

The adverse health effects of chronic cannabis use

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This paper summarizes the most probable of the adverse health effects of regular cannabis use sustained over years, as indicated by epidemiological studies that have established an association between cannabis use and adverse outcomes; ruled out reverse causation; and controlled for plausible alternative explanations. We have also focused on adverse outcomes for which there is good evidence of biological plausibility. The focus is on those adverse health effects of greatest potential public health significance – those that are most likely to occur and to affect a substantial proportion of regular cannabis users. These most probable adverse effects of regular use include a dependence syndrome, impaired respiratory function, cardiovascular disease, adverse effects on adolescent psychosocial development and mental health, and residual cognitive impairment. Copyright © 2013 John Wiley & Sons, Ltd.

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Introduction

Cannabis has probably been used for medical and quasi-medical reasons by humans for several thousand years^[1] but societal concerns about the possible adverse health effects of cannabis use has been driven by the more recent emergence of recreational cannabis use among young people.^[2] In developed countries over the past half century, psychoactive preparations of cannabis have been increasingly used by adolescents and young adults in social settings to enhance sociability and produce euphoria and relaxation. Since cannabis use was first reported over 40 years ago by US college students, its use has spread globally, first to other developed countries, and more recently, to low- and middle-income countries.^[3,4]

This paper summarizes what is known about the adverse effects of chronic use of cannabis beginning in adolescence and continuing into adulthood. We focus on the adverse effects that are of greatest potential public health significance, specifically, those health outcomes that are most likely to affect a substantial proportion of regular cannabis users. There is good evidence that cannabis use increases risks of car crashes in cannabis-impaired drivers and evidence from laboratory studies that psychomotor impairment persists for some weeks after cessation in regular cannabis users.^[5,6] This topic is not discussed further here because it is dealt with in another paper in this special issue.

Defining chronic cannabis use

We lack reliable information on the doses of delta-9-tetrahydrocannabinol (THC) and other cannabinoids (e.g. cannabidiol) that are commonly used by regular cannabis users.^[7] As a consequence, epidemiological studies have usually defined 'heavy' or 'regular' cannabis use as daily or near daily use.^[2] This pattern of use continued over years most clearly predicts increased risks of adverse health effects.^[2]

Search strategy

We searched PubMed and Thompson/Reuters Web of Science citation indexes for articles published in the last 10 years on adverse health effects of cannabis to update our earlier review.^[8] Search terms

included 'cannabis', 'marijuana abuse', 'marijuana smoking', 'epidemiologic studies', 'adverse effects', 'substance related disorders', 'lung diseases', 'respiration disorders', 'cardiovascular diseases', 'coronary disease', 'traffic accidents', 'automobile driving', 'mental disorders', and 'adolescent'. Additional papers were identified in references cited in these papers, books, edited works, and reports.

Assessing the adverse health effects of cannabis

As in our earlier paper,^[8] we looked for evidence: (1) of an association between cannabis use and the outcome in case-control and prospective studies; (2) that reverse causation was an implausible explanation of the association (evidence from prospective studies that cannabis use preceded the outcome); (3) from prospective studies that controlled for potential confounding variables (such as other drug use and characteristics on which cannabis users differed from non-users); and (4) from clinical and experimental research that a causal relationship was biologically plausible.^[2]

The health effects of chronic cannabis use

Epidemiological studies have reported associations between chronic cannabis use – defined as near daily use over a period of years during adolescence – and various adverse health outcomes in young adulthood. These associations are typically quantified as an odds ratio (ratio of the odds of the disorder

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among cannabis users to the odds among non-users) or a relative risk (the ratio of the risks of the disorder among cannabis users and non-users).

The major challenge in interpreting studies reporting association between regular cannabis use and adverse outcomes has been in ruling out alternative explanations of these associations because regular cannabis users are more likely to use alcohol, tobacco, and other illicit drugs, all of which adversely affect health.^[2] Regular cannabis users also differ from non-users in ways that may affect their risk of behavioural outcomes.^[2] Statistical control of confounding has been used to assess these relationships but there are epidemiologists who doubt that this strategy can be wholly successful.^[9]

Cannabis dependence

Cannabis dependence is characterized by impaired control over cannabis use and difficulty in ceasing use despite harms caused by it. In Australia, Canada, and the USA, cannabis dependence is the most commonly treated type of drug dependence after alcohol and tobacco,^[2] affecting an estimated 1–2% of adults in the past year, and 4–8% of adults during their lifetime.^[2,10]

The lifetime risk of dependence among all cannabis users has been estimated at about 9%.^[10] This increases to one in six among those who initiate in adolescence.^[10] The equivalent lifetime risks of dependence were 32% for nicotine, 23% for heroin, 17% for cocaine, 15% for alcohol, and 11% for stimulant users.^[11,12] Those at highest risk of cannabis dependence have a history of poor academic achievement, deviant behaviour in childhood and adolescence, rebelliousness, poor parental relationships, and a parental history of drug and alcohol problems.^[10]

In laboratory studies, animals and humans develop tolerance to many of the effects of THC.^[13] Cannabis users who seek help to quit commonly report withdrawal symptoms that include anxiety, insomnia, appetite disturbance and depression.^[14]

Over the past two decades, increased cannabis use among young adults has been accompanied by increasing numbers of persons seeking help in the USA, Europe, and Australia to stop using cannabis.^[2,15] Some of this increase may be explained by more diversion of users into treatment by the courts but increases have also occurred in the Netherlands where cannabis use has been decriminalized.^[16] The adverse health and social consequences of cannabis use reported by those who seek treatment for dependence are probably less severe than those reported by persons with comparable levels of alcohol or opioid dependence.^[2,17]

The respiratory and cardiovascular risks of cannabis smoking

Regular cannabis smokers report more symptoms of chronic bronchitis (wheeze, sputum production, and chronic coughs) than non-smokers.^[18] The immunological competence of the respiratory system in cannabis-only smokers is also impaired, leading to increased health-service use for respiratory infections.^[19]

The effects of long-term cannabis smoking on respiratory function are less clear.^[18] A longitudinal study of 1037 New Zealand youths followed until the age of 26^[20] found impaired respiratory function in dependent cannabis users but this finding was not replicated in a longer-term follow-up of US users.^[19] Chronic cannabis smoking has not been found to increase the risk of emphysema in 8–20-year follow-ups in cannabis smokers in the USA^[21,22] and New Zealand.^[23]

Respiratory cancers

Cannabis smoke contains many of the same carcinogens as tobacco smoke, some at higher levels^[24] and it is mutagenic and carcinogenic in the mouse skin test. In some studies, chronic cannabis smokers have shown pathological changes in lung cells that precede the development of lung cancer in tobacco smokers,^[25] but epidemiological studies have not consistently found increased risks of upper respiratory tract cancers in cannabis smokers. Sidney *et al.*^[26] found no increased risk of respiratory cancer in an 8.6-year follow-up of 64 855 members of the Kaiser Permanente Medical Care Program. Zhang *et al.*^[27] reported an increased risk (odds ratio (OR) of 2) of squamous cell carcinoma of the head and neck among cannabis users in 173 cases and 176 controls that persisted after adjusting for cigarette smoking, alcohol use, and other risk factors. Three other case-control studies of these cancers have failed to find an association with cannabis use.^[28]

Case-control studies of lung cancer have produced more consistent associations but cannabis smoking has often been confounded by cigarette smoking.^[29] A Tunisian case-control study of 110 cases of hospital diagnosed lung cancer and 110 community controls found an association with cannabis use (OR = 8.2) that persisted after adjustment for cigarette smoking. A pooled analysis of three Moroccan case-control studies also found an elevated risk of lung cancer among cannabis smokers but they all also smoked tobacco.^[30] A New Zealand case-control study of lung cancer in 79 adults under the age of 55 years and 324 community controls^[31] found a dose-response relationship between frequency of cannabis use and lung cancer risk. A US case-control study found a simple association between cannabis smoking and head and neck and lung cancers but these associations were no longer significant after controlling for tobacco use.^[32] Larger cohorts and better designed case-control studies are needed to clarify the lung-cancer risks from chronic cannabis smoking.^[28]

Cardiovascular effects

Cannabis smoking and THC increase heart rates in a dose-related way. Healthy young adults who use cannabis daily, rapidly develop tolerance^[33,34] to these effects but this may not be true in older adults with cardiovascular disease who use less frequently.^[33,34] A case-crossover study by Mittleman *et al.*^[35] of 3882 patients who had had a myocardial infarction found that cannabis use quadrupled the risk of a myocardial infarction in the hour after use. A prospective study of 1913 of these adults found a dose-response relationship between cannabis use and mortality over 3.8 years.^[36] These findings are supported by laboratory studies which show that smoking cannabis provokes angina in patients with heart disease.^[37] A French study found that that 9.5% of 200 cannabis-related hospitalizations in the Toulouse area between January 2004 and December 2007 involved cardiovascular disorders, including several myocardial infarctions and a fatal stroke in young adults with no other known risk factors for these disorders.^[38]

Chronic cannabis use and brain function

Cognitive impairment

It is unclear from cross-sectional studies whether chronic cannabis use impairs cognitive performance or whether persons with poorer cognitive functioning are more likely to become regular cannabis users.^[39] Studies that have matched users and non-users on estimated intellectual function before using cannabis,^[39] or on

cognitive performance assessed before cannabis use,^[40] have found cognitive impairments in frequent and/or long-term cannabis users.^[40]

Deficits in verbal learning, memory, and attention are the most consistently reported in heavy cannabis users but these have been variously related to duration of use, frequency of use, and cumulative dose of THC.^[41,42] Debate continues about whether these deficits can be attributed to the acute cognitive effects of cannabis, residual effects of chronic use, or the effects of cumulative THC exposure on brain functioning.^[42]

It is also unclear whether cognitive function completely recovers after cessation of cannabis use. Solowij^[39,41] found partial recovery after two years' abstinence but brain event-related potentials still showed a correlation between impaired information processing and years of cannabis use. Bolla *et al.*^[43] found persistent dose-related impairment in neurocognitive performance after 28 days of abstinence in heavy young users (5 years of use) but Pope *et al.*^[44] reported recovery after 28 days' abstinence.

A recent New Zealand longitudinal study assessed changes in IQ between age 13 (before cannabis use) and at age 38 in 1037 New Zealanders born in Dunedin in 1972 or 1973.^[45] They found that early and persistent cannabis users showed an eight-point decline in IQ compared to those who had not used cannabis or not used it in this way. Detailed analyses pointed to persistent cannabis use being the most plausible explanation for the decline.

First, the decline in IQ was largest in those who began using cannabis in adolescence and used regularly throughout adulthood. The relationship persisted after statistical adjustment for other factors that may affect IQ (such as recent cannabis use, alcohol, tobacco and other drug use, and schizophrenia). Second, the same effects were observed in cannabis users who finished high school, and the decline persisted after statistically controlling for educational level attained. Third, there was some recovery in IQ if users quit, but recovery was limited in participants who started smoking cannabis in adolescence and had stopped using for a year or less. There was no IQ decline in cannabis users who started in young adulthood and had not used for a year or more before follow-up.

Brain structure and function

Regular cannabis use produces a down-regulation of cannabinoid receptors that can be detected by positron emission tomography (PET) and persist for up to a month after abstinence has been achieved.^[46] Functional imaging studies^[47] have also shown reduced activity in brain regions involved in memory and attention in chronic cannabis users after 28 days of abstinence.^[40]

Structural changes have been reported in the hippocampus, prefrontal cortex, and cerebellum in chronic cannabis users. Yücel *et al.*^[48] reported reduced hippocampal and amygdala volumes in 15 long-term users who had smoked 5 or more joints a day for 10 or more years. These reductions increased with the duration of use. Brain-imaging studies on larger samples of long-term cannabis users are needed to see if cognitive impairments in long-term users are correlated with structural changes in brain areas implicated in memory and emotion.^[49]

The psychosocial consequences of adolescent cannabis use

Educational outcomes

Regular cannabis use and poor educational attainment are associated^[50] but it is uncertain whether such use: (1) is a contributory cause of poor school performance; (2) is more likely to occur in

young people with poor educational attainment; or (3) implies that cannabis use and poor educational attainment are caused by common factors.^[50] Explanations (1) and (2) could both be true if poor school performance made regular cannabis use more likely and this in turn further impaired school performance.

Longitudinal studies have typically found a relationship between cannabis use before the age of 15 and early school leaving that has persisted after adjustment for confounders.^[51] A recent meta-analysis of three Australian and New Zealand longitudinal studies^[52] confirmed this finding by showing that the earlier the age of first cannabis use, the lower the chances of completing school and post-secondary training. This effect persisted after adjustment for confounders. They estimated that early use of cannabis may contribute to as much as 17% of the risk of failing to complete high school or post-secondary training.

It is plausible that impaired educational outcomes are attributable to a combination of a higher pre-existing risk of educational problems in regular cannabis users, the adverse effects of regular cannabis use on learning in school, increased affiliation by regular cannabis users with peers who reject school, and a strong desire among younger cannabis users to make an early transition to adulthood by leaving school.^[50]

Other illicit drug use

In the United States, Australia, and New Zealand: (1) regular cannabis users are most likely to later use heroin and cocaine; and (2) the earlier the age at which a young person first uses cannabis, the more likely they are to do so.^[53] Three explanations have been offered for these patterns of drug use: (1) cannabis users have more opportunities to use other illicit drugs because these are supplied by the same black market as cannabis; (2) early cannabis users are more likely to use other illicit drugs for reasons that are unrelated to their cannabis use; and (3) the pharmacological effects of chronic cannabis increase a young person's propensity to use other illicit drugs.^[2]

There is support for the first two hypotheses. Young people in the USA who have used cannabis report more opportunities to use cocaine at an earlier age.^[54] Socially deviant young people (who are more likely to use cocaine and heroin) start using cannabis at an earlier age than their peers.^[55] A simulation study^[56] indicates that the second hypothesis may explain the relationships observed between cannabis and other illicit drug use.

The second hypothesis has also been tested in longitudinal studies by assessing whether cannabis users are more likely to report heroin and cocaine use after statistically controlling for confounders.^[57] Adjustment for confounders (including unmeasured fixed ones using fixed effects regression)^[58] weakened but did not eliminate the relationship between regular cannabis use and the use of other illicit drugs.^[59]

Studies of twins discordant for cannabis use have tested the hypothesis that the association is explained by a shared genetic vulnerability to use cannabis and other illicit drugs. Lynskey *et al.*^[60] found that the twin who had used cannabis was more likely to have used other illicit drugs than the co-twin who had not, and the relationship persisted after controlling for non-shared environmental factors.

Cannabis use and mental health

Psychosis and schizophrenia

Regular cannabis use has been associated with psychotic symptoms (disordered thinking, hallucinations, and delusions) and with psychotic disorders. The latter include schizophrenia which is

diagnosed in persons who report severe psychotic symptoms over months, and who often experience substantial social disability, a loss of motivation, disturbed behaviour, and cognitive deficits.^[61]

A 15-year follow-up of 50 465 Swedish male conscripts found that those who had tried cannabis by age 18 were 2.4 times more likely to be diagnosed with schizophrenia than those who had not.^[62] Those who had used cannabis 10 or more times by age 18 were 2.3 times more likely to be diagnosed with schizophrenia than those who had not, after statistical adjustment for a limited set of confounding variables (a personal history of psychiatric disorder by age 18 and parental divorce).

Zammit *et al.*^[63] reported a 27-year follow-up of the same cohort that also found a dose–response relationship between frequency of cannabis use at age 18 and risk of schizophrenia during the follow-up. This persisted after statistically controlling for the effects of other confounding factors. They estimated that 13% of cases of schizophrenia could be averted if all cannabis use were prevented. These results were recently confirmed in a 35-year follow-up of the Swedish cohort.^[64] The Swedish findings have been supported by longitudinal studies in the Netherlands,^[65] Germany,^[66] and New Zealand,^[67,68] all of which found that the relationship persisted after adjustment for confounders.

A meta-analysis of longitudinal studies reported a pooled odds ratio of 1.4 [95% confidence interval (CI): 1.20, 1.65] of psychotic symptoms or psychotic disorder among those who had ever used cannabis.^[69] The risk of psychotic symptoms or psychotic disorders was higher in regular users (odds ratio of 2.09 [95% CI: 1.54, 2.84]). Reverse causation was addressed in most of these studies, by excluding cases reporting psychotic symptoms at baseline, or by statistically adjusting for pre-existing psychotic symptoms. The common cause hypothesis was harder to exclude because the association between cannabis use and psychosis was attenuated after statistical adjustment for potential confounders and no study assessed all confounders.

The evidence is conflicting on whether the incidence of schizophrenia has increased as cannabis use has increased among young adults, as would be expected if the relationship were causal. An Australian study did not find clear evidence of increased psychosis incidence after steep increases in cannabis use during the 1980s and 1990s.^[70] One British study^[71] suggested that it was too early to detect any increased incidence in Britain in the 1990s. A British^[72] and a Swiss study^[73] reported an increased incidence of psychoses in recent birth cohorts but another British study failed to do so.^[61] It will be difficult to discern whether cannabis use has had any effects on incidence because cannabis use produces a modest increase in risk (assuming that the relationship is causal) and the interpretation of data on the incidence of psychoses have been complicated by changes in diagnosis, the availability of psychiatric services for psychosis, and in the quality of data on treated incidence of psychosis.

The risk of developing a psychosis roughly doubles from around 7 in 1000 in non-users^[74] to 14 in 1000 for regular cannabis users. A doubling of risk is important in persons with an affected first degree relative among whom the risk increases from around 10% to 20%.^[75] Even if we assume that cannabis use increases the population incidence of psychosis, it will be difficult to reduce incidence by preventing cannabis uptake: among men aged 20 to 24, an estimated 4700 men would have to be dissuaded from smoking cannabis to prevent one case of schizophrenia.^[60]

Cannabis use and affective disorders

Less consistent, weaker relationships have been found between cannabis use and depression.^[76] In a follow-up of the Swedish cohort, for example, Manrique-Garcia *et al.* found an increased risk of depression (1.5 times) in those who reported the heaviest cannabis use at age 18. The association disappeared after adjustment for confounders.^[77] Fergusson and Horwood^[78] found a dose–response relationship between frequency of cannabis use by age 16 and depressive disorder but the relationship was no longer statistically significant after adjusting for confounders. A meta-analysis of these studies^[69] found a modest association between cannabis use and depressive disorders (OR = .49 [95% CI: 1.15, 1.94]) but the authors argued that most studies had not adequately controlled for confounders, or excluded the possibility that depressed young people are more likely to use cannabis. Similar conclusions were drawn from a combined analysis of data from four Australasian birth cohorts.^[79]

Bipolar disorders

Surveys of clinical populations report higher rates of cannabis use disorders among persons diagnosed with bipolar disorders.^[80–82] In a longitudinal study, cannabis use at baseline predicted an increased likelihood of manic symptoms in a 3-year follow-up of a representative sample of young adults.^[83] There are also clinical studies suggesting that people with bipolar disorders who continue to use cannabis have more manic episodes and are less satisfied with their lives than affected peers who do not use cannabis.^[82] These findings suggest that regular cannabis use may play a contributory causal role in bipolar disorders but the case is not yet compelling because these studies have not adequately controlled for confounding variables or ruled out reverse causation.^[82]

Suicide

Several case–control and cohort studies have found associations between cannabis use and suicide in adolescents and young adults but it is unclear whether the relationship is causal. For example, a New Zealand case–control study^[84] of serious suicide attempts resulting in hospitalization found that 16% of the 302 suicide attempters had a cannabis disorder compared with 2% of the 1028 community controls. Controlling for social disadvantage, depression and alcohol dependence substantially reduced but did not eliminate the association (odds ratio of 2).

The evidence from prospective studies is mixed. Fergusson and Horwood,^[78] for example, found a dose–response relationship between frequency of cannabis use by age 16 and a self-reported suicide attempt but the association did not persist after controlling for confounders. A recent analysis of the data from this cohort^[85] using sophisticated econometric methods found that more than weekly cannabis use increased the likelihood of reporting suicidal ideation *in males*. Patton *et al.*^[86] by contrast, found that cannabis was only associated with self-harmful behaviour in females, a relationship that persisted after controlling for depression and alcohol use. Rasic *et al.*^[87] reported that heavy cannabis use increased the risk of depression but did not affect suicide risk. A meta-analysis^[69] found that these studies were too heterogeneous to quantify risk, and the authors argued that most of these studies had not excluded reverse causation or controlled for confounding.

The health effects of increased THC in cannabis products

The average THC content of cannabis products increased during the late 1990s and early 2000s in many developed countries.^[88,89] It is unclear whether increased THC content has been accompanied by changes in levels of CBD, a cannabinoid that some argue moderates the adverse effects of THC on mental health. Any adverse health effects of increased potency will also depend on whether users are able to titrate their dose of THC and on users' experience with cannabis. A higher THC content may increase anxiety, depression and psychotic symptoms in naïve users, which may deter continued use. At the same time, more potent products may increase the risks of developing dependence and psychotic symptoms in regular users if these users do not titrate their doses. Adverse effects on the respiratory and cardiovascular systems may be reduced if regular users titrate their dose of THC by reducing the amount that they smoke. This is a high priority for research.

Summary of the adverse health effects of cannabis

Chronic cannabis use can produce a dependence syndrome in 1 in 10 users. Regular users have higher risks of chronic bronchitis and possibly impaired respiratory function; and psychotic symptoms and disorders, especially if they have a history of psychotic symptoms or a family history of these disorders. The most *probable* adverse psychosocial effect among adolescents who become regular users is impaired educational attainment. Regular adolescent cannabis users are more likely to use other illicit drugs although the explanation of this relationship remains contested.

There is uncertainty about whether a number of other adverse effects associated with regular cannabis use are causally related to its use. This is because of the possible confounding effects of tobacco smoking in the case of respiratory cancers. In the case of depressive disorders and suicide, the direction of the relationship is uncertain. In the case of cognitive performance, the size and reversibility of the impairment is unclear. These outcomes, and studies of the typical doses of THC and other cannabinoids in commonly used cannabis preparations, should be priorities for research on the health effects of cannabis.

Text boxes

Box 1: The most probable adverse health effects of *chronic* cannabis smoking

- A cannabis dependence syndrome (in around 1 in 10 users).
- Chronic bronchitis and impaired respiratory function in regular smokers.
- Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders.
- Impaired educational attainment among adolescents who use regularly.
- Residual cognitive impairment for up to a month after abstinence.
- Cognitive impairment in those who initiate early and use daily for a decade or more.

Box 2: Possible adverse effects of regular cannabis use of which the causal significance remains to be assessed

- Respiratory cancers
- Depressive disorders, mania, and suicide
- Use of other illicit drugs by adolescents

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References

- [1] E.L. Abel. *Marihuana: The First Twelve Thousand Years*, Plenum Press, New York, **1980**.
- [2] W.D. Hall, R. Pacula. *Cannabis Use and Dependence: Public Health and Public Policy*. Cambridge University Press, Cambridge, **2010**.
- [3] L. Degenhardt, C. Bucello, B. Calabria, P. Nelson, A. Roberts, W.D. Hall *et al.* What data are available on the extent of illicit drug use and dependence globally? Results of four systematic reviews. *Drug Alcohol Depend.* **2011**, *117*, 85.
- [4] UNODC. *World Drug Report 2012*. United Nations Office on Drugs and Crime, Vienna, **2012**.
- [5] M. Asbridge, J.A. Hayden, J. Cartwright. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. *BMJ* **2012**, *344*, 14.
- [6] W.M. Bosker, E.L. Karschner, D. Lee, R.S. Goodwin, J. Hirvonen, R.B. Innis *et al.* Psychomotor function in chronic daily cannabis smokers during sustained abstinence. *PLoS One* **2013**, *8*, e53127.
- [7] M. Norberg, J. Mackenzie, J. Copeland. Quantifying cannabis use with the timeline followback approach: A psychometric evaluation. *Drug Alcohol Depend.* **2012**, *121*, 247.
- [8] W.D. Hall, L. Degenhardt. The adverse health effects of nonmedical cannabis use. *Lancet* **2009**, *374*, 1383.
- [9] J. Macleod, R. Oakes, A. Copello, I. Crome, M. Egger, M. Hickman *et al.* Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* **2004**, *363*, 1579.
- [10] J. Anthony. *Cannabis Dependence: Its Nature, Consequences and Treatment*, (Eds: R.A. Roffman, R.S. Stephens). Cambridge University Press, Cambridge, **2006**, pp. 58–105.
- [11] J. Anthony, L. Warner, R. Kessler. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: Basic findings from the National Comorbidity Survey. *Exp. Clin. Psychopharmacol.* **1994**, *2*, 244.
- [12] W.D. Hall, M. Teesson, M. Lynskey, L. Degenhardt. The 12-month prevalence of substance use and ICD-10 substance use disorders in Australian adults: Findings from the national survey of mental health and well-being. *Addiction* **1999**, *94*, 1541.
- [13] A. Lichtman, B. Martin. Cannabinoid tolerance and dependence. *Handb. Exp. Pharmacol.* **2005**, *168*, 691.
- [14] A. Budney, J. Hughes. The cannabis withdrawal syndrome. *Curr. Opin. Psychiat.* **2006**, *19*, 233.
- [15] WHO. *ATLAS on Substance Use (2010): Resources for the Prevention and Treatment of Substance Use Disorders*. World Health Organization, Geneva, **2010**.

- [16] Dutch National Alcohol and Drug Information System. Treatment demand of cannabis clients in outpatient addiction care in the Netherlands (1994–2001). *LADIS Bull.* **2004**, April, 1–4.
- [17] L. Degenhardt, W.D. Hall. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet* **2012**, 379, 55.
- [18] J. Tetrault, K. Crothers, B. Moore, R. Mehra, J. Concato, D. Fiellin. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Arch. Intern. Med.* **2007**, 167, 221.
- [19] D. Tashkin, G. Baldwin, T. Sarafian, S. Dubinett, M.D. Roth. Respiratory and immunologic consequences of marijuana smoking. *J. Clin. Pharmacol.* **2002**, 42, 71S.
- [20] D. Taylor, D. Fergusson, B. Milne, L. Horwood, T. Moffitt, M. Sears *et al.* A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction* **2002**, 97, 1055.
- [21] M. Pletcher, E. Vittinghoff, R. Kralhan, J. Richman, M. Safford, S. Sidney *et al.* Association between marijuana exposure and pulmonary function over 20 years. *JAMA* **2012**, 307, 173.
- [22] D. Tashkin. Smoked marijuana as a cause of lung injury. *Monaldi Arch. Chest Dis.* **2005**, 63, 93.
- [23] S. Aldington, M. Williams, M. Nowitz, M. Weatherall, A. Pritchard, A. McNaughton *et al.* Effects of cannabis on pulmonary structure, function and symptoms. *Thorax* **2007**, 62, 1058.
- [24] D. Moir, W. Rickert, G. Levasseur, Y. Larose, R. Maertens, P. White *et al.* A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem. Res. Toxicol.* **2008**, 21, 494.
- [25] D. Tashkin. In *The Health Effects of Cannabis*. (Eds: H. Kalant, W. Corrigall, W.D. Hall, R. Smart), Centre for Addiction and Mental Health, Toronto, **1999**, pp. 311–345.
- [26] S. Sidney, C. Quesenberry, G. Friedman, I. Tekawa. Marijuana use and cancer incidence (California, United States). *Cancer Causes Control* **1997**, 8, 722.
- [27] Z. Zhang, H. Morgenstern, M. Spitz, D. Tashkin, G. Yu, J. Marshall *et al.* Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiol. Biomarkers Prev.* **1999**, 8, 1071.
- [28] M. Hashibe, K. Straif, D. Tashkin, H. Morgenstern, S. Greenland, Z. Zhang. Epidemiologic review of marijuana use and cancer risk. *Alcohol* **2005**, 35, 265.
- [29] R. Mehra, B. Moore, K. Crothers, J. Tetrault, D. Fiellin. The association between marijuana smoking and lung cancer: A systematic review. *Arch. Intern. Med.* **2006**, 166, 1359.
- [30] J. Berthiller, K. Straif, M. Boniol, N. Voirin, V. Benhaim-Luzon, W.B. Ayoub, *et al.* Cannabis smoking and risk of lung cancer in men: A pooled analysis of three studies in Maghreb. *J. Thorac. Oncol.* **2008**, 3, 1398.
- [31] S. Aldington, M. Harwood, B. Cox, M. Weatherall, L. Beckert, A. Hansell *et al.* Cannabis use and risk of lung cancer: A case–control study. *Eur. Respir. J.* **2008**, 31, 280.
- [32] M. Hashibe, H. Morgenstern, Y. Cui, D. Tashkin, Z. Zhang, W. Cozen *et al.* Marijuana use and the risk of lung and upper aerodigestive tract cancers: Results of a population-based case–control study. *Cancer Epidemiol. Biomarkers Prev.* **2006**, 15, 1829.
- [33] R. Jones. Cardiovascular system effects of marijuana. *J. Clin. Pharmacol.* **2002**, 42, 58S.
- [34] S. Sidney. Cardiovascular consequences of marijuana use. *J. Clin. Pharmacol.* **2002**, 42, 64S.
- [35] M.A. Mittleman, R. Lewis, M. Maclure, J. Sherwood, J. Muller. Triggering myocardial infarction by marijuana. *Circulation* **2001**, 103, 2805.
- [36] K. Mukamal, M. Maclure, J. Muller, M. Mittleman. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *Am. Heart J.* **2008**, 155, 465.
- [37] L. Gottschalk, W. Aronow, R. Prakash. Effect of marijuana and placebo-marijuana smoking on psychological state and on psychophysiological and cardiovascular functioning in angina patients. *Biol. Psychiatry* **1977**, 12, 255.
- [38] E. Jouanjus, F. Leymarie, M. Tubery, M. Lapeyre-Mestre. Cannabis-related hospitalizations: Unexpected serious events identified through hospital databases. *Brit. J. Clin. Pharmacol.* **2011**, 71, 758.
- [39] N. Solowij. Cannabis and Cognitive Functioning. Cambridge University Press, Cambridge, UK, **1998**.
- [40] R. Block, D. O'Leary, R. Hichwa, J. Augustinack, L. Ponto, M. Ghoneim *et al.* Effects of frequent marijuana use on memory-related regional cerebral blood flow. *Pharmacol. Biochem. Behav.* **2002**, 72, 237.
- [41] N. Solowij, N. Pesa. In *Marijuana and Madness*, (Eds: D. Castle, R.M. Murray, D.C. D'Souza), Cambridge University Press, New York, **2012**, pp. 91–102.
- [42] N. Solowij, R. Stephens, R. Roffman, T. Babor, R. Kadden, M. Miller *et al.* Marijuana Treatment Project Research Group. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* **2002**, 287, 1123.
- [43] K. Bolla, K. Brown, D. Eldreth, K. Tate, J. Cadet. Dose-related neurocognitive effects of marijuana use. *Neurology* **2002**, 59, 1337.
- [44] H. Pope, A. Gruber, J. Hudson, M. Huestis, D. Yurgelun-Todd. Neuropsychological performance in long-term cannabis users. *Arch. Gen. Psychiatry* **2001**, 58, 909.
- [45] M. Meier, A. Caspi, A. Ambler, H. Harrington, R. Houts, R. Keefe *et al.* Persistent cannabis users show neuropsychological decline from childhood to midlife. *P. Natl. Acad. Sci. USA.* **2012**, 109, E2657.
- [46] J. Hirvonen, R.S. Goodwin, C.T. Li, G.E. Terry, S.S. Zoghbi, C. Morse *et al.* Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Mol. Psychiatry* **2012**, 17, 642.
- [47] J. Quickfall, D. Crockford. Brain neuroimaging in cannabis use: A review. *J. Neuropsychiatry Clin. Neurosci.* **2006**, 18, 318.
- [48] M. Yücel, N. Solowij, C. Respondek, S. Whittle, A. Fornito, C. Pantelis *et al.* Regional brain abnormalities associated with long-term heavy cannabis use. *Arch. Gen. Psychiatry* **2008**, 65, 694.
- [49] N. Solowij, M. Yucel, V. Lorenzetti, D. Lubman. *Marijuana and Madness*, (Eds: D. Castle, R.M. Murray, D.C. D'Souza). Cambridge University Press, New York, **2012**, pp. 103–113.
- [50] M. Lynskey, W.D. Hall. The effects of adolescent cannabis use on educational attainment: A review. *Addiction* **2000**, 96, 433.
- [51] P. Ellickson, K. Bui, R. Bell, K. McGuigan. Does early drug use increase the risk of dropping out of high school? *J. Drug Issues* **1998**, 28, 357.
- [52] L. Horwood, D. Fergusson, M. Hayatbakhsh, J. Najman, C. Coffey, G. Patton *et al.* Cannabis use and educational achievement: Findings from three Australasian cohort studies. *Drug Alcohol Depend.* **2010**, 110, 247.
- [53] D. Kandel. *Stages and Pathways of Drug Involvement: Examining the Gateway Hypothesis*. Cambridge University Press, New York, **2002**.
- [54] F. Wagner, J. Anthony. Into the world of illegal drug use: Exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *Am. J. Epidemiol.* **2002**, 155, 918.
- [55] D. Fergusson, J. Boden, L. Horwood. The developmental antecedents of illicit drug use: Evidence from a 25-year longitudinal study. *Drug Alcohol Depend.* **2008**, 96, 165.
- [56] A. Morral, D. McCaffrey, S. Paddock. Reassessing the marijuana gateway effect. *Addiction* **2002**, 97, 1493.
- [57] J. Lessem, C. Hopfer, B. Haberstick, D. Timberlake, M. Ehringer, A. Smolen *et al.* Relationship between adolescent marijuana use and young adult illicit drug use. *Behav. Genet.* **2006**, 36, 498.
- [58] D. Fergusson, J. Boden, L. Horwood. Cannabis use and other illicit drug use: Testing the cannabis gateway hypothesis. *Addiction* **2006**, 101, 556.
- [59] W.D. Hall, M. Lynskey. Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs. *Drug Alcohol Rev.* **2005**, 24, 39.
- [60] M. Lynskey, A. Heath, K. Buchholz, W. Slutske. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA* **2003**, 289, 427.
- [61] Advisory Council on the Misuse of Drugs. *Cannabis: Classification and Public Health*. Home Office, London, **2008**.
- [62] S. Andréasson, A. Engstrom, P. Allebeck, U. Rydberg. Cannabis and schizophrenia: A longitudinal study of Swedish conscripts. *Lancet* **1987**, 2, 1483.
- [63] S. Zammit, P. Allebeck, S. Andréasson, I. Lundberg, G. Lewis. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: Historical cohort study. *Brit. Med. J.* **2002**, 325, 1199.
- [64] E. Manrique-García, S. Zammit, C. Dalman, T. Hemmingsson, S. Andréasson, P. Allebeck. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. *Psychol. Med.* **2012**, 42, 1321.
- [65] J. van Os, M. Bak, M. Hanssen, R.V. Bijl, R. de Graaf, H. Verdoux. Cannabis use and psychosis: A longitudinal population-based study. *Am. J. Epidemiol.* **2002**, 156, 319.
- [66] C. Henquet, L. Krabbendam, J. Spauwen, C. Kaplan, R. Lieb, H. Wittchen *et al.* Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *Brit. Med. J.* **2004**, 330, 11.

- [67] D. Fergusson, L. Horwood, N. Swain-Campbell. Cannabis dependence and psychotic symptoms in young people. *Psychol. Med.* **2003**, *33*, 15.
- [68] L. Arseneault, M. Cannon, R. Poulton, R. Murray, A. Caspi, T. Moffitt. Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *Brit. Med. J.* **2002**, *325*, 1212.
- [69] T. Moore, S. Zammit, A. Lingford-Hughes, T. Barnes, P. Jones, M. Burke *et al.* Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* **2007**, *370*, 319.
- [70] L. Degenhardt, W.D. Hall, M. Lynskey. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend.* **2003**, *71*, 37.
- [71] M. Hickman, P. Vickerman, J. Macleod, J. Kirkbride, P. Jones. 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* **2007**, *102*, 597.
- [72] J. Boydell, J. van Os, A. Caspi, N. Kennedy, E. Giouroukou, P. Fearon *et al.* Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. *Psychol. Med.* **2006**, *36*, 1441.
- [73] V. Ajdacic-Gross, C. Lauber, I. Warnke, H. Haker, R. Murray, W. Rossler. Changing incidence of psychotic disorders among the young in Zurich. *Schizophr. Res.* **2007**, *95*, 9.
- [74] S. Saha, D. Chant, J. Welham, J. McGrath. A systematic review of the prevalence of schizophrenia. *PLoS Med.* **2005**, *2*, e141.
- [75] I.I. Gottesman. Schizophrenia Genesis: The Origins of Madness. W. H. Freeman, New York, **1991**.
- [76] L. Degenhardt, W.D. Hall, M. Lynskey, C. Coffey, G. Patton. in *Marijuana and Madness*, (Eds: D. Castle, R. Murray, D. D'Souza). Cambridge University Press, New York, **2012**, pp. 114–128.
- [77] E. Manrique-Garcia, S. Zammit, C. Dalman, T. Hemmingsson, P. Allebeck. Cannabis use and depression: A longitudinal study of a national cohort of Swedish conscripts. *BMC Psychiatry* **2012**, *12*, 112. DOI: 10.1186/1471
- [78] D. Fergusson, L. Horwood. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction* **1997**, *92*, 279.
- [79] L. Horwood, D. Fergusson, C. Coffey, G. Patton, R. Tait, D. Smart *et al.* Cannabis and depression: An integrative data analysis of four Australasian cohorts. *Drug Alcohol Depend.* **2012**, *126*, 369.
- [80] H. Lai, T. Sitharthan. Exploration of the comorbidity of cannabis use disorders and mental health disorders among inpatients presenting to all hospitals in New South Wales, Australia. *Am. J. Drug Alcohol Abuse* **2012**, *38*, 567.
- [81] S. Lev-Ran, F.B. Le, K. McKenzie, T.P. George, J. Rehm. Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates. *Psychiatry Res.* **2013**, DOI:10.1016/j.psychres.2012.12.014
- [82] C. Silberberg, D. Castle, D. Koethe. *Marijuana and Madness*, (Eds: D. Castle, R. Murray, D. D'Souza). Cambridge University Press, New York, **2012**, pp. 129–136.
- [83] C. Henquet, L. Krabbendam, R. de Graaf, M. ten Have, J. van Os. Cannabis use and expression of mania in the general population. *J. Affect. Disord.* **2006**, *95*, 103.
- [84] A. Beautrais, P. Joyce, R. Mulder. Cannabis abuse and serious suicide attempts. *Addiction* **1999**, *94*, 1155.
- [85] J. van Ours, J. Williams, D. Fergusson, L. Horwood. Cannabis use and suicidal ideation. *J. Health Econ.* **2013**, *32*, 524.
- [86] G. Patton, J. Harris, M. Schwartz, G. Bowes. Adolescent suicidal behaviors: A population-based study of risk. *Psychol. Med.* **1997**, *27*, 715.
- [87] D. Rasic, S. Weerasinghe, M. Asbridge, D. Langille. Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students. *Drug Alcohol Depend.* **2013**, *129*, 49.
- [88] J. McLaren, W. Swift, P. Dillon, S. Allsop. Cannabis potency and contamination: A review of the literature. *Addiction* **2008**, *103*, 1100.
- [89] D. Slade, Z. Mehmedic, S. Chandra, M. ElSohly. *Marijuana and Madness*, (Eds: D. Castle, R. Murray, D. D'Souza). Cambridge University Press, New York, **2012**, pp. 35–52.

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