CANNABINOIDS TOXICITY

Cannabis is a collective term referring to the bioactive substances from Cannabis sativa.

The C. sativa plant contains a group of more than 60 chemicals (C21 group) called cannabinoids.

The major cannabinoids are cannabinol, cannabidiol, and tetrahydrocannabinol
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The principal psychoactive cannabinoid is Δ9-tetrahydrocannabinol (THC).

Marijuana is the common name for a mixture of dried leaves and flowers of the C. sativa plant.
Hashish and hashish oil are the pressed resin and the oil expressed from the pressed resin, respectively.
The concentration of THC varies from 1% in low-grade marijuana up to 50% in hash oil. Pure THC and a synthetic cannabinoid are available by prescription with the generic names of dronabinol and nabilone, respectively. Currently, marijuana is the most commonly used illicit xenobiotic in the United States.

MEDICAL USES

Cannabinoids are proposed for use in the management of many clinical conditions , but have generally only been approved for the control of chemotherapy-related nausea and vomiting that are resistant to conventional antiemetics, for breakthrough postoperative nausea and vomiting,

and for appetite stimulation in human immunodeficiency virus (HIV) patients with anorexia-cachexia syndrome.

Medical Conditions Proposed for Cannabinoid Use

Anorexia-cachexia syndrome secondary to HIV infection[a]
Anxiety
Asthma
Depression
Epilepsy
Glaucoma
Head injury
Insomnia
Migraine headaches
Multiple sclerosis
Muscle spasticity and spasms
Nausea and vomiting (resistant)[a]
Neurologic disorders
Pain
Parkinson disease
Tourette syndrome

[a] FDA approved use.

Δ9-THC (sometimes referred to in the literature as Δ1-THC) was isolated in 1964. After that, two specific G protein–coupled cannabinoid-binding receptors were identified: CB1 (or Cnr1) and CB2 (or Cnr).

Both receptors inhibit adenylyl cyclase and stimulate potassium channel conductance. CB1 receptors are distributed throughout the brain.

CB1 receptors are located presynaptically and their activation inhibits the release of acetylcholine, L-glutamate, γ-aminobutyric acid, noradrenaline, dopamine, and 5-hydroxytryptamine.?

CB2 receptors are located peripherally in immune system tissues (splenic macrophages), B lymphocytes, peripheral nerve terminals, and the vas deferens. ?

Other brain regions in which the CB1 receptors are found include areas responsible for anxiety, pain, sensory perception, motor coordination, and endocrine function. This distribution is consistent with the clinical effects elicited by cannabinoids.

CB2 receptors are believed to participate in the regulation of immune responses and inflammatory reactions.

Activity at the CB1 receptors is believed to be responsible for the clinical effects of cannabinoids, including the regulation of cognition, memory, motor activities, nociception, and nausea and vomiting.

Chronic administration of a cannabinoid agonist reduces CB1 receptor density in several regions of the rat brain. ?

Cannabis is available in several forms:

1. Marijuana is a combination of the *C sativa* flowering tops and leaves. The THC content is 0.5-5%.
2. Hashish is dried resin collected from the flowering tops. The THC concentration is 2-20%. Hash oil is a liquid extract; it contains 15% THC.

Absorption:

The route of administration determines the absorption of the cannabis product, as follows:

- Smoking – Onset of action is rapid (within minutes); it results in 10-35% absorption of the available THC; peak plasma concentrations occur within 8 minutes.
- Ingestion – Onset occurs within 1-3 hours (unpredictable); 5-20% is absorbed due to stomach acid content and metabolism; peak plasma levels occur 2-6 hours after ingestion.

Absorption of synthetic forms is as follows:

- Dronabinol (Marinol) – 10% absorption; peak concentration 2-3 hours after ingestion.
- Nabilone (Cesanet) – Up to 90% absorption; peak concentration in 2 hours after ingestion.

Distribution:

THC has a steady-state volume of distribution of approximately 2.5 to 3.5 L/kg. Cannabinoids are lipid soluble and accumulate in fatty tissue in a biphasic pattern. Initially, THC is distributed to highly vascularized tissues such as the liver, kidneys, heart, and muscle.

Following smoking or intravenous administration, the distribution half-life is less than 10 minutes. After the initial distribution phase, THC accumulates more slowly in less vascularized tissues and body fat. Once administration of Δ8-THC stopped, the cannabinoids were slowly released from fat stores as adipose tissue turned over.

THC crosses the placenta and enters the breast milk. Concentrations in fetal serum are 10% to 30% of maternal concentrations.

Daily marijuana smoking by a nursing mother resulted in concentrations of THC in breast milk that are eightfold higher than concomitant maternal serum concentrations.

Metabolism:
THC is nearly completely metabolized by hepatic microsomal hydroxylation and oxidation by the cytochrome P450 system (primarily CYP2C9 and CYP3A4).

The primary metabolite (11-hydroxy-Δ9-THC or 11-OH-THC) is active and is subsequently oxidized to the inactive 11-nor-Δ9-THC carboxylic acid metabolite (THC-COOH) and many other metabolites.

Clinical Manifestation:

The clinical effects of THC use, including time of onset and duration of effect, vary with the dose, the route of administration (ingestion is slower in onset than inhalation), the experience of the user, the user's vulnerability to psychoactive effects, and the setting in which the drug is used.

The concomitant use of central nervous system depressants such as ethanol, or stimulants such as cocaine, alters the psychological and physiologic effects of cannabis.

ACUTE TOXICITY:

Acute toxicity may include decreases in coordination, muscle strength, and hand steadiness. Lethargy, sedation, postural hypotension, inability to concentrate, decreased psychomotor activity, slurred speech, and slow reaction time also may occur.

In young children, the acute ingestion of cannabis is potentially life threatening. Ingestion of estimated amounts of 250 to 1000 mg of hashish resulted in obtundation in 30 to 75 minutes. Tachycardia (>150 beats/min) was found in one-third of the children.

Less commonly reported findings include apnea, cyanosis, bradycardia, hypotonia, and opisthotonus.

ACUTE ADVERSE REACTIONS

Cannabis users occasionally may experience distrust, dysphoria, fear, or panic reactions. Transient psychotic episodes are associated with cannabis use.

Commonly reported adverse reactions at the prescribed dose of dronabinol or nabilone include postural hypotension, dizziness, sedation, xerostomia, abdominal discomfort, nausea, and vomiting. Life-threatening ventricular tachycardia (200 beats/min) has been reported.

Large doses of THC may produce confusion, amnesia, delusions, hallucinations, anxiety, and agitation. Most episodes remit rapidly.

However, a clear relationship exists between long-term cannabis use and mental health problems. Substance-abusing adolescents commonly suffer one or more comorbid health or behavioral problems. Several studies have demonstrated marijuana abuse to coexist with attention deficit hyperactivity disorder, other learning disabilities, depression, and anxiety. Cohort and well-designed cross-sectional studies suggest a modest association between early, regular, or heavy cannabis use and depression

CHRONIC USE ADVERSE EFFECTS

Long-term use of cannabis is associated with a number of adverse effects.

Cardiovascular effects

These include the following:

- Naive users may experience a sudden 20-100% rise in heart rate, lasting up to 2-3 hours
- Peripheral vasodilatation causes postural hypotension, which may lead to dizziness or syncope
- Cardiac output increases by as much as 30%, and cardiac oxygen demand is also increased; tolerance to these effects can develop within a few days of use
- Naive users can experience angina; in addition, users with preexisting coronary artery disease or cerebrovascular disease may experience myocardial infarctions, congestive heart failure, and strokes

Respiratory effects:

Respiratory effects include the following:

- Transient broncho-dilatation may occur after an acute exposure.

- With chronic heavy smoking, users experience increased cough, sputum production, and wheezing. These complaints are augmented by concurrent tobacco use.

- One study sites that the rate of decline of respiratory function in an 8-year period was greater among marijuana smokers than among tobacco smokers.

- Aside from nicotine, marijuana cigarettes contain some of the same components as tobacco smoke, including bronchial irritants, tumor initiators (mutagens), and tumor promoters. The amount of tar in a marijuana cigarette is 3 times the amount in a tobacco cigarette when smoked, with one-third greater deposition in the respiratory tract.
- Chronic cannabis use is associated with bronchitis, and emphysema.

- Several case reports strongly suggest a link between cannabis smoking and cancer of the aerodigestive system, including the oropharynx and tongue, nasal and sinus epithelium, and larynx.

Most illegally obtained marijuana is contaminated with *Aspergillus* species, which can cause invasive pulmonary aspergillosis in immunocompromised users.

Reproductive effects

These include the following:

- High-dose THC in animals causes a drop in testosterone levels, decreased sperm production, and compromised sperm motility and viability.

- THC alters the normal ovulatory cycle.

Cannabis administration during pregnancy reduces birth-weight in animals. However, studies are equivocal in humans. No evidence exists that cannabis increases the risk of birth defects.

Abuse, Dependence, and Withdrawal:

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, defines marijuana abuse as repeated instances of use under hazardous conditions; repeated, clinically meaningful impairment in social/occupational/educational functioning; or legal problems related to marijuana use.

The amount, frequency, and duration of cannabis use required to develop dependence are not well established.
Much of the support for cannabis dependence is based on the existence of a withdrawal syndrome.
In animals repeatedly given cannabis, the administration of a CB1 receptor antagonist produced signs of withdrawal.
In humans, chronic users experience unpleasant effects when abstaining from cannabis. The time of onset of withdrawal symptoms is not well characterized. The most reliably reported effects are irritability- restlessness-nervousness and appetite and sleep disturbances. Other reported acute withdrawal manifestations include tremor, diaphoresis, fever, and nausea. These symptoms and signs are reversed by the oral administration of THC42.
The duration of withdrawal manifestations, without treatment, is not clearly established

Management:

Gastrointestinal decontamination is not recommended for patients who ingest cannabis products, nabilone, or dronabinol because clinical toxicity is rarely serious and responds to supportive care.

In addition, a patient with a significantly altered mental status, such as somnolence, agitation, or anxiety, has risks associated with gastrointestinal decontamination that outweigh the potential benefits of the intervention.

Agitation, anxiety, or transient psychotic episodes should be treated with quiet reassurance and benzodiazepines (lorazepam 1–2 mg intramuscularly or diazepam 5–10 mg intravenously) or antipsychotics (haloperidol, ziprasidone) as needed.

There are no specific antidotes for cannabis. Coingestants, such as cocaine or ethanol, should be identified and their effects anticipated and treated as indicated.

Lysergic Acid Diethylamide (LSD)

LSD was first synthesized on November 16, 1938 by Swiss chemist Albert Hofmann at the Sandoz Laboratories in Basel, Switzerland as part of a large research program searching for medically useful ergot alkaloid derivatives.
Lysergic acid diethylamide (LSD) is the synthetic diethylamide derivative of ergot alkaloids, and was originally synthesized exclusively from these alkaloids produced by the fungus Claviceps purpurea, which is a contaminant of rye and certain other grains.

Today, most LSD is synthesized entirely in the laboratory, and typically sold to addicts as liquid-impregnated blotting paper or sugar cubes, tiny tablets ("microdots"), gelatin squares ("window panes"), liquid, or powder. LSD is said to be the most powerful of all hallucinogens, and is active in doses of 50 to 100 mg. It occurs as a water-soluble, colorless, tasteless and odorless powder.

Drugs related to LSD (lysergamides) also occur naturally in plants such as “Morning glory” (Rivea corymbosa) and “Hawaiian baby woodrose” (Ipomoea violacea).

Seeds of morning glory contain lysergic acid hydroxyethylamide, which is 1/10th as powerful as LSD. At least 200 to 300 seeds have to be pulverized—intact seed coat resists digestion—and ingested, for inducing hallucinogenic effects.

Mode of Intake

The LSD is almost always ingested. Other less common routes of intake include intranasal, sublingual, smoking, conjuctival instillation, and very rarely injection.

Mode of Action

The LSD is structurally related to serotonin (5-hydroxy- tryptamine) and is an agonist at the 5-HT1 receptor. Serotonin modulates many psychological and physiological processes including mood, personality, affect, appetite, sexual desire, motor function, temperature regulation, pain perception, and sleep induction. LSD inhibits central raphe neurons of brainstem through stimulation of 5-HT1A receptors, which are coupled to adenylcyclase. LSD is also an agonist at 5-HT2A, 2C receptors, which are not located presynaptically on serotonergic cell bodies but on certain subpopulations of neurons in postsynaptic regions. The majority of 5-HT2 receptors in the brain are located in the cerebral cortex. Animal experiments have shown that LSD is anatomically distributed maximally in the visual and auditory cortex, and the limbic cortex (besides the pituitary, pineal, and hypothalamic areas), which parallels the finding of high concentration of 5-HT2 receptors in human cerebral cortex. Recent studies also suggest that activation of D1 (dopamine) receptors may contribute to the neurochemical effects of LSD.

The LSD has a half-life of 2.5 hours, while the duration of effects lasts for up to 8 hours. But psychotropic effects can occur for several days, and urine-screen is usually positive for 100 to 120 hours. The route of metabolism is hepatic hydroxylation. The usual dose of abuse is 100 to 300 mcg. Doses over 0.2 mg/kg are potentially lethal.

Clinical (Toxic) Features

- **Acute Poisoning:**
- A.Physical:
- Mydriasis, hippus. – Vertigo. – Tachycardia, hypertension. – Sweating, piloerection. – Hyperthermia. – Tachypnoea. – Muscle weakness, ataxia. – Hyperactivity. – Coma.
- **B. Psychological**:
- Euphoria or dysphoria,
- hallucinations,
- Bizarre perceptual changes: People's faces and body parts appear distorted, objects undulate, sounds may be magnified and distorted, colors seem brighter with halos around objects. Occasionally there is depersonalisation, and the hallucinating person may feel as if he is observing an event instead of being involved in it.

•Chronic Poisoning:

a. Prolonged psychotic reactions, which are mainly schizophrenic in nature.

b. Severe depression.

c. Flashback phenomena: The person relives the LSD experience periodically in the absence of drug intake for months or years.

d. Post-hallucinogen perception disorder: A persistent perceptual disorder often described by the person as if he is residing in a bubble under water in a “purple haze”, with trailing of lights and images. Associated anxiety, panic, and depression are common.

Diagnosis

•Radioimmunoassay of serum or urine (limit of detection 0.1ng/ml).

•HPTLC (high performance thin layer chromatography) can detect LSD in urine in concentrations less than 1 mcg/litre.

•HPLC (high pressure/performance liquid chromatography) of serum and urine.

•GC-MS (gas chromatography–mass spectrometry) can confirm positive LSD urine levels to a lower limit of 5 pg/ml.

Treatment

- Avoid gut decontamination as LSD is ingested in micro- quantities and rapidly absorbed, rendering decontamination procedures totally redundant.
- Do not use restraints in agitated patients; it will only exacerbate the condition.
- Because of the short half-life and few serious medical reactions, elimination enhancement procedures such as haemodialysis, haemoperfusion, etc. are not warranted.
- Treat acute panic attacks with quiet environment, reas- surance, supportive care, and administration of diazepam (5–10 mg IV) or haloperidol (in severe cases).
- Treat acute psychotic reactions with cautious administration of neuroleptics such as haloperidol. Avoid phenothiazine, which can cause hypotension, sedation, extrapyramidal reactions, lowered seizure threshold, and potentiation of anticholinergic effects.
- Treat flashbacks with psychotherapy, anti-anxiety agents, and neuroleptics.
- Treat post-hallucinogen perception disorder with long- lasting benzodiazepines such as clonazepam, and to lesser extent anticonvulsants such as valproic acid and carbamazepine. This approach must be combined with behavioral therapy. The patient must be instructed not to consume alcohol, cannabis, caffeine, and other drugs, which can intensify the disorder.