The clinical toxicology of cannabis
Leo J Schep, Robin J Slaughter, Paul Glue, Paul Gee

ABSTRACT
Cannabis is one of the most widely used recreational drugs in the world. Tetrahydrocannabinol (THC) is the psychoactive principal constituent of the cannabis plant (Cannabis sativa). It is taken either orally or by inhalation, resulting in sedation, euphoria, relaxation and loss of social inhibition. Adverse effects from higher doses can include fear, distrust and a profound state of unease, hallucinations, ataxia, stupor and seizures. Long-term use can result in respiratory and cardiovascular toxicity and has been associated with a range of psychiatric conditions. Cannabinoid hyperemesis syndrome can occur with chronic use. Driving under the influence of THC is associated with approximately double the risk of motor vehicle crashes. The intensity and duration of symptoms is proportional to the concentration of THC in the blood. Following acute use, THC only remains in the blood for several hours before it is converted into a carboxylic derivative of THC and this partitions into the fat, from where it leaches out and can be detected in urine for weeks after use. Treatment of acute intoxication mainly consists of appropriate symptom-directed supportive care. Children are more susceptible to cannabis toxicity, particularly seizures and coma, and therefore may require additional supportive care for these potential symptoms. The aim of this narrative review is to provide a brief overview of the acute and chronic effects of cannabis, its pharmacokinetics, toxicity and the medical management of intoxication.

Natural cannabis is one of the most widely used recreational drugs in the world. The active constituent, trans-Δ9-tetrahydrocannabinol (THC), is one of approximately 64 different cannabinoids found within the cannabis plant (Cannabis sativa). This cannabinoid is psychoactive (affects the mind), whereas cannabidiol, present in very low concentrations in the plant, has some activity that is thought to offer some protection against some of the harmful effects of THC on cognition. The highest concentration of THC is found in the flowering tops of the female plant, with lesser concentrations in the leaves and minimal amounts in the stem, seeds and roots. Users of the drug typically smoke dried plant matter, though ingestion has become more popular, especially in countries where cannabis and its products have been legalised. Cannabis preparations, including hash oil and hashish, are also consumed. Refined cannabis extracts have been processed into candies or other products for ingestion and are commonly referred to as ‘edibles’. With the increasing popularity of e-cigarettes for nicotine administration, there has also been a rising prevalence of vaping cannabis. Vaping entails the vaporisation of cannabis in the form of concentrated THC oil extracts or dried cannabis buds or leaves by heating them to a temperature that releases a mixture of water vapour and THC for inhalation.

The percentage of THC in plant products smoked by users, as determined from confiscated samples, has been steadily increasing from about 3% in 1995 to 12% in 2012. In New Zealand this increase has risen from 1-3% in the 1960s up to 6-25% in the early 2000s (see Table 1). The associated doses consumed per cigarette have proportionally increased from 10-83mg per cigarette. Doses taken will be greater when users smoke cigar-like products.

Signs and symptoms
Recreational use of cannabis in adults produces a range of variable psychoactive effects. A low to moderate dose of cannabis may lead to signs and symptoms of either
sedation or stimulation, along with elevated mood/euphoria, relaxation, loss of social inhibition, increased appetite, increased heart rate, dilated pupils and conjunctival injection.\(^5,6\) Higher doses may produce more severe adverse effects including vomiting, hypertension, confusion, time-space distortions, hallucinations, tremors, ataxia, stupor and seizures.\(^6,8\) Occasionally, fear, paranoia/distrust, dysphoria (a profound state of unease or dissatisfaction that often occurs with depression, anxiety or agitation) or panic occurs after use.\(^8\) Impaired short-term memory, judgment and attention span may additionally occur.\(^8\)

Children tend to be more susceptible to severe toxicity. Toxicity can occur following ingestion of cannabis plant material or edible cannabis products. In children, central nervous system (CNS) depression is more common than excitatory effects.\(^8,10,11\) In severe cases rapid-onset sedation, ataxia, tachycardia, respiratory depression, coma and seizures may occur.\(^8,10\)

With the discovery of the endocannabinoid system, investigators have recognised the presence of endocannabinoid receptors (CBR) in not only the CNS and gastrointestinal tract but also the heart and peripheral vasculature. Case reports and studies have associated cannabis use with myocardial infarction, cardiac arrhythmias, cardiomyopathies, sudden death arteritis and stroke.\(^12\) In many reports, patients are young, healthy men with no prior cardiovascular risk factors. Increasing potency of natural cannabis can lead to an increasing risk of such complications occurring.

Another active cannabis constituent is cannabidiol, which acts as a CNS depressant. It is believed to antagonise some of the negative effects of THC such as agitation, anxiety and panic.\(^1\) Selective cannabis plant breeding has led to cultivars with a higher ratio of THC to cannabidiol.

Adverse effects of using THC products in vaping devices have also occurred, notably acute lung injury, although this, in part, may be due to additives, such as vitamin E acetate, added to the THC vaping products.\(^13,14\)

Subjects operating machinery or driving a motor vehicle are at risk of impaired performance resulting in an increased risk of injury. Evidence suggests that driving under the influence of THC is associated with approximately double the risk of motor vehicle crashes.\(^15,16\) In New Zealand, recent evidence from ESR, covering motor vehicle crashes between 2014 to 2018, showed that 27% of 787 blood samples obtained from deceased drivers killed in crashes had evidence of cannabis use, and, from 1,619 drivers who provided blood samples following a traffic accident, 37% of drivers had used cannabis.\(^17\) Consequently, Parliament has recently proposed legislation empowering police officers to perform random roadside oral fluid (saliva) testing for cannabis.\(^18\)

**Chronic use**

Chronic cannabis use can lead to a range of adverse effects, though many of the effects have not been fully established. Following chronic cannabis use, loss of cognitive ability and memory function may occur and the chances of experiencing psychotic symptoms and/or psychotic disorders are elevated, particularly if use began in adolescence and continued into adulthood.\(^16\) Pre-existing psychotic disorders may be exacerbated by cannabis use.\(^19\) Longitudinal studies in the Netherlands,\(^20\) Germany\(^21\) and New Zealand\(^22\) all indicate that the association of psychosis and cannabis use persists after adjustment for confounders. These investigations, and a recent meta-analysis,\(^23\) report a dose–response relation between frequency and amount of cannabis use.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Source</th>
<th>THC (%)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried plant matter</td>
<td>Cigarettes (1960–70s)</td>
<td>1–3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Cigarettes (1980–2000s)</td>
<td>6–25</td>
<td>20–83</td>
</tr>
<tr>
<td>Cannabis resin</td>
<td>Bricks, cakes, slabs</td>
<td>10–20</td>
<td></td>
</tr>
<tr>
<td>Hashish oil</td>
<td>Solvent extraction</td>
<td>15–65</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1:** Some forms of cannabis available in New Zealand and their THC content.
in individuals aged 18 years and subsequent risk of schizophrenia. It is estimated that 13% of schizophrenia cases could be averted if cannabis use was prevented. A large US population-based study reported significant associations (odds ratios; OR) between cannabis use and psychosis of 1.27 for lifetime cannabis use, 1.79 for lifetime cannabis abuse, and 3.69 for lifetime cannabis dependence. A systematic review and meta-analysis of 11 longitudinal and prospective studies reported that adolescent cannabis consumption was associated with increased risk of developing depression (pooled OR 1.3; 95% CI, 1.16–1.62; I²=0%) and suicidal ideation (OR 1.5; 95% CI, 1.11–2.03) and suicide attempts (OR 3.46; 95% CI, 1.53–7.84) in young adulthood.

Some users may display evidence of ‘amotivational syndrome’, which is a state of withdrawal, apathetic indifference, general mental and physical deterioration, along with a range of social problems. Further problems with oral, respiratory and cardiovascular health may occur. Tolerance and dependence may also develop. Research has suggested one in 10 regular cannabis users develops dependence. Additionally, long-term use of high doses of cannabis can lead to a condition called cannabis hyperemesis syndrome (CHS), characterised by excessive cyclic vomiting usually accompanied by abdominal pain without any obvious cause.

Overall, the risks of negative outcomes associated with chronic cannabis use seem to be most common in those who begin using in early to mid-adolescence, and/or use frequently, and/or are dependent.

**Toxicity**

The degree of impairment following use of THC is associated with plasma concentrations. One study, which examined the relationship between plasma THC concentrations and changes in heart rate and subjective effects following smoking of 19 mg THC, reported associations between these parameters (time to achieve peak concentration and pharmacodynamic effects, plus their respective durations). A more nuanced evaluation of pharmacokinetic/pharmacodynamic interactions has been reported using a compartmental model, taking into account distribution into various compartments. These authors reported a direct relationship between predicted THC and its active hydroxymetabolite effect-site concentrations and psychoactive effects.

There is, however, no clear demarcation between doses that achieve symptoms desired by a marijuana user and noxious effects. Variation will occur between different subjects. The associated peak plasma concentration may vary, depending on the route of exposure, the strength of the THC formulation, the dose consumed and, when smoked, the method of smoking.

Investigations with human volunteers have shown that smoking cannabis with doses of THC at 0.5 and 2.9% weight for weight (w/w) resulted in mild physiological changes with an elevated heart rate (increase in heart rate of 15 BPM and 57 BPM respectively). When normalised to an administered THC dose per kilogram body weight, at a low dose of either 0.12mg/kg oral or 0.05mg/kg smoking, volunteers reported mild changes in mood (typically euphoric), and altered sense of time, and visual and auditory perception, whereas at higher doses (0.3 to 0.48mg/kg oral and 0.2 to 0.25mg/kg smoked), subjects reported hallucinogenic effects.

Behavioural and physiologic effects appear rapidly after inhalation of a single cigarette containing 3.55% THC, correlating with plasma concentrations of 18ng/mL. Some research suggests THC psychoactive effects associated with 7–10ng/mL of THC can be equivalent to those associated with blood ethanol concentration of approximately 50mg/dL.

Clinical case reports of THC blood concentrations are rare. A 19-year-old male patient was found comatose, sweating with muscle rigidity after smoking a substance allegedly containing THC; a thorough clinical investigation revealed a blood specimen contained 180ng/mL (equivalent to a plasma concentration of 300ng/mL) by radioimmunoassay analysis.

**Pharmacokinetics**

THC, the primary psychoactive constituent of cannabis, is very lipophilic; upon absorption (typically following smoking plant matter or vaping, or ingesting edibles)
it is rapidly distributed in the body, particularly to the CNS, and to the adipose tissue, liver and lungs. The average bioavailability via smoking is 10–35% and, due to first pass metabolism, is reduced to 4–12% following ingestion. The volume of distribution of THC is 523–742L. Vaporisation and smoking provide comparable cannabinoid pharmacokinetics.

Peak THC blood concentrations occur within 5–9 minutes following smoking and 1–2 hours after oral ingestion. Due to rapid absorption and distribution following smoking, blood THC concentrations often briefly peak and then fall within 1–2 hours. In one study, for example, volunteers smoked approximately 33.8mg THC; peak concentrations averaged 162ng/mL and it was predominantly eliminated within 1.2 hours. Following ingestion, the peak is typically flatter and THC is more persistent in the blood. In one study, for example, ingestion of 15mg THC resulted in a median peak value of 3.6ng/mL at approximately 1–2 hours post-ingestion, and remained detectable for eight hours. Given the concentration of THC in available products has increased over the last few decades (see Table 1), the doses consumed have increased, thereby increasing the associated peak blood concentrations and related increased risk of adverse effects.

Vaping produces comparable drug effects and the time to achieve peak effects is similar to traditional smoking. However, when the same amounts of THC are vaped and smoked, vaporisation produces higher concentrations of THC and its metabolites in whole blood when compared to smoking.

Heavy smokers of cannabis can have evidence of THC remaining in the bloodstream for several days and it can still be detectable in excess of seven days post-consumption. In contrast, passive smoking can result in plasma concentrations ranging from 2–4ng/mL.

THC is metabolised to form an active metabolite, namely 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-THC). This metabolite is then rapidly metabolised to form a second, more persistent, non-active metabolite 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol (11-COOH-THC) (see Figure 1). The plasma half-life of THC following smoking is 1.6 hours but is typically extended up to 27 hours in chronic users. The acute half-lives of the two metabolites 11-OH-THC and 11-COOH-THC are 2.4 and 5.1 hours respectively. These values are higher in chronic users.

The 11-COOH-THC metabolite is eliminated from the body, but it also partitions into adipose tissue, where it can remain after consumption of the drug. The metabolite will then slowly leach from fat into the blood and be eliminated in the urine; 11-COOH-THC will be detectable in urine and will persist longer in regular drug users (urinary half-life 10–19 days) than for occasional users (urinary half-life ~3 days). The presence and persistence of this metabolite in the urine forms the basis of workplace drug testing.

**Treatment**

It is rare for smokers of natural cannabis to require medical assistance following occasional or light use. In most instances

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**Figure 1:** The metabolism of THC to form 11-OH-THC before undergoing further metabolism to form the carboxylic metabolite 11-COOH-THC.

![THC Metabolism Diagram](image)
of acute toxicity, treatment is supportive care. However, the use of products with increasing strengths of THC and devices that efficiently deliver THC may increase the risk of adverse effects such as seizures, respiratory or cardiovascular toxicity or injuries resulting from impaired driving or workplace accidents.

Children are more susceptible to the acute adverse effects of cannabis than adults.11 Edible cannabis products are available in many jurisdictions where cannabis has been legalised. These pose a special risk to children as they are often attractive to toddlers and a large dose can accidentally be ingested, and may lead, in some instances, to life-threatening symptoms.45,46 Paediatric patients may present with varying degrees of neurologic symptoms including altered mental status, ataxia, hypotonia and coma.45 Furthermore, there is the additional risk of seizures. Benzodiazepines are suggested as first-line treatment. Consciousness level and cardiorespiratory function must be monitored closely for deterioration.

In most instances with adults, management only requires observation and monitoring in a quiet environment with the administration of a benzodiazepine, when necessary. Additional supportive care may be required in cases where the patient has presented with symptoms following exposure to a substantial dose of cannabis. Their cardiovascular status may need to be monitored. Patients should be checked for hyperthermia or hypothermia. In instances of hypotension they may be managed with fluids and monitoring.

If patients are experiencing chest pain, they should be assessed for potential pneumothorax and pneumopericardium, acute coronary syndrome or myocardial infarction. Patients who present with cannabinoid hyperemesis syndrome should be checked for complications such as dehydration, kidney injury and Mallory-Weiss tears. Frequent hot showering is commonly reported to relieve symptoms and can trigger suspicion that CHS is the cause for vomiting when cannabis smoking has not been disclosed.27 CHS is usually resistant to conventional antiemetics. Haloperidol or droperidol by IV administration appear to be the most effective drugs to control nausea and vomiting.47,48 The application of capsaicin cream to the abdomen creates a sensation of heat on the skin and is reported to relieve mild symptoms—this may operate via the same unknown mechanism by which hot showers provide relief. Definitive treatment requires stopping the use of cannabis.27

Conclusions

In summary, use of the psychoactive constituent of cannabis, THC, can cause mild to moderate psychoactive effects including impairment of driving, that may persist for 2–3 hours after cannabis was used. At higher doses more serious adverse effects can occur, including fear, distrust and a profound state of unease, hallucinations, ataxia, stupor and seizures. Chronic use increases the risk of respiratory and cardiovascular toxicity and has been associated with a range of acute and chronic psychiatric conditions. THC remains in the blood for several hours only after acute use. It is metabolised into the carboxylic metabolite which then partitions into, and slowly leaches out of, adipose tissue. It can remain detectable in the urine for several weeks after use. Supportive care is the mainstay of treatment following acute toxicity. Children are more susceptible to cannabis toxicity and may require additional support.
Competing interests:
Dr Schep reports financial activities outside the submitted work from Toxinform Ltd. Dr Glue reports other from Douglas Pharmaceuticals, other from Janssen Pharmaceuticals, outside the submitted work.

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