

REVIEW ARTICLE

Adverse effects of cannabis and cannabinoids

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The use of cannabis for both recreational and medicinal purposes dates back for thousands of years.^{15–91} It is perceived widely by recreational users as a harmless drug, a view fostered by some sections of the press and even (surprisingly) by a leading medical journal.⁷³ The opinions of 74% of doctors in a British Medical Association survey⁹² and of a Select Committee of the House of Lords⁵⁹ that cannabis should again be available on prescription (as it was until 1971) appear to support this belief. Therapeutic uses of cannabis have recently been reviewed by the British Medical Association¹⁷ which concluded that herbal cannabis is unsuitable for medical use. Nevertheless, it was recommended that research on the value of individual pure cannabinoids in a variety of conditions, including multiple sclerosis, spinal cord injury, chronic pain and palliative care, should be encouraged. Synthetic cannabinoids such as nabilone (in the UK) and dronabinol (in the USA) already have an established use as antiemetics in nausea and vomiting associated with cancer chemotherapy. However, no drug is without unwanted effects. It is timely to review the adverse effects of cannabis, especially in view of the increased prevalence of its recreational use in the UK, increased potency of modern preparations and present interest in the therapeutic possibilities of cannabinoids.

This review is based on a Medline search of articles on the pharmacology and effects of cannabis and cannabinoids 1980–1998, supplemented by comprehensive books and compendia, and standard books and articles from the older literature. Relevant books and articles were hand-searched for additional references. The search was conducted originally for reports commissioned by the Department of Health,⁷ the British Medical Association¹⁷ and the Ministry of Defence (unpublished), but has since been updated. The articles quoted in this review were selected from a very large bibliography as having relevance to the recreational use of cannabis and the medical use of cannabinoids in the UK today. Constraints on the number of references permitted meant further selection of original data, but most important

articles omitted here are cited in the reviews mentioned. Thus the review is not claimed to be comprehensive but aims to give a balanced view of the available information on the known and potential adverse effects of cannabis and cannabinoids in humans.

Prevalence and patterns of cannabis consumption in the UK

The prevalence of recreational cannabis use has increased markedly over the past decade among young people in the UK.¹¹¹ Surveys of schoolchildren show that more than 40% of 15–16 yr olds and up to 59% of 18-yr-old students have tried it at least once.^{10 98 109 142} Among university students (all faculties), more than 50% have some experience and 20% report weekly or more frequent use.¹³⁸ Of medical students, 41% report cannabis use and 10% take it at least weekly.¹³⁹ Nearly 30% of a sample of junior hospital doctors report current use and 11% use it weekly or monthly.¹³ There is also a considerable but unknown population, which includes 1% of schoolchildren and unemployed youths, who smoke cannabis daily or several (5–15) times a day¹²³ (North East Council for Addictions, personal communication). Such heavy users smoke to obtain a high level of intoxication and, because of the slow elimination of cannabinoids, may be chronically intoxicated. Other groups with a high prevalence of cannabis use are alcohol and illicit drug abusers⁸⁸ and psychiatric patients.⁹⁶

Most of today's regular cannabis users in the 20–30 yr age group started while still at school and are thus long-term users. Studies in the USA and Australia^{51 52} indicate that approximately 10% who ever use cannabis become daily users and another 20–30% use the drug weekly. These studies also suggest that most users stop in their mid- to late-20s. However, follow-up studies are needed to verify this conclusion among the present generation of users; increasing evidence, described below, suggests that regular users find it difficult to give up.

Table 1 Preparations of cannabis (US and UK) ^{44 94 126 129}

Form	Source	THC content (this is extremely variable and the values are approximate)
Marijuana (US) Cannabis (UK) (Herbal cannabis)	Dried leaves/stalks/flowers/seeds	
	Traditional cigarette (reefer) of 1960s and 1970s	1–3% THC (10 mg/reefer)
	Modern cigarette (joint) of 1980–90s, result of intensive cultivation and more potent subspecies (sinsemilla, skunkweed, Netherweed, and others)	6–20% THC (60–150 mg/joint, more than 300 mg if laced with hashish oil)
Hashish (US) Cannabis resin (UK) Hashish oil	Resin secreted by plant	10–20% THC
	Bricks, cakes, slabs	15–30% THC (sometimes up to 65%)
	Product of extraction by organic solvents	

Pharmacology of cannabis and cannabinoids

Plant sources and constituents of cannabis

Cannabis is obtained from the plant *Cannabis sativa* and some of its subspecies. The plant is unique in producing the chemicals known as cannabinoids, of which more than 61 have been identified.⁸⁷ The pharmacology of most of these substances is unknown but the most potent psychoactive agent is Δ^9 -tetrahydrocannabinol (THC), which is probably of greatest importance in the recreational use of cannabis. In addition to cannabinoids, the plant contains approximately 340 other chemical compounds, and the smoke from a cannabis cigarette contains carbon monoxide and the same tars, irritants and carcinogens that are present in tobacco smoke, some of them in greater concentrations.¹⁰³

Potency of cannabis preparations

The average THC content of cannabis preparations has increased in recent years as a result of sophisticated cultivation and plant breeding techniques which have produced high potency subspecies and preparations.^{2 51 129} In the early 1970s, the average reefer contained approximately 10 mg of THC; a modern joint may contain 60–150 mg or more (Table 1). In the UK at present, high potency varieties are favoured, obtained either from Holland or home-grown (exact details of how to grow cannabis can be obtained on the Internet). Thus today's cannabis smokers may be exposed to doses of THC many times greater than their counterparts in the 'flower power' days of the 1960s and 1970s. This fact is important because most of the effects of THC are dose-related and most of the research suggesting that cannabis had few harmful effects was carried out in the 1970s. Much of this early research may now be obsolete.⁴⁴

Pharmacokinetics of cannabinoids

Approximately 50% of the THC and other cannabinoids present in a cannabis cigarette enter the mainstream smoke and are inhaled. The amount absorbed through the lungs depends on smoking style. In experienced smokers, who inhale deeply and hold the smoke in the lungs for some seconds before exhaling, virtually all of the cannabinoids present in the mainstream smoke enter the bloodstream.^{3 20 87} Subjective and objective effects are perceptible within

seconds and fully apparent within minutes from the start of smoking. THC 2.5 mg in a cigarette is enough to produce measurable psychological and physical effects in occasional cannabis users.^{9 44 87} If cannabis is taken orally, the amount of cannabinoids absorbed is 25–30% of that obtained by smoking and the onset of effects is 0.5–2 h, although duration of action may be prolonged.⁸⁷

On entering the bloodstream, cannabinoids are distributed rapidly throughout the body, reaching first the tissues with the highest blood flow (brain, lungs, liver, etc.). Within the brain, cannabinoids are differentially distributed, reaching high concentrations in neocortical areas (especially the frontal cortex), limbic areas (hippocampus and amygdala), sensory areas (visual and auditory), motor areas (basal ganglia and cerebellum) and the pons.⁹⁰ Being highly fat soluble, cannabinoids accumulate in fatty tissues from which they are very slowly released back into other body compartments, including the brain. The plasma elimination half-life of THC is approximately 56 h in occasional users and 28 h in chronic users.²⁰ However, because of sequestration in fat, the tissue half-life is approximately 7 days and complete elimination of a single dose may take up to 30 days.⁸⁷ With repeated dosage, high concentrations of cannabinoids can accumulate in the body and continue to reach the brain.

Cannabinoids are metabolized in the liver, forming more than 20 metabolites, some of which are psychoactive and many of which have plasma elimination half-lives of the order of 50 h. Further metabolism produces inactive metabolites of which 15–30% are excreted in urine. Active and inactive metabolites are also excreted into the intestine and bile and approximately 15% are reabsorbed, prolonging the action of cannabis, while 35–65% are finally eliminated in the faeces.⁸⁷

Pharmacodynamics of cannabinoids

Cannabinoids exert many of their effects by combining with specific receptors in the brain and periphery. CB₁ receptors are present in the brain,^{32 86} particularly in regions involved in cognition, memory, reward, anxiety, pain, sensory perception, motor co-ordination and endocrine function.^{2 56 100} CB₂ receptors⁹⁹ are found in the spleen and other peripheral tissues and may play a role in the immuno-

suppressive actions of cannabinoids. The physiological ligands for these receptors appears to be a family of anandamides,^{33 114} which are derivatives of arachidonic acid, related to prostaglandins. It appears that there is an endogenous system of cannabinoid receptors and anandamides which normally modulate neuronal activity by effects on cyclic AMP formation and Ca²⁺ and K⁺ ion transport.^{29 60 86 100 114} The physiological function of this system is not understood but it is thought to have important interactions with opioid, GABAergic, dopaminergic, noradrenergic, serotonergic, cholinergic, glucocorticoid and prostaglandin systems.^{2 41 82 133} The many effects of exogenous cannabinoids derived from cannabis almost certainly result from perturbation of this complex system, but the exact mechanisms are not clear.

Actions of cannabis in humans

Acute effects

The acute toxicity of cannabis is extremely low. No deaths caused by direct toxicity have been reported, although coma has occasionally occurred after inadvertent ingestion by children. The pharmacological actions of cannabinoids are many and complex; they include a unique combination of some of the effects of alcohol, tranquillizers, opioids and hallucinogens, such as LSD. Almost every body system is affected.⁷

Effects on mood

Euphoria. The euphoriant potential of cannabis, the ability to produce a 'high', is probably the most important single action sustaining its widespread and often chronic recreational use. In a survey of university students¹³⁸ the reason given for taking cannabis was 'pleasure' by 75%, and 'relaxation' was the main effect reported by cannabis users in a community survey.²³ The euphoriant effect varies greatly with dose, mode of administration, expectation, environment and personality of the taker. When small doses are taken in social gatherings, the main effects are a pleasant euphoria and loquaciousness and sometimes fatuous laughter—responses very similar to those of social doses of alcohol. A 'high' can be induced by doses as small as THC 2.5 mg in a cigarette and includes feelings of intoxication and detachment, with decreased anxiety, alertness, depression and tension,⁹ in addition to perceptual changes. The intensity of the 'high' is dose-dependent, being increased with higher doses.

Cannabinoids have recently been shown to have actions in common with other 'rewarding' or addictive drugs, including nicotine, alcohol, opioids and amphetamines. In common with these drugs, THC releases dopamine from the nucleus accumbens in the rat.¹³³ The effect was similar in magnitude to that of heroin and was blocked by the opioid antagonist, naloxone. These findings suggest strongly that cannabinoids have a dependence-producing potential similar to other recreational drugs, a suggestion supported

by the evidence of tolerance, dependence and withdrawal effects discussed below.

Dysphoria. Dysphoric reactions to cannabis are not uncommon, especially in naive subjects. Such reactions may include severe anxiety and panic, unpleasant somatic sensations and paranoid feelings. Anxiety-panic reactions are the most common adverse psychological effects of cannabis use. They may include restlessness, depersonalization, derealization, sense of loss of control and fear of dying.^{16 134} In some subjects euphoria and dysphoria, laughing and crying, may alternate.

Flashbacks. Flashbacks, in which the original drug experience (usually dysphoria) is relived weeks or months later without further exposure to the drug, have been reported frequently.¹⁶ These are similar to the flashbacks described with hallucinogens such as LSD. It is possible, as they are often associated with a dysphoric or frightening cannabis experience, that they represent a psychological reaction similar to that of post-traumatic stress disorder.

Sedative and anxiolytic effects

After an initial period of excitement after an acute dose, cannabis exerts a generalized central nervous system depressant effect leading to drowsiness and sleep towards the end of a period of intoxication.¹¹² These effects are similar to those of alcohol and benzodiazepines.

Effects on perception

Perceptual changes induced by cannabis and THC affect all sensory modalities.¹¹² Colour and sound perception may be heightened and musical appreciation increased. Temporal and spatial perception is distorted so that judgement of distance and time are impaired. Experimental studies of time perception^{22 34} have found that subjects consistently overestimate the passage of time even after small doses (e.g. four puffs of a cigarette containing 3.6% THC). Persistent subjective visual changes, lasting for months after cessation of chronic cannabis use, have been described.⁷² These may represent prolonged functional disturbance of visual pathways and have also been reported after use of LSD.

Effects on motor function

An initial stage of excitement and increased motor activity after acute administration of cannabis is followed by a state of physical inertia with ataxia, dysarthria and general incoordination, which may last for some hours, depending on the dose. Impaired motor performance has been shown in many studies in humans, including measurements of body sway, tracking ability, pursuit rotor performance, hand-eye co-ordination, reaction time, physical strength and many others.^{46 102 112} The impairments are demonstrable after commonly used social doses of cannabis in experienced users, although (as with alcohol) some degree of compensation is possible.

Effects on cognition and memory

The effects of cannabis on thought processes are characterized initially by a feeling of increased speed of thought,

Table 2 Effects of cannabis which impair driving and piloting skills^{19 64 65 76 94 101}

Slowed complex reaction time
Poor detection of peripheral light stimuli
Poor oculomotor tracking
Space and time distortion
Impaired co-ordination
Brake and accelerator errors, poor speed control
Poor judgement, increased risks in overtaking
Impaired attention, especially for divided attention tasks
Impaired short-term memory
Additive effects with alcohol and other drugs

flights of ideas which may seem unusually profound and crowding of perceptions.¹¹² Such feelings can also occur at certain stages of alcohol intoxication and are common with LSD. With higher doses of cannabis, thoughts may get out of control, become fragmented and lead to mental confusion.

Cannabis causes a specific deficit in short-term memory, an effect which is demonstrable even after small doses in experienced cannabis users.⁴⁵ Memory impairment induced by cannabis has been investigated in a large variety of tests, including immediate free recall of digits, prose material and word–picture combinations.⁴⁶ The deficit appears to be in acquisition of memory and may result from an attentional deficit combined with an inability to filter out irrelevant information¹²⁹ and the intrusion of extraneous thoughts. Memory lapses may account in part for the time distortion⁴⁶ and may contribute to poor psychomotor performance in complex tasks. Effects of chronic use are discussed below.

Effects on psychomotor performance

The effects of cannabis on perception, memory and cognition, motor co-ordination and general arousal level combine to affect various types of psychomotor performance. Laboratory investigations show that ‘social’ doses of cannabis have minimal effects on performance in simple motor tasks and simple reaction times.^{46 52 102 112} However, even small doses (THC 5–15 mg) can cause significant impairment of performance in complex or demanding tasks, such as those involving fine hand–eye co-ordination, complex tracking, divided attention tasks, visual information processing, digit code tests, alternate addition–subtraction tasks and many others. Performance in all of these tasks deteriorates as the dose increases and can last for 2 h or more after single doses.^{55 71} These results have implications for performance in a variety of real-life situations and across a range of occupations.

Effects on car driving ability. Car driving ability after taking cannabis has been tested using a driving simulator, actual car driving on a closed course and car driving in real traffic conditions.^{82 94 102 121} All of these studies have shown dose-related deficits across a range of driving skills (Table 2). The effects are evident after small doses (THC 5–10 mg in a cigarette), increase with increasing dose and can last 4–8 h after a single dose. Although alcohol and cannabis taken alone produce different patterns of impairment in driving tests, their effects together are additive, so that

concurrent use produces greater impairment than the same dose of either drug taken alone.¹⁰²

The extent to which cannabis use contributes to road traffic accidents is controversial.⁵¹ Nevertheless, there is a large body of evidence linking cannabis use with such accidents, and some observers suggest that these risks have been underestimated.^{19 44 57} In many countries, cannabis is the most common drug, apart from alcohol, to be detected in individuals involved in traffic accidents. In the UK, a 1989 Department of Transport study³⁹ of 1273 road accident fatalities found cannabis post-mortem in the tissues of 33 victims; in 60% of these, no alcohol was detected. In 1998, a DETR survey³¹ showed that the prevalence of cannabis use in a sample of 284 drivers killed in road accidents had increased to 10% and in 80% of these alcohol was either not present or below the legal limit. The report pointed out that these figures applied only to fatal accidents and did not include non-fatal accidents.

Similar findings on the prevalence of cannabis use in killed or seriously injured drivers, reckless drivers and drivers suspected of being under the influence of drugs have been reported in Canada, the USA, Europe, New Zealand and Australia.^{25 35 42 66 81 104 132} For example, the Australian Road Safety Committee³⁵ reported that cannabis was present in the blood of 23% of surviving drivers of vehicle collisions involving death or life-threatening injuries (11% cannabis alone; 12% cannabis and alcohol). In Norway, 56% of 425 suspected drug-impaired drivers testing negative for alcohol were found to have positive blood samples for THC.⁴² In the USA, cannabis was detected in 37.8% of 1842 impaired drivers.¹⁰⁴

These studies indicate that cannabis, both with and without alcohol (and possibly with other central nervous system depressants such as benzodiazepines), contributes to road traffic accidents. However, rigorous proof is lacking as there is no simple roadside test to measure the degree of cannabis intoxication from blood, saliva or urine concentrations. Cannabinoids can be detected in body fluids days or weeks after the last dose but there is a very poor correlation between THC concentration and the level of intoxication.

Effects on aircraft piloting. Piloting an aeroplane is a much more complex task than driving a car, and it is not surprising that cannabis has been shown to impair piloting skills. In double-blind, placebo-controlled studies, gross decrements of performance in flight simulator tasks were found in 10 trainee pilots after smoking cannabis (2.1% THC)^{64 65} and in 10 experienced licensed pilots after smoking a single cigarette containing THC 19 or 20 mg.^{76 145} Performance deficits included increased errors, altitude deviations, poor alignment on landing, difficulties in remembering the flight sequence and time distortion: significant impairments were noted for more than 24 h after a single marijuana cigarette⁷⁶ (Fig. 1) and by this time the pilots were unaware of their reduced performance. A multi-dose study (THC 0, 10 and 20 mg in cigarettes) with two levels

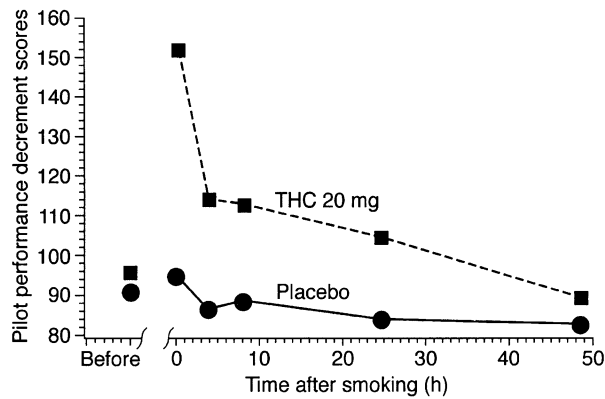


Fig 1 Effect of smoking a cannabis cigarette containing THC 20 mg on pilot performance in flight simulator tasks. Performance on six simulator tasks included in one flight session was standardized to give mean decrement scores; nine pilots performed the tasks under both drug and placebo conditions.⁷⁶

of difficulty (calm and turbulent simulated flying) was carried out in nine 'old' and nine 'young' pilots.⁷⁵ It was found that older pilots (aged 30–48 yr) made more mistakes than younger pilots (aged 18–29 yr) and that the effect of THC dose, age and task difficulty were cumulative. At least one aircraft crash in which the pilot was known to have taken cannabis some hours before flying has been reported.⁷⁶ The error was a landing misalignment similar to those observed in experimental studies.

Railroad and other accidents. Nahas¹⁰¹ reported that cannabis has been implicated in several major railroad accidents. In one case, a freight train rammed a passenger train travelling at full speed, resulting in 16 dead and 43 passenger injuries. The driver of the freight train had ignored three red signals before the crash; cannabinoids were detected in his body fluids. In another case, cannabis was detected in a railway switch man after a derailment in which 25 people were injured. It is likely that cannabis-related impairments shown in car drivers and aeroplane pilots apply equally to train drivers, signal men, air traffic controllers and other operators of complex machinery, including anaesthetists!

Psychosis

Although the most common adverse psychiatric effect of cannabis is anxiety, it can cause an acute toxic psychosis, a non-specific acute brain syndrome which can occur with other intoxicants. The clinical picture is one of delirium with confusion, prostration, disorientation, derealization and auditory and visual hallucinations.¹⁰² Acute paranoid states, mania or hypomania with persecutory and religious delusions and schizophreniform psychosis may also occur.⁵⁷ These reactions are relatively uncommon and usually dose-related but appear to be becoming more common with the advent of potent preparations such as Skunkweed.¹⁴⁴ They are usually self-limiting over a few days, but schizophreniform psychosis in addition to depression and depersonaliza-

tion can last for weeks and are often, but not always, associated with a family history of psychosis.^{85 89 134}

Patients with mental illness and those with a family history of schizophrenia appear to be particularly vulnerable to the adverse psychiatric effects of cannabis. There are numerous reports of schizophrenic illness being aggravated or precipitated by cannabis,^{58 78 83 134} and these reports also suggest that cannabis can antagonize the therapeutic effects of antipsychotic drugs in previously well controlled schizophrenic patients. The question of whether cannabis can actually cause schizophrenia in patients who would not otherwise develop it is more vexed.^{5 135} It seems most likely that cannabis use is an associated risk factor rather than a cause, and rates of cannabis use in schizophrenic patients are high, probably more than 40%.⁹⁶

Aggression and violence

Although historically linked to aggressive acts in assassins (from which the term hashish is derived), cannabis in most recreational settings decreases aggressive feelings in humans and increases sociability. However, occasional predisposed individuals, especially if under stress, become aggressive after taking cannabis.¹⁰² Violent behaviour may also be associated with acute paranoid or manic psychosis induced by cannabis intoxication, and polydrug use, mainly cannabis, appears to increase the risk of aggression and violence in affective disorders or schizophrenia.^{37 48} An investigation of criminal behaviour¹³⁰ found that 30% of 73 cannabis users incarcerated for homicide had taken the drug within 24 h of the crime. Although usually alcohol or other drugs had also been taken, 18 prisoners said that cannabis had contributed to their homicidal act. Thus cannabis, in common with alcohol, appears to be a potential contributor to violence and possibly to criminal behaviour.

Chronic effects

As described above, the effects of single moderate doses of cannabis (THC 20 mg) on complex tasks can last for more than 24 h. The slow tissue elimination of cannabinoids and consequent accumulation with repeated doses suggest that the effects of larger doses and of chronic use would be of greater duration and magnitude. For this reason there have been many studies comparing the performance of long-term heavy cannabis users with non-users. Do regular users show long-lasting impairments? If so, are the impairments reversible or can cannabis produce permanent changes in brain function? What are the long-term effects on other body systems (e.g. immune systems), and what are the effects of smoke constituents other than cannabinoids (e.g. on the respiratory system)?

Tolerance, dependence and withdrawal effects

Tolerance. One mechanism tending to limit the effects of regular doses of cannabis is the development of tolerance. Repeated use induces considerable tolerance, within days or weeks, to the behavioural and pharmacological effects.

Reviews and several studies^{57 68 69 102 113} have noted tolerance to the effects of cannabis on mood, memory, psychomotor performance, sleep, EEG, heart rate, arterial pressure, body temperature and antiemetic effects. However, tolerance is not complete; the rate of onset and degree of tolerance depend on the dose and frequency of administration and differ between different effects. For this reason it is difficult to predict the degree of tolerance in an individual or the extent to which a particular task is impaired by a given dose of cannabis or THC. However, casual cannabis smokers usually show more impairment of psychomotor and cognitive performance in response to a given acute dose than do habitual users.⁴⁶ Cross-tolerance between cannabis and alcohol, barbiturates, opioids, prostaglandins and chlorpromazine has been observed,^{102 113} indicating that all of these drugs may have some actions in common.

Tolerance to the recreationally desired 'high' has been observed in several studies and this has led to escalation of the dose over a period of 2–3 weeks in free-choice laboratory investigations.^{93 94} Such tolerance has led some authors to suggest that cannabis can act as a 'gateway' drug, introducing users to the more potent thrills obtainable from other illicit drugs,^{43 113} although this issue remains controversial.⁵² Certainly there is a high correlation between the use of cannabis and the use of other illicit drugs and alcohol.^{43 116 138} Whether or not cannabis acts as a 'gateway' drug, there is little doubt that increased cannabis consumption after tolerance to the 'high' increases the likelihood of adverse consequences, physical and mental, associated with higher doses.¹⁰²

Dependence, withdrawal syndrome. That a degree of physical and psychological dependence to cannabis develops is suggested by the advent of a withdrawal syndrome on cessation of use after chronic use. A cannabis withdrawal reaction has been demonstrated in laboratory studies in both animals^{30 113} and humans.^{94 95 102} In rats, acute withdrawal from a synthetic CB₁ agonist precipitated by a specific antagonist is accompanied by a marked release of corticotrophin releasing factor (CRF) and a distinct pattern of activation (Fos immunoreactivity) in the amygdala (a key nucleus in the 'reward' system of the brain).³⁰ These changes are similar to those observed in opioid, cocaine and alcohol withdrawal. They have not been observed in humans, but the human cannabis withdrawal syndrome has similarities to alcohol and opioid withdrawal states and includes restlessness, anxiety, dysphoria, irritability, insomnia, anorexia, muscle tremor, increased reflexes and several autonomic effects (Table 3). A daily oral dose of THC 180 mg (equivalent to one or two 'good quality' joints) for 11–21 days was found to be sufficient to produce a well defined withdrawal syndrome in a placebo-controlled study.⁶⁸ The reaction appeared approximately 10 h after cessation of THC, reached maximum intensity at 48 h and then declined slowly.

It is usually claimed that the cannabis withdrawal syndrome is mild and short-lived.^{1 57} However, some symptoms

Table 3 Cannabis withdrawal symptoms and signs^{68 94 95.101}

Mood changes	Hyperactivity
Disturbed sleep	Weight loss
Decreased appetite	Haemoconcentration
Restlessness	Salivation
Irritability	Tremor
Perspiration	Loose bowel movements
Chills	Body temperature increase
Feverish feeling	Sleep EEG eye movement rebound
Nausea	Waking EEG changes
Tremulousness	Intraocular pressure increase

may be protracted¹²⁸ and there is increasing evidence that people are seeking professional help in withdrawal.^{124 125 131} Community surveys have shown that many cannabis users have difficulty in stopping, despite wanting to, and that they experience difficulties in withdrawal, including sleep difficulties, increased anxiety, mood swings, depression, irritability and problems controlling temper. Prevalence rates for withdrawal symptoms in chronic cannabis users have been estimated as 16–29%^{134 141} and it is claimed that 10 000 people in the USA seek treatment for marijuana dependence each year.¹⁴⁰

Long-term cognitive impairment

The possibility that chronic heavy cannabis use may lead to long-term or permanent cognitive impairment has been reviewed recently¹¹⁸ and examined in depth.¹²⁹ The old idea of a cannabis-induced 'amotivational syndrome' can be explained as a state of chronic intoxication in frequent users. Computed tomography (CT) studies in humans have revealed no evidence of gross structural brain changes, such as cerebral atrophy. However, in rhesus monkeys exposed for 2–3 months to marijuana smoke at doses comparable with human use, brain ultrastructural changes, including synaptic abnormalities especially in the hippocampus, septal region and amygdala, have been reported.⁵⁴ Such changes do not appear to have been observed post-mortem in the brains of human cannabis users.

Nevertheless, there is accumulating evidence that chronic cannabis use may be associated with functional brain changes manifested by subtle impairments in cognitive function, and that such changes depend on dose and duration of use. A comparison of US college students¹¹⁹ found that after 19 h of abstinence, 65 long-term daily cannabis users performed less well than 64 long-term light users in cognitive tests of attentional and executive function. In a study of 12th grade US schoolchildren¹⁴ which included 144 chronic heavy cannabis users (seven or more times daily), who had abstained for 24 h, and 72 non-users previously matched for IQ in the 4th grade, the users were found to display deficits in mathematical skills, verbal expression and memory retrieval. Lighter cannabis users, although still using the drug at least weekly, did not show significant impairments. Another study¹²⁶ found impairment of short-term visual and verbal memory persisting for 6 weeks after cessation of cannabis use in 10 adolescents who were daily users compared with nine non-user control

subjects matched for age and IQ. This author emphasized the potential adverse effects of persisting memory deficits in academic performance in schoolchildren and college students and suggested that adolescents and those with borderline or low IQ might be particularly susceptible.¹²⁶

Cognitive performance after longer periods of abstinence in heavy cannabis users has been investigated in a series of studies by Solowij.¹²⁹ The ability of ex-cannabis users to focus attention and to filter out irrelevant information was measured by an EEG evoked potential response ('processing negativity') to a complex selective attention task. In one such study this response was measured in 218 ex-cannabis users who had taken cannabis regularly for a mean of 9 yr and had ceased for 3 months to 6 yr, 16 continuing long-term users (mean duration of use 10.1 yr), 16 continuing short-term users (mean duration 3.3 yr) and 16 non-user controls. Frequency of cannabis use (10–19 days each month) was similar in all user groups. The results showed impairment of attentional function compared with controls in both groups of continuing users. The ex-users showed partial improvement of function compared with current users, but their performance was still significantly below that of controls, even after allowing for alcohol consumption and other possible conflicting variables. The degree of impairment was related to duration of cannabis use and there was no improvement with increasing length of abstinence. The findings were interpreted to suggest that there is incomplete recovery of attentional function after cessation of chronic cannabis use and that changes, which are only partially reversible, occur in the brain as a result of prolonged exposure to cannabis. Such changes, although subtle, could affect everyday functioning, particularly among individuals in occupations requiring high levels of cognitive capacity.¹²⁹

Psychopathology

The psychopathology associated with chronic cannabis use has been less systematically studied than cognitive performance. However, a high proportion of long-term cannabis users, drawn from both non-psychiatric community samples and psychiatric in-patients, develop paranoid ideation, delusions and hallucinations.^{48 129} These symptoms appear to increase with duration of use and to continue after cessation of cannabis use.

Somatic effects and associated health risks

Apart from its actions in the central nervous system, cannabis exerts effects on many other body systems, including the cardiovascular, respiratory, immune, endocrine and reproductive systems, all of which may carry health hazards, especially with chronic use. Some of these effects are caused by cannabinoids; some, particularly respiratory effects, are caused mainly by other smoke constituents, while some may be a result of a combination of both.

Cardiovascular system. Acute doses of cannabis cause a marked tachycardia with peripheral vasodilatation, sometimes resulting in postural hypotension, and a slight decrease

in body temperature. Cardiac output may be increased by as much as 30%, accompanied by increased cardiac work and oxygen demand. These changes are of little importance in young healthy users, and tolerance develops rapidly. However, in individuals with pre-existing heart disease, the condition may be aggravated. Myocardial ischaemia, cardiac infarction and transient ischaemic attacks have been reported in previously healthy young men in their twenties.^{74 79 94 102}

A contributory factor to long-term cardiac risks may be the relatively large amounts of carbon monoxide absorbed when smoking cannabis. Cannabis smoke contains a volume of carbon monoxide similar to that of tobacco smoke but, because of the deep inhalations and long inspiratory times adopted by cannabis smokers, the increase in carboxyhaemoglobin concentration per cigarette is approximately five times greater than with a tobacco cigarette.^{12 143} Increased carboxyhaemoglobin concentrations are thought to be a major factor in atheromatous disease associated with tobacco smoking and are likely to be a health risk in chronic cannabis smokers.

Respiratory system. The smoke from a cannabis joint or pipe contains the same constituents (apart from nicotine) as tobacco smoke, including bronchial irritants, tumour initiators (mutagens), tumour promoters and carcinogens. The tar from cannabis smoke also contains greater concentrations of benzanthracenes and benzpyrenes, both of which are carcinogens, than the tar in tobacco smoke.^{62 103} Furthermore, smoking a cannabis cigarette results in a threefold greater increase in the amount of tar inhaled, and retention in the respiratory tract of one-third more tar, than smoking a tobacco cigarette.¹⁴³ Chronic cannabis smoking is associated with bronchitis, emphysema and squamous metaplasia (a pre-cancerous change) of the tracheobronchial epithelium. These changes are more frequent in those who have only smoked cannabis than in those who have only smoked tobacco.⁵⁰ Furthermore, chronic cannabis smokers who also smoke tobacco have higher rates of respiratory symptoms and histopathological changes than those who only smoke tobacco or only smoke cannabis.⁵⁰ It is estimated that 3–4 cannabis cigarettes daily are equivalent to 20 or more tobacco cigarettes per day in terms of the incidence of acute and chronic bronchitis and damage to the bronchial epithelium.¹⁴³

There have been several case reports which strongly suggest a link between cannabis smoking and cancer of the aerodigestive tract (oropharynx and tongue, nasal and sinus epithelium and larynx).^{51 101} Some of these cases have involved young patients who were heavy cannabis smokers but had not used tobacco or alcohol. This type of cancer is rare in those less than 40 yr of age, even in those who smoke and drink alcohol. The impact of chronic cannabis smoking on the respiratory and aerodigestive systems is still not clear as prospective epidemiological studies which distinguish between cannabis and tobacco are lacking but, as with tobacco, the effects of cannabis are probably cumulative and any increased incidence in today's young

chronic cannabis smokers will only become apparent after a latent period of 10–20 yr.

Immunosuppressant effects. Tobacco smoke is known to suppress both humoral and cell-mediated immune systems. Smoke from cannabis cigarettes would be expected to have similar effects and some *in vitro* and animal studies suggest that cannabis impairs the bactericidal activity of lung alveolar macrophages and may depress intrapulmonary antibacterial defence systems.^{44 87} However, there is no clear evidence that cannabis smoke produces significant immunological damage in humans. Fatal invasive aspergillosis in already immunocompromised individuals has been reported after smoking cannabis contaminated with this organism, but a large prospective study of 4954 HIV-positive men indicated that cannabis use did not increase the risk of progression to AIDS.⁵²

Reproductive system. Cannabis is antiandrogenic and cannabinoids, including THC, bind to androgen receptors.⁴⁴ Chronic cannabis smoking appears to be associated with decreased sperm counts, decreased sperm motility and abnormal sperm morphology in animals and humans.^{44 87 102} However, strictly controlled studies taking into account the use of other drugs and alcohol have not been conducted and the effects, if any, on human fertility are unclear.

In women, regular cannabis smoking may be associated with suppression of ovulation, an effect also observed in primates.^{57 87} Acute cannabis smoking decreases prolactin concentrations, but chronic use may cause increased prolactin concentrations and may lead to galactorrhoea in women and gynaecomastia in men.^{44 57} Effects on fertility have not been fully studied. Endocrine changes resulting from cannabis use may be of relatively little importance in adults, but they may be significant in prepubertal males and females in whom cannabis may suppress sexual maturation in addition to social and personal development and learning of stress-coping skills.^{43 57}

During pregnancy, cannabinoids enter the embryo or fetus. There is no evidence of teratogenicity but some, although not all, studies suggest that chronic maternal cannabis smoking, in common with cigarette smoking, is associated with low neonatal birthweight.^{51 102 110} This effect may be related to the carbon monoxide content of smoke causing fetal hypoxia. There is evidence that cannabis smoking may increase the risks of complications during labour^{44 58 102} and that infants of cannabis-smoking mothers may show delay in cognitive development⁵¹ but the clinical significance of these effects is not clear. A retrospective study of 204 case-control pairs¹²² found a 10-fold increased risk of developing non-lymphoblastic leukaemia in the offspring of mothers who had taken marijuana during or just before pregnancy. This was followed by two other studies suggesting an increased risk of rhabdomyosarcoma and astrocytoma in the children of mothers who had used cannabis during pregnancy.⁵¹ Additional studies on this issue are needed.

It is clear that the recreational use of cannabis carries

Table 4 Some adverse effects and potential costs of recreational cannabis use

Personal	Community
Short-term (acute effects)	
Psychomotor impairment	Traffic accidents (road, rail, air)
Cognitive impairment	Accident at work and home
	Educational under-attainment (school, university, work training)
	Impaired work performance
	NHS and prison costs
Psychiatric effects	
Anxiety/panic, acute psychosis	
Aggravation of schizophrenia	
?Increased risk of violence, crime	
Long-term (chronic effects)	
Dependence and withdrawal reactions	NHS and voluntary service costs
?Long-term cognitive impairment	Impaired work performance
?Association with polydrug abuse	NHS and social costs
Respiratory and cardiovascular health risks	NHS costs
Bronchitis, emphysema, ?lung and oropharyngeal cancer, aggravation of heart disease	
Effects on reproduction	NHS and social costs
Decreased sperm count	
Increased birth complications	
Neonatal risks	

risks both to the community and the individual. These risks are summarized in Table 4.

Effects of cannabis and cannabinoids of particular relevance to anaesthetists

Administration of anaesthesia

It is likely that a considerable proportion of young patients requiring anaesthesia may be occasional or regular users of cannabis. Up to 10–20% of those in the age group 18–25 yr may take it weekly or more often. Because of the slow elimination of cannabinoids, the drugs may be present in the tissues of users for some weeks after the last exposure. Some of the residual effects of cannabis may be of particular concern to anaesthetists, although this subject has not been investigated systematically.

First, cannabis may enhance the sedative–hypnotic effects of other central nervous system depressants. Apart from alcohol, animal work has shown additive effects and/or cross-tolerance of cannabis with barbiturates, opioids, benzodiazepines and phenothiazines.^{102 113} There is little human work in this area but such interactions are likely.⁵² Second, cannabis smoking is associated with similar impairment of lung function as tobacco smoking. In addition, cannabis smoking can cause oropharyngitis and uvular oedema which may sometimes result in acute airway obstruction in patients receiving a general anaesthetic.⁸⁰ These authors caution that elective operations should not be performed in patients who have recently been exposed to cannabis smoke. Third, the cardiovascular effects of cannabis may interact with other drugs affecting heart rate or arterial pressure. Interactions with propranolol and physostigmine have been reported.⁵² Fourth, it is theoretically possible that adverse psychiatric and autonomic reac-

tions to cannabis, including withdrawal effects, may interfere with induction of anaesthesia and postoperative recovery. These possibilities make it advisable for anaesthetists to inquire into the drug history of young patients and to be aware of the potential effects of cannabis on anaesthetic procedures.

Therapeutic use of cannabinoids for nausea and vomiting, chronic pain management and palliative care

Antiemetic use

Cannabinoids have an established use in the prevention of nausea and vomiting caused by anticancer drugs. Nabilone and dronabinol (synthetic THC), and other synthetic cannabinoids, have been shown to be as effective or more effective than phenothiazines, metoclopramide and domperidone for this indication,¹⁷ although they have not been tested against the more recently introduced 5-HT₃ antagonists such as ondansetron. The recommended dose of nabilone for this indication is 4–8 mg day⁻¹ orally in divided doses in short courses of a few days during cancer chemotherapy. On such a regimen, adverse effects are frequent and may be severe. The incidence of drowsiness, dizziness and lethargy is 50–100%. Psychological effects include euphoria, dysphoria, anxiety, confusion, impaired memory, depersonalization, paranoia, hallucinations and depression. Physical effects include dry mouth, ataxia (incidence more than 50%), blurred vision, inco-ordination, muscle weakness, tremor, palpitations, tachycardia and postural hypotension.¹⁷ Nevertheless, in many studies, patients preferred nabilone to standard drugs.^{4 11 28 38 67 70 77 105 137}

Appetite stimulation

Cannabinoids also stimulate appetite and it has been suggested that they may have a use in palliative care for anorexia, nausea and vomiting caused by opioids, antiviral drugs AIDS-related illnesses^{11 117} or terminal cancer.^{8 17} For these indications smaller doses of nabilone, either on its own or as an adjuvant to other drugs, may be effective and less liable to cause adverse effects, although clinical experience is lacking.

Pain management

Cannabinoids have analgesic, muscle relaxant and anti-inflammatory actions.¹¹⁴ In addition, they exert anxiolytic, hypnotic and antidepressant effects^{21 40 61 120} and some have anticonvulsant actions.^{26 27} Furthermore, the analgesic effects appear to be exerted by non-opioid mechanisms as, unlike the 'rewarding' effects (release of dopamine from the nucleus accumbens), cannabinoid-induced analgesia is not reversed by naloxone.^{26 53 97 127} These properties suggest that cannabinoids would be ideal candidates for use in chronic pain management, either on their own or in combina-

tion with other drugs, including opioids, antidepressants, muscle relaxants and anticonvulsants.

Despite this theoretical promise, there have been very few controlled studies of cannabinoids as analgesics. Noyes and colleagues^{107 108} found that THC provided significant relief compared with placebo in patients with cancer pain and that oral THC 20 mg was equivalent in analgesic potency to codeine 120 mg. Sedation and mental clouding were common side effects of THC. Jain and colleagues⁶³ found that a single i.m. dose of the synthetic cannabinoid levonantradol 1.5–3 mg gave significant analgesia for postoperative pain compared with placebo, but drowsiness was common with levonantradol. A few controlled studies^{24 115 136} (involving a total of only 20 patients) showed that oral THC 2.5–15 mg day⁻¹ relieved spasticity and tremor and improved general well being in some patients with multiple sclerosis. Several patients experienced a 'high' and some became dysphoric. Greenberg and colleagues⁴⁷ compared the effects of smoking cannabis (1.54% THC) or placebo in 10 patients with multiple sclerosis and 10 controls and found that cannabis impaired posture and balance in all subjects, causing greater impairment in the patients. No other objective changes were noted, although some patients reported subjective improvement and some experienced a 'high' on cannabis. Martyn, Illis and Thom⁸⁴ studied a single patient with multiple sclerosis who took nabilone 1 mg on alternate days for two periods of 4 weeks, alternating with 4-week periods of placebo. There was a clear improvement in pain from muscle spasms, frequency of nocturia and general well being during the two periods on nabilone. The patient experienced a brief period of mild sedation after taking nabilone but no other adverse symptoms.

Most other studies of cannabis or cannabinoids in painful conditions consist of open studies, questionnaire surveys or anecdotal reports.^{17 49} For example, Dunn and Davies³⁶ questioned 10 patients who smoked cannabis for a range of problems arising from spinal cord injury. Of these patients, five of eight reported improvement in spasticity; four of nine reported improvement in phantom limb pain; one of nine noted worsening of bladder spasm, and two of 10 worsening of urinary retention. Notcutt, Price and Chapman¹⁰⁶ described results with individualized doses of nabilone in patients attending a pain relief clinic who had chronic pain that had not responded to other treatments. Six of 13 patients with multiple sclerosis, seven of nine with back pain, three of seven with peripheral neuropathy, one of five with central neurogenic pain, three of three with various types of cancer pain and four of six so-called 'heartsink' patients with physical, psychological and social problems obtained partial or complete pain relief. They also reported better sleep, increased appetite, decreased use of other drugs and increased general well being. Three patients stopped nabilone because of dysphoria but six went on to smoke cannabis instead because they found it better than

Table 5 Adverse effects of nabilone in doses recommended for nausea and vomiting associated with cancer chemotherapy^{17,18}

Sedation, dizziness, lethargy
Additive effects with other CNS depressants
Psychological effects
Euphoria, dysphoria, anxiety, depression
Mental clouding, impaired memory
Depersonalization, paranoia, hallucinations
Physical effects
Dry mouth, ataxia, inco-ordination, blurred vision, weakness, tremor, palpitations, tachycardia, postural hypotension
(Cautions: cardiovascular disease, psychosis, liver disease, elderly)
Chronic use
Tolerance, withdrawal reactions

nabilone. Three patients found nabilone still effective after 2–3 yr.

Other clinical uses

Other clinical uses of cannabis which may be of value in chronic pain or palliative care, such as bronchodilator, anxiolytic, hypnotic and antidepressant effects, and use in glaucoma, in addition to their drawbacks, are described in the British Medical Association publication.¹⁷

Adverse effects in clinical use

The cannabinoid most likely to be prescribed for clinical use in the UK is nabilone. Adverse effects of this drug in doses recommended for nausea and vomiting associated with cancer chemotherapy are shown in Table 5. However, this dose is probably excessive for the other clinical indications mentioned above, especially in elderly and ill patients, and many unwanted effects could be prevented by using smaller doses. Unfortunately, nabilone is supplied only in 1-mg capsules, although it is a potent drug, up to 10 times more potent than THC.⁶ Notcutt, Price and Chapman¹⁰⁶ found that for some patients with pain conditions it was necessary to administer nabilone 0.25 mg, at least initially, and to give the first dose at night because of the hypnotic effects. The dose was then increased gradually depending on clinical effects. Smaller doses were obtained by opening the capsules and dividing the powder inside, an impractical and inaccurate procedure for many patients. It is hoped that nabilone will become available in smaller dose formulations.

Nabilone has a shorter half-life than THC; the plasma elimination half-life of the parent drug is 2–4 h, that of its metabolites 20 h, and 84% of a single dose is eliminated in 7 days.⁶ Reported dose regimens for pain conditions and multiple sclerosis vary from 1 mg three times daily to less than 1 mg daily on alternate days. It is not clear to what extent tolerance develops to various effects with chronic use. However, withdrawal reactions, sometimes severe (see Table 3), have been observed after long-term therapeutic use (personal communications). For this reason it is advisable to taper the dose gradually (possibly in 0.25-mg steps) if nabilone has been used for several weeks or months.

In view of the widespread recreational use of cannabis,

it is advisable that prescribed nabilone should not be identified as a cannabinoid and that patients should be warned to keep it in a place inaccessible to others, especially children and adolescents. Although nabilone is believed to have a low abuse potential and is unlikely to be abused by patients, some studies have concluded that in high doses the euphoriant effect is seven times more potent than that of THC.⁶ Thus there is a risk that it could enter the illicit drugs market. Other adverse effects of cannabinoids in clinical use are discussed in the British Medical Association publication.¹⁷

Conclusions

The prevalence of recreational cannabis use among young people and the potency of available cannabis preparations has increased markedly over the past decade in the UK. This widespread use carries health and other risks to the individual involved and to the community. Over the same period, interest in the use of cannabinoids as therapeutic agents has re-awakened and it seems possible that cannabinoids could provide a valuable addition to chronic pain management and palliative care.

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