SCIENCE AND SOCIETY

Cannabis, the mind and society: the hash realities

Robin M. Murray, Paul D. Morrison, Cécile Henquet and Marta Di Forti

Abstract | Cannabis has been known for at least 4,000 years to have profound effects on the mind — effects that have provoked dramatically divergent attitudes towards it. Some societies have regarded cannabis as a sacred boon for mankind that offers respite from the tribulations of everyday life, whereas others have demonized it as inevitably leading to 'reefer madness'. The debate between the protagonists and prohibitionists has recently been re-ignited, but unfortunately this debate continues mainly in ignorance of our new understanding of the effects of cannabis on the brain and of studies that have quantified the extent of the risks of long-term use.

The classical Greek term *pharmakon* indicates that a substance can be a remedy as well as a poison, and in many traditional societies cannabis was considered to have both of these properties. However, as the twentieth century progressed, cannabis gradually lost its status as a useful remedy, and fewer and fewer people regarded it as harmful. Indeed, by the 1990s, the prevailing medical wisdom held that smoking cannabis did not cause long-term harm to health[1]. Recreational use became normalized to the extent that use of cannabis was seen, like that of alcohol, nicotine and caffeine, as a culturally acceptable lifestyle choice (TIMELINE).

Recently, however, cannabis has re-emerged as both a potential medicine and a potentially harmful drug. On the one hand, cannabis-based drugs have been shown to be of value to people with chronic pain, and to control spasticity in patients with multiple sclerosis[2]. On the other hand, a number of reports have claimed that heavy use of cannabis increases the risk of psychotic illnesses, such as schizophrenia. If the latter is true for even a small minority of cannabis users, this would be of considerable public health importance, because cannabis is the world's third most-popular recreational drug (FIG. 1), after alcohol and tobacco.

In this Perspective, we briefly outline recent research into the endocannabinoid system[3–8] and discuss how exogenous cannabinoids might disrupt interneuronal signalling and information processing in the brain. We then consider the evidence as to whether cannabis can induce acute and chronic psychosis, whether it is addictive and whether its use leads on to the use of hard drugs, such as heroin and cocaine. Finally, we discuss how different societies are attempting to deal with cannabis use.

The endocannabinoid system

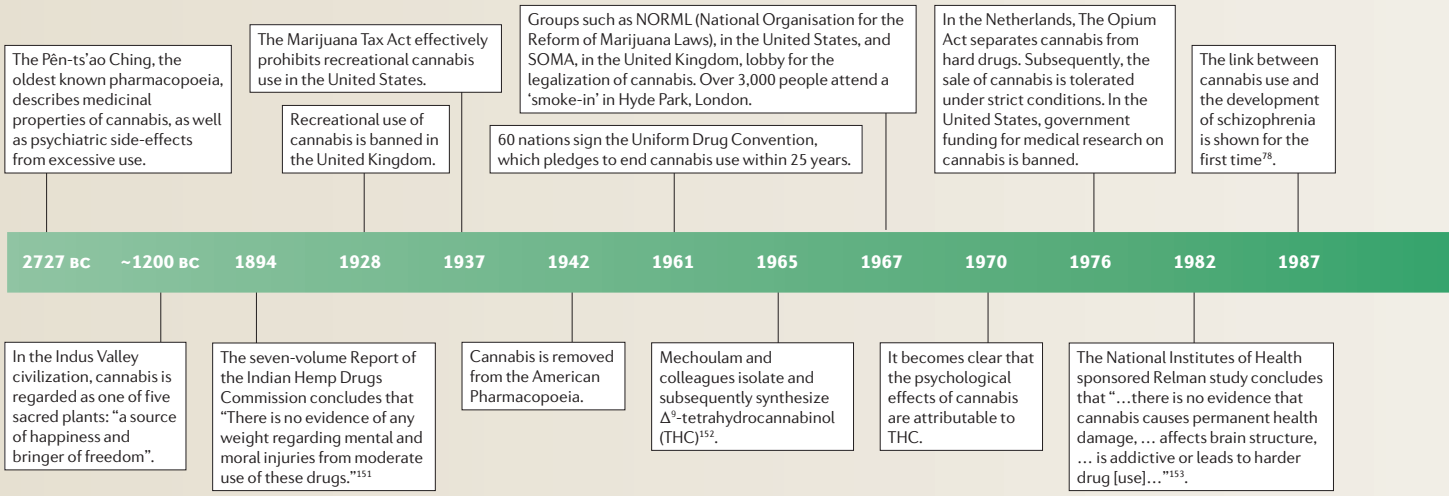
The major psychoactive ingredient of cannabis is Δ^9-tetrahydrocannabinol (THC), the structure of which was elucidated by Raphael Mechoulam and colleagues in the 1960s[9]. THC elicits its psychological effects by stimulation of the cannabinoid 1 (CB1) receptor[10], which was identified in 1988 (REF. 11) and cloned in 1990 (REF. 12). The CB1 receptor is the most common G-protein-coupled receptor in the brain[7]. Its expression is particularly high in the hippocampus, the cerebellum, the basal ganglia and the neocortex, consistent with the major psychological and motor effects of THC administration[13–16]. Expression of CB1 in peripheral nerve fibres, the dorsal root ganglion, the spinal dorsal horn and the peri-aquaductal grey probably accounts for the analgesic properties of THC[17–19]. A second cannabinoid receptor, CB2 (REF. 20), which was once believed to be restricted to immune cells, is also expressed in CNS neurons, although at lower levels than CB1 receptors[21–23].

The discovery of these receptors prompted a search for their endogenous agonists. The first of these endocannabinoids to be discovered, arachidonoylethanolamide, was termed anandamide, from the Sanskrit word *ananda*, signifying 'bliss'[24]. A second endocannabinoid, 2-arachidonoylglycerol, was discovered in 1995 (REFS 25,26), and others soon followed. Unlike conventional neurotransmitters, endocannabinoids are not stored in vesicles, but are synthesized 'on demand' from membrane phospholipids[6].

Endocannabinoids act as retrograde signals at CNS synapses[8,27] (FIG. 2a). They are synthesized in dendrites but act presynaptically to inhibit the release of fast-acting amino-acid neurotransmitters. Ultrastructural analyses have located key enzymes for endocannabinoid synthesis at dendritic spines, and have detected CB1 receptors on the terminals of neighbouring GABA (γ-aminobutyric acid)-releasing and glutamatergic neurons[15,28,29]. In the neocortex, the striatum and the hippocampus, CB1-receptor expression is considerably higher on GABA-releasing than on glutamatergic terminals[15,16,30,31]. The reason for this, and whether this pattern is seen throughout the CNS, remains unknown. However, this fact might explain the bidirectional effects of THC, and also why, for example, THC can be either pro- or anti-convulsant, depending on the dose[32,33].

Endocannabinoids are synthesized by principal output neurons, such as Purkinje cells in the cerebellum, pyramidal neurons in the hippocampus and the cortex, medium spiny neurons in the striatum, and dopaminergic neurons in the midbrain[34]. It seems that these neurons regulate their excitatory and inhibitory inputs by releasing endocannabinoids. In this way, endocannabinoids add another layer of modulation of plasticity at glutamate synapses to that which is provided by conventional transmitters, such as dopamine and serotonin[35].

Timeline | **A brief history of cannabis**



Cannabinoids and synaptic plasticity. Endocannabinoids have emerged as essential mediators of several forms of transient (5–30 second) and long-term (longer than 1 hour) plasticity in the cortex, the limbic system, the basal ganglia and the cerebellum[27,36–40]. So far, in all cases, endocannabinoid-dependent plasticity is expressed presynaptically as a decreased probability of neurotransmitter release.

At the behavioural level, intact endocannabinoid signalling is required for cerebellum-dependent motor learning[41] and for the extinction of aversive memories in the amygdala[42]. At CA3–CA1 synapses in the hippocampus, endocannabinoids appear to facilitate memory encoding. Activity-driven synthesis of 2-arachidonylglycerol in the dendritic spines of pyramidal neurons leads to long-term depression of neighbouring GABA and cholecystokinin (CCK) terminals, such that adjacent excitatory synapses are primed for strengthening by a reduction in their thresholds for long-term potentiation (LTP)[43–46].

As mentioned above, CB1 receptors are present on glutamatergic terminals in the hippocampus[29,47], albeit at much lower levels than on GABA and CCK terminals[30]. It might be that in hippocampal circuits the endocannabinoid system serves as a local amplifier that comes 'ready equipped' with a self-limiting feedback mechanism. Thus, although preferential inhibition of GABA inputs amplifies neighbouring excitatory synapses, prolonged or excessive excitation releases additional endocannabinoids that terminate further glutamatergic drive and act in a neuroprotective fashion[48] (FIG. 2a). Experimental work using conditional knockout mice has demonstrated that CB1 receptors on glutamatergic terminals are both necessary and sufficient to protect against experimentally induced hippocampal seizures[49].

In contrast to the subtle effects of endocannabinoids, acute administration of exogenous cannabinoids markedly disrupts neuronal signalling and circuit dynamics (FIG. 2b). Consequently, THC and other exogenous CB1-receptor agonists decrease synchronized neuronal firing in the hippocampus, inhibit theta oscillations[50] and LTP[51] and, at the behavioural level, impair learning and memory.

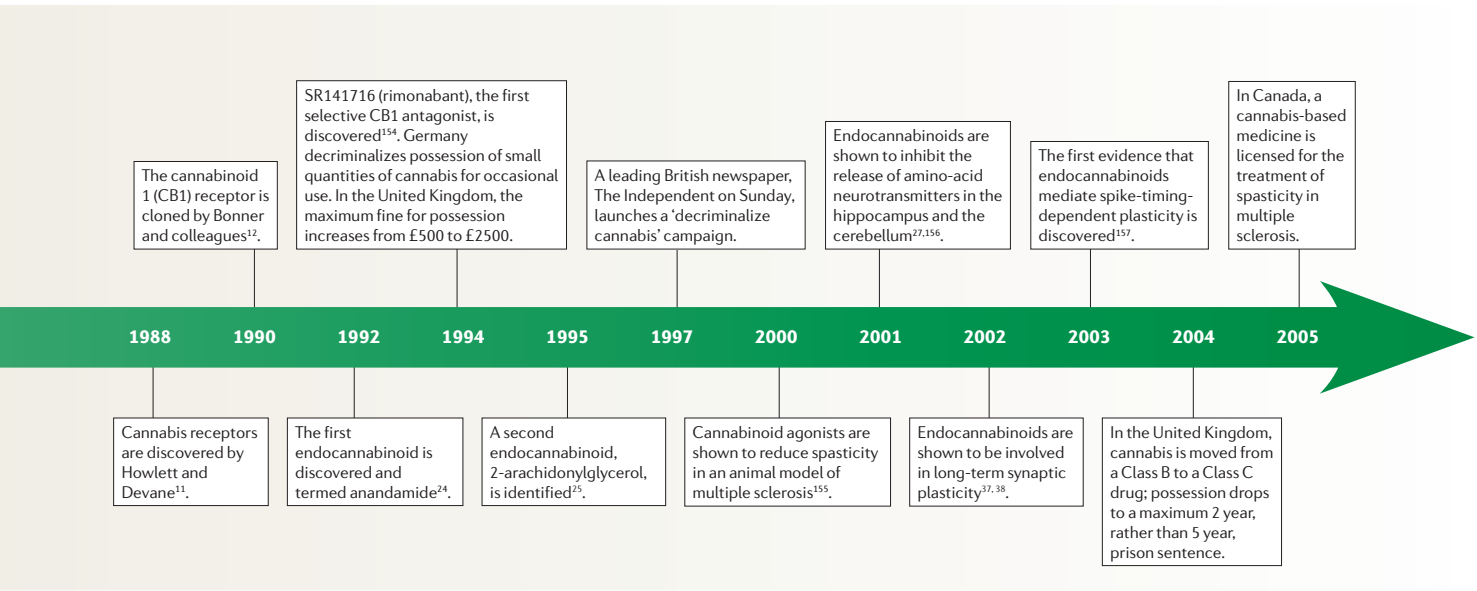
The acute effects of cannabis

Cannabis is so widely used because its effects are enjoyable. The most frequently reported reasons for taking it are pleasure-seeking and liking the experience of being relaxed or 'high'[52,53]; a small but growing minority take it for its possible medicinal properties. However, its ability to induce paranoia was noted as early as 1845. The French psychiatrist Moreau de Tours, who experimented in the appropriately named Club de Haschischins, published the results of studies in which he took cannabis himself (most probably up to several hundred milligrams) and gave it to some of his students and patients. He concluded that cannabis could precipitate "acute psychotic reactions, generally lasting but a few hours, but occasionally as long as a week"[54].

In 1958, Ames exposed medical staff to controlled doses of cannabis[55] and noted the emergence of delusions and visual hallucinations. With higher doses, paranoid ideas became common, with subjects reporting fears of being hypnotized, of being monitored by a hidden tape recorder and of secretly being given shock therapy. Other early studies[56,57] confirmed the ability of cannabis and THC to induce visual and auditory hallucinations and persecutory delusions[58,59]. Recently, D'Souza and colleagues investigated the acute effects of intravenous administration of 2.5 and 5 mg of THC in a double-blind placebo-controlled study[60], and found that THC produced transient psychotic symptoms that were dose-dependent.

Of the other constituents of cannabis, cannabidiol (CBD) has aroused the most interest. CBD is not hallucinogenic and, in contrast to THC, it appears to have anxiolytic properties; surprisingly, it has even been suggested to have antipsychotic effects[61].

Effects on cognition. Acute administration of cannabis causes impairment of cognitive functioning[60,62], specifically in executive functions, such as attention and working memory, and in hippocampus-dependent learning and memory. The latter is not surprising considering that, as described above, endocannabinoids are key components in the neuroplastic mechanisms that are believed to underlie these processes. The effect of the different constituents of cannabis on cognition varies, and therefore the effect of the cannabis that an individual consumes depends on the relative proportions of THC to CBD. Most, but not all[63], studies have shown that THC impairs memory function; by contrast, CBD administration has been found to have no adverse effect on



cognition in animals[64], and it might even reverse the working memory deficits that are induced by THC[65].

People who use cannabis chronically show cognitive impairment, but there is controversy over whether this impairment persists after the drug use has ceased. For example, Fried *et al.* found no evidence of cognitive deficits in cannabis users after three months of abstention[66], whereas Bolla *et al.* found persisting deficits in decision-making and brain activity among heavy cannabis users who had been abstinent for 25 days[67]. One possible explanation for these contradictory findings is that the effects of cannabis on cognition might depend on the age at which the use of the drug began. Accordingly, in one study of adults who regularly used cannabis, cannabis use before, but not after, the age of 16 predicted poorer performance in a task that required focused attention[68]. Similarly, Pope and colleagues found that the initiation of cannabis use before, but not after, the age of 17 was associated with lower verbal IQ scores in long-term heavy cannabis users[69].

Animal studies that address whether the cognitive effects of cannabis persist are few in number, but their results are intriguing. In rats that were chronically treated with THC, hippocampal LTP was abolished for 3 days following the last dose of THC, but it had recovered completely after 14 days[70]. Similar to findings in humans, immature, but not adult, rats that were repeatedly exposed to a potent CB1 agonist showed deficits in working memory and sensorimotor gating, and displayed increased social anxiety even after a drug-washout period of more than 20 days[71,72].

Cannabis and the risk of psychosis

It has long been accepted that cannabis intoxication can cause brief psychotic episodes[73–75], as can intoxication with a number of other psychoactive drugs, such as amphetamines, cocaine, ketamine and phencyclidine. From the 1990s onwards, reports started to appear that demonstrated that, among patients with established psychosis, those who persisted in smoking cannabis had a worse outcome than those who did not[76]. For example, it was shown that continued use of cannabis by people with a recent onset of psychosis was associated with earlier relapse of psychosis, more frequent hospitalization and poorer psychosocial functioning over the next 4 years[77].

Numerous studies have shown that psychotic patients take more cannabis than the populations from which they are drawn. But does cannabis actually cause psychosis? In an attempt to answer this question, researchers have carried out longitudinal studies in general populations and related cannabis consumption to subsequent onset of psychosis. Thus, Andreasson *et al.*[78], who examined almost 50,000 young Swedish male conscripts, found that men who had smoked cannabis by the age of conscription had double the risk of schizophrenia in the ensuing 15 years. In addition, they found that men who had smoked cannabis on at least 50 occasions were six times more likely to later receive a diagnosis of schizophrenia. These findings were confirmed in a follow-up study of the cohort 25 years later[79].

In another influential study, a birth cohort of 1,034 children born in Dunedin, New Zealand, were asked about their drug consumption at the ages of 15 and 18, and at 26 years of age 96% of the sample were interviewed using a standardized psychiatric assessment[80]. Those who had used cannabis by the ages of 15 or 18 reported significantly more psychotic symptoms at 26 years of age compared with non-users. Furthermore, 10% of those who used cannabis by the age of 15 were diagnosed with schizophreniform psychosis when they were 26 years old, compared with 3% of the non-using control group.

Another seven cohort or general-population studies have reported similar findings. These are summarized in TABLE 1, and have been extensively reviewed[81–83].

Criticisms. Some have claimed that the studies discussed above might have been confounded by the effect of other psychoactive drugs, such as amphetamines and LSD, which are known to be psychotogenic. However, the association between cannabis use and later schizophrenia in the Dunedin, Dutch and Swedish studies held even when the researchers adjusted for the use of other psychotogenic drugs[79,80,84].

A second criticism has been that the cannabis might have been taken in an attempt to self-medicate against psychotic symptoms. The best information concerning this comes from the Christchurch study, in which data on both cannabis use and psychotic symptoms were collected from a cohort that was studied at the ages of 18, 21 and 25 (REFS 85,86). The investigators were therefore able to study both the effects of cannabis use on later psychotic symptoms and also the

effect of psychotic symptoms on later cannabis use. As expected, cannabis use at the age of 18 was associated with more psychotic symptoms 3 and 7 years later. However, the presence of psychotic symptoms at the age of 18 appeared to inhibit, rather than encourage, subsequent cannabis use. This suggests a causal link between cannabis use and the development of psychotic symptoms and does not support the 'self-medication' explanation.

Thus, the epidemiological evidence strongly suggests, although it cannot prove, that heavy cannabis use increases the risk of both psychotic symptoms and schizophrenia. These conditions have a multifactorial aetiology in which a number of environmental factors interact with a genetic predisposition to cause illness[87,88]. Recent meta-analyses have suggested that cannabis acts as a component cause that increases the risk of psychotic illness between 1.4 and 1.9 times, and that might account for between 8% and 14% of cases of schizophrenia in different countries[82,83].

Few studies have investigated a possible link between cannabis use and more common psychiatric disorders. In their meta-analysis, Moore and colleagues came to the conclusion that the evidence for an effect of cannabis use on anxiety, depression and suicide was much less convincing than that concerning psychosis[83].

How might cannabis cause psychotic symptoms? Acutely psychotic patients show dopamine sensitization. For example, they release excessive striatal dopamine in response to an amphetamine challenge, and the degree of dopamine release correlates positively with the severity of the psychotic symptoms[89]. The probable mechanism is the increased dopamine[90] resulting in increased attention and excessive significance (salience) being attributed to everyday stimuli[91]. In this way, an unexpected sound, the comments of a TV newsreader or eye contact with a stranger, for example, are transformed from trivial everyday occurrences into highly salient events of great personal meaning to the psychotic individual. Delusions can be understood as an attempt to explain these experiences and resolve the resultant perplexity, confusion and dysphoria[92].

Cannabis markedly increases dopaminergic neuronal firing, including burst-firing, and increases the release of dopamine at terminal fields in the striatum[93–96]. It is tempting therefore to suggest that this is the mechanism by which it exerts its psychotogenic effects. No investigations have directly tested this in humans, although in one imaging study a subject broke the protocol by smoking cannabis during a pause between imaging sessions, and the resulting brain scans showed evidence that suggested the occurrence of a cannabis-induced increase in synaptic dopaminergic activity[97].

Who is vulnerable? Why do only a small minority of people who take cannabis, even in large quantities, develop psychoses? Individuals differ in their sensitivity to acute administration of THC, with a minority developing full-blown paranoia in response to doses that barely have an effect in others[98]. Verdoux studied the acute effects of cannabis in everyday situations, and assessed her subjects using a questionnaire that measured subclinical psychotic experiences[99]. Individuals without evidence of any predisposition to psychosis generally responded to cannabis by feeling more at ease with the world, and experienced only minor perceptual changes. However, those who were identified as psychosis-prone reported more marked perceptual changes, and feelings of increased suspicion and hostility after taking cannabis[53].

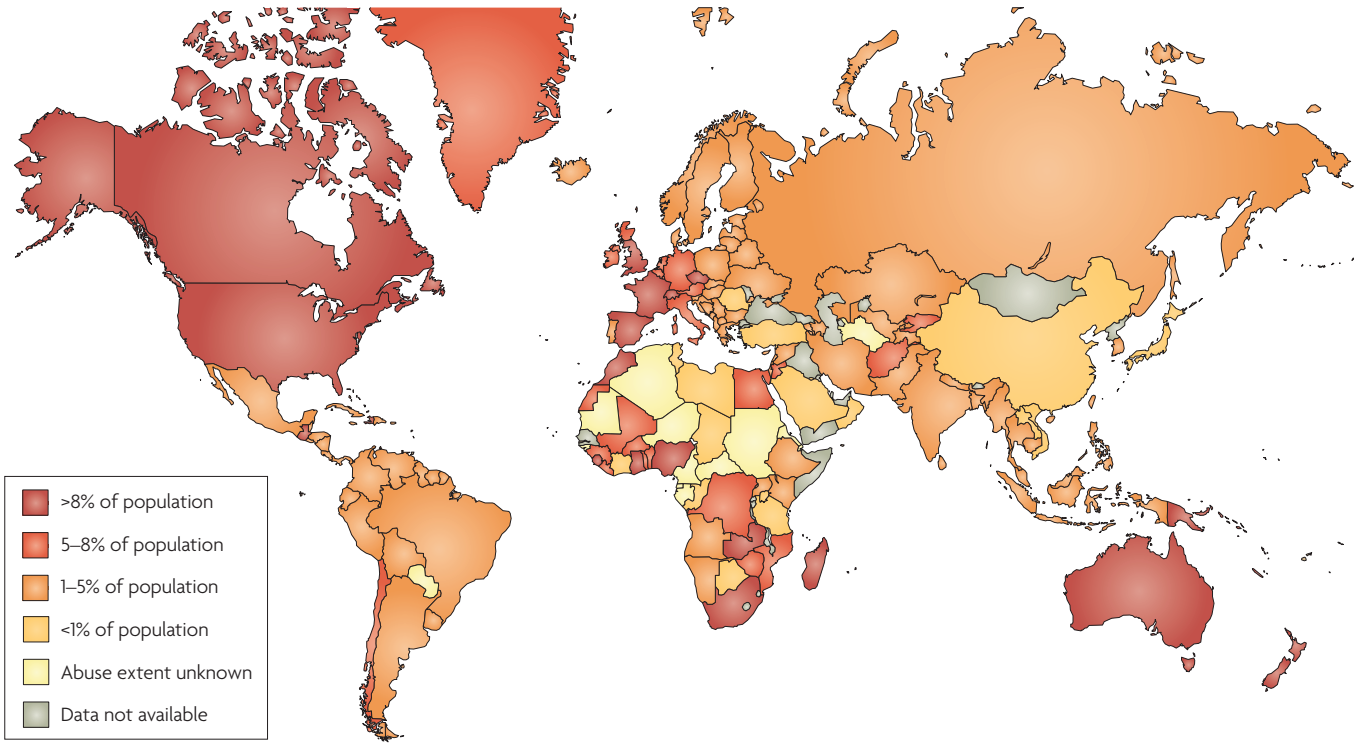


Figure 1 | **Global cannabis use between 2003 and 2004.** The map shows the prevalence of cannabis use around the world between 2003 and 2004. Darker colours indicate higher levels of cannabis use, with the darkest colour indicating that >8% of the population have used cannabis during the previous year. Grey areas indicate countries for which data were not available; yellow areas indicate countries for which the extent of cannabis use is unknown. Figure reproduced, with permission, from REF. 129 © (2006) United Nations Office on Drugs and Crime.

Henquet and colleagues prospectively studied 2,400 young Germans. People who were categorized as psychosis-prone at baseline were no more likely than the rest of the sample to use cannabis 4 years later. However, among psychosis-prone individuals, use of cannabis at baseline was associated with a 24% increased risk for psychotic symptoms at follow-up, whereas in non-predisposed individuals who used cannabis the risk was increased by only 6% (REF. 100). Thus, psychosis-prone individuals were especially likely to develop psychotic symptoms after using cannabis.

Caspi and colleagues reasoned that this vulnerability might have a genetic basis. They therefore studied how the interaction between cannabis use and variation in the gene that encodes catechol-O-methyltransferase (COMT), an enzyme that is involved in the breakdown of dopamine in the synapse, correlated with the risk of psychosis in subjects in the Dunedin study that was discussed earlier. Owing to a functional polymorphism that involves a Val-to-Met substitution at codon 158, this gene has two common allelic variants that influence the efficiency with which dopamine is broken down in the prefrontal cortex. The Val allele is thought to be associated with increased dopamine levels in

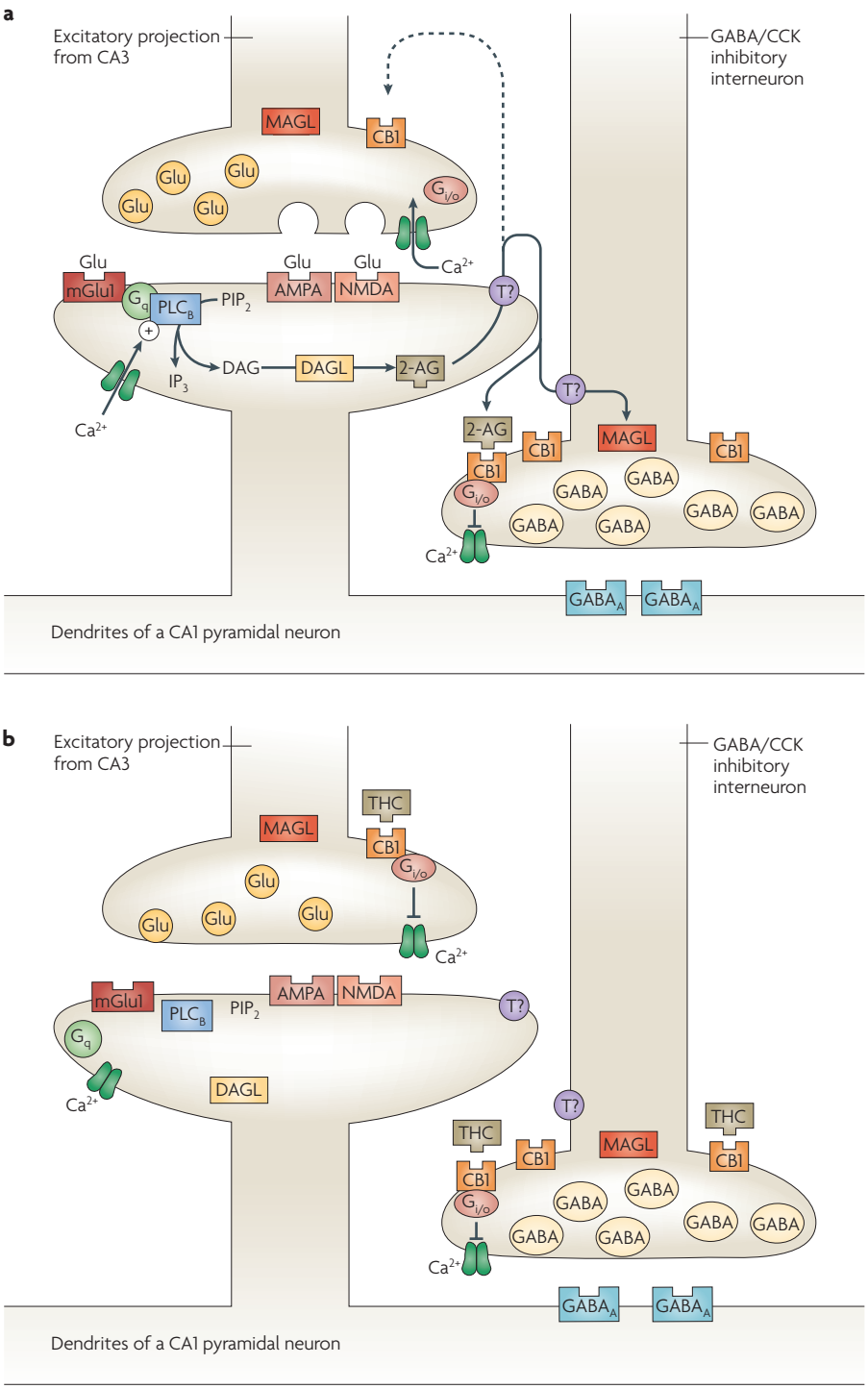


Figure 2 | **Endocannabinoids and THC affect neurotransmission in the hippocampus.** **a** | Endocannabinoids 'fine-tune' neurotransmission. In the CA1 area of the hippocampus, pyramidal neurons synthesize and release the endocannabinoid 2-arachidonylglycerol (2-AG), which acts at cannabinoid 1 (CB1) receptors on adjacent nerve terminals. Synthesis of 2-AG is driven by the stimulation of the metabotropic glutamate receptor mGlu1, or by Ca^{2+} entry through voltage-operated channels[36]. Compelling pharmacological evidence indicates the existence of an as-yet uncharacterized bidirectional endocannabinoid transporter (T?)[142]. Consistent with a retrograde mode of action for 2-AG, the 2-AG-synthetic enzyme sn1 diacylglycerol lipase (DAGL) is localized to dendritic spines[28,29], whereas the 2-AG-catabolic enzyme monoacylglycerol lipase (MAGL) is localized to presynaptic terminals[143–145]. Endocannabinoid-dependent plasticity is expressed presynaptically as a transient (5–30 second) or prolonged (longer than 1 hour) reduction in neurotransmitter release[36]. Inhibitory GABA (γ-aminobutyric acid) and cholecystokinin (CCK) terminals in the hippocampus express more CB1 receptors than do excitatory terminals[30], and consequently they are more sensitive to cannabinoids (reflected pictorially by the use of solid and dashed arrows to represent the effects of 2-AG on inhibitory and excitatory terminals, respectively)[30,146]. In the CA1 area, locally released 2-AG depresses GABA inhibitory tone, thereby facilitating long-term potentiation (LTP) at adjacent glutamatergic excitatory synapses[43–46]. CB1 receptors on glutamatergic terminals might serve to limit the extent of 2-AG synthesis and arrest the progression to seizures and excitotoxicity[48,49]. **b** | Δ^9-tetrahydrocannabinol (THC) disrupts neuromodulation in the hippocampus. Exogenous cannabinoids, such as THC, disrupt rather than mimic the subtleties of the endocannabinoid system in the hippocampus. THC inhibits the long-term-potentiation of CA3–CA1 synapses by activating CB1 receptors on glutamatergic terminals, inhibiting Ca^{2+} influx and suppressing glutamate release[36,51]. This mechanism appears to underlie the detrimental effect of THC on hippocampus-dependent learning and memory[36,51]. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DAG, diacylglycerol; $G_{i/o}$ and G_q, G-proteins; IP_3, inositol trisphosphate; NMDA, *N*-methyl D-aspartate ; PIP_2, phosphatidylinositol-4,5-bisphosphate; PLCβ, phospholipase C_β.

Table 1 | **General population studies of the effect of cannabis use on the risk of psychosis**

Country in which the study was conducted	Number of participants	Follow up	Odds ratio (95% confidence interval)	Study design	References
United States	4,494	NA	2.4 (1.2, 7.1)	Population based	147
Sweden	50,053	25 years	2.1 (1.2, 3.7)	Conscript cohort	78,79
The Netherlands	4,045	3 years	2.8 (1.2,6.5)	Population based	84
Israel	9,724	4–15 years	2.0 (1.3, 3.1)	Population based	148
New Zealand (Christchurch)	1,265	3 years	1.8 (1.2, 2.6)	Birth cohort	85
New Zealand (Dunedin)	1,253	15 years	3.1 (0.7,13.3)	Birth cohort	80
The Netherlands	1,580	14 years	2.8 (1.79,4.43)	Population based	149
Germany	2,436	4 years	1.7 (1.1, 1.5)	Population based	100
United Kingdom	8,580	18 months	1.5 (0.55,3.94)	Population based	150

NA, not applicable.

midbrain neurons that project to the ventral striatum[101]. Caspi and colleagues found that the use of cannabis in adolescence had no effect on the subsequent risk of psychosis in individuals who were homozygous for the *COMT* Met allele. However, adolescent smokers who were homozygous for the Val allele were at least five times more likely to develop schizophreniform psychosis than were people with the same genotype who did not take cannabis[102] (FIG. 3).

The number of psychotic subjects in the Caspi *et al.* study is small, and as yet there has been no direct attempt at replicating the study in an epidemiological sample. However, examining the COMT-variation–cannabis-use interaction experimentally, Henquet gave study volunteers 300 μg of THC per kg of body weight, or a placebo, and noted that carriers of the *COMT* Val allele were more likely to develop an impairment of memory and attention than carriers of the Met allele. Those with the homozygous Val genotype were also more sensitive to the effects of THC on psychotic symptoms, but this was dependent on their pre-existing proneness to psychosis[103].

Is cannabis addictive?

Epidemiological surveys show that approximately one in nine cannabis users satisfy the clinical criteria for dependence on cannabis[104] (BOX 1). Although cannabis dependence is moderate rather than severe, the number of people requesting treatment for it has been rising, particularly in Australia and the United States, where between 1993 and 1999, the annual number doubled to 232,105.

Animal studies support the idea that cannabis can induce dependence. Animals will press levers repeatedly to obtain intravenous injections of addictive drugs such as morphine and cocaine[105,106]. Similarly, rodents and monkeys self-administer THC at doses that are comparable to those taken by humans who smoke cannabis[107–110]. When given a choice, laboratory animals will choose a compartment that has been repeatedly paired with the experience of receiving an addictive drug, such as heroin, over one that is associated with receiving a placebo. THC also produces this effect, but only at low doses[107,110]; at high doses THC appears to induce conditioned place-aversion[110].

Following repeated dosing, tolerance develops to the psychological and analgesic effects of THC. Tolerance is mediated through the internalization of CB1 receptors[5,34]. Some researchers have pointed to the lack of a significant cannabis withdrawal syndrome as evidence of non-addictiveness. However, the CB1-receptor antagonist rimonabant can trigger a pronounced cannabis withdrawal reaction in animals and humans[5]. It seems that, in the usual situation among cannabis users, the slow clearance of cannabis from the body masks withdrawal symptoms.

Habit-forming drugs share the ability to increase the release of dopamine in the nucleus accumbens, and this property is believed to be central to the addictive process[111]. Cannabis is no exception[112]. Indeed, the ability of alcohol, nicotine and opiates to enhance dopamine release in the nucleus accumbens is blocked by CB1-receptor antagonists and is absent in mice that lack the CB1 receptor[110]. Similarly, at the behavioural level, knocking out the CB1-receptor gene or blocking the receptor in rodents abolishes conditioned place-preference by, and self-administration of, alcohol, nicotine and opiates[110].

Cannabis use and hard-drug abuse

Abusers of 'hard' drugs most commonly report that cannabis was the first recreational drug, other than alcohol or tobacco, that they used[113]. Two main theories have been proposed to explain this finding. First, the 'gateway' theory argues that cannabis use can facilitate the subsequent use or misuse of other drugs[114]. Second, the 'correlated vulnerabilities' theory postulates that some individuals have a general predisposition to using drugs, including cannabis; this could

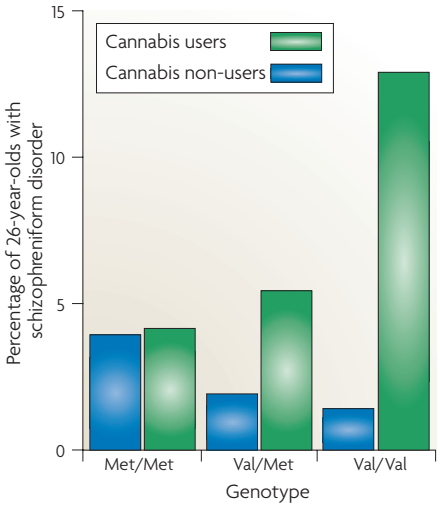


Figure 3 | **Modulation of the effect of adolescent cannabis use on psychosis by COMT genotype.** Owing to a functional polymorphism that involves a Val-to-Met substitution at codon 158, the gene for catechol-O-methyltransferase (COMT) has two common allelic variants that influence the efficiency with which dopamine is broken down in the prefrontal cortex. One study that genotyped this polymorphism in 800 individuals found that cannabis use during adolescence significantly increased the risk of developing a schizophreniform disorder at age 26, but only in those individuals who carried one or two of the Val alleles. Although the number of psychotic subjects in this study was small, the results indicate that vulnerability to cannabis-induced psychosis might have a genetic basis. Figure modified, with permission, from REF. 102 © (2005) Elsevier Science.

be mediated by a risk-taking personality[115]. Until recently, most experts favoured the second of these explanations, but recent evidence has revived the 'gateway' theory.

Fergusson and co-workers used data from the Christchurch study, which we discussed earlier, to examine the developmental sequence of drug use from 15 to 21 years of age. Early use of cannabis was associated with an increased risk of subsequent abuse of or dependence on other drugs, even after family and social circumstances were controlled for in the analysis[116].

Lynskey and colleagues examined the possible mechanisms behind this finding by studying the drug histories of more than 300 twin pairs who were discordant for early cannabis use. The individuals who had used cannabis by the age of 17 were between two and five times more likely than their non-using co-twins to report subsequent other drug use, and drug and alcohol dependence. These associations persisted when early-onset alcohol or tobacco use, childhood sexual abuse and conduct disorder were controlled for[117]. Thus, either a pharmacological effect of cannabis increases the probability of transition to hard drugs, or an environmental factor that is unique to the drug-taking co-twin underlies both adolescent cannabis use and later hard-drug use.

Results from animal studies support the first possibility: they show that THC affects the developmental plasticity of the reward system. Thus, pre-treatment of rats with THC from postnatal days 4 through 14 lowers the threshold for heroin-induced conditioned place-preference at 8 weeks of age[118]. Furthermore, exposure to THC prenatally or during adolescence enhances opiate self-administration in adulthood[119–121], but only under a fixed-ratio-1 schedule (in which one lever press results in one injection). This indicates that pre-exposure to THC does not alter heroin's rewarding efficacy *per se,* but that the enhanced responses in the fixed-ratio schedule might be explained by cross-tolerance[119]. This possibility is supported by an impressive body of pharmacological literature that describes multiple interactions between the endocannabinoid and opiate systems and includes evidence for cross-tolerance (for a review, see REF. 110).

A frequent criticism of the idea that cannabis is a gateway drug has been that most hard-drug users started smoking tobacco before they began using cannabis. This was indeed the traditional pattern, and longitudinal studies of teenagers from the United States that were carried out in the 1970s and 1980s reported that tobacco use preceded and predicted subsequent use of cannabis[122]. However, more recent studies have shown that, in young people, use of tobacco has decreased whereas use of cannabis has increased, such that cannabis use now appears to be a predictor of tobacco smoking. Thus, studies in both Australia and Scotland have shown that cannabis use during the teens and early adulthood is associated with an increased subsequent risk of initiation of tobacco use and progression to nicotine dependence[123,124].

Nevertheless, whether early use of cannabis increases the risk of subsequent abuse of hard drugs remains highly contentious. Most cannabis users do not escalate to the use of heroin or cocaine, but the recent studies have put the gateway theory back into contention.

Cannabis and society

Historically, some societies have idealized cannabis whereas others have demonized it and, recently, Western society has tended to oscillate between the two. In reality, as cannabis derivatives have the potential for causing both good and harm, the important question for society is how to maximize the former and minimize the latter.

Cannabis-based medicines. Interest in the potential value of cannabis-based medicines has been steadily rising. In the 1980s, THC (Dronabinol) was licensed for the treatment of chemotherapy-induced nausea and vomiting and for the stimulation of appetite in AIDS patients. More recently, trials have shown that cannabis-based medicines provide symptomatic relief for spasticity, pain and sleep disturbance in patients with multiple sclerosis[125–127]. In 2005, Sativex, which is an oromucosal spray that contains THC and CBD in a 1/1 ratio, gained approval in Canada for the relief of neuropathic pain in people with multiple sclerosis, and recently, Health Canada announced its intention to approve Sativex for the treatment of cancer pain. Cannabis-based medicines are also promising treatments for particular symptoms of Tourette's syndrome and glaucoma, and might prove useful as neuroprotective agents in the treatment of head injury, inflammatory disorders and some forms of cancer[2,4].

The CB1-receptor antagonist SR141716A (rimonabant) has been shown to be an effective treatment for nicotine dependence; indeed, pre-clinical studies suggest that CB1-receptor antagonists such as rimonobant might be effective against craving in a range of disorders, such as substance abuse and obesity[110,128]. However, there have been concerns that rimonabant might be associated with depression and suicidal thoughts and, although it is available in Europe for the treatment of metabolic syndrome associated with obesity, the FDA has not yet granted a licence for it in the United States.

It is likely that further advances in our understanding of the endocannabinoid system will lead to the development of new cannabis-based medicines. In a rational world, the introduction of such medicines would not be influenced by attitudes towards the recreational use of cannabis. Sadly, however,

Box 1 | Addiction and dependence

Addictive behaviour includes not only the misuse of psychoactive substances, but also other activities, such as excessive gambling, eating and sexual behaviour. It is defined as a repetitive pattern that increases the risk of disease and associated personal and social problems. The individual usually has a loss of control and seeks immediate gratification, then suffers delayed, deleterious effects. They often relapse when trying to quit.

The concept of dependence was developed by Edwards and Gross in 1976 (REF. 140); it is applied almost exclusively to drugs. In the International Classification of Mental Disorders 10 (ICD 10), three or more of the following criteria are required for the diagnosis of the dependence syndrome[141]:

- Increased tolerance to the drug (the requirement that greater dosages of a given drug be used to produce an identical effect as time passes).
- A physiological withdrawal state when substance use has ceased or been reduced. This is usually evidenced by the need to use the same substance to relieve or avoid the withdrawal symptoms.
- Difficulties in controlling substance-taking behaviour in terms of its onset, termination or amount used.
- Increased salience of drug-seeking behaviour (obtaining and using the drug becomes the priority in the person's life).
- Narrowing of the behavioural repertoire of the drug taking.
- Rapid reinstatement after abstinence.

the two tend to become confused in the public mind, and there is a danger that useful medicines might not be licensed because of rising concerns about the recreational use of cannabis.

Recreational use of cannabis. This rising concern led the United Nations to devote the bulk of its 2006 Annual Report on Drug Abuse to cannabis[129]. The report estimates that 160 million people, equivalent to 4% of the world's adult population, use cannabis each year. The report indicates that consumption rose in all continents during the last quarter of the twentieth century, with consumption currently highest in Western Europe, North America and, in particular, Australia and New Zealand. Traditionally, cannabis has been mainly available as a herb or as resin. The herb (known as marijuana, grass and ganja, among others) is comprised of the flowering tops and leaves of the plant, whereas resin (also known as hashish) consists of the secretions of the plant that are emitted when it is flowering. World production of the herb almost doubled between the early 1990s and 2005, reaching a total of 45,000 metric tons; the production of resin has also risen steadily, reaching a global total of 7,500 tons in 2004. Seizures show the same trend (FIG. 4).

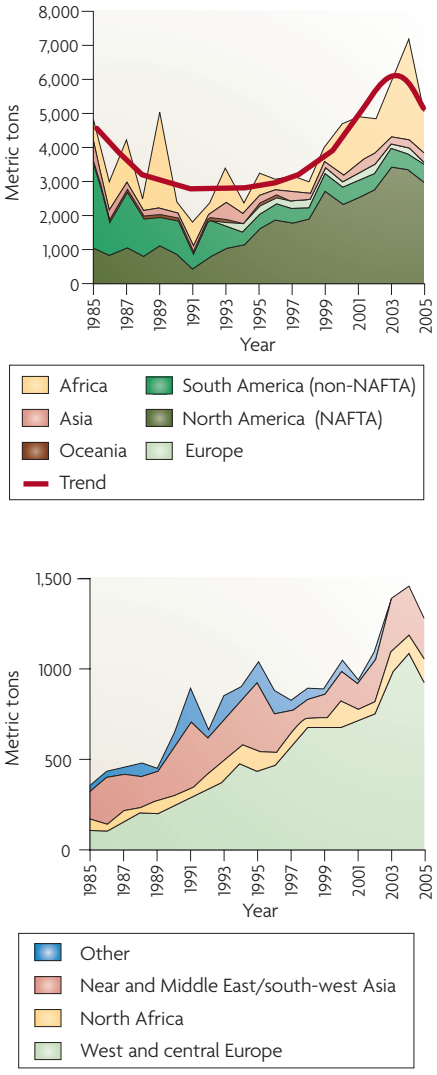


Figure 4 | **Worldwide trends in cannabis seizures.** The graphs show the amounts of cannabis herb (top panel) and resin (bottom panel) that were seized in the period 1985–2005, broken down by region. The overall trend in herb seizures is represented by the red line. NAFTA, North American Free Trade Agreement. Figures reproduced, with permission, from REF. 131 © (2007) United Nations Office on Drugs and Crime.

There are two other recent trends in cannabis use and production. First, in many countries the concentration of THC in street preparations of cannabis has risen. This is a consequence of the availability of more potent varieties of cannabis, which are variously termed sinsemilla or skunk; these are often produced indoors using greenhouse techniques. Until recently, the concentration of THC in cannabis was 1–4%, but by 2003, the average concentration in street preparations seized in the USA had risen to 7%. In European countries cannabis potency also increased: between 1996 and 2004, the average THC concentration in sinsemilla doubled from 6% to 12% in England and Wales, and at the extreme it reached 20% in some forms in the Netherlands[129].

A second cause for concern is the decreasing age of first-time cannabis users. For example, between 1992 and 1996, the number of children in the Netherlands who had started using cannabis by the age of 13 doubled[130]. In Europe as a whole, 40% of 15–16-year-old adolescents have now tried the drug[129]. However, although there are suspicions that adolescents are more prone to the cognitive and psychotogenic effects of cannabis, this is far from proven[80,83]. Furthermore, since 2005, the production and consumption of cannabis have fallen slightly on all continents except Africa[131]. This might be a consequence of a greater awareness of the risks of cannabis among young people[131].

Legal policies. There is huge variation both in the prevalence of cannabis use and in the legal constraints on its use in different countries. The two are not necessarily linked. For example, both Sweden and the Netherlands provide models that have been much admired. Sweden has a highly restrictive policy, low cannabis consumption and few problems associated with cannabis use. The Netherlands has a liberal approach in which cannabis is available in designated 'coffee shops', and it has a consumption level that is near the European average but is well below that of France, Spain and the United Kingdom.

The confusion concerning legal policies is exemplified by the United Kingdom, where there has been a raucous argument between pro- and anti-cannabis lobbies[132]. Following the advice of the Advisory Council on Misuse of Drugs that use of cannabis had no serious adverse psychological effects[133], the UK Government decided in 2002 to reduce the illegality status of cannabis so that pos-

Glossary

Component cause
A risk factor that acts with some other factor or factors to have a causal influence on the risk for a disease.

Conditioned place-aversion
The aversion to environmental stimuli that have previously been associated with a negative reward.

Conditioned place-preference
The preference for environmental stimuli that have previously been associated with a positive reward or drug effects.

Cross-tolerance
A decrease in the response to a substance as a result of continued exposure to a different substance that has a similar pharmacological action.

Dopamine sensitization
The process whereby repeated, intermittent stimulant exposure produces a permanent change in dopaminergic responses.

Long-term depression
(LTD). An enduring decrease in the strength of neurotransmission at a synapse. LTD is believed to underpin learning and memory.

Long-term potentiation
(LTP). An enduring increase in the strength of neurotransmission at a synapse. LTP is believed to underpin learning and memory.

Psychosis
A mental disturbance characterized by aberrations of perception (hallucinations) and thought (delusions) that causes a person to lose touch with external reality.

Psychosis-proneness
An increased genetic vulnerability to developing psychotic illness, as evidenced by the occurrence of subclinical psychotic experiences.

Schizophreniform psychosis
A schizophrenia-like psychosis in which the symptoms last for at least 1 month (as opposed to 6 months for a diagnosis of schizophrenia).

Sensorimotor gating
The neural filtering process that allows attention to be focused on one stimulus.

session of small quantities became largely a non-arrestable offence. However, no sooner had they announced their decision than reports of the relationship between cannabis use and psychosis started to appear.

The implications of this link have been much discussed in the United Kingdom. Hickman and colleagues predicted that by 2010 a substantial increase in the incidence of schizophrenia should be apparent. Under a conservative model in which heavy use of cannabis carries a twofold risk of schizophrenia, they calculated that the drug would be responsible for 10% of new schizophrenia cases, rising to 25% if light use of the drug also carries this risk[134]. Recent studies by Boydell and co-workers are compatible with this view. During the period 1965–1999, the incidence of schizophrenia in South London doubled[135], and there was a large increase in the proportion of cases that had used cannabis in the 12 months before diagnosis; this increase was much greater than that in non-schizophrenic controls[136].

In consequence, British newspapers and opposition politicians pressed for the reinstatement of the previous classification, oblivious to the fact that the reclassification had actually been accompanied by a decrease in the consumption of cannabis[131]. In 2005, the Advisory Council on Misuse of Drugs reversed its previous benign view of cannabis and accepted the evidence that linked cannabis to psychosis[137]. However, it did not recommend a change in classification; this was based on the consideration that its overall harmfulness did not equate with that of other drugs in the next category. By 2007, the media clamour had reached such a pitch that a further review of the classification was announced.

Similarly confusing and contradictory legal steps are being taken in other countries. For example, the famously liberal Netherlands have been closing coffee shops, while by contrast Switzerland has come near to legalizing cannabis in the face of an increase in the incidence of schizophrenia in young people[138]. Of course, decisions concerning the legal status of cannabis need to take into account a range of factors other than health effects. For example, some suggest that more harm comes from the expensive enforcement of criminal penalties, school dropout and the black-market that is associated with the criminalization of cannabis than from the deleterious effects of cannabis on mental health[139]. One thing is certain: politicians find it difficult to balance the enjoyment that cannabis brings to the majority of users with the dependence, cognitive difficulties and psychosis it induces in a minority. Swings in popular prejudice tend to push legislators towards alternately tightening and loosening the legal constraints on cannabis use. Public education about the risks of excessive use of cannabis appears to have a greater influence on consumption levels than alterations in the legislative status of cannabis; however (and curiously), governments rarely adopt this approach.

Robin M. Murray, Paul D. Morrison and Marta Di Forti are at the Institute of Psychiatry, Psychological Medicine, De Crespigny Park, Denmark Hill, London, SE5 8AF, UK.

Cécile Henquet is at the Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, the Netherlands.

Correspondence to R.M.M.
e-mail: Robin.murray@iop.kcl.ac.uk

doi:10.1038/nrn2253
Published online 10 October 2007

1. Deglamorising cannabis. *Lancet* **346**, 1241 (1995).
2. Pacher, P., Batkai, S. & Kunos, G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol. Rev.* **58**, 389–462 (2006).
3. Iversen, L. Cannabis and the brain. *Brain* **126**, 1252–1270 (2003).
4. Mackie, K. Cannabinoid receptors as therapeutic targets. *Annu. Rev. Pharmacol. Toxicol.* **46**, 101–122 (2006).
5. Pertwee, R. G. Cannabinoid pharmacology: the first 66 years. *Br. J. Pharmacol.* **147** (Suppl. 1), S163–S171 (2006).
6. Piomelli, D. The molecular logic of endocannabinoid signalling. *Nature Rev. Neurosci.* **4**, 873–884 (2003).
7. Di Marzo, V., Bifulco, M. & De Petrocellis, L. The endocannabinoid system and its therapeutic exploitation. *Nature Rev. Drug Discov.* **3**, 771–784 (2004).
8. Elphick, M. R. & Egertova, M. The neurobiology and evolution of cannabinoid signalling. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **356**, 381–408 (2001).
9. Mechoulam, R. & Hanus, L. A historical overview of chemical research on cannabinoids. *Chem. Phys. Lipids* **108**, 1–13 (2000).
10. Huestis, M. A. *et al.* Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Arch. Gen. Psychiatry* **58**, 322–328 (2001).
11. Devane, W. A., Dysarz, F. A., III, Johnson, M. R., Melvin, L. S. & Howlett, A. C. Determination and characterization of a cannabinoid receptor in rat brain. *Mol. Pharmacol.* **34**, 605–613 (1988).
12. Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C. & Bonner, T. I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **346**, 561–564 (1990).
13. Herkenham, M., Lynn, A. B., de Costa, B. R. & Richfield, E. K. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Res.* **547**, 267–274 (1991).
14. Egertova, M. & Elphick, M. R. Localisation of cannabinoid receptors in the rat brain using antibodies to the intracellular C-terminal tail of CB. *J. Comp. Neurol.* **422**, 159–171 (2000).
15. Eggan, S. M. & Lewis, D. A. Immunocytochemical distribution of the cannabinoid CB1 receptor in the primate neocortex: a regional and laminar analysis. *Cereb. Cortex* **17**, 175–191 (2007).
16. Matyas, F. *et al.* Subcellular localization of type 1 cannabinoid receptors in the rat basal ganglia. *Neuroscience* **137**, 337–361 (2006).
17. Calignano, A., La Rana, G., Giuffrida, A. & Piomelli, D. Control of pain initiation by endogenous cannabinoids. *Nature* **394**, 277–281 (1998).
18. Ahluwalia, J., Urban, L., Capogna, M., Bevan, S. & Nagy, I. Cannabinoid 1 receptors are expressed in nociceptive primary sensory neurons. *Neuroscience* **100**, 685–688 (2000).
19. Hohmann, A. G. *et al.* An endocannabinoid mechanism for stress-induced analgesia. *Nature* **435**, 1108–1112 (2005).
20. Munro, S., Thomas, K. L. & Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **365**, 61–65 (1993).
21. Van Sickle, M. D. *et al.* Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science* **310**, 329–332 (2005).
22. Onaivi, E. S. *et al.* Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. *Ann. NY Acad. Sci.* **1074**, 514–536 (2006).
23. Gong, J. P. *et al.* Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. *Brain Res.* **1071**, 10–23 (2006).
24. Devane, W. A. *et al.* Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **258**, 1946–1949 (1992).
25. Mechoulam, R. *et al.* Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem. Pharmacol.* **50**, 83–90 (1995).
26. Sugiura, T. *et al.* 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem. Biophys. Res. Commun.* **215**, 89–97 (1995).
27. Wilson, R. I. & Nicoll, R. A. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. *Nature* **410**, 588–592 (2001).
28. Yoshida, T. *et al.* Localization of diacylglycerol lipase-α around postsynaptic spine suggests close proximity between production site of an endocannabinoid, 2-arachidonoyl-glycerol, and presynaptic cannabinoid CB1 receptor. *J. Neurosci.* **26**, 4740–4751 (2006).
29. Katona, I. *et al.* Molecular composition of the endocannabinoid system at glutamatergic synapses. *J. Neurosci.* **26**, 5628–5637 (2006).
30. Kawamura, Y. *et al.* The CB1 cannabinoid receptor is the major cannabinoid receptor at excitatory presynaptic sites in the hippocampus and cerebellum. *J. Neurosci.* **26**, 2991–3001 (2006).
31. Uchigashima, M. *et al.* Subcellular arrangement of molecules for 2-arachidonoyl-glycerol-mediated retrograde signaling and its physiological contribution to synaptic modulation in the striatum. *J. Neurosci.* **27**, 3663–3676 (2007).
32. Alger, B. E. Endocannabinoids and their implications for epilepsy. *Epilepsy Curr.* **4**, 169–173 (2004).
33. Smith, P. F. Cannabinoids as potential anti-epileptic drugs. *Curr. Opin. Investig. Drugs* **6**, 680–685 (2005).
34. Freund, T. F., Katona, I. & Piomelli, D. Role of endogenous cannabinoids in synaptic signaling. *Physiol. Rev.* **83**, 1017–1066 (2003).
35. Bailey, C. H., Giustetto, M., Huang, Y. Y., Hawkins, R. D. & Kandel, E. R. Is heterosynaptic modulation essential for stabilizing Hebbian plasticity and memory? *Nature Rev. Neurosci.* **1**, 11–20 (2000).
36. Chevaleyre, V., Takahashi, K. A. & Castillo, P. E. Endocannabinoid-mediated synaptic plasticity in the CNS. *Annu. Rev. Neurosci.* **29**, 37–76 (2006).
37. Gerdeman, G. L., Ronesi, J. & Lovinger, D. M. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. *Nature Neurosci.* **5**, 446–451 (2002).
38. Robbe, D., Kopf, M., Remaury, A., Bockaert, J. & Manzoni, O. J. Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. *Proc. Natl Acad. Sci. USA* **99**, 8384–8388 (2002).
39. Kreitzer, A. C. & Regehr, W. G. Cerebellar depolarization-induced suppression of inhibition is mediated by endogenous cannabinoids. *J. Neurosci.* **21**, RC174 (2001).
40. Kreitzer, A. C. & Malenka, R. C. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. *Nature* **445**, 643–647 (2007).
41. Kishimoto, Y. & Kano, M. Endogenous cannabinoid signaling through the CB1 receptor is essential for cerebellum-dependent discrete motor learning. *J. Neurosci.* **26**, 8829–8837 (2006).
42. Marsicano, G. *et al.* The endogenous cannabinoid system controls extinction of aversive memories. *Nature* **418**, 530–534 (2002).

43. Zhu, P. J. & Lovinger, D. M. Persistent synaptic activity produces long-lasting enhancement of endocannabinoid modulation and alters long-term synaptic plasticity. *J. Neurophysiol.* **97**, 4386–4389 (2007).
44. Chevaleyre, V. & Castillo, P. E. Heterosynaptic LTD of hippocampal GABAergic synapses: a novel role of endocannabinoids in regulating excitability. *Neuron* **38**, 461–472 (2003).
45. Chevaleyre, V. & Castillo, P. E. Endocannabinoid-mediated metaplasticity in the hippocampus. *Neuron* **43**, 871–881 (2004).
46. Carlson, G., Wang, Y. & Alger, B. E. Endocannabinoids facilitate the induction of LTP in the hippocampus. *Nature Neurosci.* **5**, 723–724 (2002).
47. Takahashi, K. A. & Castillo, P. E. The CB1 cannabinoid receptor mediates glutamatergic synaptic suppression in the hippocampus. *Neuroscience* **139**, 795–802 (2006).
48. Panikashvili, D. *et al.* An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. *Nature* **413**, 527–531 (2001).
49. Monory, K. *et al.* The endocannabinoid system controls key epileptogenic circuits in the hippocampus. *Neuron* **51**, 455–466 (2006).
50. Robbe, D. *et al.* Cannabinoids reveal importance of spike timing coordination in hippocampal function. *Nature Neurosci.* **9**, 1526–1533 (2006).
51. Hampson, R. E. & Deadwyler, S. A. Cannabinoids, hippocampal function and memory. *Life Sci.* **65**, 715–723 (1999).
52. Arendt, M. *et al.* Testing the self-medication hypothesis of depression and aggression in cannabis-dependent subjects. *Psychol. Med.* **37**, 935–945 (2007).
53. Verdoux, H., Gindre, C., Sorbara, F., Tournier, M. & Swendsen, J. D. Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. *Psychol. Med.* **33**, 23–32 (2003).
54. Moreau, J. J. *Hashish and Mental Illness* (Raven, New York, 1973).
55. Ames, F. A clinical and metabolic study of acute intoxication with *Cannabis sativa* and its role in the model psychoses. *J. Ment. Sci.* **104**, 972–999 (1958).
56. Talbott, J. A. & Teague, J. W. Marihuana psychosis. Acute toxic psychosis associated with the use of cannabis derivatives. *JAMA* **210**, 299–302 (1969).
57. Chopra, G. S. & Smith, J. W. Psychotic reactions following cannabis use in East Indians. *Arch. Gen. Psychiatry* **30**, 24–27 (1974).
58. Isbell, H. *et al.* Effects of (–)Δ^9-trans-tetrahydrocannabinol in man. *Psychopharmacologia* **11**, 184–188 (1967).
59. Melges, F. T. Tracking difficulties and paranoid ideation during hashish and alcohol intoxication. *Am. J. Psychiatry* **133**, 1024–1028 (1976).
60. D'Souza, D. C. *et al.* The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* **29**, 1558–1572 (2004).
61. Leweke, F. M., Schneider, U., Radwan, M., Schmidt, E. & Emrich, H. M. Different effects of nabilone and cannabidiol on binocular depth inversion in man. *Pharmacol. Biochem. Behav.* **66**, 175–181 (2000).
62. Solowij, N. & Michie, P. T. Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia? *J. Psychiatry Neurosci.* **32**, 30–52 (2007).
63. Makela, P. *et al.* Low doses of Δ^9 tetrahydrocannabinol (THC) have divergent effects on short-term spatial memory in young, healthy adults. *Neuropsychopharmacology* **31**, 462–470 (2006).
64. Winsauer, P. J., Lambert, P. & Moerschbaecher, J. M. Cannabinoid ligands and their effects on learning and performance in rhesus monkeys. *Behav. Pharmacol.* **10**, 497–511 (1999).
65. Fadda, P., Robinson, L., Fratta, W., Pertwee, R. G. & Riedel, G. Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. *Neuropharmacology* **47**, 1170–1179 (2004).
66. Fried, P. A., Watkinson, B. & Gray, R. Neurocognitive consequences of marihuana — a comparison with pre-drug performance. *Neurotoxicol. Teratol.* **27**, 231–239 (2005).
67. Bolla, K. I., Eldreth, D. A., Matochik, J. A. & Cadet, J. L. Neural substrates of faulty decision-making in abstinent marijuana users. *Neuroimage* **26**, 480–492 (2005).
68. Ehrenreich, H. *et al.* Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology (Berl.)* **142**, 295–301 (1999).
69. Pope, H. G., Jr *et al.* Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend.* **69**, 303–310 (2003).
70. Hoffman, A. F., Oz, M., Yang, R., Lichtman, A. H. & Lupica, C. R. Opposing actions of chronic Δ^9-tetrahydrocannabinol and cannabinoid antagonists on hippocampal long-term potentiation. *Learn. Mem.* **14**, 63–74 (2007).
71. O'Shea, M., Singh, M. E., McGregor, I. S. & Mallet, P. E. Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. *J. Psychopharmacol.* **18**, 502–508 (2004).
72. Schneider, M. & Koch, M. Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology* **28**, 1760–1769 (2003).
73. Negrete, J. C., Knapp, W. P., Douglas, D. E. & Smith, W. B. Cannabis affects the severity of schizophrenic symptoms: results of a clinical survey. *Psychol. Med.* **16**, 515–520 (1986).
74. Thornicroft, G. Cannabis and psychosis. Is there epidemiological evidence for an association? *Br. J. Psychiatry* **157**, 25–33 (1990).
75. Mathers, D. C. & Ghodse, A. H. Cannabis and psychotic illness. *Br. J. Psychiatry* **161**, 648–653 (1992).
76. Linszen, D. H., Dingemans, P. M. & Lenior, M. E. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch. Gen. Psychiatry* **51**, 273–279 (1994).
77. Grech, A., van Os, J., Jones, P. B., Lewis, S. W. & Murray, R. M. Cannabis use and outcome of recent onset psychosis. *Eur. Psychiatry* **20**, 349–353 (2005).
78. Andreasson, S., Allebeck, P., Engstrom, A. & Rydberg, U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* **2**, 1483–1486 (1987).
79. Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I. & Lewis, G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ* **325**, 1199 (2002).
80. Arseneault, L. *et al.* Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* **325**, 1212–1213 (2002).
81. Arseneault, L., Cannon, M., Witton, J. & Murray, R. M. Causal association between cannabis and psychosis: examination of the evidence. *Br. J. Psychiatry* **184**, 110–117 (2004).
82. Henquet, C., Murray, R., Linszen, D. & van Os, J. The environment and schizophrenia: the role of cannabis use. *Schizophr. Bull.* **31**, 608–612 (2005).
83. Moore, T. H. *et al.* Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **370**, 319–328 (2007).
84. van Os, J. *et al.* Cannabis use and psychosis: a longitudinal population-based study. *Am. J. Epidemiol.* **156**, 319–327 (2002).
85. Fergusson, D. M., Horwood, L. J. & Swain-Campbell, N. R. Cannabis dependence and psychotic symptoms in young people. *Psychol. Med.* **33**, 15–21 (2003).
86. Fergusson, D. M., Horwood, L. J. & Ridder, E. M. Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction* **100**, 354–366 (2005).
87. Di Forti, M., Morrison, P. D., Butt, A. & Murray, R. M. Cannabis use and psychiatric and cogitive disorders: the chicken or the egg? *Curr. Opin. Psychiatry* **20**, 228–234 (2007).
88. Morrison, P. D. & Murray, R. M. Schizophrenia. *Curr. Biol.* **15**, R980–R984 (2005).
89. Laruelle, M. *et al.* Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc. Natl Acad. Sci. USA* **93**, 9235–9240 (1996).
90. Abi-Dargham, A. *et al.* Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am. J. Psychiatry* **155**, 761–767 (1998).
91. Kapur, S., Mizrahi, R. & Li, M. From dopamine to salience to psychosis — linking biology, pharmacology and phenomenology of psychosis. *Schizophr. Res.* **79**, 59–68 (2005).
92. Krabbendam, L. *et al.* Hallucinatory experiences and onset of psychotic disorder: evidence that the risk is mediated by delusion formation. *Acta Psychiatr. Scand.* **110**, 264–272 (2004).
93. Cheer, J. F., Wassum, K. M., Heien, M. L., Phillips, P. E. & Wightman, R. M. Cannabinoids enhance subsecond dopamine release in the nucleus accumbens of awake rats. *J. Neurosci.* **24**, 4393–4400 (2004).
94. Riegel, A. C. & Lupica, C. R. Independent presynaptic and postsynaptic mechanisms regulate endocannabinoid signaling at multiple synapses in the ventral tegmental area. *J. Neurosci.* **24**, 11070–11078 (2004).
95. French, E. D., Dillon, K. & Wu, X. Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra. *Neuroreport* **8**, 649–652 (1997).
96. Tanda, G., Pontieri, F. E. & Di Chiara, G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ_1 opioid receptor mechanism. *Science* **276**, 2048–2050 (1997).
97. Voruganti, L. N., Slomka, P., Zabel, P., Mattar, A. & Awad, A. G. Cannabis induced dopamine release: an *in-vivo* SPECT study. *Psychiatry Res.* **107**, 173–177 (2001).
98. Favrat, B. *et al.* Two cases of "cannabis acute psychosis" following the administration of oral cannabis. *BMC Psychiatry* **5**, 17 (2005).
99. Konings, M., Bak, M., Hanssen, M., van Os, J. & Krabbendam, L. Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. *Acta Psychiatr. Scand.* **114**, 55–61 (2006).
100. Henquet, C. *et al.* Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* **330**, 11 (2005).
101. Meyer-Lindenberg, A. & Weinberger, D. R. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature Rev. Neurosci.* **7**, 818–827 (2006).
102. Caspi, A. *et al.* Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol. Psychiatry* **57**, 1117–1127 (2005).
103. Henquet, C. *et al.* An experimental study of catechol-o-methyltransferase Val^{158}Met moderation of Δ-9-tetrahydrocannabinol-induced effects on psychosis and cognition. Neuropsychopharmacology **31**, 2748–2757 (2006).
104. Hall, W. & Degenhardt, L. Prevalence and correlates of cannabis use in developed and developing countries. *Curr. Opin. Psychiatry* **20**, 393–397 (2007).
105. Bergman, J. & Paronis, C. A. Measuring the reinforcing strength of abused drugs. *Mol. Interv.* **6**, 273–283 (2006).
106. Gardner, E. L. What we have learned about addiction from animal models of drug self-administration. *Am. J. Addict.* **9**, 285–313 (2000).
107. Braida, D., Iosue, S., Pegorini, S. & Sala, M. Δ^9-tetrahy-drocannabinol-induced conditioned place preference and intracerebroventricular self-administration in rats. *Eur. J. Pharmacol.* **506**, 63–69 (2004).
108. Justinova, Z., Tanda, G., Redhi, G. H. & Goldberg, S. R. Self-administration of Δ9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. *Psychopharmacology (Berl.)* **169**, 135–140 (2003).
109. Tanda, G., Munzar, P. & Goldberg, S. R. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. *Nature Neurosci.* **3**, 1073–1074 (2000).
110. Gardner, E. L. Endocannabinoid signaling system and brain reward: emphasis on dopamine. *Pharmacol. Biochem. Behav.* **81**, 263–284 (2005).
111. Di Chiara, G. & Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc. Natl Acad. Sci. USA* **85**, 5274–5278 (1988).
112. Lupica, C. R. & Riegel, A. C. Endocannabinoid release from midbrain dopamine neurons: a potential substrate for cannabinoid receptor antagonist treatment of addiction. *Neuropharmacology* **48**, 1105–1116 (2005).
113. Golub, A. & Johnson, B. D. Variation in youthful risks of progression from alcohol and tobacco to marijuana and to hard drugs across generations. *Am. J. Public Health* **91**, 225–232 (2001).
114. Kandel, D. B. Does marijuana use cause the use of other drugs? *JAMA* **289**, 482–483 (2003).
115. Morral, A. R., McCaffrey, D. F. & Paddock, S. M. Reassessing the marijuana gateway effect. *Addiction* **97**, 1493–1504 (2002).

116. Fergusson, D. M., Boden, J. M. & Horwood, L. J. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. *Addiction* **101**, 556–569 (2006).
117. Lynskey, M. T. *et al.* Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA* **289**, 427–433 (2003).
118. Singh, M. E., McGregor, I. S. & Mallet, P. E. Perinatal exposure to Δ^9-tetrahydrocannabinol alters heroin-induced place conditioning and Fos-immunoreactivity. *Neuropsychopharmacology* **31**, 58–69 (2006).
119. Solinas, M., Panlilio, L. V. & Goldberg, S. R. Exposure to Δ-9-tetrahydrocannabinol (THC) increases subsequent heroin taking but not heroin's reinforcing efficacy: a self-administration study in rats. *Neuropsychopharmacology* **29**, 1301–1311 (2004).
120. Ellgren, M., Spano, S. M. & Hurd, Y. L. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. *Neuropsychopharmacology* **32**, 607–615 (2007).
121. Spano, M. S., Ellgren, M., Wang, X. & Hurd, Y. L. Prenatal cannabis exposure increases heroin seeking with allostatic changes in limbic enkephalin systems in adulthood. *Biol. Psychiatry* **61**, 554–563 (2007).
122. Kandel, D. B., Yamaguchi, K. & Chen, K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *J. Stud. Alcohol* **53**, 447–457 (1992).
123. Patton, G. C., Coffey, C., Carlin, J. B., Sawyer, S. M. & Lynskey, M. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. *Addiction* **100**, 1518–1525 (2005).
124. Amos, A., Wiltshire, S., Bostock, Y., Haw, S. & McNeill, A. 'You can't go without a fag ... you need it for your hash' — a qualitative exploration of smoking, cannabis and young people. *Addiction* **99**, 77–81 (2004).
125. Zajicek, J. *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* **362**, 1517–1526 (2003).
126. Rog, D. J., Nurmikko, T. J., Friede, T. & Young, C. A. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* **65**, 812–819 (2005).
127. Collin, C., Davies, P., Mutiboko, I. K. & Ratcliffe, S. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur. J. Neurol.* **14**, 290–296 (2007).
128. Van Gaal, L. F., Rissanen, A. M., Scheen, A. J., Ziegler, O. & Rossner, S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* **365**, 1389–1397 (2005).
129. UNODC World Drug Report. United Nations Office on Drugs and Crime [online] http://www.unodc.org/unodc/en/world_drug_report_2006.html (2006).
130. Monshouwer, K., Smit, F., de Graaf, R., van Os, J. & Vollebergh, W. First cannabis use: does onset shift to younger ages? Findings from 1988 to 2003 from the Dutch National School Survey on Substance Use. *Addiction* **100**, 963–970 (2005).
131. UNODC World Drug Report. United Nations Office on Drugs and Crime [online] http://www.unodc.org/unodc/en/world_drug_report.html (2007).
132. Owen, J. Cannabis: an apology. *Independent on Sunday (Lond.)* 1–2 (18 Mar 2007).
133. Advisory Council on the Misuse of Drugs. The classification of cannabis under the Misuse of Drugs Act 1971. Home Office [online] http://drugs.homeoffice.gov.uk/publication-search/acmd/cannabis-class-misuse-drugs-act (2002).
134. Hickman, M., Vickerman, P., Macleod, J., Kirkbride, J. & Jones, P. B. Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales. *Addiction* **102**, 597–606 (2007).
135. Boydell, J. *et al.* Incidence of schizophrenia in south-east London between 1965 and 1997. *Br. J. Psychiatry* **182**, 45–49 (2003).
136. Boydell, J. *et al.* Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. *Psychol. Med.* **36**, 1441–1446 (2006).
137. Advisory Council On the Misuse of Drugs. Further consideration of the classification of cannabis under the Misuse of Drugs Act 1971. Home Office [online] http://drugs.homeoffice.gov.uk/publication-search/acmd/cannabis-reclass-2005 (2005).
138. Rossler, W. *et al.* Psychotic experiences in the general population: a twenty-year prospective community study. *Schizophr. Res.* **92**, 1–14 (2007).
139. MacCoun, R. & Reuter, P. Evaluating alternative cannabis regimes. *Br. J. Psychiatry* **178**, 123–128 (2001).
140. Edwards, G. & Gross, M. M. Alcohol dependence: provisional description of a clinical syndrome. *BMJ* **1**, 1058–1061 (1976).
141. *International Classification of Mental Disorders, ICD 10*. (World Health Organization Press, Geneva, 1992).
142. Hermann, A., Kaczocha, M. & Deutsch, D. G. 2-Arachidonoylglycerol (2-AG) membrane transport: history and outlook. *AAPS J.* **8**, E409–E412 (2006).
143. Dinh, T. P. *et al.* Brain monoglyceride lipase participating in endocannabinoid inactivation. *Proc. Natl Acad. Sci. USA* **99**, 10819–10824 (2002).
144. Makara, J. K. *et al.* Selective inhibition of 2-AG hydrolysis enhances endocannabinoid signaling in hippocampus. *Nature Neurosci.* **8**, 1139–1141 (2005).
145. Hashimotodani, Y., Ohno-Shosaku, T. & Kano, M. Presynaptic monoacylglycerol lipase activity determines basal endocannabinoid tone and terminates retrograde endocannabinoid signaling in the hippocampus. *J. Neurosci.* **27**, 1211–1219 (2007).
146. Hajos, N. & Freund, T. F. Pharmacological separation of cannabinoid sensitive receptors on hippocampal excitatory and inhibitory fibers. *Neuropharmacology* **43**, 503–510 (2002).
147. Tien, A. Y. & Anthony, J. C. Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. *J. Nerv. Ment. Dis.* **178**, 473–480 (1990).
148. Weiser, M., Knobler, H. Y., Noy, S. & Kaplan, Z. Clinical characteristics of adolescents later hospitalized for schizophrenia. *Am. J. Med. Genet.* **114**, 949–955 (2002).
149. Ferdinand, R. F. *et al.* Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction* **100**, 612–618 (2005).
150. Wiles, N. J. *et al.* Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British National Psychiatric Morbidity Survey. *Br. J. Psychiatry* **188**, 519–526 (2006).
151. Kaplan, J. (ed.) *Marijuana: Report of the Indian Hemp Drugs Commission, 1893–1894*. (Thomas Jefferson Co., Silver Springs, Maryland, USA, 1969).
152. Mechoulam, R. & Gaoni, Y. A total synthesis of DL-Δ-1-tetrahydrocannabinol, the active constituent of hashish. *J. Am. Chem. Soc.* **87**, 3273–3275 (1965).
153. Relman, A. (ed.) *Marijuana and Health (Report of a Study by a Committee of the Institute of Medicine, Division of Health Sciences Policy)*. (National Academy Press, Washington, D.C., 1982).
154. Rinaldi-Carmona, M. *et al.* SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett.* **350**, 240–244 (1994).
155. Baker, D. *et al.* Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* **404**, 84–87 (2000).
156. Maejima, T., Hashimoto, K., Yoshida, T., Aiba, A. & Kano, M. Presynaptic inhibition caused by retrograde signal from metabotropic glutamate to cannabinoid receptors. *Neuron* **31**, 463–475 (2001).
157. Sjöström, P., Turrigiano, G. & Nelson, S. Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. *Neuron* **39**, 641–654 (2003).

DATABASES

Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
CB1 | CB2 | COMT

FURTHER INFORMATION

Robin M. Murray's homepage: http://www.iop.kcl.ac.uk/staff/profile/default.aspx?go=10328&local=True

ALL LINKS ARE ACTIVE IN THE ONLINE PDF