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Long-term effects of exposure to cannabis

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The long-term use of cannabis, particularly at high intake levels, is associated with several adverse psychosocial features, including lower educational achievement and, in some instances, psychiatric illness. There is little evidence, however, that long-term cannabis use causes permanent cognitive impairment, nor is there is any clear cause and effect relationship to explain the psychosocial associations. There are some physical health risks, particularly the possibility of damage to the airways in cannabis smokers. Overall, by comparison with other drugs used mainly for 'recreational' purposes, cannabis could be rated to be a relatively safe drug.

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Abbreviations
THC Δ^9-tetrahydrocannabinol

Introduction

Cannabis is the most commonly used illicit drug. In many countries, more than 50% of young people have used it at least once and it is widely perceived as relatively safe. Many people believe that there are genuine medical uses for cannabis-based medicines and it seems likely that such products will gain official approval in several Western countries. Concurrently, there is a move towards relaxation of the criminal penalties associated with the recreational use of cannabis — ranging from the down-grading of criminal penalties in the UK to the possibility of full legalization in Canada and Switzerland. In light of these changes in attitude, it is timely to consider again the adverse effects associated with long-term cannabis use over a period of years, as no drug can ever be considered completely safe.

Effects on cognition

Several studies have addressed the question of whether severe deficits in cognitive function develop in chronic heavy users of cannabis, or in animals treated for prolonged periods with the drug. Most reports have shown that there are deficits in the performance of complex cognitive tasks in long-term cannabis users, although there is little evidence that these are qualitatively or quantitatively more severe than those seen after acute drug use [1].

More controversial is the question of whether long-term cannabis use can cause irreversible deficits in higher brain function that persist after drug use stops. Human studies are fraught with difficulties, as described in detail by Earleywine [1]. Indeed, many studies have suffered from poor design. One confounding factor in human studies is that comparisons have to be made between groups of drug users versus non-users; however, it is usually impossible to compare the baseline performance of these groups before cannabis use to see if they are properly matched. Pope *et al.* [2], for example, tested 69 early-onset heavy cannabis users (who began smoking before the age of 17) in a battery of neuropsychological tests after a two-week period of abstinence. The group performed significantly worse than late-onset users or controls, but also displayed a lower verbal IQ. When the data were adjusted for this, all differences between early-onset users and others ceased to be significant.

It is not sufficient to identify a group of cannabis users and simply to test them after stopping cannabis use. One study, for example, recruited 63 current heavy users who had smoked cannabis at least 5000 times in their lives and 72 control subjects [3]. The subjects underwent a 28-day washout from cannabis use, monitored by urine assays. At days 0, 1 and 7, the heavy users scored significantly below control subjects on a battery of neuropsychological tests, particularly in recall of word lists. However, by day 28, there were no differences between the groups in any of the test results, and no significant association between cumulative lifetime cannabis use and test scores. The fact that drug-induced effects on cognitive performance can persist for up to a week after stopping the drug (perhaps because of the persistence of Δ^9-tetrahydrocannabinol [THC] in the body, or because of a subtle withdrawal syndrome) means that many earlier studies that did not allow a sufficiently long washout period might be invalid.

One way of assessing cognitive function is to measure IQ. Fried *et al.* [4] tested the effects of cannabis use in a group of 70 young people by subtracting each person's IQ score at nine years of age (before drug use) from their score at age 17-20 years. Current cannabis use was found to be significantly correlated in a dose-dependent manner with a decline in IQ scores. However, no such decline was seen

in subjects who had formerly been heavy cannabis users and had stopped taking the drug. The authors concluded that cannabis does not have a long-term effect on global intelligence.

This general conclusion was also supported by a review of the 40 published studies that met adequate criteria, which failed to detect any consistent evidence of persisting neuropsychological deficits in cannabis users — although some studies reported subtle impairments in the ability to learn and remember new information [5].

Cannabis and psychiatric illness

There has been a long-standing concern that cannabis use might precipitate mental illness in some users. It is clear that an acute schizophrenia-like psychosis can occur in response to a high dose of cannabis [6•], but whether cannabis use can cause persistent psychiatric illness in people who had not previously shown psychotic symptoms remains contentious. A recent re-analysis of the results of a large scale study of >50 000 Swedish men (age 18–20 years) conscripted into the Swedish army between 1969 and 1970 suggested that those who had used cannabis >50 times before the age of 18 years had a 6.7-fold increased risk of developing schizophrenia in later life [7]. A review of this and four other longitudinal cohort studies also concluded that early cannabis use might be a causal factor for schizophrenia-like illness in later life [8••]. However, the interpretation of such studies is fraught with many difficulties, as reviewed by Macleod *et al.* [9••]. These authors highlighted that proof of a causal relationship is subject to many confounding factors. When known confounding factors were applied to the Swedish army data, for example, the odds ratio was reduced from 6.7 to 3.1 [7]. This, in turn, suggests that other residual unidentified confounding factors are also likely to exist. The published studies show that the existence of 'prodromal' symptoms of psychosis clearly increased the risk of subsequent psychiatric illness in cannabis users [8••]. This factor was adequately controlled for in only one of the five published longitudinal studies [10]. In this New Zealand cohort, even when those exhibiting prodromal symptoms of psychosis were eliminated, those who started cannabis use by age 15 years (but not those who started later) showed a fourfold increase in the risk of developing schizophrenia-like illness by age 26 years. However, the number of subjects involved was small (there were 26 15-year old cannabis users, of whom three developed mental illness) so the statistical power of this study was limited. Degenhardt *et al.* [11] sought to test the hypothesis of a causal relationship between cannabis use and schizophrenia by a careful examination of the incidence of schizophrenia in Australia during the past 30 years. Although the prevalence of cannabis use had increased markedly during this period, there was no evidence of a significant increase in the incidence of schizophrenia. The question of whether cannabis use can precipitate psychiatric illness in a vulnerable minority of previously well people remains unanswered. One could equally argue that a tendency to psychotic illness might increase the likelihood of early cannabis use [9••]. It is possible that cannabis may precipitate schizophrenic illness earlier in vulnerable people who exhibit 'schizophreniform' tendencies. Such a conclusion is supported by the results of a study of 122 newly admitted schizophrenia patients in the Netherlands, which showed a strong association between cannabis use and the age of onset of the first psychotic episode in men, with users experiencing their first psychotic episode 6.9 years earlier than non-users [12].

Other studies have explored the association between cannabis use and depression. One longitudinal study in Australia reported that daily use of cannabis by teenage girls (but not boys) led to an approximately twofold increased risk for depression/anxiety in later life [13]. A review of other studies of this type suggested that heavy cannabis use may increase depressive symptoms in some users, but whether this represents a causal relationship is again unclear [14].

Psychosocial sequelae of cannabis use

Apart from the potential risk of mental illness, there has been a long standing concern that adolescent use of cannabis could lead to reduced educational achievement and reduced motivation — sometimes referred to as an 'amotivational syndrome' [1].

Cherek *et al.* [15] attempted to assess this experimentally in a study in which human participants earned money by responding on a complex lever-pressing schedule. There was a significant reduction in the number of responses, time spent and money earned when the subjects were re-tested while smoking cannabis, indicating a drug-induced reduction in motivation.

Various longitudinal studies have sought to establish the relationship between cannabis use and subsequent educational achievement. A study of 1265 New Zealand children [16] showed that cannabis use was dose-dependently related to an increased risk of leaving school without qualifications, failure to enter university and failure to obtain a university degree. A similar conclusion was reached in reviews of other published studies of this type [9••,17]. The review by Macleod *et al.* [9••] was particularly comprehensive; the authors studied 48 published longitudinal studies on the use of cannabis, of which 16 were considered to provide the most robust evidence. Their conclusions for cannabis use were, firstly, a consistent association with reduced educational achievement; secondly, a consistent association with use of other drugs; thirdly, an inconsistent association with psychological problems of various types; and finally, an inconsistent association with antisocial or other

problematic behaviours. They concluded that ''Available evidence does not support an important causal relation between cannabis use and psychosocial harm, but cannot exclude the possibility that such a relation exists''.

Whatever the nature of the association, it seems clear that long-term heavy cannabis use carries a variety of negative attributes. A case control study compared 108 heavy-use long-term cannabis users, who had on average smoked 18 000 times, with 72 age-matched controls who had smoked cannabis <50 times [18••]. The heavy-use cannabis smokers reported significantly lower educational attainment and lower income than did controls. When asked to rate the subjective effects of cannabis on cognition, memory, career, social life, physical and mental health and various quality-of-life measures, a large majority of heavy-use cannabis smokers reported negative effects of their drug use.

Cannabis and substance dependence

Although it was previously thought that cannabis was not a drug of addiction, it is now recognized that cannabis use can lead to substance dependence in perhaps as many as 10% of regular users, according to the internationally accepted DSMIV definition of 'substance dependence' [6•]. In both animals and humans, a clear withdrawal syndrome can be identified [6•]. In rodents, chronic administration of THC or synthetic cannabinoids leads to downregulation and desensitization of cannabinoid CB_1 receptors in the brain [19]. This might partly explain the tolerance that develops in both animals and humans on repeated use of the drug. In regular cannabis users, abstinence leads to a withdrawal syndrome characterized by negative mood (irritability, anxiety, misery), muscle pain, chills, sleep disturbance and decreased appetite. A placebo-controlled study showed that these symptoms were significantly reduced by oral administration of THC, suggesting that the withdrawal syndrome and underlying substance dependence were related to effects of THC on the cannabinoid CB_1 receptor, rather than to any other component of herbal cannabis [20].

Other potentially toxic effects of long-term cannabis use

Some of the most serious adverse effects of smoked cannabis are on the respiratory system. Although little progress has been made recently in quantifying such risks, warnings continue to be issued about the potential for long-term damage or even malignancy in the airways [21]. It is known that lung macrophages isolated from cannabis smokers exhibit impaired anti-bacterial activity, and one experimental study showed that this might be caused, in part, by reduced expression of inducible nitric oxide synthase and decreased production of nitric oxide [22]. A review of the evidence for immunosuppressant effects of cannabis concluded that, with the exception of the effects of cannabis smoking on broncho-alveolar immunity, there is no evidence that cannabis causes any other serious immunosupression in users [23]. The authors suggested that the effects on lung macrophages might be related to the ability of cannabis in animal studies to cause a shift from Th1 to Th2 cytokine production.

With increasing use of cannabis, there remains a concern that cannabis use during pregnancy might impair foetal development. Reviews of data from humans, however, suggest that such effects are minimal for cannabis users when compared with the well-documented adverse effects of tobacco or alcohol use [24,25•]. Nevertheless, treatment of pregnant rats with high doses of THC did lead to significant reductions in expression of neural adhesion molecule L1 in the foetal brain — a key protein for brain development [26].

Conclusions

A review of the literature suggests that the majority of cannabis users, who use the drug occasionally rather than on a daily basis, will not suffer any lasting physical or mental harm. Conversely, as with other 'recreational' drugs, there will be some who suffer adverse consequences from their use of cannabis. Some individuals who have psychotic thought tendencies might risk precipitating psychotic illness. Those who consume large doses of the drug on a regular basis are likely to have lower educational achievement and lower income, and may suffer physical damage to the airways. They also run a significant risk of becoming dependent upon continuing use of the drug. There is little evidence, however, that these adverse effects persist after drug use stops or that any direct cause and effect relationships are involved.

In contrast, cannabis might have beneficial effects in some medical indications. There is considerable literature obtained from animal studies to suggest that cannabis has analgesic effects [27]. Until recently, however, there has been a dearth of controlled clinical studies to validate such effects in patients. This has now changed, with the publication in the past two years of a number of double-blind placebo-controlled trials showing the effectiveness of cannabinoids in relieving chronic neuropathic pain [28,29] or pain associated with multiple sclerosis [30••, 31]. The largest of these trials involved 630 multiple sclerosis patients and showed significant pain relief after 15 weeks of treatment with either pure THC or cannabis extract [30]. It seems likely that medicinal cannabis will re-enter the Pharmacopoeia.

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