkinetic/dystonic disorders, occurring in both Huntington's and Parkinson's disease.

Endogenous lig and. Devane et al. (1992) demonstrated the existence of an endogenous cannabimimetic ligand, anandamide. The fact that anandamide could inhibit the N-type calcium channel current through the cannabinoid receptors (Mackie and Hille, 1992) could suggest a physiological role of this compound in the regulation of the release of other neurotransmitters (Mackie et al., 1993). Anandamide has only been tested in vivo in rodents and it was shown that the effects of this compound (hypomotility, hypothermia and nociception) have a rapid onset but shorter duration than other cannabinoids (Fride and Mechoulam, 1993; Crawley et al., 1993). Besides anandamide, other receptor selective agonists are: A-THC, CP 55940, WIN 55,212-2, levonantradol and nabilone. The activation of cannabinoid receptors is associated with a decrease of cyclic adenosine monophosphate (cAMP). A selective receptor antagonist is not known yet (The RBI hand book of receptor classification, 1994).

Tolerance

Tolerance to repeated use of marijuana has long been suspected, given the fact that experienced users are capable of consuming enormous quantities of the drug with few or no obvious ill effects (Cohen, 1976). Tolerance to cannabinoids in animals has also been reported (Carlini, 1968). Recently, it has been demonstrated that chronic administration of the selective
cannabinoid receptor agonists A9-THC and CP 55940, induced a receptor down-regulation. This indicates that tolerance to cannabinoids in vivo could occur (Oviedo et al., 1993).

Withdrawal syndrome

Discontinuation of cannabis after chronic heavy use induces a mild withdrawal syndrome in humans, characterized by irritability, restlessness, loss of appetite, sleeplessness, tremor, perspiration and sometimes nausea, vomiting and diarrhoea (Jones, 1983; Goldstein, 1994). In animals, withdrawal symptoms did not occur following cessation of cannabinoid use (McMillan et al., 1971).

1.2.3. Hallucinogens

The family of the hallucinogens is a very diverse one, with many naturally occurring and synthetic compounds with similar mind-altering effects.

Natural occurring compounds:

• psilocin is obtained from a fungus and is structurally related to serotonin (5-HT, Wasson, 1980).
Chapter 1 Definition of terms and classification of dependence-producing drugs

Written by Suzanne Cappendijk
Sunday, 03 January 2010 00:00

• mescaline is derived from a Mexican cactus (peyote). Its structure is almost identical to that of amphetamine, which in its turn is closely related to that of DA (Jaffe, 1990).

Synthetic compounds:

• LSD is chemically related to 5-HT and is considered as one of the most potent hallucinogenic drugs (Schultes and Hofmann, 1979).

• MDMA (3,4-methylenedioxymethamphetamine, "ecstasy") belongs to the group of phenethylamines and is chemically related to amphetamines. In rats, MDMA causes massive destruction of 5-HT neurons (Rosecrans et al., 1988). The neurotoxic effect may be due not to MDMA itself, but rather to a product of the metabolism of MDMA in the body. Although there are not yet hard evidences that MDMA could cause brain damage in humans, it is striking that relatively many people die after MDMA intake (Henry et al., 1992). In the last years, a lot of phenethylamine derivatives are brought on the market. These derivatives, sold in the form of pills are mostly used during house-parties and in combination with alcohol are causing severe side-effects (respiration problems, hyperthermia) and could even lead to death.

• PCP (phencyclidine, "angel dust"), chemically resembling to ketamine, induces an increased locomotor activity, stereotyped movements and ataxia, although in animals depressant rather than stimulant effects predominate (Sanger and Jackson, 1989).

Action on cellular level

Many hallucinogens affect the serotonergic (5-HT-ergic) system in the brain, causing a massive discharge of 5-HT from the 5-HT-ergic neurons, followed by prolonged depletion of the neurotransmitter (Strassman, 1992).
LSD acts as a 5-HT antagonist in peripheral tissue, but in CNS it is believed mainly to work as an agonist. Neurophysiological studies show that LSD directly inhibits the firing of 5-HT-containing neurons in the raphe nuclei, apparently by activation of inhibitory autoreceptors of these cells (Aghajanian, 1981).

PCP interacts with NMDA receptors as a noncompetitive antagonist (Kemp et al., 1987). It was shown that following chronic infusion of PCP a significant decrease of D2 receptors in rat striatum occurred (Spain et al., 1985). PCP and also MDMA are relatively selective neurotoxins, affecting mainly 5-HT neurons (Rosecrans et al., 1988).

Tolerance

LSD. Tolerance to the effects of LSD develops quite quickly, and there is crosstolerance between this drug and most other hallucinogens. Animals trained to discriminate LSD respond almost identical to the presentation of psilocybin (Carlton, 1983).

PCP. Chronic PCP administration has been shown to produce tolerance to the behavioral actions of PCP (Nabeshima et al., 1985).

Withdrawal syndrome

LSD induces psychic- but not physical dependence (Stolerman, 1992).

PCP, in contrast to LSD, acts consistently as a primary reinforcer in animals experiments,
inducing drug dependence (Carlton, 1983; Stolerman, 1992). Withdrawal of PCP after infusion for 7 days resulted in an abstinence syndrome in rats, comparable to that of opioids (piloerection, increased susceptibility to audiogenic sounds, weight loss). The first withdrawal's signs occurred around 4 h after termination of infusion, and in the following 20 h, the abstinence syndrome subsides (Spain and Klingman, 1985). Buspirone is used for the treatment of PCP (and cocaine) withdrawal syndrome (Giannini et al., 1993).

1.2.4. Tobacco

Nicotine appears to be the only pharmacologically active substance in tobacco smoke, apart from carcinogenic tars. It is proved to be extreme difficult to induce animals to selfadminister nicotine. This has led to the incorrect idea that nicotine is not addictive. However, a recent study demonstrated that stimulation of the mesolimbic DA system could be considered of major importance for the rewarding and dependence producing properties of nicotine (Nisell et al., 1994).

Action on cellular level

Nicotine affects several neurotransmitter systems, but its main effect is on central nAChRs. Several studies have revealed that nAChRs not only are present on cholinergic neurons (Clarke, 1993), but appear to be also located on a variety of pre- and postsynaptic sites of noncholinergic neurons (Rosecrans and Karan, 1993). This may indicate that several neuronal pathways are involved in the tobacco dependence phenomena. Recently, it has been shown that the presynaptic nicotinic binding site in mouse could be involved in the DA release (Grady et al., 1994). Systematically administered nicotine increases frontocortical 5-HT release, probably due to the activation of the nicotinic receptors on raphe neurons (Ribeiro et al., 1993).

Tolerance

An upregulation of brain nicotinic receptors during tolerance to nicotine was ascribed to receptor desensitization (Marks et al., 1993). Cross-tolerance with nicotine has been shown for alcohol (De Fiebre and Collins, 1993).
Withdrawal syndrome

A withdrawal syndrome occurs in both humans and experimental animals following the cessation of regular nicotine administration. Its main features are impaired performance of psychomotor tasks, aggressiveness and sleep disturbance (Griffith and Henningfield, 1982; Goldstein, 1994). The physical withdrawal syndrome disappears in 2-3 weeks, though craving for cigarettes persists for much longer. The withdrawal syndrome is much less severe than that produced by opioids and it can be alleviated not only by nicotine but also by amphetamine. This latter point suggests that the effect of nicotine may be partly due to catecholamine release in the brain, an hypothesis advanced for other dependence-producing drugs (Koob and Bloom, 1988).

Various therapeutic products have been developed in order to help the nicotine user to get rid of their addiction. This so called "nicotine replacement therapy" includes the followings:

- Clonidine is shown to decrease dose-dependently the tobacco withdrawal craving (Gourlay et al., 1994), perhaps by reducing the sympathetic arousal (Hughes, 1993).

- Sertraline, a 5-HT reuptake inhibitor, counteracts the hyperphagia and rapid weight gain associated with nicotine withdrawal, and might be a useful adjunct to smoking cessation (Levin et al., 1993).

- The skin patches are claimed to improve a smoking cessation both by reducing nicotine withdrawal effects and by reducing the reward of slips back to smoking (Levin et al., 1994).

- Transdermal nicotine is effective even given without psychotherapy, but does not consistently decrease postcessation weight gain, which is similar for the nicotine gum (Hughes, 1993). However, controversial results on the effectiveness of both nicotine gum and patch were reported (Tang et al., 1994).
Until now, no uniform therapy for helping nicotine-addicts is available. Recently, treatment with antidepressant drugs has started, but there are no results in respect to the treatment of nicotinic addiction come out yet.

1.2.5. Volatile solvents

Harmful use of volatile substances, also referred to as glue sniffing is defined as "the deliberate inhalation of a gas or of fumes given off from a substance at room temperature for its intoxicating effect" (cited by Chalmers, 1991). These category of drugs include a variety of chemical products such as petrol, anaesthetic gases, volatile nitrites, organic solvents, and are present in an array of household and commercial products, aerosols, fire extinguisher chemicals and natural gases (Chalmers, 1991).

Epidemiological study of deaths from harmful use of volatile substances in people under 18 years showed that 605 people died in United Kingdom in the period 1981-1990, and nearly as four times as many deaths occurred in the social lower class (Esmail et al., 1993).

Action on cellular level

There are indications that these drugs could act on GABA receptors in much the same way as alcohol does, however the precise mechanism of action is still unclear (Goldstein, 1994).

1.2.6. Opioids and Psychostimulants

The opioids and psychostimulants were used in our experimental studies and therefore, are discussed in more details (see chapter 2 and chapter 8).

References
Chapter 1 Definition of terms and classification of dependence-producing drugs


Carlini EA, Tolerance to chronic administration of cannabis sativa (marihuana) in rats, Pharmacology 1: 135-142, 1968.


De Armendi AJ, Tonner PH, Bugge B, Miller KW and Phil D, Barbiturate action is dependent on the conformational state of the acetylcholine receptor, Anesthesiology 79: 1033-1041, 1993.

De Fiebre CM and Collins AC, A comparison of the development of tolerance to ethanol and cross-tolerance to nicotine after chronic ethanol treatment in long- and short sleep mice, J Pharmacol Exp Ther 266: 1398-1406, 1993.


Fride E and Mechoulam R, Pharmacological activity of the cannabinoid receptor agonist


Jones RT, Cannabis and Health Hazards, KO Fehr and H Kalant (eds.), Springer-Verlag, New York, pp. 617-689, 1983.


Chapter 1 Definition of terms and classification of dependence-producing drugs

Korpi ER and Seeburg PH, Natural mutation of GABA \( \text{A} \) receptor \( \text{a6} \) subunit alters benzodiazepine affinity but not allosteric GABA effects, Ear J Pharmacol 247: 23-27, 1993.


Nagasawa HT, DeMaster EG, Redfern B, Shiruta FN and Goon DJW, Evidence for nitroxyl in the catalase-mediated bioactivation of the alcohol deterrent agent cyanamide, J Med Chem 33:
Chapter 1 Definition of terms and classification of dependence-producing drugs

Written by Suzanne Cappendijk
Sunday, 03 January 2010 00:00

3120-3122, 1990.


Nisell M, Nomikos GG and Svensson TH, Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area, Synapse 16: 36-44, 1994.


Chapter 1 Definition of terms and classification of dependence-producing drugs

Written by Suzanne Cappendijk
Sunday, 03 January 2010 00:00


