Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis

Robin M. Murray, Harriet Quigley, Diego Quattrone, Amir Englund, Marta Di Forti

Institute of Psychiatry, Psychology and Neuroscience, King's College, De Crespigny Park, London, SE5 8AF, UK

Epidemiological evidence demonstrates that cannabis use is associated with an increased risk of psychotic outcomes, and confirms a dose-response relationship between the level of use and the risk of later psychosis. High-potency cannabis and synthetic cannabinoids carry the greatest risk. Experimental administration of tetrahydrocannabinol, the active ingredient of cannabis, induces transient psychosis in normal subjects, but this effect can be ameliorated by co-administration of cannabidiol. This latter is a constituent of traditional hashish, but is largely absent from modern high-potency forms of cannabis. Argument continues over the extent to which genetic predisposition is correlated to, or interacts with, cannabis use, and what proportion of psychosis could be prevented by minimizing heavy use. As yet, there is not convincing evidence that cannabis use increases risk of other psychiatric disorders, but there are no such doubts concerning its detrimental effect on cognitive function. All of the negative aspects are magnified if use starts in early adolescence. Irrespective of whether use of cannabis is decriminalized or legalized, the evidence that it is a component cause of psychosis is now sufficient for public health messages outlining the risk, especially of regular use of high-potency cannabis and synthetic cannabinoids.

Key words: Cannabis, psychosis, marijuana, synthetic cannabinoids, cognitive function, brain structure, genetic predisposition, early adolescence

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The use of cannabis has been illegal in most countries since the 1930s, but this has not deterred use[1]. Currently, cannabis is used by around 180 million people globally[2]. The tensions produced by this unsatisfactory situation have resulted in much attention being paid to the legal status of cannabis.

Possession of the drug in small quantities has been decriminalized officially in countries such as Portugal and the Netherlands, and unofficially in many more. In 2013, Uruguay became the first nation to legalize the sale, cultivation and distribution of cannabis[3]. Four US states have also legalized recreational use, and another twenty-five US states as well as Canada permit so-called "medicinal marijuana". While Uruguay has strict rules concerning access, laws vary state by state in the US, with policy being increasingly driven by entrepreneurs in search of profit, and law makers in search of taxes.

Given the above, it seems likely that consumption of cannabis will increase rather than decrease. This makes it imperative to understand the possible adverse consequences of use, even if they only affect a minority of users. In this paper we start by reviewing cannabinoids and the endocannabinoid system. We then focus on cannabis use and risk of psychiatric disorder, particularly psychosis, before touching on the effects on cognition and brain structure.

CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM

Cannabis contains over one hundred cannabinoids[4], the most important of which are tetrahydrocannabinol (THC) and cannabidiol (CBD). These are produced in tiny crystal formations around the flowering tops. Recreational cannabis has been traditionally available as herb (marijuana, grass, weed) or resin (hashish, hash). In some countries such as the US it is smoked by itself, while in much of Europe it is smoked with tobacco. When smoked or inhaled, effects come on after a few minutes and last 2-3 hours; if eaten it can take 2 hours for the effects to be felt and they can last up to 8 hours.

Cannabinoids exert their effects primarily by interacting with the endocannabinoid system, which comprises endogenous ligands, their receptors, and the enzymes that synthesize and degrade them[5].

There are two specific receptors: cannabinoid receptor type-1 (CB1) and cannabinoid receptor type-2 (CB2). The CB1 receptor is widespread throughout the brain, with high concentrations in the neocortex, basal ganglia and hippocampus[6]. CB1 receptors are located pre-synaptically on the terminals of GABAergic and glutamatergic neurons, where they act homeostatically to counteract the over- or under-activity of these systems by modulating pre-synaptic neurotransmitter release[7]. The CB2 receptor, initially thought to be confined to immune cells and peripheral tissues[8], has recently also been found in the cerebellum and brain stem.

The best known endogenous cannabinoid receptor ligands are N-arachidonoylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). These are biosynthesized post-synaptically in an activity-dependent manner before being cleared by a reuptake mechanism and enzymatic hydrolysis.

THC is responsible for the euphoria and feelings of increased sociability and insightfulness, "the high" that users enjoy. It is a partial agonist at the CB1 receptor[9]. As the endocannabinoid system normally operates "on-demand" in an activity-dependent manner[10], exogenous THC appears to overwhelm the endogenous system[11-15], with resulting lower levels, for example, of AEA[16].

Administering THC to healthy volunteers impairs learning, attention and memory in a dose-response manner[17-22]. Such impairment is likely why drivers, under the influence of cannabis, are at double risk of traffic accidents[23]. Experimental studies have also shown that a sufficiently high dose of intravenous THC can induce short-lived psychotic symptoms, including paranoia and hallucinations[19,24,25]. It also increases paranoid thoughts in a virtual reality setting[26].

CBD lacks significant affinity for the CB1 receptor[27,28], but it is able to displace THC at low nanomolar concentrations[29]. It may act antagonistically against CB1 agonists via a non-orthosteric binding site[30]. It appears to block or ameliorate many of the effects of THC. For example, the co-administration of CBD significantly reduces THC-induced tachycardia[31], the anxiogenic effects of THC[32], and the detrimental effects of THC on perception[33,34] and memory[35].

THE CHANGING NATURE OF RECREATIONAL CANNABINOIDS

The proportion of THC in the commonly used herbal cannabis (marijuana) and resin (hashish) was 3% or less in the 1960s, but subsequently it began to rise. Growers cross-bred plants to increase potency. Then, they found that preventing pollination increased THC, as in this situation the female plant converts its energy into producing more cannabinoids rather than seeds[36]. This type of cannabis is referred to as *sinsemilla*, which means "without seed" in Spanish, but is sometimes colloquially termed "skunk", because of its strong smell. Plants bred to produce a high concentration of THC cannot simultaneously produce a lot of CBD, so the product contains only traces of the latter[37].

By the early years of the 21th century, the average proportion of THC had risen to 16 and 20% in England and Holland respectively, and *sinsemilla* had taken over much of the traditional market from resin[37,38]. Similarly, Australia saw a shift towards high-potency cannabis, with mean THC around 15%[39], while in the US potency reached an average of 12% by 2014[40].

In the US states where recreational cannabis or "medicinal marijuana" have been legalized, an increasingly wide variety of products are becoming available, including oils and "edibles" such as biscuits, chocolates and cakes. Novel ways of extracting THC from the plant have produced resin oil with up to 80% THC content, while other innovations delivering high THC concentrations include "vaping" and "wax dabbing".

J.W. Huffman spent over 25 years seeking to synthetize cannabinoids for therapeutic use[41]. However, in the late 2000s, some of his compounds started to be used as "legal highs", often termed "Spice". Subsequently, the use of such synthetic cannabinoids increased dramatically, often taken sprayed on herbal mixtures. While THC is a partial agonist with weak affinity for the CB1 receptor, synthetic cannabinoids are full agonists and generally have higher affinity. Not surprisingly, they pose a greater health risk compared to plant cannabis[42-44]. A survey of 80,000 drug users showed that those who used synthetic cannabinoids were thirty times more likely to end up in an emergency unit than users of traditional cannabis[45]. Acute physical reactions include nausea and vomiting, breathlessness, hypertension, tachycardia, chest pain, and occasionally acute renal failure.

Over 200 synthetic cannabinoids have been reported available on the Internet[46]. As each has a slightly different molecular structure, they can have unpredictable side effects. Furthermore, they cannot be detected by routine drug tests, making them particularly attractive to those in prison and in the army.

PSYCHOSIS

Concern that use of cannabis might induce psychosis is not new. For example, in 1896, the Scottish psychiatrist T. Clouston visited the Cairo asylum and noted that 40 out of 253 people in the hospital had insanity attributed to the use of hashish[47]. However, by the 1960s, this view was commonly ridiculed as "reefer madness", with the implication that it was those who believed that cannabis could induce psychosis who were mad, rather than those who consumed the drug.

In the first prospective study to explore whether cannabis played a causal role in psychosis, Andréasson et al[48] traced 45,750 young men who had been asked about their drug use when they were conscripted into the Swedish army. Those who had used cannabis more than fifty times were six times more likely to develop schizophrenia over the next fifteen years than those who had never used it. Surprisingly, the findings were mostly ignored. Even *The Lancet*, which had published Andréasson et al's paper in 1987, carried an editorial in 1995 stating the prevailing view that "the smoking of cannabis, even long term, is not harmful to health"[49].

However, there has now been a raft of longitudinal prospective studies[50,51]. Nine out of twelve found that cannabis use was associated with a significantly increased risk of psychotic symptoms or psychotic illness; the remaining three showed a trend in the same direction[52-64] (Table 1). Marconi et al[65] performed a meta-analysis and showed that the more extensive the cannabis use the greater the risk for psychosis in all of the studies included. There was an odds ratio of almost four for risk of psychosis-related outcomes among the heaviest users compared to the non-users.

Is use of higher potency types of cannabis more risky than traditional forms? Di Forti et al[66] examined 410 patients with their first episode of psychotic disorder and 390 healthy controls. People using high-potency cannabis on a daily basis were five times more likely than non-users to suffer from a psychotic disorder. Use of hashish was not related to an increased risk of psychosis, possibly due to its lower THC content combined with the presence of CBD[66-68].

Table 1 Longitudinal studies concerning the role of cannabis as a risk factor for psychosis

Study	Country	Design	No. participants	Follow-up (years)	OR (95% CI) (adjusted risk)
Tien & Anthony[52]	US	Population based	4,494	1	2.4 (1.2-7.1)
Zammit et al[53]	Sweden	Conscript cohort	50,053	27	3.1 (1.7-5.5)
Manrique-Garcia et al[54]				35	1.8 (1.3-2.3)
van Os et al[55]	The Netherlands	Population based	4,045	3	2.8 (1.2-6.5)
Weiser et al[56]	Israel	Population based	9,724	4-15	2.0 (1.3-3.1)
Fergusson et al[57]	New Zealand	Birth cohort	1,265	3	1.8 (1.2-2.6)
Arseneault et al[58]	New Zealand	Birth cohort	1,034	15	4.5 (1.1-18.2)
Ferdinand et al[59]	The Netherlands	Population based	1,580	14	2.8 (1.79-4.43)
Henquet et al[60]	Germany	Population based	2,437	4	1.7 (1.1-1.5)
Wiles et al[61]	UK	Population based	8,580	1.5	1.5 (0.55-3.94)
Rössler et al[62]	Switzerland	Community survey	591	30	1.8 (0.96-3.2)
Gage et al[63]	UK	Birth cohort	1,756	2	1.1 (0.76-1.65)
Rognli et al[64]	Sweden	Cohort of discharged prisoners	6,217	5	2.6 (1.40-5.0)

Similarly, in a Dutch survey of 2,000 cannabis users, those who preferred cannabis with the highest CBD content had experienced fewer psychotic-like experiences[69]. Morgan and Curran[70], who tested hair for cannabinoids, showed that users with both detectable THC and CBD had fewer psychotic symptoms than those with only THC. Finally, in an experimental study of 48 healthy volunteers, treatment with oral CBD before administration of intravenous THC significantly reduced the occurrence of psychotic symptoms[35].

Reports have begun to emerge of cases of psychosis following the use of types of cannabis with much higher THC content, for example "wax dabs"[71]. Psychiatric symptoms are also increasingly being reported consequent upon use of synthetic cannabinoids[72]. Papanti et al[73] carried out a systematic review and reported that agitation, anxiety, paranoia and psychosis can result; these reactions are sometimes referred to as "spiceophrenia". Mounting evidence suggests that more chronic psychotic disorders can occur in persistent users of synthetic cannabinoids[74].

The existence of a cannabis psychosis distinct from schizophrenia is dubious. It is true that sudden high consumption can induce a state of acute intoxication which usually rapidly resolves. This is not uncommon with consumption of edibles, where it is more difficult to titrate one's ingestion than with smoked cannabis. Use of plant or synthetic cannabinoids for a relatively short time may induce an acute psychosis from which people recover over a period of days or weeks. But the longer use continues, the more the clinical picture merges into that of schizophrenia-like psychosis[54,64].

Nevertheless, there are differences between people with a cannabis-associated psychosis and non-using psychotic patients. Cannabis-using patients tend to have a significantly earlier onset than psychosis patients who never used cannabis[75]. One study showed a dose-response association, with daily users of high-potency cannabis experiencing their first episode of psychosis, on average, 6 years younger than never users[68].

Cannabis-using psychotic patients also tend to have higher IQ and better neurocognition than non-using psychotic patients[76,77]. They also have higher premorbid IQ and better premorbid social function[78] and are less likely to show neurological soft signs[79]. The likely explanation is that many non-drug-using schizophrenic patients have some neurodevelopmental impairment and consequent poor premorbid cognition and social function. In contrast, those who have used cannabis are often initially clever and sociable; introduced to cannabis by their friends, they are sufficiently socially adept to be able to conceal their habit from their parents.

CRITICISMS OF THE CAUSAL HYPOTHESIS

Most European and Australasian experts are now convinced that cannabis is one of a number of contributory causes of schizophrenia. However, three sceptical articles have recently appeared from North America[80-82]. We will now review the main criticisms.

One suggestion has been that those who use cannabis may be psychologically more vulnerable than those who do not. However, the Dunedin study from New Zealand controlled for psychotic symptoms at age 11, and still found a link between cannabis use and later psychotic symptoms[58].

Might some people be taking cannabis in an attempt to self-medicate symptoms of psychosis or its precursors? There is little evidence for this. A second New Zealand study, this time from Christchurch, showed that once minor psychotic symptoms developed, people tended to smoke less[83]. Further-

more, when psychotic patients are asked why they use cannabis, they report the same hedonic reasons as the rest of the population, i.e., for enjoyment[84]. Indeed, even though many know that they will develop paranoid ideas, the immediate "high" outweighs this.

A common suggestion has been that those cannabis users who go psychotic have also been using other drugs. However, a number of studies have addressed this question and not found the effect sufficient to negate the impact of cannabis[58], even when use of tobacco was accounted for[66,67].

Another argument states that cannabis use became more common in the latter part of the 20th century without an obvious change in the incidence of schizophrenia. In fact, there is little reliable information on temporal trends in the incidence of schizophrenia, so it is difficult to know whether this is true or not. To our knowledge, the only competent study spanning several decades and using the same research criteria for schizophrenia reported that the incidence doubled between 1965 and 1999, and that the proportion of schizophrenic patients using cannabis increased disproportionally compared with other psychiatric patients[85].

GENETIC PREDISPOSITION OR GENE X ENVIRONMENT INTERACTION?

A popular explanation for the association between cannabis use and psychosis is shared genetic vulnerability[80,81,86]. Cannabis-using psychotic patients not uncommonly have other relative(s) who are psychotic[87]. However, often the other psychotic member(s) of the family are also using cannabis.

One can now examine the relationship between predisposition to psychosis, as measured by the polygenic risk score for schizophrenia, and cannabis use. Power et al[88] examined the effect of the polygenic risk score on cannabis use in a large sample of Australians. The score was responsible for only a very small proportion of cannabis consumption. In a similar manner, Gage et al[89] suggested that those who used high-potency cannabis might be especially genetically predisposed to psychosis. However, Di Forti et al[90], who examined the polygenic risk score for schizophrenia in users of low- and high-potency cannabis, found no evidence to support this view.

A more likely possibility is that some individuals are more vulnerable to the psychotogenic effects of cannabis than others. No published study has yet examined a possible interaction between the polygenic risk score for schizophrenia and cannabis use in causing psychosis. However, schizophrenia patients with large, rare deletions are less likely to have comorbid cannabis abuse over their lifetime than those without such copy number variants[91]. This provides support for a threshold model of risk, with those carrying a copy number variant needing fewer adverse environmental exposures to become frankly psychotic.

Other work has examined candidate genes involved in the dopamine system. Caspi et al[92] suggested that variation in the catechol-O-methyltransferase (COMT) gene might moderate lability to cannabis-induced psychosis, but attempted replications have been inconsistent. Most recently, an experimental study[93] found no effect of this COMT polymorphism on THC-induced psychotic symptoms, but those with the val/val genotype had a greater decrement in working memory.

Two case-control studies have reported that a variant of AKT1 increases risk of psychotic illness among cannabis users, and a third has shown that those who carry this variant show a greater psychotogenic response to smoked cannabis[94-96]. Another report indicates that a variant in the D2 receptor gene may also increase psychosis risk, and that the risk is even greater in carriers of both this variant and the above-mentioned AKT1 polymorphism[97].

WHAT IS THE MECHANISM OF ACTION?

Bianconi et al[84] showed that cannabis-using psychotic patients appeared to be more sensitive to both the positive and negative effects of the drug. Similar findings have been reported from individuals at high clinical risk of developing psychosis[98]. D'Souza et al[24] showed that people with schizophrenia had a stronger reaction to the psychotogenic and cognitive effects of intravenous THC compared to healthy controls.

In animal studies, administration of THC reliably leads to increased dopamine release, but human studies have been more equivocal. One positron emission tomography (PET) study reported an increase in striatal dopamine release, but another found no significant effect. A re-analysis combining data from the two studies reported a small but significant increase in THC-induced dopamine release[99].

Several PET studies have shown that cannabis users, like other drug abusers, have a low capacity to synthetize and release striatal dopamine. However, Volkow et al[100] reported that, unlike other drug abusers, cannabis users show no alteration in striatal D2/D3 receptors. Furthermore, following an amphetamine challenge, psychotic patients who use cannabis, despite the absence of marked elevation in dopamine release, present a greater exacerbation of their symptoms compared to patients who never used it. These findings might be explained by cannabis use inducing post-synaptic dopamine supersensitivity[101], as was found by Ginovart et al[102] in their study of animals given chronic THC. This hypothesis is strengthened by the genetic evidence, reviewed above, that variation in post-synaptic genes may predispose to cannabis-associated psychosis.

OUTCOME AND TREATMENT

A recent meta-analysis showed that psychotic patients who continued cannabis use had higher relapse rates, longer hospital admissions, and more severe positive symptoms than either former users who discontinued cannabis or never-users[103].

Unfortunately, persuading cannabis users to stop is not easy. A variety of therapies, especially cognitive behavior therapy and motivational interviewing, have been tried, but so far without great success. Given tokens for cannabis-free urine tests is currently under trial. The only pharmacological treatment that has had any success is clozapine: a double-blind trial showed it to have a useful effect in diminishing craving for cannabis[104].

OTHER PSYCHIATRIC DISORDERS

Cannabis dependence

Withdrawal symptoms are usually relatively minor, because cannabis remains in the body for several weeks. However, anxiety and craving, irritability, insomnia, appetite disturbance, dysphoria and depression can develop.

Almost 10% of users will become dependent[105,106], and some claim that the rate goes as high as 17% if use starts in adolescence[107]. Certainly, cannabis dependence is an increasingly common cause of help seeking in Australia, UK, continental Europe and North America[23,108]. An Internet survey[109] reported that high-potency cannabis use was associated with an especially increased likelihood of dependence.

Depression and anxiety disorders

Cross-sectional studies report a high prevalence of depression and anxiety disorders in cannabis users[110-113], but the direction of effect remains unclear[112,114-116].

The Swedish conscript cohort showed no evidence of increased risk of depression in cannabis users[117], and systematic reviews have provided only weak evidence that cannabis use increases the risk of affective outcomes[118,119]. However, one such review concluded that cannabis use was associated with a modestly increased risk for depression, with heavy use accounting for a slightly stronger risk[120].

On the other hand, a prospective study of a large US cohort found that cannabis use was associated with increased odds of alcohol, nicotine and other drug use, but not of mood or anxiety disorders[121].

Post-traumatic stress disorder

People with post-traumatic stress disorder (PTSD) are especially likely to use cannabis[122-124], but again the nature of this relationship is uncertain. Some studies show that traumatic experiences and subsequent PTSD increase the risk of drug abuse[125,126].

Cannabis has become popular among US military veterans suffering from PTSD, and several US states have approved its medicinal use for such symptoms. However, as yet there is no evidence concerning the safety or efficacy of this practice.

Attention-deficit/hyperactivity disorder

There is a high prevalence of attention-deficit/hyperactivity disorder (ADHD) in adults seeking treatment for cannabis use disorders[127]. Prospective studies show that cannabis use increases risk of adult ADHD[128], while childhood hyperactivity/impulsivity predicts early substance use[129].

It remains controversial whether medicinal use of cannabis reduces the use of stimulant medication. A small placebo controlled trial on adults with ADHD is underway[130].

Summary

The evidence that cannabis use increases the risk of depression, anxiety disorders, PTSD or ADHD is much less convincing than that for psychosis. Indeed, it remains possible, but not proven, that cannabis may be helpful for people with PTSD and ADHD.

EFFECTS ON BRAIN AND COGNITION

There are many reports that cannabis use can alter brain structure. However, many of the studies are small, the control groups are inadequate, and most have not fully controlled for the effects of alcohol consumption (heavy cannabis users also tend to be heavy alcohol users)[131].

Two recent large studies found no main effect of cannabis on brain structure[132,133]. However, the former study[132] stands out in that the investigators found an interaction with the polygenic risk score for schizophrenia, such that individuals with a high (but not low) polygenic risk score who used cannabis did show decreased cortical thickness. Thus, people with a vulnerability to schizophrenia may also be more vulnerable to the adverse effects of cannabis on the brain.

Potency has not generally been taken into consideration in imaging studies. However, Yucel et al[134] found that those using high-potency cannabis showed hippocampal volume decrements, while those who had used preparations containing CBD did not. Similarly, in another study, cannabis users with hair samples higher in CBD were found to show less decrement in the volume of the right hippocampus than users with less CBD[135]. A further magnetic resonance imaging study found that use of high-potency cannabis was associated with disturbed white matter connections in the corpus callosum, an effect which was absent in hashish users[136].

Cannabis users perform worse on executive function, attention, verbal ability and memory tasks than non-users[137,138]. Follow-up of the Dunedin cohort showed a decline in IQ scores of six points between ages 13 and 38 among those who had been repeatedly diagnosed with cannabis use disorder[139]. However, other shorter studies have failed to replicate this finding[140,141]. Recently, in a study following up 5,115 young men and women for 25 years, past exposure to marijuana was

associated with worse verbal memory, but did not appear to affect executive function or processing speed[142].

As recently summarized by Hall and Lynskey[143], "case-control studies have generally found poorer verbal learning, memory, and attention in those who regularly use marijuana than in controls; the size of these differences usually has been related to the duration and frequency of marijuana use". Some studies suggest that cognition can recover fully when use stops[144], while others indicate that only partial recovery is possible[142].

Once again, CBD may ameliorate the negative impact of THC. A naturalistic study with 134 users found that participants using cannabis higher in CBD displayed no cognitive impairment[145]. The same group explored memory functioning in 120 users: participants whose hair tested positive for CBD and THC displayed significantly better performance than those with only THC[146].

ARE ADOLESCENTS ESPECIALLY VULNERABLE?

Some brain imaging studies have found greater brain changes in those who started heavy cannabis use in adolescence as opposed to adult life, including decreased volume in several cortical and subcortical regions, together with evidence of white matter disruption and abnormal brain activation responses to cognitive tasks[138]. These reports await confirmation.

Pope et al[147] found that the initiation of cannabis use before age 17 was associated with lower verbal IQ scores in long-term heavy cannabis users. There was also greater IQ decline in those Dunedin cohort members who started use in adolescence[148], but social decline was not so associated with age of onset[149].

Silins et al[150] reviewed 2,500 young people in Australasia and found that daily cannabis use before age 17 was associated with "clear reductions" in the likelihood of completing high school and obtaining a university degree. Similarly, a 1-year follow-up of 1,155 adolescents found that weekly cannabis use was related to poorer performance in maths and English tests[151].

In the original report from the Dunedin cohort concerning psychosis, those who started to use cannabis at age 18 or later showed only a small, non-significant increase in the risk of schizophrenia-like psychosis by age 26, but the risk increased fourfold among those starting at age 15 or earlier[58].

A possible explanation for the above reports is that the brain is still developing in those who start cannabis in their teens. Exposing the juvenile brain to the drug might permanently impair the endocannabinoid system, and impact adversely on brain and neurotransmitter function[138].

THERAPEUTIC USE OF CANNABIS AND ITS COMPONENTS

The problems associated with the recreational use of cannabis should not blind us to the possibility that some of its constituents may have useful therapeutic effects, as for example with opiates.

A German clinical trial[152] found that CBD had antipsychotic actions equivalent to a standard antipsychotic, amisulpride, in patients with schizophrenia. Furthermore, in a study of psychotic patients only partially responding to antipsychotics, the addition of CBD rather than placebo led to a significant improvement in the score on a psychosis scale[153].

Cannabinoid receptors modulate pain perception, so not surprisingly there are reports of therapeutic use of exogenous cannabinoids in human pain. A beneficial effect of smoked THC on the pain of HIV-associated neuropathy has been reported[154], and inhaled cannabis was found to provide short-term relief from chronic neuropathic pain, with a number-needed-to-treat of 5.6[155].

Several cannabinoid drugs are already available. For example, THC has long been used as an antiemetic. THC or a combination product of THC and CBD, marketed in some countries as an oromucosal spray (nabiximols), can be a useful option for pain or painful spasms in patients with multiple sclerosis[156,157]. CBD may be effective in the treatment of some patients with epilepsy[158-161], but the data are insufficient to provide definitive evidence[162].

CONCLUSIONS

As there is no good animal model of psychosis, it is difficult to conclusively prove any environmental cause. Thus, it is unclear what changes an exogenous cannabinoid would need to induce in an animal in order to provide definitive proof that cannabis can cause psychosis. Given the lack of an equivalent of painting tobacco tar on mice to demonstrate its carcinogenicity, is it sensible to wait for absolute proof that exogenous cannabinoids are a component cause of psychosis?

Gage et al[163], who exhaustively scrutinized the epidemiological literature for possible confounding, bias, misclassification, reverse causation and other explanations for the association, concluded that "epidemiologic studies provide strong enough evidence to warrant a public health message that cannabis use can increase the risk of psychotic disorders".

Of course, it is important not to overstate our knowledge in any public health campaign. For example, there is still uncertainty over the extent to which cannabis use can induce psychosis in the absence of genetic vulnerability. There remains argument over the proportion of psychosis that could be prevented if nobody used cannabis; estimates range from 8 to 24%[66]. The effects of cannabis on the brain also remain to be clarified. Moreover, we need to take care that public education does not get confused with the highly charged debate for and against decriminalization or legalization[164].

On the other hand, changes in legislation in several countries provide "natural" experiments concerning the effects of population exposure to cannabis. Will legalization result in an increase in consumption? Early reports are contradictory[165,166].

Will liberalization of laws lead to use of more potent forms of cannabis, or will it popularize safer varieties? Will educational campaigns focusing on the risks of regular use of high-potency cannabis or synthetic cannabinoids be effective? Will diminution of legal constraints on adult use result in greater use by those in their early teens who seem most susceptible to adverse effects? Will the mental health and addiction services be able to cope? It is important that researchers take the opportunity to monitor changes in the legal status of cannabis use and their effects on mental health.

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