

Seminar

Adverse effects of cannabis

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Cannabis is the most widely used illicit drug in many developed societies. Its health and psychological effects are not well understood and remain the subject of much debate, with opinions on its risks polarised along the lines of proponents' views on what its legal status should be. An unfortunate consequence of this polarisation of opinion has been the absence of any consensus on what health information the medical profession should give to patients who are users or potential users of cannabis. There is conflicting evidence about many of the effects of cannabis use, so we summarise the evidence on the most probable adverse health and psychological consequences of acute and chronic use. This uncertainty, however, should not prevent medical practitioners from advising patients about the most likely ill-effects of their cannabis use. Here we make some suggestions about the advice doctors can give to patients who use, or are contemplating the use, of this drug.

In many western societies, cannabis has been used by a substantial minority, and in some a majority, of young adults, even though its use is prohibited by law.¹ Debate about the justification for continuing to prohibit cannabis use has polarised opinion about the seriousness of its adverse health effects.² In addition, the possible therapeutic effects of cannabinoids have become entangled in the debate about prohibition of recreational cannabis use (see Further reading). The health effects of cannabis use, especially of long-term use, remain uncertain because there is very little epidemiological research and because of disagreements about the interpretation of the limited epidemiological and laboratory evidence.² Here we summarise the evidence on the most probable adverse health effects of cannabis use acknowledging where appropriate the uncertainty that remains.

Cannabis the drug

Cannabis preparations are largely derived from the female plant of *Cannabis sativa*. The primary psychoactive constituent is δ -9-tetrahydrocannabinol (THC).³ The THC content is highest in the flowering tops, declining in the leaves, lower leaves, stems, and seeds of the plant. Marijuana (THC content 0.5–5.0%) is prepared from the dried flowering tops and leaves; hashish (THC content 2–20%) consists of dried cannabis resin and compressed flowers; and hashish oil may contain between 15% and 50% THC.³ Sinsemilla and Netherwood varieties of cannabis may have a THC content of up to 20%.³

Cannabis may be smoked in a "joint", which is the size of a cigarette, or in a water pipe. Tobacco may be added to assist burning. Smokers typically inhale deeply and hold their breath to maximise absorption of THC by the lungs. Marijuana and hashish may also be eaten, but

cannabis is mostly smoked because this is the easiest way to achieve the desired psychoactive effects.²

A typical joint contains between 0.5 g and 1.0 g of cannabis. The THC delivered varies between 20% and 70%,² its bioavailability ranging from 5% to 24%.³ As little as 2–3 mg of available THC will produce a "high" in occasional users, but regular users may smoke five or more joints a day.

Cannabinoids act on a specific receptor that is widely distributed in the brain regions involved in cognition, memory reward, pain perception, and motor coordination.³ These receptors respond to an endogenous ligand, anandamide, which is much less potent and has a shorter duration than THC.³ The identification of a specific cannabinoid antagonist promises to improve our understanding of the role of cannabinoids in normal brain function.³

Patterns of cannabis use

Cannabis has been tried by many European young adults and by most young adults in the USA and Australia.¹ Most cannabis use is intermittent and time-limited: most users stop in their mid to late 20s, and very few engage in daily cannabis use over a period of years.⁴ In the USA and Australia, about 10% of those who ever use cannabis become daily users, and another 20–30% use the drug weekly.^{1,4}

Because of uncertainties about THC content, heavy cannabis use is generally defined as daily or near daily use.² This pattern of use over years places users at greatest risk of adverse health and psychological consequences.² Daily cannabis users are more likely to be male, to be less well educated, to use alcohol and tobacco regularly, and to use amphetamines, hallucinogens, psychostimulants, sedatives, and opioids.⁵

Acute effects of cannabis

Cannabis produces euphoria and relaxation, perceptual alterations, time distortion, and the intensification of ordinary sensory experiences, such as eating, watching films, and listening to music.² When used in a social

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setting it may produce infectious laughter and talkativeness. Short-term memory and attention, motor skills, reaction time, and skilled activities are impaired while a person is intoxicated.²

The most common unpleasant side-effects of occasional cannabis use are anxiety and panic reactions.² These effects may be reported by naïve users, and they are a common reason for discontinuation of use; more experienced users may occasionally report these effects after receiving a much larger than usual dose of THC.²

Cannabis smoking or ingestion of THC increases heart rate by 20–50% within a few minutes to a quarter of an hour; this effect lasts for up to 3 h.² Blood pressure is increased while the person is sitting, and decreased while standing.² These effects are of negligible clinical significance in healthy young users because tolerance develops to them.²

The acute toxicity of cannabinoids is very low.² There are no confirmed published cases worldwide of human deaths from cannabis poisoning, and the dose of THC required to produce 50% mortality in rodents is extremely high compared with other commonly used drugs.²

Psychomotor effects and driving

Cannabis produces dose-related impairments in cognitive and behavioural functions that may potentially impair driving a motor vehicle or operating machinery.⁶ These impairments are larger and more persistent for difficult tasks that depend on sustained attention.⁶ The most serious possible consequence of acute cannabis use is a road-traffic accident if a user drives while intoxicated.²

The effects of recreational doses of cannabis on driving performance in laboratory simulators and standardised driving courses have been reported by some researchers as being similar to the effects when blood alcohol concentrations are between 0.07% and 0.10%.² However, studies of the effects of cannabis on driving under more realistic conditions on roads have shown much more modest impairments,^{7,8} probably because cannabis users are more aware of their impairment and less inclined to take risks than alcohol users.^{7,8}

Results of epidemiological studies of road-traffic accidents are equivocal because most drivers who have cannabinoids in their blood also have high blood alcohol concentrations.² In two studies with reasonable numbers of individuals who had only used cannabis, there was no clear evidence of increased culpability in these drivers.⁹ The separate effects of alcohol and cannabis on psychomotor impairment and driving performance in laboratory tasks are roughly additive,⁹ so the main effect of cannabis use on driving may be in amplifying the impairments caused by alcohol, which is often used with the drug.²

Effects of chronic cannabis use

Cellular effects and the immune system

Cannabis smoke may be carcinogenic; it is mutagenic in vitro and in vivo.¹⁰ Cannabinoids impair cell-mediated and humoral immunity in rodents, decreasing resistance to infection, and non-cannabinoids in cannabis smoke impair alveolar macrophages.¹¹ The relevance of these findings to human health is uncertain because the doses of THC used in animal studies have been very high, and tolerance may develop to the effects on immunity in human beings.¹²



Figure 1: *Cannabis sativa*

A few studies that have pointed to the adverse effects of cannabis on human immunity have not been replicated.¹² There is no conclusive evidence that consumption of cannabinoids impairs human immune function, as measured by numbers of T lymphocytes, B lymphocytes, or macrophages, or immunoglobulin concentrations.¹² Two prospective studies of HIV-positive homosexual men have shown that cannabis use is not associated with an increased risk of progression to AIDS concentrations.^{13,14} David

Respiratory system

Chronic heavy cannabis smoking is associated with increased symptoms of chronic bronchitis, such as coughing, production of sputum, and wheezing.^{15,16} Lung function is significantly poorer and there are significantly greater abnormalities in the large airways of marijuana smokers than in non-smokers. Tashkin and colleagues^{16,17} have reported evidence of an additive effect of marijuana and tobacco smoking on histopathological abnormalities in lung tissue.

Bloom and colleagues¹⁵ reported similar additive effects on bronchitic symptoms in an epidemiological study of the respiratory effects of smoking "non-tobacco" cigarettes in 990 individuals aged under 40 years in Tucson, Arizona, USA. Non-tobacco smokers reported more coughing, phlegm production, and wheeze than non-smokers, irrespective of whether they also smoked tobacco. Those who had never smoked any substance had the best respiratory functioning, followed in order of decreasing function by current tobacco smokers, current non-tobacco smokers, and current smokers of both tobacco and non-tobacco cigarettes. Non-tobacco smoking alone had a larger effect on respiratory function



Figure 2: Resin and dried leaves

than tobacco smoking alone, and the effect of both types of smoking was additive.¹⁵

In 1997, Tashkin and colleagues¹⁸ reported that the rate of decline in respiratory function over 8 years among marijuana smokers did not differ from that in non-smokers. This finding contrasted with that of a follow-up of the Tucson cohort,¹⁹ in which there was a greater rate of decline in respiratory function among marijuana-only smokers than in tobacco-only smokers and additive effects of tobacco and marijuana smoking. Both studies showed that long-term cannabis smoking increased bronchitic symptoms.

In view of the adverse effects of tobacco smoking, the similarity between tobacco and cannabis smoke, and the evidence that cannabis smoking produces histopathological changes that precede lung cancer,¹⁷ long-term cannabis smoking may also increase the risks of respiratory cancer.²⁰ There have been reports of cancers in the aerodigestive tract in young adults with a history of heavy cannabis use.^{21,22} These reports are worrying since such cancers are rare among adults under the age of 60, even those who smoke tobacco and drink alcohol.²⁰ Case-control studies of the role of cannabis smoking in these cancers are urgently needed.

Reproductive effects

Chronic administration of high doses of THC to animals lowers testosterone secretion, impairs sperm production, motility, and viability, and disrupts the ovulatory cycle.²³ Whether cannabis smoking has these effects in human beings is uncertain because the published evidence is small and inconsistent.²

Cannabis administration during pregnancy reduces birthweight in animals.²⁴ The results of human epidemiological studies have been more equivocal.² The stigma of using illicit drugs during pregnancy discourages honest reporting,²⁵ and when associations are found, they are difficult to interpret because cannabis users are more likely than non-users to smoke tobacco, drink alcohol, and use other illicit drugs during pregnancy, and they differ in social class, education, and nutrition.²⁶ Several studies have suggested that cannabis smoking in pregnancy may reduce birthweight.² In the best controlled of these studies, this relation has persisted after statistical control for potential confounding variables,²⁷ but other studies²⁸ have not shown any such association. The effect of cannabis on birthweight in the studies that have found an association has been small compared with that of tobacco smoking.²⁶

That cannabis use during pregnancy increases the risk of birth defects is unlikely. Early case reports have not been supported by large well-controlled epidemiological studies. For example, the study by Zuckerman et al²⁷ included a large sample of women with a substantial prevalence of cannabis use that was verified by urine analysis, and there was no increase in birth defects.

There is suggestive evidence that infants exposed in utero to cannabis have behavioural and developmental effects during the first few months after birth.²⁶ Between the ages of 4 and 9 years, children who were exposed in utero have shown deficits in sustained attention, memory, and higher cognitive functioning.²⁹ The clinical significance of these effects remains unclear since they are small compared with the effects of maternal tobacco use.²⁹

Summary of adverse effects of cannabis

Acute effects

- Anxiety and panic, especially in naïve users.
- Impaired attention, memory, and psychomotor performance while intoxicated.
- Possibly an increased risk of accident if a person drives a motor vehicle while intoxicated with cannabis, especially if cannabis is used with alcohol.
- Increased risk of psychotic symptoms among those who are vulnerable because of personal or family history of psychosis.

Chronic effects (uncertain but most probable)

- Chronic bronchitis and histopathological changes that may be precursors to the development of malignant disease.
- A cannabis dependence syndrome characterised by an inability to abstain from or to control cannabis use.
- Subtle impairments of attention and memory that persist while the user remains chronically intoxicated, and that may or may not be reversible after prolonged abstinence.

Possible adverse effects (to be confirmed)

- Increased risk of cancers of the oral cavity, pharynx, and oesophagus; leukaemia among offspring exposed in utero.
- Impaired educational attainment in adolescents and underachievement in adults in occupations requiring high-level cognitive skills.

Groups at higher risk of experiencing these adverse effects

- Adolescents with a history of poor school performance, who initiate cannabis use in the early teens, are at increased risk of using other illicit drugs and of becoming dependent on cannabis.
- Women who continue to smoke cannabis during pregnancy may increase their risk of having a low-birthweight baby.
- People with asthma, bronchitis, emphysema, schizophrenia, and alcohol and other drug dependence, whose illnesses may be exacerbated by cannabis use.

Three studies have shown an increased risk of non-lymphoblastic leukaemia,³⁰ rhabdomyosarcoma,³¹ and astrocytoma³² in children whose mothers reported using cannabis during their pregnancies. None of these was a planned study of the association; cannabis use was one of many potential confounders included in statistical analyses of the relation between the exposure of interest and childhood cancer. Their replication is a priority.

Behavioural effects in adolescence

There is a cross-sectional association between heavy cannabis use in adolescence and the risk of leaving high-school education and of experiencing job instability in young adulthood.³³ However, the strength of this association is reduced in longitudinal studies when statistical adjustments are made for the fact that, compared with their peers, heavy cannabis users have poor high-school performance before using cannabis.^{33,34}

There is some evidence that heavy use has adverse effects on family formation, mental health, and involvement in drug-related crime.³³ In each case, the strong associations in cross-sectional studies are more modest in longitudinal studies after statistical control for associations between cannabis use and other pre-existing characteristics that independently predict these adverse outcomes.³⁴

A consistent finding in the USA has been the regular sequence of initiation into drug use in which cannabis use has typically preceded involvement with "harder" illicit drugs such as stimulants and opioids.^{5,33,35} The interpretation of this sequence remains controversial.

The less compelling hypothesis is that cannabis use directly increases the use of other drugs in the sequence. There is better support for two other hypotheses—namely, that there is a selective recruitment into cannabis use of non-conforming adolescents who have a propensity to use other illicit drugs, and that once recruited to cannabis use, social interaction with drug-using peers, and greater access to illicit-drug markets, they are more likely to use other illicit drugs.^{2,34}

Dependence syndrome

Animals develop tolerance to the effects of repeated doses of THC,³⁶ and studies suggest that cannabinoids may affect the same reward systems as alcohol, cocaine, and opioids.³⁷ Heavy smokers of cannabis also develop tolerance to its subjective and cardiovascular effects,³⁶ and some report withdrawal symptoms on the abrupt cessation of cannabis use.^{36,38}

There is evidence that a cannabis dependence syndrome occurs with heavy chronic use in individuals who report problems in controlling their use and who continue to use the drug despite experiencing adverse personal consequences.^{2,39} There is some clinical evidence of a dependence syndrome analogous to that for alcohol.² In the USA, cannabis dependence is among the most common forms of illicit-drug dependence in the population.⁴⁰ About one in ten of those who ever use cannabis become dependent on it at some time during their 4 or 5 years of heaviest use.⁴⁰ This risk is more like the equivalent risk for alcohol (15%) than for nicotine (32%) or opioids (23%).⁴⁰

Cognitive effects

The long-term heavy use of cannabis does not produce the severe or grossly debilitating impairment of memory, attention, and cognitive function that is found with chronic heavy alcohol use.² Electrophysiological and neuropsychological studies show that it may produce more subtle impairment of memory, attention, and the organisation and integration of complex information.^{41–43} The longer cannabis has been used, the more pronounced the cognitive impairment.⁴¹ These impairments are subtle, so it remains unclear how important they are for everyday functioning, and whether they are reversed after an extended period of abstinence.² Early studies that suggested gross structural brain damage with heavy use have not been supported by better controlled studies with better methods.⁴¹ Research in animals has shown that chronic cannabinoid administration may compromise the endogenous cannabinoid system^{3,41} (its function is unclear, but it has roles in memory, emotion, and cognitive functioning, as mentioned above). These results are consistent with the subtlety of the cognitive effects of chronic cannabis use in human beings.⁴¹

Psychosis

Large doses of THC produce confusion, amnesia, delusions, hallucinations, anxiety, and agitation.⁴⁴ Such reactions are rare, occurring after unusually heavy cannabis use; in most cases they remit rapidly after abstinence from cannabis.²

There is an association between cannabis use and schizophrenia. A prospective study of 50 000 Swedish conscripts⁴⁵ found a dose-response relation between the frequency of cannabis use by age 18 and the risk of a

diagnosis of schizophrenia over the subsequent 15 years. A plausible explanation is that cannabis use can exacerbate the symptoms of schizophrenia,^{2,46} and there is prospective evidence that continued use predicts more psychotic symptoms in people with schizophrenia.⁴⁷ A declining incidence of treated cases of schizophrenia over the period when cannabis use has increased suggests, however, that cannabis use is unlikely to have caused cases of schizophrenia that would not otherwise have occurred.⁴⁸ This observation suggests that chronic use may precipitate schizophrenia in vulnerable individuals, an effect that would not be expected to change incidence.⁴⁵

Premature mortality

There have been two prospective epidemiological studies of mortality among cannabis users. A Swedish study of mortality during 15 years among male military conscripts showed an increased risk of premature death among men who had smoked cannabis 50 or more times by age 18.⁴⁹ Violent and accidental death was the main contributor to this excess. However, the association between mortality and cannabis use disappeared after multivariate statistical adjustment for alcohol and other drug use.⁴⁹

Sydney and colleagues⁵⁰ reported a 10-year study of mortality in cannabis users aged between 15 and 49 years among 65 171 members of the Kaiser Permanente Medical Care Program. The sample consisted of 38% who had never used cannabis, 20% who had used fewer than six times, 20% who were former users, and 22% who were current users. Regular cannabis use had a small association with premature mortality (RR 1.33), which was wholly explained by increased deaths from AIDS in men, probably because marijuana use was a marker for male homosexual behaviour in this cohort. It is too early to conclude from the study that marijuana use does not increase mortality because the average age at follow-up was only 43 years, and cigarette smoking and alcohol use were only modestly associated with premature mortality.⁵⁰

Possible effects of increased THC content of cannabis

The average THC content of cannabis has probably increased over the past several decades, but without good data by how much is unclear.² This situation probably reflects a combination of an increased market for more potent cannabis products among regular users,² and improved methods of growing high-THC-content.³ The net health consequences of any increase in potency are uncertain.² Among naïve users, higher THC content may increase adverse psychological effects, including psychotic symptoms, thereby discouraging some from continuing to use. Among those who continue to use cannabis, increased potency may increase the risks of developing dependence, having accidents if driving while intoxicated, and experiencing psychotic symptoms. If experienced users can regulate their dose of THC, the respiratory risks of cannabis smoking may be marginally reduced.

Health advice for cannabis users

Uncertainty about the adverse health effects of acute, and especially chronic, cannabis use, should not prevent medical practitioners from advising patients who use cannabis about the most probable ill-effects of their cannabis use with emphasis on the uncertainty. In the absence of other risk factors, this should include advice about the possibility of being involved in a motor-vehicle

accident if patients drive while intoxicated by cannabis; the higher risk of an accident if they drive when intoxicated by both alcohol and cannabis; the respiratory risks of long-term cannabis smoking, which are substantially increased if they also smoke tobacco; an increased risk of developing dependence if they are daily users of cannabis; and the possibility of subtle cognitive impairment if they use regularly over several years.

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