Cannabinoids

GENERAL INFORMATION

Cannabis is the abbreviated name for the hemp plant *Cannabis sativa*. The common names for cannabis include marijuana, grass, and weed. Other names for cannabis refer to particular strains; they include bhang and ganja. The most potent forms of cannabis come from the flowering tops of the plants or from the dried resinous exudate of the leaves, and are referred to as hashish or hash. *Cannabis sativa* contains more than 450 substances and only a few of the main active cannabinoids have been evaluated.

Cannabis is the most commonly used illicit drug. In 2001, 83 million Americans and 37% of those aged 12 and older had tried marijuana [1]. The long history of marijuana use both as a recreational drug and as a herbal medicine for centuries has been reviewed [2].

In different Western countries the possible therapeutic use of cannabinoids as antiemetics in patients with cancer or in patients with multiple sclerosis has been debated, because of the prohibition of cannabis, and has polarized opinion about the seriousness of its adverse effects [3,4].

Pharmacology

The primary active component of cannabis is Δ9-tetrahydrocannabinol (THC), which is responsible for the greater part of the pharmacological effects of the cannabis complex. Δ8-THC is also active. However, the cannabis plant contains more than 400 chemicals, of which some 60 are chemically related to Δ9-THC, and it is evident that the exact proportions in which these are present can vary considerably, depending on the way in which the material has been harvested and prepared. In man, Δ9-THC is rapidly converted to 11-hydroxy-Δ9-THC [5], a metabolite that is active in the central nervous system. A specific receptor for the cannabinoids has been identified; it is a member of the G-protein-linked family of receptors [6]. The cannabinoid receptor is linked to the inhibitory G-protein, which is linked to adenylyl cyclase in an inhibitory fashion [7]. The cannabinoid receptor is found in highest concentrations in the basal ganglia, the hippocampus, and the cerebellum, with lower concentrations in the cerebral cortex.

When cannabis is smoked, usually in a cigarette with tobacco, the euphoric and relaxant effects occur within minutes, reach a maximum in about 30 minutes, and last up to 4 hours. Some of the motor and cognitive effects can persist for 5–12 hours. Cannabis can also be taken orally, in foods such as cakes (for example “space cake”) or sweetmeats (for example hashish fudge) [8].

Many variables affect the psychoactive properties of cannabis, including the potency of the cannabis used, the route of administration, the smoking technique, the dose, the setting, the user’s past experience, the user’s expectations, and the user’s biological vulnerability to the effects of the drug.

In research on the effects of cannabinoids the routes of administration include smoking a plant-derived cigarette, oral dronabinol (synthetic delta 9-tetrahydrocannabinol, THC), or intravenous THC. Each method has specific characteristics: cigarettes deliver a wide range of dosages, dronabinol has a slower onset of action and lower potency, and intravenous THC offers precise dose and timing [9]. Careful screening of subjects’ medical backgrounds and status and close monitoring during research participation are essential.

Animal and in vitro toxicology

Δ9-tetrahydrocannabinol, the active component in herbal cannabis, is very safe. Laboratory animals (rats, mice, dogs, monkeys) can tolerate doses of up to 1000 mg/kg, equivalent to some 5000 times the human intoxicant dose. Despite the widespread illicit use of cannabis, there are very few, if any, instances of deaths from overdose [10].

Long-term toxicology studies with THC were carried out by the National Institute of Mental Health in the late 1960s [11]. These included a 90-day study with a 30-day recovery period in both rats and monkeys and involved not only Δ9-THC but also Δ8-THC and a crude extract of marijuana. Doses of cannabis or cannabinoids in the range 50–500 mg/kg caused reduced food intake and lower body weight. All three substances initially depressed behavior, but later the animals became more active and were irritable or aggressive. At the end of the study the weights of the ovaries, uterus, prostate, and spleen were reduced and the weight of the adrenal glands was increased. The behavioral and organ changes were similar in monkeys, but less severe than those seen in rats. Further studies were carried out to assess the damage that might be done to the developing fetus by exposure to cannabis or cannabinoids during pregnancy. Treatment of pregnant rabbits with THC at doses up to 5 mg/kg had no effect on birth weight and did not cause any abnormalities in the offspring [11].

A similarly detailed toxicology study was carried out with THC by the National Institute of Environmental Health Sciences in the USA, in response to a request from the National Cancer Institute [12]. Rats and mice were given THC up to 500 mg/kg five times a week for 13 weeks; some were followed for a period of recovery over 9 weeks. By the end of the study more than half of the rats treated with the highest dose (500 mg/kg) had died, but all of the remaining animals appeared to be healthy, although in both species the higher doses caused lethargy and increased aggressiveness. The THC-treated animals ate less food and their body weights were consequently significantly lower than those of untreated controls at the end of the treatment period, but returned to normal during recovery. During this period the animals were sensitive to touch and some had convulsions. There was a trend towards reduced uterine and testicular weights.

In further studies rats were treated with doses of THC up to 50 mg/kg and mice with up to 500 mg/kg five times a week for 2 years in a standard carcinogenicity test [12]. After 2 years, more treated animals had survived than controls, probably because the treated animals ate less and had lower body weights. The treated animals also had a significantly lower incidence of the various cancers normally seen in aged rodents in testes, pancreas, pituitary gland, mammary glands, liver, and uterus. Although there
was an increased incidence of precancerous changes in the thyroid gland in both species and in the mouse ovary after one dose (125 mg/kg), these changes were not dose-related. The conclusion was that there was “no evidence of carcinogenic activity of THC at doses up to 50 mg/kg.” This was also supported by the failure to detect any genetic toxicity in other tests designed to identify drugs capable of causing chromosomal damage. For example, THC was negative in the so-called “Ames test,” in which bacteria are exposed to very high concentrations of a drug to see whether it causes mutations. In another test, hamster ovary cells were exposed to high concentrations of the drug in tissue culture; there were no effects on cell division that might suggest chromosomal damage.

By any standards, THC must be considered to be very safe, both acutely and during long-term exposure. This probably partly reflects the fact that cannabinoid receptors are virtually absent from those regions at the base of the brain that are responsible for such vital functions as breathing and blood pressure control. The available animal data are more than adequate to justify its approval as a human medicine, and indeed it has been approved by the FDA for certain limited therapeutic indications (generic name = dronabinol) [10].

**Respiratory**

There have been several attempts to address this question by exposing laboratory animals to cannabis smoke. After such exposure on a daily basis for periods of up to 30 months, extensive damage has been observed in the lungs of rats [13], dogs [14], and monkeys [15], but it is very difficult to extrapolate these findings to man, as it is difficult or impossible to imitate human exposure to cannabis smoke in any animal model.

**Nervous system**

Animal studies on neurotoxicity have yielded conflicting results. Treatment of rats with high doses of THC given orally for 3 months [16] or subcutaneously for 8 months [17] produced neural damage in the hippocampal CA3 zone, with shrunken neurons, reduced synaptic density, and loss of cells. But in perhaps the most severe test of all, rats and mice treated on 5 days each week for 2 years had no histopathological changes in the brain, even after 50 mg/kg/day (rats) or 250 mg/kg/day (mice) [12]. Although claims were made that exposure of a small number of rhesus monkeys to cannabis smoke led to ultrastructural changes in the septum and hippocampus [18,19], subsequent larger-scale studies failed to show any cannabis-induced histopathology in monkey brain [20].

Studies of the effects of cannabinoids on neurons in vitro have also yielded inconsistent results. Exposure of rat cortical neurons to THC shortened their survival: twice as many cells were dead after exposure to THC 5 µmol/l for 2 hours than in control cultures [21]. Concentrations of THC as low as 0.1 µmol/l had a significant effect. The effects of THC were accompanied by release of cytochrome c, activation of caspase-3, and DNA fragmentation, suggesting an apoptotic mechanism. All of the effects of THC could be blocked by the antagonist AM-251 or by pertussis toxin, suggesting that they were mediated through CB1 receptors. Toxic effects of THC have also been reported in hippocampal neurons in culture, with 50% cell death after exposure to THC 10 µmol/l for 2 hours or 1 µmol/l for 5 days [22]. The antagonist rimonabant blocked these effects, but pertussis toxin did not. The authors proposed a toxic mechanism involving arachidonic acid release and the formation of free radicals. On the other hand, other authors have failed to observe any damage in rat cortical neurons exposed for up to 15 days to THC 1 µmol/l, although they found that this concentration killed rat C6 glioma cells, human astrocytoma U373MG cells, and mouse neuroblastoma N18TG12 cells [23]. In a remarkable study, injection of THC into solid tumors of C6 glioma in rodent brain led to increased survival times, and there was complete eradication of the tumors in 20–35% of the treated animals [24]. A stable analogue of anandamide also produced a drastic reduction in the tumor volume of a rat thyroid epithelial cell line transformed by the KRAS oncogene, implanted in nude mice [25]. The antiproliferative effect of cannabinoids has suggested a potential use for such drugs in cancer treatment [26].

Some authors have reported neuroprotective actions of cannabinoids. WIN55212-2 reduced cerebral damage in rat hippocampus or cerebral cortex after global ischemia or focal ischemia in vivo [27]. The endocannabinoid 2AG protected against damage elicited by closed head injury in mouse brain, and the protective effects were blocked by rimonabant [28]. THC had a similar effect in vivo in protecting against damage elicited by ouabain [29]. Rat hippocampal neurons in tissue culture were protected against glutamate-mediated damage by low concentrations of WIN55212-2 or CP-55940, and these effects were mediated through CB1 receptors [30]. But not all of these effects seem to require mediation by cannabinoid receptors. The protective effects of WIN55212-2 did not require either CB1 or CB2 cannabinoid receptors in cortical neurons exposed to hypoxia [27], and there were similar findings for the protective actions of anandamide and 2-AG in cortical neuronal cultures [31]. Both THC and cannabidiol, which is not active at cannabinoid receptors, protected rat cortical neurons against glutamate toxicity [32] and these effects were also independent of CB1 receptors. The authors suggested that the protective effects of THC might be due to the antioxidant properties of these polyphenolic molecules, which have redox potentials higher than those of known antioxidants (for example ascorbic acid).

**Pregnancy**

In animals, THC can cause spontaneous abortion, low birth weight, and physical deformities [33]. However, these were only seen after treatment with extremely high doses of THC (50–150 times higher than human doses), and only in rodents and not in monkeys.

**Tolerance and dependence**

Many animal studies have shown that tolerance develops to most of the behavioral and physiological effects of THC.
Dependence on cannabinoids in animals is clearly observable, because of the availability of CB1 receptor antagonists, which can be used to precipitate withdrawal. Thus, a behavioral withdrawal syndrome was precipitated by rimonabant in rats treated for only 4 days with THC in doses as low as 0.5–4.0 mg/kg/day [35]. The syndrome included scratching, face rubbing, licking, wet dog shakes, arched back, and ptosis, many of the signs that are seen in rats undergoing opiate withdrawal. Similar withdrawal signs occurred when rats treated chronically with the synthetic cannabinoid CP-55940 were given rimonabant [36]. Rimonabant-induced withdrawal after 2 weeks of treatment of rats with the cannabinoid HU-120 was accompanied by a marked increase in release of the stress-related neuropeptide corticotropin-releasing factor in the amygdala, a result that also occurred in animals undergoing heroin withdrawal [37]. An electrophysiological study showed that precipitated withdrawal was also associated with reduced firing of dopamine neurons in the ventral tegmental area of rat brain [38].

These data clearly show that chronic administration of cannabinoids leads to adaptive changes in the brain, some of which are similar to those seen with other drugs of dependence. The ability of THC to cause selective release of dopamine from the nucleus accumbens [39] also suggests some similarity between THC and other drugs in this category.

Furthermore, although many earlier attempts to obtain reliable self-administration behavior with THC were unsuccessful [34], some success has been obtained recently. Squirrel monkeys were trained to self-administer low doses of THC (2 micrograms/kg per injection), but only after the animals had first been trained to self-administer cocaine [40]. THC is difficult to administer intravenously, but these authors succeeded, perhaps in part because they used doses comparable to those to which human cannabis users are exposed, and because the potent synthetic cannabinoids are far more water-soluble than THC, which makes intravenous administration easier. Mice could be trained to self-administer intravenous WIN55212-2, but CB1 receptor knockout animals could not [41].

Another way of demonstrating the rewarding effects of drugs in animals is the conditioned place preference paradigm, in which an animal learns to approach an environment in which it has previously received a rewarding stimulus. Rats had a positive THC place preference after doses as low as 1 mg/kg [42].

Some studies have suggested that there may be links between the development of dependence to cannabinoids and to opiates [43]. Some of the behavioral signs of rimonabant-induced withdrawal in THC-treated rats can be mimicked by the opiate antagonist naloxone [44]. Conversely, the withdrawal syndrome precipitated by naloxone in morphine-dependent mice can be partly relieved by THC [45] or endocannabinoids [46]. Rats treated chronically with the cannabinoid WIN55212-2 became sensitized to the behavioral effects of heroin [47]. Such interactions can also be demonstrated acutely. Synergy between cannabinoids and opiate analogues has been described above. THC also facilitated the antinociceptive effects of RB 101, an inhibitor of enkephalin inactivation, and acute administration of THC caused increased release of Met-enkephalin into microdialysis probes placed into the rat nucleus accumbens [48].

The availability of receptor knockout animals has also helped to illustrate cannabinoid–opioid interactions. CB1 receptor knockout mice had greatly reduced morphine self-administration behavior and less severe naloxone-induced withdrawal signs than wild type animals, although the antinociceptive actions of morphine were unaffected in the knockout animals [41]. The rimonabant-precipitated withdrawal syndrome in THC-treated mice was significantly attenuated in animals with knockout of the pro-enkephalin gene [49]. Knockout of the μ opioid (OP3) receptor also reduced rimonabant-induced withdrawal signs in THC-treated mice, and there was an attenuated naloxone withdrawal syndrome in morphine-dependent CB1 knockout mice [50,51].

These findings clearly point to interactions between the endogenous cannabinoid and opioid systems in the CNS, although the neuronal circuitry involved is unknown. Whether this is relevant to the so-called “gateway” theory is unclear. In the US National Household Survey of Drug Abuse, respondents aged 22 years or over who had started to use cannabis before the age of 21 years were 24 times more likely than non-cannabis users to begin using hard drugs [52]. However, in the same survey the proportion of cannabis users who progressed to heroin or cocaine use was very small (2% or less). Mathematical modeling using the Monte Carlo method suggested that the association between cannabis use and hard drug use need not be causal, but could relate to some common predisposing factor, for example “drug-use propensity” [53].

### Tumorigenicity

THC does not appear to be carcinogenic, but there is plenty of evidence that the tar derived from cannabis smoke is. Bacteria exposed to cannabis tar develop mutations in the standard Ames test for carcinogenicity [54], and hamster lung cells in tissue culture develop accelerated malignant transformations within 3–6 months of exposure to tobacco or cannabis smoke [55].

Three different associations of cannabinoids with cancer have been discussed [56]. Firstly, there is a possible direct carcinogenic effect. In in vitro studies and in mice tetrahydrocannabinol alone does not seem to be carcinogenic or mutagenic. However, cannabis smoke is both carcinogenic and mutagenic and contains similar carcinogens to those in tobacco smoke. Cannabis is possibly linked to digestive and respiratory system cancers. Case reports support this association but epidemiological cohort studies and case-control studies have provided conflicting evidence. Secondly, there is conflicting evidence on the beneficial effects of tetrahydrocannabinol and other cannabinoids in patients with cancer. In some in vitro and in vivo studies, tetrahydrocannabinol and synthetic cannabinoids had antineoplastic effects, but in others tetrahydrocannabinol had a negative effect on the immune system. Thirdly, cannabis may palliate some of the symptoms and adverse effects of cancer. Cannabis may improve appetite, reduce nausea and vomiting, and alleviate moderate neuropathic pain in patients with cancer. The authors defined the challenge for the medical use of
cannabinoids as the development of safe, effective, and therapeutic methods of using it that are devoid of the adverse psychoactive effects. Lastly, they discussed the possible associations between cannabis smoking and tumors of the prostate and brain, noting the need for larger, controlled studies.

**General adverse effects and adverse reactions in humans**

The evidence related to the adverse effects of acute and chronic use of cannabis has been summarized [57]. The effects of acute usage include anxiety, impaired attention, and increased risk of psychotic symptoms. Probable risks of chronic cannabis consumption include bronchitis and subtle impairments of attention and memory.

Adverse reactions to cannabis can be considered under two main headings, reflecting psychoactive and autonomic effects, in addition to which there are direct toxic effects. The most frequently reported psychoactive effects include enhanced sensory perception (for example, a heightened appreciation of color and sound). Cannabis intoxication commonly heightens the user’s sensitivity to other external stimuli as well, but subjectively slows the appreciation of time. In high doses, users may also experience depersonalization and derealization. Various forms of psychomotor performance, including driving, are significantly impaired for 8–12 hours after using cannabis. The most serious possible consequence of cannabis use is a road accident if a user drives while intoxicated.

Adverse reactions have been reported at relatively low doses and principally affect the psyche, leading to anxiety states, panic reactions, restlessness, hallucinations, fear, confusion, and rarely toxic psychosis. These reactions appear to be reversible [58]. Ingestion of cake containing cannabis by people who seldom use or have never used cannabis before can result in mental changes, including confusion, anxiety, loss of logical thinking, fits of laughter, hallucinations, hypertension, and/or paranoid psychosis, which can last as long as 8 hours.

The autonomic effects of cannabis lead to tachycardia, peripheral vasodilatation, conjunctival congestion, hyperthermia, bronchodilatation, dry mouth, nystagmus, tremor, ataxia, hypotension, nausea, and vomiting, that is a spectrum of effects that closely resembles the consequences of overdose with anticholinergic agents. Some individuals have sleep disturbances. Increased appetite and dry mouth are other common effects of cannabis intoxication.

Hypersensitivity reactions are rare, but a few have been reported after inhalation. Delayed hypersensitivity reactions, particularly affecting vascular tissue, have been recorded with chronic systemic administration. Tumor-inducing effects are difficult to attribute to cannabis alone. Animal studies have shown neoplastic pulmonary lesions superimposed on chronic inflammation, but such pathology may be primarily associated with the “tar” produced by burning marijuana. The most serious potential adverse effects of cannabis use come from the inhalation of the same carcinogenic hydrocarbons that are present in tobacco, and some data suggest that heavy cannabis users are at risk of chronic respiratory diseases and lung cancer.

**DRUG STUDIES**

**Observational studies**

In an open trial the safety, tolerability, dose range, and efficacy of the whole-plant extracts of Cannabis sativa were evaluated in 15 patients with advanced multiple sclerosis and refractory lower urinary tract symptoms [59]. The patients took extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg per spray) for 8 weeks followed by THC only for a further 8 weeks. Urinary urgency, the number and volume of incontinence episodes, frequency, and nocturia all reduced significantly after treatment with both extracts. Patients’ own assessments of pain, spasticity, and quality of sleep improved significantly, and the improvement in pain continued for up to a median of 35 weeks. Most of the patients had symptoms of intoxication, such as mild drowsiness, disorientation, and altered time perception, during the dose titration period. Three had single short-lived hallucinations that did not occur when the dose was reduced. All complained of a worsening of dry mouth that was already present from other treatments and two complained of mouth soreness at the site of drug administration.

Of 220 patients with multiple sclerosis in Halifax, Canada 72 (36%) reported ever having used cannabis [60]. Ever use of cannabis for medicinal purposes was associated with male sex, the use of tobacco, and recreational use of cannabis. Of the 34 medicinal cannabis users, 10 reported mild, 8 moderate and 1 strong adverse effects; none reported severe adverse effects. The most common adverse effects were feeling “high” (n=24), drowsiness [21], dry mouth [15], paranoia [3], anxiety [3], and palpitation [3].

**Placebo-controlled studies**

Cannabis has been used to treat many medical conditions, especially those involving pain and inflammation. Many studies with improved designs and larger sample sizes are providing preliminary data of efficacy and safety in conditions such as multiple sclerosis and chronic pain syndromes.

The effects of oral cannabinoids (dronabinol or Cannabis sativa plant extract) in relieving pain and muscle spasticity have been studied in 16 patients with multiple sclerosis (mean age 46 years, mean duration of disease 15 years) in a double-blind, placebo-controlled, crossover study [61]. The initial dose was 2.5 mg bd, increasing to 5 mg bd after 2 weeks if the dose was well tolerated. The plant extract was more likely to cause adverse events; five patients had increased spasticity and one rated an adverse event of acute psychosis as severe. All physical measures were in the reference ranges. There were no significant differences in any measure of efficacy score that would indicate a therapeutic benefit of cannabinoids. This study is the largest and longest of its kind, but the authors acknowledged some possible shortcomings. The route of administration could affect subjective ratings, since the gastrointestinal tract is a much slower and more inefficient route than the lungs. Another possibility is that the dose was too small to have the desired therapeutic effects.
In a parallel group, double-blind, randomized, placebo-controlled study undertaken at three sites in 160 patients with multiple sclerosis a cannabis-based medicinal extract containing equal amounts of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) at doses of 2.5–120 mg of each daily in divided doses for 6 weeks, spasticity scores were significantly improved by cannabis [62]. However, when the changes in symptoms were measured using the Primary Symptoms Scale, there were no significant differences between cannabis and placebo. The main adverse events were dizziness (33%), local discomfort at the site of application (26%), fatigue (15%), disturbance in attention (8.8%), disorientation (7.5%), a feeling of intoxication (5%), and mouth ulcers (5%).

In a randomized, double-blind, placebo-controlled, crossover trial the effect of the synthetic delta-9-tetrahydrocannabinol dronabinol on central neuropathic pain was evaluated in 24 patients with multiple sclerosis [63]. Oral dronabinol reduced central pain. Adverse events were reported by 96% of the patients compared with 46% during placebo treatment. They were more common during the first week of treatment. The most common adverse events during dronabinol treatment were dizziness (58%), tiredness (42%), headache (25%), myalgia (25%), and muscle weakness (13%). There was increased tolerance to the adverse effects over the course of treatment and with dosage adjustments.

Three cannabis-based medicinal extracts in sublingual form recently became available for use against pain. In a randomized, double-blind, placebo-controlled, crossover study for 12 weeks in 34 patients with chronic neuropathic pain THC extracts were effective in symptom control [64]. Drowsiness and euphoria/dysphoria were common in the first 2 weeks. Dizziness was less of a problem. Anxiety and panic were infrequent but occurred during the run-in period. Dry mouth was the most common complaint.

**ORGANS AND SYSTEMS**

**Cardiovascular**

Marijuana has several effects on the cardiovascular system, and can increase resting heart rate and supine blood pressure and cause postural hypotension. It is associated with an increase in myocardial oxygen demand and a decrease in oxygen supply. Peripheral vasodilation, with increased blood flow, orthostatic hypotension, and tachycardia, can occur with normal recreational doses of cannabis. High doses of THC taken intravenously have often been associated with ventricular extra beats, a shortened PR interval, and reduced T wave amplitude, to which tolerance readily develops and which are reversible on withdrawal. While the other cardiovascular effects tend to decrease in chronic smokers, the degree of tachycardia continues to be exaggerated with exercise, as shown by bicycle ergometry.

**Hypotension**

Postural syncope after marijuana use has been studied in 29 marijuana-experienced volunteers, using transcranial Doppler to measure cerebral blood velocity in the middle cerebral artery in response to postural changes [65]. They were required to abstain from marijuana and other drugs for 2 weeks before the assessment, as confirmed by urine drug screening. They were then given marijuana, tetrahydrocannabinol, or placebo and lying and standing measurements were made. When marijuana or tetrahydrocannabinol was administered, 48% reported a dizziness rating of three or four and had significant falls in standing cerebral blood velocity, mean arterial blood pressure, and systolic blood pressure. Eight subjects were so dizzy that they had to be supported. The authors suggested that marijuana interferes with the protective mechanisms that maintain standing blood pressure and cerebral blood velocity. All but one of the subjects who took marijuana or tetrahydrocannabinol reported some degree of dizziness. Women tended to be dizzier. As the postural dizziness was significant and unrelated to plasma concentrations of tetrahydrocannabinol or other indices, the authors raised concerns about marijuana use in those who are medically compromised or elderly.

Activation of cannabinoid CB1 receptors by cannabis or delta-9 tetrahydrocannabinol (THC) is associated with reduced blood pressure. The effects of rimonabant, a CB1 receptor antagonist, on blood pressure have been reported in 63 male cannabis smokers [66]. The smokers were assigned to eight groups and were pretreated with oral rimonabant (1, 3, 10, 30, 90 mg) or placebo. They smoked active (2.64% THC) or placebo marijuana cigarettes 2 and 6 hours after rimonabant. Cannabis alone had no consistent effect on blood pressure but 22% reported hypotensive symptoms (dizziness, lightheadedness) as did 20–33% of rimonabant recipients (1, 3, or 10 mg). Subjects who had symptomatic hypotension had higher mean peak plasma THC concentrations than those who did not. Rimonabant had a dose-dependent effect on the hypotensive response to cannabis. Subjects receiving the two highest doses, 30 and 90 mg, did not have symptomatic hypotension.

**Myocardial ischemia**

Marijuana use is most popular among young adults (18–25 years old). However, with a generation of post-1960s smokers growing older, the use of marijuana in the age group that is prone to coronary artery disease has increased. The cardiovascular effects may present a risk to those with cardiovascular disorders, but in adults with normal cardiovascular function there is no evidence of permanent damage associated with marijuana [58,67,68], and it is not known whether marijuana can precipitate myocardial infarction, although mixed use of tobacco and cannabis make the evaluation of the effects of cannabis very difficult.

Investigators in the Determinants of Myocardial Infarction Onset Study have reported that smoking marijuana is a rare trigger of acute myocardial infarction [69]. Interviews of 3882 patients (1258 women) were conducted on an average of 4 days after infarction. Reported use of marijuana in the hour preceding the first symptoms of myocardial infarction was compared with use in matched controls. Among the patients, 124 reported smoking marijuana in the previous year, 37 within 24 hours, and 9 within 1 hour of cardiac symptoms. The risk of myocardial
infarction was increased 4.8 times over baseline in the 60 minutes after marijuana use and then fell rapidly. The authors emphasized that in a majority of cases, the mechanism that triggered the onset of myocardial infarction involved a ruptured atherosclerotic plaque secondary to hemodynamic stress. It was not clear whether marijuana has direct or indirect hemodynamic effects sufficient to cause plaque rupture.

- Two young men, aged 18 and 30 years, developed retrosternal pain with shortness of breath, attributed to acute coronary syndrome [70]. Each had smoked marijuana and tobacco and admitted to intravenous drug use. Urine toxicology was positive for tetrahydrocannabinol. Aspartate transaminase and creatine kinase activities and troponin-I and C-reactive protein concentrations were raised. Echocardiography in the first patient showed hypokinesia of the posterior and inferior walls and in the second hypokinesia of the basal segment of the anterolateral wall. Coronary angiography showed normal coronary anatomy with coronary artery spasm. Genetic testing for three common genetic polymorphisms predisposing to acute coronary syndrome was negative.

The authors suggested that marijuana had increased the blood carboxyhemoglobin concentration, leading to reduced oxygen transport capacity, increased oxygen demand, and reduced oxygen supply.

Two other cases have been reported [71].

- A 48-year-old man, a chronic user of cannabis who had had coronary artery bypass grafting 10 years before and recurrent angina over the past 18 months, developed chest pain. An electrocardiogram showed intermittent resting ST segment changes and coronary angiography showed that of the three previous grafts, only one was still patent. There was also subtotal occlusion of a stent in the left main stem. After 24 hours he had a cardiac arrest while smoking cannabis and had multiple episodes of ventricular fibrillation, requiring both electrical and pharmacological cardioversion. He then underwent urgent percutaneous coronary intervention which involved stenting of his left main stem. He eventually stabilized and recovered for discharge 11 weeks later.

- A 22-year-old man had two episodes of tight central chest pain with shortness of breath after smoking cannabis. He had been a regular marijuana smoker since his mid-teens and had used more potent and larger amounts during the previous 2 weeks. An electrocardiogram showed resting ST segment elevation in leads V1–5, with reciprocal ST segment depression in the inferior limb leads. A provisional diagnosis of acute myocardial infarction was made. Thrombolysis was performed, but the electrocardiographic changes continued to evolve. Angiography showed intermittent resting ST segment changes and coronary angiography showed that the three previous grafts, only one was still patent. There was also subtotal occlusion of a stent in the left main stem. After 24 hours he had a cardiac arrest while smoking cannabis and had multiple episodes of ventricular fibrillation, requiring both electrical and pharmacological cardioversion. He then underwent urgent percutaneous coronary intervention which involved stenting of his left main stem. He eventually stabilized and recovered for discharge 11 weeks later.

- A 38-year-old Afro-Caribbean man was admitted after 3 months of severe constant ischemic pain and numbness affecting the right foot. The pain was worse at night. He also had intermittent claudication after walking 100 yards. He had a chronic history of smoking cannabis about 1 ounce/day, mixed with tobacco in the early years of usage. However, at the time of admission, he had not used tobacco in any form for over 10 years. He had patchy necrosis and ulceration of the toes and impalpable pulses in the right foot. The serum cotinine concentrations were consistent with those found in non-smokers of tobacco. Angiography of his leg was highly suggestive of Buerger’s disease (thromboangiitis obliterans).

Remarkably, this patient, despite having abstained from tobacco for more than 10 years, developed a progressive arteritis leading to ischemic changes. While arterial pathology with cannabis has been reported before, it has been difficult to dissociate the effects of other drugs.

In a case of cannabis-associated arteritis aspirin treatment resulted in revascularization [75].

- A 48-year-old woman developed necrosis of the right big toe and ultrasound showed complete occlusion of the large arteries below the knees bilaterally, but without atherosclerosis of the iliofemoral arteries, which might be expected in peripheral vascular disease. She stopped using marijuana and took aspirin 100 mg/day. Within 6 months all the arteries in the leg were patent and the toe had healed.

The authors suggested that aspirin could be effective in early intervention for cannabis-associated arteritis, making it important to distinguish arteritis from peripheral vascular disease.

Popliteal artery entrapment occurred in a patient with distal necrosis and cannabis-related arteritis, two rare or exceptional disorders that have never been described in association [76].

- A 19-year-old man developed necrosis in the distal third right toe, with loss of the popliteal and foot pulses. Arteriography showed posterior popliteal artery compression in the right leg and unusually poor distal vascularization in both legs. An MRI scan did not show a cyst and failed to identify the type of compression and the causal agent. Surgery showed that the patient had type III entrapment. Surprisingly, the pain failed to regress and the loss of distal pulses persisted despite a perfect result on the postoperative MRA scan. The patient then admitted consuming cannabis 10 times a day for 4 years, which suggested a Buerger-type arteritis related to cannabis.
consumption. A 21-day course of intravenous vasodilators caused the leg pain to disappear and the toe necrosis to regress. An MRA scan confirmed permanent occlusion of three arteries on the right side of the leg and the peroneal artery on the left side. Capillaroscopy excluded Buerger’s disease.

The authors suggested that popliteal artery entrapment in a young patient with non-specific symptoms should raise the suspicion of a cannabis-related lesion. Their review of literature suggested that this condition affects young patient and that complications secondary to popliteal artery entrapment did not occur in those who were under 38 years age.

**Cardiac dysrhythmias**
The dysrhythmogenic properties of cannabis appear to be influenced by the effects of tetrahydrocannabinol on action potential shortening and on vagal tone hyperstimulation. A case of Brugada-like syndrome has been reported [77].

- A healthy 19-year-old man suffered an attack of syncope lasting 2 minutes after heavy cannabis smoking. An electrocardiogram showed 2 mm ST segment elevation in leads V1 and V2. Two-dimensional echocardiography showed normal left ventricular function without any structural abnormalities. Investigation of vasovagal mediated syncope was negative. Urine and blood toxicology showed tetrahydrocannabinol. After resolution of the ST segment abnormalities, a procainamide induction test failed to elicit ST-T wave changes.

The authors suggested that the ST segment abnormalities may have been related to partial sodium channel opening secondary to marijuana.

Paroxysmal atrial fibrillation has been reported in two cases after marijuana use [78].

- A healthy 32-year-old doctor, who smoked marijuana 1–2 times a month, had paroxysmal tachycardia for several months. An electrocardiogram was normal and a Holter recording showed sinus rhythm with isolated supraventricular extra beats. He was treated with propranolol. He later secretly smoked marijuana while undergoing another Holter recording, which showed numerous episodes of paroxysmal atrial tachycardia and atrial fibrillation lasting up to 2 minutes. He abstained from marijuana for 12 months and maintained stable sinus rhythm.

- A 24-year-old woman briefly lost consciousness and had nausea and vomiting several minutes after smoking marijuana. She had hyporeflexia, atrial fibrillation (maximum 140/minute with a pulse deficit), and a blood pressure of 130/80 mmHg. Echocardiography was unremarkable. Within 12 hours, after metoprolol, propafenone, and intravenous hydration with electrolytes, sinus rhythm was restored.

The authors discussed the possibility that Δ9-THC can cause intra-atrial re-entry by several mechanisms and thereby precipitate atrial fibrillation.

Sustained atrial fibrillation has also been attributed to marijuana [79].

- A 14-year-old African-American man with no cardiac history had palpitation and dizziness, resulting in a fall, within 1 hour of smoking marijuana. After vomiting several times he had a new sensation of skipped heartbeats. The only remarkable finding was a flow murmur. The electrocardiogram showed atrial fibrillation. Echocardiography was normal. Serum and urine toxicology showed cannabis. He was given digoxin, and about 12 hours later his cardiac rhythm converted to sinus rhythm. Digoxin was withdrawn. He abstained from marijuana over the next year and was symptom free.

The authors noted that marijuana’s catecholaminergic properties can affect autonomic control, vasomotor reflexes, and conduction-enhancement of perinodal fibers in cardiac muscle, and thus lead to an event such as this.

- A 34-year-old man developed palpitation, shortness of breath, and chest pain. He had smoked a quarter to a half an ounce of marijuana per week and had taken it 3 hours before the incident. He had ventricular tachycardia at a rate of 200/minute with a right bundle branch block pattern. Electrical cardioversion restored sinus rhythm. Angiography showed a significant reduction in left anterior descending coronary artery flow rate, which was normalized by intra-arterial verapamil 200 micrograms.

The authors thought that marijuana may have enhanced triggered activity in the Purkinje fibers along with a reduction in coronary blood flow, perhaps through coronary spasm.

In terms of its potential for inducing cardiac dysrhythmias, cannabis is most likely to cause palpitation due to a dose-related sinus tachycardia. Other reported dysrhythmias include sinus bradycardia, second-degree atrioventricular block, and atrial fibrillation. Also reported are ventricular extra beats and other reversible electrocardiographic changes. Supraventricular tachycardia after the use of cannabis has been reported [80].

- A 35-year-old woman with a 1-month history of headaches was found to be hypertensive, with a blood pressure of 179/119 mmHg. She smoked 20 cigarettes a day and used cannabis infrequently. Her family history included hypertension. Electrocardiography suggested left ventricular hypertrophy but echocardiography was unremarkable. She was given amiodipine 10 mg/day and the blood pressure improved. While in the hospital, she smoked marijuana and about 30 minutes later developed palpitation, chest pain, and shortness of breath. The blood pressure was 233/120 mmHg and the pulse rate 150/minute. Electrocardiography showed atrial flutter with a 2:1 atrioventricular block. Cardiac troponin was normal at 12 hours. Urine toxicology was positive for cannabis only. Two weeks later, while she was taking amlodipine 10 mg/day and atenolol 25 mg/day, her blood pressure was 117/85 mmHg.

The authors reviewed the biphasic effect of marijuana on the autonomic nervous system. At low to moderate doses it causes increased sympathetic activity, producing a tachycardia and increase in cardiac output; blood pressure therefore increases. At high doses it causes increased parasympathetic activity, leading to Bradycardia and hypotension. They thought that this patient most probably had adrenergic atrial flutter.

**Respiratory**
Acute inhalation of marijuana or THC causes bronchodilation, but with chronic use resistance in the bronchioles increases [81,82]. Prolonged use of cannabis by inhalation can cause chronic inflammatory changes in the bronchial tree, in part related to the inhalants that accompany the smoke. In some cases attacks of asthma and glottal and uvular angioedema can occur. Reduced respiratory gas exchange has been reported in long-term smokers, and under experimental conditions THC can depress
respiratory function slightly and act as a respiratory irritant. In fact, chronic marijuana cigarette smoking and chronic tobacco cigarette smoking produce very similar changes, but these occur after smoking fewer cigarettes when marijuana is smoked, compared with tobacco-smoking. With marijuana inhalation, when a filter is never used, inhalation is deeper and the smoke is held in the lungs for longer than when smoking commercially produced tobacco-based cigarettes [83]. There is therefore a greater build-up of carbon monoxide, reduction in carboxyhemoglobin saturation, and alveolar cellular irritation with depression of macrophages [84]. Pneumothorax, pneumopericardium, and pneumomediastinum have been reported when positive pulmonary pressure is applied or a Valsalva maneuver used, as often happens [85,86].

Cannabis smoking can cause serious damage to the lungs [87]. “Bong lung” is a term that is used to refer to a histological change that occurs in the lungs of chronic cannabis smokers, characteristic of irregular emphysema [88,89]. Patients with cannabis-induced recurrent pneumothorax often undergo resection of bullae. In Australia, the histopathology of resected lung was examined in 10 cannabis smokers, 5 heavy tobacco smokers, and 5 non-smokers. All marijuana smokers had irregular emphysema with cystic blebs and bullae in the lung apices. There was also massive accumulation of intra-alveolar pigmented histiocytes or “smoker’s macrophages” throughout the pulmonary parenchyma, but sparing of the peribronchioles, similar to desquamative interstitial pneumonia.

- A 39-year-old man developed weight loss, fever, dry cough, and pleuritic chest pain. His cannabis and cigarette smoking history had started at age 12 and his current habit was 3 g of cannabis daily and 50 cigarette packs per year. A CT scan of the lung showed a pattern of large peripheral paraseptal bullae.

The authors compared this patient’s CT scan with one from a cigarette smoker. The second scan illustrated a strikingly different pattern of emphysema, with smaller panacinar bullae in a uniformly distributed centrilobular pattern. An explanation of the differences in lung findings due to cannabis and cigarettes would take into account a number of variables. Cannabis smoking requires longer inhalation and breath-holding time. Inhaled cannabis through a bong is at a higher temperature. A cannabis joint, which lacks a filter, also has a greater delivery of exposure.

Four men, who smoked both tobacco and marijuana, developed large, multiple, bilateral, peripheral bullae at their lung apices, with normal parenchymal tissue elsewhere [90]. Three patients with large bullae in the upper lung lobe have been reported [91]. All had been heavy marijuana smokers over 10–24 years. However, they all had at least nine pack-years of cigarette exposure and so marijuana may not have been the only cause of their lung bullae. Nevertheless, the authors recommended that all those who present with upper lung bullae should be screened for cannabis use.

While Δ9-THC may not contribute directly to lung bullae, it is possible that the respiratory dynamics of smoking the drug explains it. Typically, a draw on a marijuana joint has, on average, a depth of inspiration that is one-third greater, a volume two-thirds greater, and a breath-holding time four times longer than a draw on a cigarette. The marijuana joint lacks a filter tip, and the practice of smoking “leads to a fourfold greater delivery of tar and a five times greater increase in carboxyhemoglobin per cigarette smoked” [81]. Smoking three to four joints of marijuana per day is reported to produce a symptom profile and damage to the respiratory airways similar to that caused by smoking 20 tobacco cigarettes daily.

In 10 marijuana smokers with respiratory problems (mean age 41 years, 8 men), who had smoked marijuana regularly for at least 12 months, bullous lung disease was identified by high-resolution CT scanning [92]. Their presenting problems included dyspnea (n = 4), pneumothorax (n = 4), and lung infection (n = 2). In four patients the chest X-ray was normal; in five cases lung function tests were normal. The authors suggested that people who smoke cannabis present at a young age with significant respiratory problems and changes.

Cannabis smoking can cause pneumothorax [93].

- A 23-year-old man who had smoked cannabis regularly for about 10 years developed severe respiratory distress. He had bilateral pneumothoraces with complete collapse of the left lung.

No obvious reason for the problem was found and the authors suggested that coughing while breath-holding during cannabis inhalation had caused the problem.

Nervous system

Propriospinal myoclonus has been reported after cannabis use [94].

- A 25-year-old woman developed spinal myoclonus 18 months after having experienced acute-onset repetitive involuntary flexion and extension spasms of her trunk immediately after smoking cannabis. The jerks, which lasted 2–5 seconds, involved the trunk, neck, and to a lesser extent the limbs. The attacks occurred in clusters lasting up to 2 weeks and she was asymptomatic for 2–3 months between clusters. The myoclonus was not present during sleep. During a bout of jerks, myoclonus would occur every few minutes and continue for up to 9 hours, with associated fatigue and back pain. Neurological examination showed repetitive flexion jerks of the trunk with no other abnormal signs. An electroencephalogram, an MRI scan of the head and spine, and a full-length myelogram were all normal. Multi-channel surface electromyography with parallel frontal electroencephalography showed propriospinal myoclonus of mid-thoracic origin.

There have been no previous reports of propriospinal myoclonus precipitated by marijuana. The etiology was not clear but may have involved cannabinoid receptors located in the brain and spinal cord as well as the peripheral nervous system.

Amnesia

Transient global amnesia, an amnesia of sudden onset regarding events in the present and recent past, typically occurs in elderly people. Transient amnesia has been reported after marijuana use [95].

- A 40-year-old healthy man with a long history of cannabis use was hospitalized with an acute memory disturbance after
smoking for several hours a strong type of marijuana called “superskunk.” After smoking, he had difficulty recollecting recent events and would ask the same questions repeatedly. While his routine laboratory results were within the reference ranges, his urine and blood toxic screens had very high concentrations of cannabinoids (and no other drugs). He was alert and oriented to his name, address, date, and place of birth, but could not recall his marital status, whether he had children, or the nature of his job. He was disoriented in time. He performed normally in tests of general cognitive functioning (for example Raven’s matrices, word fluency, Rey’s complex figure) and short-term memory (for example digit span, verbal cues), but showed severe impairment in verbal and non-verbal long-term components of anterograde memory tests. He had a severe retrograde memory defect mainly affecting autobiographical memory, with a temporal gradient such that recent facts were preserved. These memory impairments lasted 4 days and then rapidly improved, leaving amnesia for the acute episode. Electroencephalography during the amnestic episode was normal, except for brief trains of irregular slow activity in the frontal areas bilaterally. A SPECT scan of his brain was normal. A week later, repeat neuropsychological examination showed normal memory and a normal electroencephalogram and MRI scan of the brain with enhancement. One year later, he had stopped using marijuana and had no further amnestic episodes.

The authors found similarities between the memory disorder seen here and transient global amnesia (see above), which consists of anterograde amnesia and a variably graded retrograde amnesia. The authors stated that although memory impairment has been reported with marijuana before, it has never involved retrieval of already learned material. They wondered if the memory impairment was due to marijuana-induced changes in cerebral blood flow and ischemia through vasospasm. However, their SPECT data did not support this theory. They considered the possibility that cannabinoid receptors, which are dense in the hippocampus, could have been occupied by marijuana, resulting in such memory loss. They cautioned that the effects of marijuana on memory may be more severe than previously thought.

Transient global amnesia following accidental marijuana ingestion has been reported in a young boy [96].

- A 6-year-old boy accidentally became intoxicated with marijuana after eating cookies laced with marijuana. He developed retentive memory deficits of sudden onset, later diagnosed as transient global amnesia. He was anxious and had a tachycardia, fine tremors in the upper and lower limbs, and an ataxic gait. His CSF was unremarkable. He had cannabinoids in his urine. His memory returned to normal after 14 hours. His mother admitted baking marijuana cookies and leaving them out on the kitchen table. Up to 12 months later he had no memory of the episode.

**Cerebrovascular disease**

Strokes have been reported after cannabis use.

- A 34-year-old woman who used cannabis 2–6 times per day and took buprenorphine 5 mg/day developed temporal lobe haemorrhage [97]. Angiography showed multifocal narrowing of arteries, without arteriovenous malformations or aneurysms. She reduced the dose of buprenorphine to 2 mg/day and reduced her consumption of cannabis to 3–4 cigarettes per week, and 3 months later angiography showed no narrowing or other abnormality in the cerebral vessels, leading the authors to conclude that the abnormality was associated with one or both drugs.

- A 37-year-old Albanian man had an uneventful medical history except that he smoked 20 cigarettes/day and marijuana joints regularly for 10 years. In the previous 6 months he had increased his marijuana smoking to 2–3 joints/week from 1 to 2 joints/month [98]. He suddenly developed left-sided hemiparesis, left-sided hemihypesthesia, and recurrent double vision 15 minutes after having smoked a joint containing about 250 mg marijuana. Most of the symptoms disappeared within 1 hour after onset. An MRI scan showed an area of impaired diffusion, 2 cm in diameter, in the right occipital area subcortically. He responded well to acetylsalicylic acid with dipipamolide and atorvastatin and was discharged 3 days later with blurred vision when looking to the left. There was no cardiac source of embolism. Other causes of stroke were carefully excluded, and it could only be attributed to the use of marijuana.

The authors of the second report, based on previous reports of the vasogenic effects of marijuana, suggested that this event may have been related to increased concentrations of catecholamine and carboxyhemoglobin, and diminishing cerebral autoregulatory capacity.

- A 36-year-old man developed acute aphasia followed by a convulsive seizure a few hours later after heavy consumption of hashish and 3–4 alcoholic beverages at a party [99]. He had no previous vascular risk factors. His blood pressure was 120/80 mmHg. An MRI scan showed two ischemic infarcts, one in the left temporal lobe and one in the right parietal lobe. Magnetic resonance angiography of the head and neck showed narrowing of the distal temporal branches of the left middle cerebral artery without involvement of its proximal segment. There was no evidence of diffuse atherosclerotic disease. There was tetrahydrocannabinol in the urine. Electroencephalography and transesophageal echocardiography were normal. He was given ticlopidine. A year later, he had a second episode of aphasia and right hemiparesis immediately after smoking marijuana. His blood pressure was 140/80 mmHg. An MRI scan showed acute left and right frontal cortical infarctions. He had a third stroke 8 months later, when he developed auditory agnosia after heavy use of hashish and 3–4 drinks of alcohol. On this occasion he was normotensive. An MRI scan showed acute infarcts in the right posterior temporal lobe and lower parietal lobe.

The authors discussed the importance of the close temporal relation between the use of cannabis and alcohol and the episodes of stroke. The mechanism was unclear. However, they speculated that a vasculopathy, either toxic or immune inflammatory, was the most likely mechanism.

- A 50-year-old male cigarette smoker with hypertension had episodes of transient right-sided hemisensory loss lasting only a few minutes [100]. Coughing while smoking marijuana was the apparent trigger. Electroencephalography was negative. An MRI scan of the brain showed chain-like low-flow infarctions in the white matter of the left parietal subcortex. Duplex sonography and digital subtraction angiography showed a subocclusive stenosis of the left internal carotid artery. Blood flow to the left middle cerebral artery was reduced and delayed and there was steal by the right middle cerebral artery. Endarterectomy of the left internal carotid resolved the symptoms.

The authors suggested that marijuana may increase the risk of reduced cerebral perfusion. Coughing may have contributed by reduced flow velocity within arteries supplying the brain and by a sudden increase in intracranial pressure.
Extrapyramidal effects
Marijuana can interact with the neurotransmitter dopamine, and the effects of marijuana on the brain in schizophrenia have been studied by single photon emission computed tomography (SPECT) [101].
- A 38-year-old man with schizophrenia secretively smoked marijuana during a neuroimaging study. A comparison of two sets of images, before and after marijuana inhalation, showed a 20% reduction in the striatal dopamine D2 receptor binding ratio, suggestive of increased synaptic dopaminergic activity.

On the basis of this in vivo SPECT study, the authors speculated that marijuana may interact with dopaminergic systems in brain reward pathways.
Consistent with this, extrapyramidal effects have been reported in a patient taking neuroleptic drugs who smoked cannabis [102].
- A 20-year-old man with no previous movement disorders, who had smoked marijuana for 4 years was given risperidone 9 mg/day and clorazepate 10–20 mg/day for paranoid schizophrenia. After 4 weeks he started using marijuana again and had least two episodes of cervical and jaw dystonia with oculargic crises, for which intramuscular biperiden was effective. He acknowledged marijuana use before each episode. He was then given oral biperiden 2–4 mg/day and risperidone was replaced by olanzapine 30 mg/day. He again started smoking marijuana and had similar episodes of dystonia and oculargic crises. No other causes of secondary extrapyramidal disorders were found.
The authors suggested a causal association between use of marijuana and extrapyramidal disorders. The research literature contains evidence that the endogenous cannabinoid system plays a role in basal ganglia transmission circuitry, possibly by interfering with dopamine reuptake. Furthermore, central cannabinoid receptors are located in two areas that regulate motor activity, the lateral globus pallidus and substantia nigra [103].

Cerebellar function
The effect of cannabis use on cerebellar function has been investigated [104]. The cerebellum has a role in motor coordination and some forms of associative learning and a key role in temporal operations, such as time estimation and rhythm production. Eye-blink conditioning (EBC) studies permit assessment of cerebellar-based timing deficits. In 14 chronic cannabis users (24 hour abstinence before study) and 10 healthy drug-free controls, an eye-blink conditioning task was administered, in which a conditioned stimulus (400 ms tone) was followed by a corneal air puff unconditioned stimulus (50 ms), eliciting a conditioned blink response. The cannabis group had significantly fewer and more poorly timed conditioned blink responses compared with controls. The two groups had no detectable differences in an EEG measure of selective attention to the conditioned stimulus (N100 auditory ERP) or the unconditioned response. It appeared that cannabis was associated with cerebellar disruption that was specific only to the acquisition of conditioned blink responses. The authors noted that this finding corroborated recent work in mice [105]. They also observed that it is not known whether cannabis abstinence results in recovery of cannabis-induced cognitive impairments.

Motor control and driving skills
To assess how high-potency (13%) THC affects motor control, 20 recreational marijuana users were given single doses of placebo, low-dose THC (250 micrograms/kg), or high-dose THC (500 micrograms/kg) in a double-blind crossover study [106]. Participants were aged 19–29 years, had no medical or psychiatric problems, and used marijuana on average 3.4 times per month. Impairments in object tracking, executive function, and planning, and response inhibition were greatest at 15–75 minutes after smoking and persisted for up to 6 hours. The authors suggested that high-potency cannabis, rather than the less commonly used low potency THC, should be assessed in future studies.
A review of the evidence has suggested that, particularly with high doses, cannabis users are 3–7 times more likely to cause motor accidents than non-drug users [107]. In a double-blind, placebo-controlled study to define the concentrations of THC needed to cause significantly impaired driving, 20 recreational cannabis users were given a series of performance tests at between 15 minutes and 6 hours after smoking 0, 250, or 500 micrograms/kg of THC [108]. The tests included measures of perceptual-motor control, motor impulsivity, and cognitive function. THC concentrations in saliva and blood were monitored throughout. At higher THC concentrations, there was impairment in an increasing proportion of trials, becoming significant at concentrations of 2–5 ng/ml for the perceptual-motor control task and at 5–10 ng/ml. The authors suggested that concentrations of THC, rather than positive versus negative drug screens, should be used to set legal standards for driving under the influence.

Sensory systems
Eyes
No consistent effects of cannabinoids on the eyes have been reported, apart from a reduction in intraocular pressure [109]. The initial reduction in intraocular pressure is followed by a rebound increase associated with increased prostaglandin concentrations.
However, bilateral angle-closure glaucoma has been reported after combined consumption of ecstasy and cannabis [110].
- A 29-year-old woman developed severe headaches, blurred vision, and malaise. Her visual acuity was <2/200/400 in the right eye and 20/40 in the left eye. Intraocular pressures were raised at 38 and 40 mmHg. Slit lamp examination showed bilateral conjunctival hyperemia, corneal edema, and shallow anterior chambers. Gonioscopy showed bilateral circular closed angles. The pupils were mid-dilated and non-reactive to light. The optic nerve heads in both eyes had slightly enlarged cups. She admitted to recreational use of ecstasy and marijuana before this ophthalmic crisis and also 2 years earlier, when she had had an episode of ophthalmic migraine with headache and transient blurred vision. Ophthalmic examination showed a narrow anterior chamber angle in both eyes.
The authors suggested that the bilateral angle-closure glaucoma had been precipitated by a combined mydriatic effect of ecstasy and cannabis.
There has been a pilot evaluation of the effect of sublingual cannabinoids (delta-9-tetrahydrocannabinol and
cannabidiol on intraocular pressure in a randomized, double-masked four-way, crossover study in six patients with ocular hypertension or early primary open-angle glaucoma [111]. A single dose of THC 5 mg was well tolerated but temporarily reduced intraocular pressure. Intraocular pressure was unaffected by cannabidiol 20 mg, but 40 mg resulted in a transient increase.

Hearing
The effect of THC, 7.5 and 15 mg, on auditory functioning has been investigated in eight men in a double-blind, randomized, placebo-controlled, crossover trial [112]. Blood concentrations of THC were measured for up to 48 hours after ingestion, and audiometric tests were carried out at 2 hours. There were no significant differences across treatments, suggesting that cannabis does not affect the basic unit of auditory perception.

Psychological
The psychological effects of cannabis vary with personal and social factors. However, some guidance to the essential effects of the drug can be derived from investigations with THC and marijuana in non-user volunteers. Blood concentrations of THC over 75 μg/ml under these conditions are associated with euphoria, and somewhat higher concentrations with dissociation of events and memory and impairment of psychomotor tasks lasting over 24 hours [58].

Memory
Cannabis use is associated with impaired memory and learning, and cannabinoid receptors are present in especially high density in the hippocampus, which has a role in forming episodic memories or new associations. Deficits in learning and memory and hippocampal functioning have been studied in cannabis users [113]. In the first experiment, 35 current cannabis users and 38 controls were given a neuropsychological test, a face-name task, which measures a person’s ability to associate faces and names and assesses hippocampal function. The cannabis users performed significantly worse in learning and short and long-term memory performance. In the second experiment, 14 current cannabis users and 14 controls were tested in a modified face-name task. Cortical and parahippocampal activity were examined by fluorescent magnetic resonance imaging (fMRI). Although the two groups performed similarly in learning, the marijuana users had hypoactivity or lower BOLD activity in the frontal and temporal cortices and hyperactivity or higher BOLD activity in the parahippocampus. The authors suggested that deficits in learning involve dysfunction in the prefrontal as well as the parahippocampal areas.

Cannabis has acute effects on memory, specifically transient deficits in immediate and delayed free recall of information presented after exposure. Recognition recall is not affected and neither is recall of information learned before exposure. These findings emerged from a literature review of 35 studies of varied populations (occasional to heavy cannabis users) and varied doses of cannabis [114]. The authors concluded that cannabinoids have significant acute effects on processes of encoding, retrieval, and consolidation of memory, but they pointed to several limitations of the studies they reviewed, including small sample sizes, sample selection, and the effects of tolerance and dependence.

Long-term heavy use of cannabis impairs mental performance, causes defects in memory (especially short-term memory), and leads to impairment of memory, attention, and organization and integration of complex information [115]. Adolescents with pre-existing disabilities in learning and cognition have experienced serious aggravation of their problem from regular use of cannabis [116].

Memory involves two components: an initial delay-independent discrimination or “encoding” and a second delay-dependent discrimination or “recall” of information. In five subjects tetrahydrocannabinol acutely impaired delay-dependent discrimination but not delay-independent discrimination [117]. In other words, smoking marijuana increased the rates of forgetting but did not alter initial discriminability.

Cognitive effects
Long-term marijuana altered the electroencephalogram during abstinence [118]. In 29 individuals who met DSM-III R criteria for marijuana dependence or abuse and 21 drug-free controls, electroencephalograms were recorded for 3 minutes [119]. Marijuana abusers had significantly lower log power for the theta and alpha1 bands during abstinence compared with controls. The authors also observed increased cerebrovascular resistance using transcranial Doppler sonography in an overlapping sample of marijuana abusers. They proposed that this combination of electroencephalographic findings and changes in cerebral blood flow may explain cognitive deficits reported in chronic marijuana users.

Delta-9-tetrahydrocannabinol (THC) activates cannabinoid receptors in frontal cortex and hippocampus. Electroencephalograms were obtained from 10 subjects who performed cognitive tasks before and after smoking marijuana or a placebo, to examine the effects on performance and neurophysiology signals of cognitive functions [120]. Marijuana increased heart rate and reduced global theta band electroencephalographic power, consistent with increased autonomic arousal. Responses in working memory tasks were slower and less accurate after smoking marijuana, and were accompanied by reduced alpha-band electroencephalographic reactivity in response to increased task difficulty. Marijuana disrupted both sustained and transient attention processes, resulting in impaired memory task performance. In the episodic memory task, marijuana use was associated with an increased tendency to identify distracter words erroneously as having been previously studied. In both tasks, marijuana attenuated stimulus-locked event-related potentials (ERP). In subjects most affected by marijuana, a pronounced ERP difference between previously studied words and new distracter words was also reduced, suggesting disruption of neural mechanisms underlying memory for recent episodes.
The effect of regular marijuana on binocular depth perception has been examined using the Binocular Depth Inversion Illusion (BDII) to identify individuals with an impairment of “top down” processing in perceptual networks in 10 regular users of marijuana and 10 healthy, non-cannabis-using controls [121]. The subjects had consumed marijuana at least every other day for a full year. The results suggested that regular marijuana users had significantly higher scores on the BDII, which implies subtle neurocognitive impairment that affects the sensory system involved in correcting ambiguous perceptions. The authors proposed that these impairments are similar to those seen in individuals with schizophrenia, and that cannabis use could be an independent risk factor for the development of schizophrenia.

In a Vietnamese study of 54 monozygotic male twin pairs who were discordant for regular marijuana use and who had not used any other illicit drug regularly the marijuana users significantly differed from the non-users on the general intelligence domain; however, within that domain only the performance of the block design subtests of Wechsler Adult Intelligence Scale-Revised reached statistical significance [122]. The marijuana users had not used it for at least 1 year, and a mean of almost 20 years had passed since the last time marijuana had been used regularly. There were no marked long-term residual effects of marijuana use on cognitive abilities.

The neurocognitive effects of marijuana have been studied in 113 young adults [123]. Marijuana users, identified by self-reporting and urinalysis, were categorized as light users (<5 joints per week) or heavy users (5 or more joints per week) and current users or former users, the latter having used the drug regularly in the past (1 or more joint per week) but not for at least 3 months. IQ, memory, processing speed, vocabulary, attention, and abstract reasoning were assessed. Current regular heavy users performed significantly worse than non-users beyond the acute intoxication period. Memory, both immediate and delayed, was most strongly affected. However, after 3 months abstinence, there were no residual effects of marijuana, even among those who had formerly had heavy use.

The effects of chronic marijuana smoking on human brain function and cognition have been further investigated [81]. Normalized regional brain blood flow and regional brain metabolism, measured using PET scanning with 15O, were compared in 17 frequent marijuana users and 12 non-users. Testing was performed after at least 26 hours of monitored abstinence in all subjects. Marijuana users had hypoactivity or reduced brain blood flow in a large region of the posterior cerebellum compared with controls. This is consistent with what was reported in the only previous PET study of chronic marijuana use [124]. The cerebellum is hypothesized to have input to aspects of cognition, specifically timing, the processing of sensory information, and attention and prediction of real-time events. Users often report that marijuana smoking is followed by alterations in the sense of time and less efficient cognitive processing.

The safety and possible benefits of long-term marijuana use have been studied in four seriously ill patients in the Missoula Chronic Clinical Cannabis Use Study with a quality-controlled sample of marijuana [125]. They were evaluated using an extensive neurocognitive battery.

The authors attributed these cognitive deficits not to marijuana use but rather to the patients’ illnesses, arguing that it is difficult for patients with painful debilitating diseases to concentrate on neurocognitive tasks. Any abnormalities in MRI imaging and electroencephalography were attributed to age-related brain deterioration. There were no significant abnormalities of respiratory function, apart from a “slight downward trend in FEV1 and FEV1/FVC ratios, and perhaps an increase in FVC” in three patients, interpretation of these findings being complicated by concomitant tobacco smoking. One patient had mild polycythemia and a raised white cell count. None had abnormal endocrine tests. This was a comprehensive study of the long-term effects of cannabis, but concomitant illnesses and use of tobacco made the results difficult to interpret.

Concerns have been raised about the possible adverse effects of acute as well as chronic medicinal and recreational use of cannabis on cognition and the body [126]. The author, while acknowledging the therapeutic role of cannabinoids in the management of pain and other conditions, expressed concern that in recent years the prevalence of recreational cannabis use (especially in the young) and the potency of the available products have markedly increased in the UK.

**Behavior**

The use of marijuana is related to risky behaviors that may result in other drug use, high-risk sexual activity, risky car driving, traffic accidents, and crime. The acute effects of marijuana on human risk taking has been investigated in a laboratory setting in 10 adults who were given three doses of active marijuana cigarettes (half placebo and half 1.77%, 1.77%, and 3.58% tetrahydrocannabinol) and placebo cigarettes [127]. There were measurable changes in risky decisions after marijuana. Tetrahydrocannabinol 3.58% increased selection of the risky response option and also caused shifts in trial-by-trial response probabilities, suggesting altered sensitivity to both reinforced and
losing risky outcomes. The authors suggested that the effect on risk taking was possibly seen only at the 3.58% dose because it created a requisite level of impairment to disrupt inhibitory processes in the mesolimbic-prefrontal cortical network.

**Psychiatric**

Through random urine testing of draftees to the Italian army, 133 marijuana users were identified, tested, and interviewed [128]. Among these marijuana users, 83% of those with cannabis dependence, 46% with cannabis abuse, and 29% of occasional users had at least one DSM-III-R psychiatric diagnosis. With greater cannabis use, the risk of associated psychiatric disabilities tended to increase progressively.

Occasional and regular users can suffer panic attacks, paranoia, hallucinations, or feelings of unreality (depersonalization and derealization). In a critical English-language literature review of the cannabis research done during the 10 years from 1994 to 2004 the relation between the rate of cannabis use, behavioral problems, and mental disorders in young people was explored [43]. Although there are shortcomings in the studies done in this area, the data suggest that early and heavy use of cannabis has negative effects on psychosocial functioning and psychopathology. Although infrequent use causes few mental health or behavioral problems, cannabis is not necessarily harmless. Accumulating evidence suggests that regular marijuana use during adolescence may have effects, whether biological, psychological, or social, that are different from those in later life. Most recent data challenge the notion that marijuana relieves psychotc or depressive symptoms.

A functional polymorphism of the catechol-0 methyltransferase gene (COMT Val158Met) may mediate an increased risk of psychosis in response to cannabis exposure. In a double-blind, placebo-controlled, crossover study, individuals with a psychotic disorder (n = 30), healthy controls (n = 32), and relatives of individuals with a psychotic disorder (n = 12) were exposed to either cannabis or placebo [129]. All underwent assessments of psychotic symptoms (Positive and Negative Syndrome Scale (PANSS)) and susceptibility to psychosis (Community Assessment of Psychic Experiences (CAPE)), a cognitive battery (including measures of attention and memory, and genotyping). Cannabis exposure most significantly increased psychotic symptoms, memory, and attention deficits among those with the Val allele compared with those with the Met allele. Susceptibility to psychosis among the Val carriers was increased most among those with CAPE scores suggesting susceptibility. The authors suggested that the increased risk of psychosis associated with the Val allele may be mediated through an additional pre-existing susceptibility.

**Psychoses**

In a systematic review of population-based or case-controlled longitudinal studies, the authors [130] identified 4804 references to studies that provided information about the risk that cannabis users versus non-cannabis users would develop a psychosis (including schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, or psychotic symptoms) or affective disorders (affective mood or bipolar disorder, affective disorder not otherwise specified, depression, suicidal ideation, suicide attempts, anxiety, neurosis, or mania); 175 references seemed adequately detailed, but 143 were excluded on reading the full paper. There were 11 papers that reported 7 cohort studies of psychosis and 24 papers that reported 15 cohort studies of affective outcomes. The authors found no evidence of publication bias among the papers they selected. This meta-analysis differed from previous meta-analyses, in that it did not include cross-sectional studies, included unadjusted results, and did not differentiate people who ever used cannabis from those who regularly used it. The risk of psychosis, which was defined as a range of symptoms from self-reported psychotic symptoms to a clinical diagnosis of schizophrenia, was increased in those who had ever used cannabis, with an odds ratio of 1.41 (95% CI = 1.21, 1.65). Six of the studies examined the effect of frequency; pooling these data showed a dose–response relationship, with an odds ratio of 2.09 (CI = 1.54, 2.84) for those who had used cannabis most often (defined differently in the studies as daily, weekly, >50 times, or meeting dependence criteria). The studies excluded people with a psychosis at baseline. The authors cautioned that the odds ratio did not imply causation. Affective outcomes were examined in 15 cohorts, but because of heterogeneity in the definition of cannabis use across the studies, no meta-analysis was performed. The authors found that these studies showed a slight increase in affective outcomes, although the confidence intervals were consistent with no effects. They concluded that there is now adequate evidence to justify issuing a warning that cannabis exposure will increase the risk of psychotic disorders.

Co-morbid substance use, beyond cannabis, may account for the increased positive symptoms observed in chronic schizophrenic cannabis users. When lifetime positive and negative symptoms were compared for those with (n = 66) or without (n = 139) cannabis abuse and dependence, there was no difference in positive symptoms between the two groups, after controlling for use of other substances; cannabis users also had fewer negative symptoms than non-cannabis users [131]. The reduction in volition and apathy was more pronounced when the analysis was restricted to those chronic schizophrenics who used cannabis and no other substances. The authors offered several hypotheses for these findings: cannabis use may be a susceptibility factor for schizophrenia in those who have a genetic predisposition for a lower severity of negative symptoms; alternatively, cannabis itself may reduce negative symptoms; lastly, those who have fewer negative symptoms may have a greater social ability to acquire the drug.

The causal relation between cannabis abuse and schizophrenia is controversial. Cannabis abuse, and particularly heavy abuse, can exacerbate symptoms of schizophrenia and can be considered as a risk factor eliciting relapse in schizophrenia [132]. Chronic cannabis use can precipitate schizophrenia in vulnerable individuals [133].

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Neurotrophins, such as nerve growth factor and brain-derived neurotrophic factor (BDNF), are implicated in neuronal development, growth, plasticity, and maintenance of function. Neurodevelopment is impaired in schizophrenia and vulnerable schizophrenic brains may be more sensitive to toxic influences. Thus, cannabis may be more neurotoxic to schizophrenic brains than to non-schizophrenic brains when used chronically. In 157 drug-naive first-episode schizophrenic patients there were significantly raised BDNF serum concentrations by up to 34% in patients with chronic cannabis abuse or multiple substance abuse before the onset of the disease [134]. Thus, raised BDNF serum concentrations are not related to schizophrenia and/or substance abuse itself but may reflect cannabis-related idiosyncratic damage to the schizophrenic brain. Disease onset was 5.2 years earlier in the cannabis-consuming group.

The effects of marijuana on psychotic symptoms and cognitive deficits in schizophrenia have been studied in 13 medicated stable patients with schizophrenia and 13 healthy subjects in a double-blind, placebo-controlled randomized study using 2.5 and 5 mg of intravenous delta-9-tetrahydrocannabinol (THC) [135]. Tetrahydrocannabinol transiently worsened cognitive deficits, perceptual alterations, and a range of positive and negative symptoms in those with schizophrenia. There were no positive effects. These results suggest a role for cannabinoid receptors in the pathophysiology of schizophrenia.

Four cases in which psychosis developed after relatively small amounts of marijuana were smoked for the first time have been reported [136]. All required hospitalization and neuroleptic drug treatment. Each had a mother with manic disorder and two had psychotic features. The authors noted that marijuana is a dopamine receptor agonist, and mania may be associated with excessive dopaminergic neurotransmission. The use of marijuana may precipitate psychosis or mania in subjects who are genetically vulnerable to major mental illness.

**Endocrine**

In animals (particularly monkeys), cannabis depresses ovarian and testicular function. In man, chronic use has been associated with reduced serum FSH and LH concentrations in a few people, often accompanied by reduced serum testosterone, oligospermia, reduced sperm motility, and gynecomasia [137]. There is no evidence of impairment of male fertility; no studies have been carried out on female fertility. There is evidence of slightly shortened gestation periods in chronic users [138]. There are variable non-specific effects on serum prolactin and growth hormone and a rise in plasma cortisol concentrations has been recorded in one study.

Cannabis use and gynecomasia or breast tissue growth were first associated in 1972 [139]. Subsequent research has shown that there may be an association [140] or not [141]. Dronabinol-induced gynecomasia has been reported [142].

- A 48-year-old man with a lengthy gastrointestinal history and severe recurrent nausea was given dronabinol (Marinol) 5 mg/day for 1 month. He had a history of testicular cancer treated with unilateral orchidectomy and 20 years before had had a benign contralateral breast mass, consistent with gynecomasia, removed. He now presented with a new right retroareolar breast mass. The mass was mobile and tender to palpation; there was no lymphadenopathy. Mammography and ultrasonography showed that the mass was a small dense focus of retroareolar parenchyma without microcalcification. Fine-needle aspiration of the mass showed normal breast tissue. Serum concentrations of testosterone, prolactin, and thyroxine were normal, as were liver function tests.

**Hematologic**

Of the hematologic changes very occasionally noted, polycythemia appears to be secondary to reduced pulmonary oxygen exchange (see the Respiratory section in this monograph).

**Gastrointestinal**

Although cannabis has been used as an antiemetic, in 19 patients it was associated with cyclical hyperemesis, and in 7 cases withdrawal was followed by the disappearance of symptoms; in 3 cases there was a positive re-challenge [143].

Cannabinoids stimulate appetite and relieve nausea in patients with cancer. These effects are mediated by cannabinoid receptors in the gut, nervous system, and immune system (CB1 receptors in the colon and ileum, inhibiting smooth muscle, and CB2 receptors in the colon, where they are involved in hypermotility, inflammation, and pain [144].

The effects of stimulating cannabinoid receptors with dronabinol on gastrointestinal transit and postprandial satiation have been studied in 30 healthy volunteers who were given either dronabinol 5 mg bd or placebo [145]. Each subject received three doses of medication and underwent non-invasive physiological tests 1 hour after the first and third doses. Dronabinol delayed gastric emptying, with a more pronounced effect in women. Men who received dronabinol had higher fasting gastric volumes, a finding that is associated with reduced postprandial symptoms and satiation after a meal and possibly greater appetite.

**Skin**

Cannabinoid-related contact dermatitis has been reported [146].

- A 29-year-old otherwise healthy female worker for the Forensic Science Service in the UK was developed urticarial wheals, headaches, and rhinitis within minutes after contact with cannabis plants. For 6 years she had grown, stripped, and ground cannabis plants; her symptoms started after 2 years and were gradually worsening, with a quicker onset after exposure. Patch tests to dried and fresh cannabis leaf, flower, and resin were positive.

This was a type I hypersensitivity reaction to cannabis, with a wheal-and-flare reaction due to urticaria.

**Reproductive system**

Cannabis is the most widely used illegal recreational drug among men and women of reproductive age. The effects
of cannabis on in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) outcomes have been reported in 221 couples undergoing IVF or GIFT at fertility centers in California [147]. Outcomes for a single cycle per couple were included. Data collection included three questionnaires for women and two for men and the medical records were accessed for information on sperm characteristics (numbers, motility, and morphology). Both the amount of cannabis use and the timing had negative effects. Women who had lifetime heavy cannabis use had 27% fewer oocytes retrieved and fewer embryos transferred. Moderate cannabis use in men or women was associated with 17% and 15% falls in infant birth weight respectfully. As to timing, women who used cannabis for 1 year before IVF/GIFT had 25% fewer oocytes retrieved and couples had 28% fewer oocytes fertilized.

Immunologic

Tetrahydrocannabinol depresses lymphocyte and macrophage activity in cell cultures, while in rats in vivo it directly suppresses natural killer cell activity and impairs T lymphocyte transformation by phytohemagglutinin in concentrations of cannabinoids achievable with the usual doses [148]. Variable results have been obtained in man in tests of circulating T cells and hormonal immunity [149].

In animals and man, chronic use often suppresses the immune system’s response to inhaled bacterial or fungal material. In this connection it is relevant to note that a contaminant mould (Aspergillus) found in cannabis can predispose immunocompromised cannabis smokers to infection. It has been suggested that baking the cannabis (at 300 °F for 15 minutes) before smoking will kill the fungus and reduce the potential risk [150].

The effects of oral cannabinoids on immune functioning were studied in 16 patients with multiple sclerosis in a crossover study of dronabinol, Cannabis sativa plant extract, or placebo for 4 weeks [151]. There was a modest increase in pro-inflammatory cytokine tumor necrosis factor alfa during cannabis plant extract treatment in all the subjects. Those with high adverse event scores (n = 7) had significant increases in pro-inflammatory plasma cytokine IL-12p40 while taking the plant extract; this was not the case with tetrahydrocannabinol. Other cytokines were not affected. Tumor necrosis factor alfa and IL-12p40 are known to worsen the course of multiple sclerosis [152]. These results are interesting because they suggest immunomodulation by cannabinoids in patients with multiple sclerosis, rather than immunosuppression, as previously reported with the plant extract [153]. More studies are needed, because these pro-inflammatory effects could have negative influence on the course of the disease.

The effects of marijuana on immune function have been reviewed [154]. The studies suggest that marijuana affects immune cell function of T and B lymphocytes, natural killer cells, and macrophages. In addition, cannabis appears to modulate host resistance, especially the secondary immune response to various infectious agents, both viral and bacterial. Lastly, marijuana may also affect the cytokine network, influencing the production and function of acute-phase and immune cytokines and modulating network cells, such as macrophages and T helper cells. Under some conditions, marijuana may be immunomodulatory and promote disease.

A severe allergic reaction after intravenous marijuana has been reported [155].

• A 25-year-old man with intermittent metamfetamine use developed facial edema, pruritus, and dyspnea 45 minutes after injecting a mixture of crushed marijuana leaves and heated water. He was anxious, and had tachypnea, respiratory stridor, wheezing, edema of the face and oral mucosa, and truncal urticaria. There was mild pre-renal uremia and urine toxicology was positive for metamfetamine and marijuana. Skin testing was not done. With appropriate medical intervention there was resolution of symptoms within a day.

The authors noted that marijuana may have contaminants, including Aspergillus, Salmonella, herbicides, and mercury, which can trigger allergic reactions.

LONG-TERM EFFECTS

Drug tolerance

Tolerance develops with heavy chronic use in individuals who report problems in controlling their use and who continue to use cannabis despite adverse personal consequences [57].

Drug dependence

Marijuana abuse and its possible associated risks in reinforcing further use, causing dependence, and producing withdrawal symptoms among adolescents with conduct symptoms and substance use disorders has been investigated in 165 men and 64 women selected and then interviewed from a group of 255 consecutive admissions to a university-based adolescent substance abuse treatment program [156]. All had DSM-III-R substance dependence, 82% had conduct disorder, 18% had major depression, and 15% had attention-deficit/hyperactivity disorder. Most (79%) met the criteria for cannabis dependence. Two-thirds of the cannabis-dependent individuals admitted serious drug-related problems and reported associated drug withdrawal symptoms according to the Comprehensive Addiction Severity Index in adolescents (CASI). For the majority, progression from first to regular cannabis use was as rapid as tobacco progression and more rapid than that of alcohol.

Drug withdrawal

Withdrawal symptoms occur after chronic heavy use [57]. Abrupt withdrawal of high-level use of cannabinoids causes irritability, restlessness, and insomnia, with a rebound increase in REM sleep, tremor, and anorexia lasting up to a week [157–159]. Occasional use does not appear to be associated with major consequences.

Tumorigenicity

Cannabis smoking is associated with an increased risk of some of the traditional tobacco-related cancers. Cannabis smoke contains tar, which has many of the same carcinogens as tobacco tar, such as vinyl chlorides, nitrosamines,
phenols, and reactive oxygen species. The smoking-associated cancers affect organs such as the lungs, upper airways, and bladder, which have long-term exposure to these carcinogens.

Transitional cell carcinoma of the bladder has been reported in a smoker of marijuana [160].

- A 45-year-old man who had a 30+ year habit of smoking of up to five marijuana cigarettes a day developed macroscopic painless hematuria. He had no history of tobacco use, chemical exposure, or family history of transitional cell carcinoma. There was a 7-cm bladder mass on CT scan and cystoscopy showed papillary lesions along the right lateral wall. The bladder tumor was resected and was a high-grade stage T1 transitional cell carcinoma. He received intravesical BCG for 6 weeks. After 3 months cytology was normal. He stopped using cannabis.

The association between cannabis and transitional cell carcinoma has been investigated in 156 men aged less than 60 years in a US Veterans Association Hospital, 52 with a transitional cell carcinoma and 104 age-matched controls, who completed self-administered questionnaires [161]. Detailed questions on tobacco and cannabis use and duration and exposure to other potential carcinogens, including radiation, Agent Orange, smoked or processed meats, and dyes, were included. There was significantly higher habitual cannabis use by 46 of the 52 patients with transitional cell carcinomas compared with 72 of the 104 age-matched controls. The former had engaged in greater cannabis use as measured in joint-years (the product of joints per day and years smoked), with a mean of 48 joint-years compared with 29 joint-years in controls. In both groups, there was high tobacco use, with rates greater than 90%.

The association between cannabis smoking and the development of lung cancer has been the subject of a systematic review of research studies written in English on adult subjects for the period 1966–1995; 19 articles out of 186 abstracts were identified and categorized [162]. There was an association between marijuana smoking and increased tar exposure, alveolar macrophage tumouricidal dysfunction, increased oxidative stress, and bronchial mucosal histopathological abnormalities compared with tobacco smokers and non-smoking controls. However, there were no significant associations between marijuana smoking and lung cancer after adjusting for use of tobacco, although the age of the participants was too young to allow conclusions based on long-term exposure.

SECOND-GENERATION EFFECTS

Pregnancy

Behavioral anomalies have been identified in the offspring of monkeys and women exposed to cannabis during pregnancy [163,164]. These include reduced visual responses, increased auditory responses, and reduced quietude. Most of the effects resolved within 4–5 weeks postpartum and there were no abnormalities at 1 year.

Teratogenicity

In animals, THC crosses the placenta and is excreted in breast milk. There is conflicting evidence concerning teratogenicity in animals, but no definitive evidence in man. However, there have been many anecdotal reports of abnormalities. Although these were without consistent characteristics, the descriptions would readily fit the fetal alcohol syndrome [165–168] and clinical evaluation of the use of cannabis during pregnancy is complicated by the frequent concomitant use of alcohol and tobacco.

Fetotoxicity

Cannabis has been implicated as having a neurodevelopmental role in conditions such as schizophrenia, substance abuse, mood and anxiety disorders, and impaired cognitive function. Exposure of the developing brain to cannabis can occur at several key periods: in utero, by crossing the placenta from mother to fetus; after birth through breast milk; and in adolescence by smoking.

Findings from two longitudinal studies of children exposed to cannabis in utero have been included in a review of neurodevelopmental effects [169]. Cannabis exposure resulted in small reductions in length, head circumference, and birth weight (about 100 g), but did not increase rates of prematurity or miscarriage. The children in these studies also had deficits in visuospatial reasoning and memory at ages 9–12 and 13–16.

The effect of maternal and prenatal marijuana exposure on offspring from birth to adolescence is being investigated [170]. The Ottawa Prenatal Prospective Study (OPPS), a longitudinal project begun in 1978, recently reported its findings in 146 low-risk, middle-class children aged 9–12 years. Their performances on neurobehavioral tasks that focus on visuoperceptual abilities (ranging from basic skills to those requiring integration and cognitive manipulation of such skills) were analysed. Performance outcomes were different in children with prenatal exposure to cigarette smoking and those with prenatal exposure to marijuana. Maternal cigarette smoking affected fundamental visuoperceptual functioning. Prenatal marijuana use had a negative effect on performance in visual problem-solving, which requires integration, analysis, and synthesis. In a second prospective study, the effects of prenatal marijuana exposure and child behavior problems were studied in 763 subjects aged 10 years [171]. Prenatal maternal marijuana exposure was associated with increased hyperactivity, impulsivity, and inattention in the children. There was also increased delinquency and externalizing problems. The authors suggested a possible pathway between prenatal marijuana exposure and delinquency, which may be mediated by the effects of marijuana exposure on symptoms of inattention.

The effects of prenatal marijuana exposure on cognitive functioning have been examined in 145 children aged 13–16 years [172]. The age breakdown was 45 13-year-olds, 36 14-year-olds, 51 15-year-olds, and 13 16-year-olds. These groups were further classified by maternal marijuana use: less than six joints per week (n=120) and six or more joints per week (n=25). A standard neurocognitive test battery was administered, and two of the tests differed significantly between non-users/light users and heavy users. On the Abstract Designs test the children of heavy users had significantly slower response times. Children in the heavy user group also scored significantly lower on the
Peabody Spelling test. These results suggest a dose-related effect of prenatal marijuana exposure on cognition. The two tests that differed across groups depend, to a lesser degree, on cognitive manipulation or comprehension and, to a greater degree, on visual memory, analysis, and integration. Unlike cigarette exposure, marijuana does not seem to affect overall intelligence. It is therefore possible that heavy marijuana use during pregnancy causes subtle deficits in visual analysis.

Cannabis is the illicit drug that is most commonly used by young women and they are not likely to withdraw until the early stages of pregnancy. The effects of early maternal marijuana use on fetal growth have been reported in pregnant women who elected voluntary saline-induced abortion at mid-gestation (weeks 17–22) [173]. Marijuana (n = 44) and non-marijuana exposed fetuses (n = 95) were compared and adjusted for maternal alcohol and cigarette use. Both fetal foot length and body weight were significantly reduced by marijuana. Fetal growth impairment was greatest in the group with moderate, regular exposure to about 3–6 joints/week and not in those with heavy maternal marijuana use. There was no significant effect on fetal body length and head circumference due to prenatal marijuana exposure.

Exposure to cannabis during pregnancy and its adverse effects on the fetus are difficult to assess, for several reasons. Concentrations of the psychoactive agents in cannabis sold on the street vary widely, from a trace of THC to as much as 20%. The amount and of drug use by expectant mothers and duration of use are also difficult to determine.

A study of altered neurobehavior in term neonates with prenatal cannabis exposure within 24–72 hours of life has been reported [174]. Between July 2001 and November 2002, 928 (25%) of 3685 infants at a hospital in Brazil were born to adolescent mothers; 26 infants (4.6%) of 561 infants who met the study criteria had marijuana exposure detected by maternal hair and neonatal meconium analysis for marijuana and cocaine metabolites. Neonates who had prenatal exposure to tobacco, alcohol, or cocaine were excluded. The infants were assessed with the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS). Infants exposed to marijuana scored significantly higher in variables of arousal, regulation, and excitability than non-exposed infants. Only one of 26 mothers who used cannabis during pregnancy revealed this during the interview.

Research on cannabis use in adolescent pregnancy is complicated by a number of variables [175]. Adolescent mothers frequently have poor nutrition, use other substances, and have poor mental health. The parenting environment of an infant born to an adolescent mother is likely to have a number of psychosocial stressors.

A systematic review of studies on neurobehavioral and cognitive outcomes associated with cannabis in utero exposure has been published [176]. To date, there have been only two longitudinal studies, the Ottawa Prenatal Prospective study (2002) and the Maternal Health Practices and Child Development Study (1998). The consequences of heavy prenatal exposure to cannabis appear to be subtle, with the prefrontal brain region negatively affected by prenatal cannabis use. There have been no studies focused on moderate or low cannabis use during pregnancy.

A small fMRI study has suggested that prenatal cannabis exposure may have effects on neural activity during tasks involving visuospatial working memory in young adults [177]. In this study, 16 prenatally exposed and 15 unexposed individuals (aged 18–22) performed a task involving visuospatial working memory while being imaged by fMRI. While there was no difference in performance between the two groups, there were differences in the neural networks that were activated during the task. Those exposed to cannabis had more activity in the left inferior and left middle frontal gyri, the left parahippocampal gyrus, the left middle occipital gyrus, and the left cerebellum, whereas they had less activity in the right inferior and right middle frontal gyri.

### SUSCEPTIBILITY FACTORS

#### Age

#### Children

In young children, accidental ingestion leads to the rapid onset of drowsiness, hypotonia, dilated pupils, and coma. Fortunately, gradual recovery occurs spontaneously, barring accidents. Passive inhalation of marijuana in infants can have serious consequences.

- A 9-month-old girl presented with extreme lethargy and a modified Glasgow coma scale of 10, after having been exposed to cigarette and cannabis smoke at the home of her teenage sister’s friend [178]. The physical examination and laboratory results were unremarkable. Cannabinoids were detected in a urine screen.

While chronic adult users can display apathy and impaired concentration, these effects are possibly in part associated with other factors. No permanent organic brain damage has been demonstrated [178,179].

#### HIV infection

The use of cannabinoids has been studied in 62 patients with HIV-1 infection [180]. Cannabinoids and HIV are of interest because there is the chance of an interaction between tetrahydrocannabinol and antiretroviral therapy. Tetrahydrocannabinol inhibits the metabolism of other drugs [181,182] and cannabinoids are broken down by the same cytochrome P-450 enzymes that metabolize HIV protease inhibitors. The subjects were randomly assigned to marijuana, dronabinol (synthetic delta-9-tetrahydrocannabinol), or placebo, given three times a day, 1 hour before meals. The amounts of HIV RNA in the blood did not increase significantly over the course of the study and there were no significant effects on CD4+ or CD8+ cell counts. However, there was significant weight gain in both cannabinoid groups compared with placebo. Although this study was of very short duration, the results suggested that either oral or smoked marijuana may be safe for individuals with HIV-1.

#### Coronary artery disease

People with pre-existing coronary artery disease may have an increased incidence of attacks of angina [183].
individuals who are vulnerable to schizophrenia, cannabis can precipitate psychoses or aggravate schizophrenia. The control of epilepsy may be impaired. Users undergoing anesthesia may react unexpectedly and may have enhanced nervous system depression. Because of impairment of judgement and psychomotor performance, users should not drive or operate machinery for at least 24 hours after administration.

**DRUG ADMINISTRATION**

**Drug contamination**

Over 3–4 months 29 patients, aged 16–33 years, all regular users of marijuana, presented to a German university hospital with lead poisoning, including one with a severe encephalopathy and a permanent palsy in his forearm [184]. When samples of the marijuana in the patients’ homes were examined, lead particles were visible. The lead may have been used to increase the weight of the marijuana (which is sold by weight) and therefore increase profits to the dealer. Contaminated marijuana could be considered when seeking a source for lead intoxication.

**DRUG–DRUG INTERACTIONS**

*See also* Buprenorphine; Indinavir; Methylenedioxymetamfetamine; Naltrexone; Nelfinavir; Neuroleptic drugs; Phenazone (antipyrine); Phosphodiesterase type V inhibitors; Theophylline and related compounds.

**Alcohol**

Additive psychoactive effects sought by users may be achieved by combinations of cannabis and alcohol, but at the same time the ability of THC to induce microsomal enzymes will increase the rate of metabolism of alcohol and so reduce the additive effects [157].

**Anticholinergic drugs**

The anticholinergic effects of cannabis [157] may result in interactions with other drugs with anticholinergic effects, such as some antidyserhythmic drugs.

**Barbiturates, short-acting**

Additive psychoactive effects sought by users may be achieved by combinations of cannabis and short-acting barbiturates, but at the same time the ability of THC to induce microsomal enzymes will increase the rate of metabolism of barbiturates and so reduce the additive effects [157].

**Disulfiram**

Concurrent administration of marijuana with disulfiram is associated with hypomania [185].

**Lysergic acid diethylamide**

“Flashbacks,” or the return of hallucinogenic effects, occur in almost a quarter of those who have used LSD, particularly if they have also used other CNS stimulants, such as alcohol or marijuana. They can experience distortions of perception of objects, space, or time, which intrude without warning into reality, resulting in delusions, panic, and unusual images. A “trailing phenomenon” has also been reported, in which the visual perception of objects is reduced to a series of interrupted pictures rather than a constant view. The frequency of these events may slowly abate over several years, but in a significant number their incidence later increases [186,187].

**Psychotropic drugs**

Cannabis alters the effects of psychotropic drugs, such as opioids, anticholinergic drugs, and antidepressants, although variably and unpredictably [157].

**Sildenafil**

Myocardial infarction has been attributed to the combination of cannabis and sildenafil.

- A 41-year-old man developed chest tightness radiating down both arms [188]. He had taken sildenafil and cannabis recreationally the night before. His vital signs were normal and he had no signs of heart failure. However, electrocardiography showed an inferior evolving non-Q-wave myocardial infarct and his creatine kinase activity was raised (431 U/l).

Cannabis inhibits CYP3A4, which is primarily responsible for the metabolism of sildenafil, increased concentrations of which may have caused this cardiac event.

**REFERENCES**


[54] Wehner FC, van Rensburg SJ, Thiel PG. Mutagenicity of cannabis-based medicinal extracts have general or specific 1404–7.

[55] Wehner FC, van Rensburg SJ, Thiel PG. Mutagenicity of cannabis-based medicinal extracts have general or specific 1404–7.


[60] Wehner FC, van Rensburg SJ, Thiel PG. Mutagenicity of cannabis-based medicinal extracts have general or specific 1404–7.


[70] Wehner FC, van Rensburg SJ, Thiel PG. Mutagenicity of cannabis-based medicinal extracts have general or specific 1404–7.


[74] Wehner FC, van Rensburg SJ, Thiel PG. Mutagenicity of cannabis-based medicinal extracts have general or specific 1404–7.


[78] Wehner FC, van Rensburg SJ, Thiel PG. Mutagenicity of cannabis-based medicinal extracts have general or specific 1404–7.


[82] Wehner FC, van Rensburg SJ, Thiel PG. Mutagenicity of cannabis-based medicinal extracts have general or specific 1404–7.


[84] Wehner FC, van Rensburg SJ, Thiel PG. Mutagenicity of cannabis-based medicinal extracts have general or specific 1404–7.
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Majmudar V, Azam NAM, Finch T. Contact urticaria to Cannabis sativa. Contact Dermatitis 2006; 54: 127.


