Time to acknowledge the mixed effects of cannabis on health: a summary and critical review of the NASEM 2017 report on the health effects of cannabis and cannabinoids

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Time to acknowledge the mixed effects of cannabis on health: a summary and critical review of the NASEM 2017 report on the health effects of cannabis and cannabinoids

This is a summary and critical review of the National Academies of Sciences, Engineering and Medicine (NASEM) report of the health effects of cannabis. The report stated that effects of cannabis are understudied, and research findings are mixed. It concluded that the underdeveloped evidence base poses a public health risk and rightly addressed complexities of cannabis research that need to be resolved collaboratively. We support NASEM's urgent call for research, but add that the mixed evidence base cannot be attributed solely to research limitations. Rather, we propose a need to acknowledge the heterogeneity in the effects of cannabis to advance the field.

INTRODUCTION

There is a world-wide shift in cannabis policies culminating in lifts in restrictions throughout several countries, as well as US states. This is a striking departure from the prohibitive 'drug-free world' policies proclaimed by the United Nations General Assembly Special Session (UNGASS) on the World Drug Problem in 1998 towards one based more on public health efforts. This call for a 'people-centred' approach to drug policy (via harm reduction policies) brings to bear not only empirical evidence of the therapeutic benefits of cannabis, but also an understanding of its associated health risks.

The shift in policies directly reflects a similar shift in public opinion. In the United States the number of proponents for legalization of cannabis has continued to rise, with most surveys reporting the majority of the population in favour of decriminalization (e.g. 53%) compared with 12% in 1969 [1]. This is notable, given that the role of public opinion with regard to cannabis seems bigger than with other substances. For example, legalization of medical and/or recreational use in some US states was initiated by voters. There is also a myriad of influential non-government organizations whose primary initiative is to move public opinion on cannabis. Given that the main dividing factor in whether or not to legalize cannabis is perception of harm, the burden of proof falls upon scientific research.

The increasing need for evidence-based arguments about potential harms and benefits of cannabis use paralleled a surge in empirical studies investigating the health impact of cannabis use, the majority of which are observational and focused upon negative health effects. Important milestones in cannabis research include proof for the existence of cannabis dependence, a clinically relevant cannabis withdrawal syndrome [2] and therapeutic pain-reducing effects [3]. However, compared with other substances of abuse, knowledge concerning the health impact of cannabis use is still limited. This highlights the need and timeliness for the National Academies of Sciences, Engineering and Medicine's (NASEM) review and research agenda of the health effects cannabis that was released in January, 2017.

The goal of this journal club paper is to summarize and review the NASEM's findings regarding the health effects of cannabis and draw attention to the NASEM's urgent call for research. To that end, we discuss the complexities of cannabis research that need to be resolved collaboratively and provide future directions for a world-wide research agenda.

REPORT OVERVIEW

Goal and conclusions

The NASEM aimed to provide a comprehensive review regarding the positive and negative health effects of using cannabis and cannabis-derived products and to provide recommendations for a research agenda that could progress the field rapidly [4]. Due to time constraints, the report was limited to 11 topics with high public health impact (see Table 1), and primacy was given to systematic reviews published since 2011 and research papers published after the most recent systematic review. Eventually, a total of 10 700 abstracts were considered. The quality of the primary research papers was guided by the Cochrane Quality Assessment [5] and the Newcastle–Ottawa scale [6]. Conclusions and recommendations were based subsequently on a categorized weighing of the evidence into conclusive, substantial, moderate, limited and no or insufficient.

A full summary of the NASEM report's conclusions regarding the positive and negative health effects of cannabis is shown in Table 1. The report concludes that the therapeutic effects are controversial and less studied than potential harmful effects. There is an urgent need for good-quality randomized trials; however, the number of studies investigating the beneficial effects of cannabis use for various health outcomes is growing steadily. Regarding harmful effects, evidence is mainly limited and most studies suffer from poor control over confounding factors and reliance on self-reported cannabis use.

Table 1 Cannabis use-related health effects: conclusions of the National Academies of Sciences, Engineering and Medicine's (NASEM) report compared with the World Health Organization (WHO) report.

NASEM health outcome	*NASEM conclusions*	*WHO conclusion*
Therapeutic effects		
Chemotherapy-induced nausea and vomiting	Conclusive evidence for anti-emetic effect, but no good-quality randomized trials	–
Chronic pain	Substantial evidence for modest pain reducing effect	–
Multiple sclerosis	Substantial evidence for moderate reduction of self-reported spasms; limited evidence for effect on clinician-measured spasms; limited evidence for reduction depressive symptoms	–
Sleep problems	Moderate evidence for improvement of short-term sleep outcomes	–
Weight gain and loss	Limited evidence for increasing appetite and decreasing weight loss in HIV; no or insufficient evidence to support or refute treatment effects in anorexia	–
Tourette; social anxiety disorder; post-traumatic stress disorder	Limited evidence for symptom reduction	–
Dementia; glaucoma	Limited evidence that cannabinoids are ineffective	–
Cancer; irritable bowel syndrome; epilepsy; spasticity after paralysis; amyotrophic lateral sclerosis; Huntington's disease; Parkinson; dystonia; addiction; schizophrenia	No or insufficient evidence to support or refute treatment effects	–
Cancer		
Non-seminoma-type testicular germ cell tumours	Limited evidence for increased risk in cannabis users	Suggestive evidence for increased risk in cannabis smokers
Lung cancer; Head and neck cancers	Moderate evidence for no association	Smoking mix of cannabis and tobacco may increase cancer risks; effect of cannabis alone is unknown
Acute leukaemia; rhabdo-myosarcoma; astrocytoma; neuro-blastoma in offspring	No or insufficient evidence to support or refute associations	
Other cancers	No or insufficient evidence to support or refute associations	
Cardiometabolic risk		
Ischaemic stroke; subarachnoid haemorrhage; pre-diabetes; acute myocardial infarction	Plausible theoretical link for triggering coronary events; limited evidence for a higher risk of suffering	Some evidence for intoxication triggered coronary events; long-term heavy use potentially triggers myocardial infarctions and strokes in young users
Diabetes; metabolic syndrome	Limited evidence for decreased risk of diabetes and metabolic syndrome; findings are counterintuitive, as THC tends to stimulate appetite, promote fat deposition, and promote adipogenesis	–
Respiratory disease		
bronchitis; respiratory symptoms	Substantial evidence for increased incidences and symptom severity in long-term cannabis users; moderate	Long-term cannabis smoking causes symptoms of bronchitis and microscopic injury to bronchial lining cells

(***Continues***)

Table 1. (Continued)

NASEM health outcome	*NASEM conclusions*	*WHO conclusion*
	evidence for improvements in respiratory symptoms after cessation of use	
Pulmonary function	Moderate evidence that acute, but not chronic use, results in bronchodilatation; moderate evidence for higher long volume, but clinical significance is unclear; poor control for tobacco smoking effects	Some studies report higher long function in cannabis smokers
Chronic obstructive pulmonary disease (COPD)	Limited evidence for increased risk in occasional cannabis smokers, controlled for tobacco smoking; insufficient evidence to support or refute associations with COPD severity	No associations
Asthma	No or insufficient evidence to support or refute associations	–
Immunity		
Immune competence; human immunodeficiency virus (HIV); oral human papilloma virus (HPV)	Animal models and cell cultures support immunosuppressive properties of cannabinoids but insufficient evidence to support or refute effects in healthy humans and humans with HIV and HPV; limited evidence for a decrease in production of several inflammatory cytokines in healthy individuals	–
Viral hepatitis C (VHC)	Limited evidence for no association	–
Injury and death		
Motor vehicle crashes	Substantial evidence for an increased risk	Acute use increases risk of traffic injuries
Cannabis overdose	Moderate evidence for a positive association of increased risk of overdose injuries; insufficient evidence to support or refute a death due to cannabis overdose	–
All-cause mortality; Occupational accidents	Insufficient evidence to support or refute associations	–
Prenatal, perinatal and neonatal exposure		
Maternal cannabis smoking	Substantial evidence for positive association with lower birth weight; limited evidence for association with pregnancy complications; insufficient evidence for negative association with later outcomes in offspring; attribution of outcomes to cannabis exposure is generally problematic	Understudied topic, but offspring demonstrate impaired attention, learning and memory, impulsivity and behavioural problems and a higher likelihood of using cannabis when they mature
Psychosocial		
Cognitive domains of learning, memory and attention	Moderate evidence association cannabis intoxication and impaired functioning; limited evidence for impairments after sustained abstinence	Cannabis intoxication is associated with impaired functioning

(***Continues***)

Table 1. (Continued)

NASEM health outcome	*NASEM conclusions*	*WHO conclusion*
Academic achievement; unemployment and/or low income; social functioning	Limited evidence for a negative association	Daily use in adolescence and young adulthood is associated with early school-leaving
Mental health and substance use		
Cannabis use disorder (CUD)	Substantial evidence that being a male tobacco smoker, frequency of use and early onset of use are risk factors, ADHD stimulant treatment is not a risk factor and CUD severity is higher in males; moderate evidence that depression, being male and polydrug use (but neither alcohol nor nicotine dependence alone) are risk factors; ADHD, anxiety, personality disorders, and bipolar disorders are not risk factors and persistence of CUD is associated with history of psychiatric treatment; limited evidence that childhood anxiety and depression are risk factors; risk factors differ with age: moderate evidence that during adolescence frequency of use, onset of alcohol and nicotine use, oppositional behaviours, parental substance use, poor school performance, antisocial behaviours and childhood sexual abuse are risk factors	The risk to develop a CUD may be 10% in ever users, 17% in adolescent users and 30% in daily users; growing evidence that adolescent heavy cannabis use is associated with more severe outcomes
Other substance use and substance use disorders (SUDs)	Moderate evidence for an association with development of other SUDs (alcohol, tobacco, and other illicit drugs); limited evidence for a higher risk of initiation of tobacco use and higher levels of other illicit substance use	Daily use in adolescence and young adulthood is associated with increased risk of using other illicit drugs
Schizophrenia, psychosis	Substantial evidence for increased dose-dependent risk; a history of cannabis use may be linked to better cognitive performance in individuals with a psychotic disorder; limited evidence of increased positive symptoms; moderate evidence of no worsening of negative symptoms	Consistent evidence for increased risk, depending on dose, duration and onset age of cannabis use; cannabis use may trigger earlier onset and exacerbated course of the illness
Bipolar disorder	Moderate evidence for that regular user increases symptom severity; limited evidence for increased risk	Existing studies are confounded
Depression	Moderate evidence for small increase in risk; no evidence to support or refute an association with the course of depression	Regular cannabis use during adolescence is associated with increased risk of depressive symptoms
Suicide (ideation, attempts, and completion)	Moderate evidence for increased incidence of ideation and attempts, with higher incidences among heavier users	Daily use in adolescence and young adulthood is associated with increased rates of suicidal ideation
Anxiety	Moderate evidence for increased incidence of social anxiety disorder in regular cannabis users; limited evidence for increased risk to develop any other type of anxiety disorder; limited evidence for increased symptoms severity in near daily users	Comorbidity is evident but not understood

(***Continues***)

Table 1. (Continued)

NASEM health outcome	*NASEM conclusions*	*WHO conclusion*
Post-traumatic stress disorder (PTSD)	No evidence to support or refute that cannabis use increased risk; moderate evidence for an association between CUD and PTSD; limited evidence for increased symptom severity among individuals with PTSD	–

The NASEM report also provided a detailed research agenda, with the main recommendation of improving the quality of cannabis research substantially through (1) increased funds for cannabis research, (2) standardization of terminology, methods and materials, (3) improvement of health surveillance systems and (4) loosening of regulatory barriers on cannabis research to create the necessary resources and infrastructure to conduct high-quality cannabis research. The suggested knowledge gaps that should be prioritized included: (1) effects of cannabis in at risk groups, such as children, pregnant women, seniors, heavy cannabis users; (2) pharmacokinetic and pharmacodynamic properties of different cannabis products; (3) health effects of understudied cannabis products, including edibles, concentrates and topicals; (4) randomized controlled trials using different forms of cannabis; (5) unstudied or understudied health outcomes (see Table 1); and (6) the economic impact of recreational and medical cannabis use on national and state public health and health-care systems, health insurance providers and patients. Moreover, to improve public safety, (1) gaps in cannabis-related knowledge and skills of health-care and public health professionals need to be addressed and (2) quality assurance, safety and packaging standards for recreational cannabis need to be evaluated.

Strengths and limitations of scope and procedure

These conclusions and research agenda should be considered in light of some important strengths and limitations of the scope and review procedure. The NASEM report appeared shortly after publication of the World Health Organization (WHO) report on the health and social effects of non-medical cannabis use [7]. Scope and conclusions of both reports largely overlap (see Table 1 for a comparison of the WHO and NASEM conclusions for each of the health topics included in the NASEM report); however, clear strengths of the NASEM report include the systematic assessment of the strength of the scientific evidence, discussion of both positive and negative health effects, inclusion of a research agenda and the discussed nuances in terms of modality, including edible products. As such, the NASEM conclusions appear more systematic and slightly more nuanced.

A clear limitation of the NASEM report is the arbitrary cut-offs that were made to narrow down the literature search to studies that would probably produce the clearest research conclusions [e.g. systematic reviews, studies with a sample size of $>$ 500 participants (p. 284)]. Although the NASEM report acknowledges this limitation (p. 276), it may underestimate evidence strength for some of the discussed health outcomes. Moreover, cognitive effects were poorly covered, discussing only behavioural effects on learning, memory and attention but not on cognitive functions that are linked strongly to risk-taking behaviour and addiction, such as inhibition, affective processing and decision-making [8,9]. Regarding the effects of acute cannabis intoxication, the existing literature indicates that there is moderate evidence for impaired inhibition and mixed evidence for impaired decision-making and heightened reward processing [10,11]. Regarding long-term effects, there is mixed evidence for impaired inhibition, impaired decision-making and heightened reward processing [10,11]. Neuroimaging studies in chronic cannabis users generally support these findings; structural and functional alterations are reported most consistently in limbic reward and memory-related areas (e.g. hippocampus, amygdala, striatum) and prefrontal brain areas; however, effects are mixed and age of onset, gender, psychopathology and cumulative cannabis exposure appear to play an important role in this [11,12].

Animal and human experimental studies were omitted from the review. The pharmacokinetics, direct (neuro) physiological effects and long-term health effects of cannabis are complex, depending on the individual, mode of administration and ratio between different cannabinoids. The NASEM report recognized this, therefore inclusion of the clinical and preclinical experimental literature could have shed light on these issues. For example, even though human research is still in its infancy, experimental studies indicate preliminary evidence that cannabidiol may protect against the negative effects of delta-9-tetrahydrocannabinol (Δ9-THC) on cognition [13], psychotic symptoms [14] and anxiety [15]. Interestingly, a recent within-subject placebo-controlled study in human adolescents and adults showed preliminary evidence for both adolescent resilience (blunted subjective, memory, physiological and

psychotomimetic effects) and vulnerability (lack of satiety and impaired inhibition) to the direct effect of cannabis (12% THC, < 1% cannabidiol) [16]. Moreover, a study investigating psychophysical effects in frequent and occasional cannabis users following placebo, smoked, vaporized and oral THC administration showed preliminary evidence for an interaction between use history and route of administration, such that impairments were more prolonged following an oral dose, specifically in occasional cannabis users [17]. Although methodologically and ethically challenging, an advantage of such experimental studies is that they allow for assessment of causal effects.

Finally, the report covered the role of biological sex and culture sparsely. A recent review concluded that there are evident but inconsistent differences between male and female cannabis users regarding brain structure, reward processing, attention, motor coordination and sensitivity to withdrawal [18]. Cannabis culture (i.e. an environment that facilitates a systematic set of cannabis-related behaviours during an extended period of time) may impact upon cannabis-related health effects [19,20]. Cross-cultural studies are largely missing; however, social factors and willingness to acknowledge cannabis use disorder (CUD) symptoms have been found to differ between legal cultures [21]. Given the world-wide changes in cannabis policy and high treatment demands, knowledge regarding the differences and similarities in cannabis-related health effects throughout different cannabis cultures may have important implications for policy, prevention and treatment. Moreover, an additional advantage of cross-cultural studies is the possibility to replicate study effects directly in independent samples.

AN URGENT CALL FOR CHANGE IN CANNABIS RESEARCH

More than 10 000 published papers led to largely inconclusive results regarding the health effects of cannabis. Despite the limitations discussed above, the NASEM report provided a comprehensive overview of the current state of evidence. We doubt if a more extensive literature review with more detailed health outcomes and experimental literature would have resulted in different conclusions. The lack of evidence-based information poses a public health risk, and we agree with the NASEM's urgent call to address the major research gaps listed above to facilitate access to research-graded cannabis products and to improve the quality of cannabis research through harmonization of terminology, methods and materials. Below, we discuss the complexities of cannabis research and provide suggestions for future studies and a world-wide research agenda.

Complexities of cannabis research that need to be resolved collaboratively

The report rightly addressed some important complexities of cannabis research. These complexities contribute strongly to the mixed findings and the need to be resolved collaboratively to progress the field. First, there is as yet no consensus on terminology. A quick glance of the literature indicated that 'heavy cannabis use' has been defined as having more than 40 occasions of use in a life-time [22] as well as having multiple occasions of use per day [23], whereas 'recreational use' has been defined as more than 20 life-time occasions of use [24], using monthly [25] and using more than weekly [26]. Moreover, as shown by multiple systematic reviews (e.g. [27,28]), many epidemiological studies grouped light and heavy users into an 'ever' user category. As such, researcher-estimated level of harm biases the research design and terminology, thereby limiting the informativeness and comparability of individual studies. To help solve these issues, future studies should use more objective terminology (e.g. monthly, weekly, daily or dependent user instead of recreational, light, heavy and chronic user) and provide clear sample characteristics regarding history of use and problem severity using consensus measures when possible (e.g. https://www.phenxtoolkit.org/).

A second limitation is the difficulty in measuring cannabis exposure objectively. Most studies rely fully upon self-reports, including variable assessment methods. Reliance upon self-reports is considered a primary limitation of many studies; however, the use of self-reports in cannabis research may be especially problematic. Differences in social acceptance throughout users and countries, inconsistent terminology and large variability in chemical composition of cannabis and related products impact upon the reliability and comparability of self-reports. Conversely, standardized units of use exist in other substances such as alcohol and tobacco, thus findings regarding health effects in these substances are more clear. Complicating cannabis research even further, existing objective measures of cannabis use are limited to recent use; (sub)acute cannabis exposure can be measured from urine, oral fluids and blood [29], whereas hair analysis can be used as a qualitative indicator of near-daily cannabis use within the past 3 months [30]. Of note, mental health outcomes, including diagnostic criteria, are subjective and all substantial evidence regarding some of the discussed health outcomes (see Table 1) are based largely upon consistent research results with self-reports. Although the use of self-reports does not necessarily compromise research quality, given the fact that subjective measures are highly variable and there is only moderate consistency between objective and subjective cannabis

use measures [31,32], researchers should include multiple assessment methods and invest in the cross-validation and harmonization of these methods.

A third limitation general to substance use research concerns polysubstance use, pre-existing vulnerability factors and comorbid mental problems. Cannabis users often differ in many more aspects from a control population. Approximately 70% of cannabis users also smoke tobacco, and cannabis is often combined with tobacco in cannabis cigarettes [33]. Controlling statistically for tobacco use can potentially remove valuable variance associated with cannabis use, raising the question of how to balance specificity with generalizability. The same problem holds for the high co-occurrence of cannabis use with attention deficit hyperactivity disorder (ADHD), depression and anxiety [34], therefore attributing a certain health outcome to cannabis use proves to be difficult. One approach that researchers could consider is including control groups with specific comorbidities to allow the investigation of common and unique health effects [35]. Longitudinal studies could also help in unravelling causal and consequential effects. Given the high costs and protracted results of such studies, investment in the longitudinal extension of existing studies may prove to be a fruitful avenue to progress the field rapidly.

A final limitation posing a large problem in the United States is the limited access to good-quality cannabis and cannabis products for cannabis administration research. Due to federal regulation barriers (classification of cannabis as a schedule I substance, with the highest level of restriction), research-graded cannabis production is currently restricted to the University of Mississippi. As such, researchers have problems obtaining the right quantity, potency and product type to address current public health issues [4]. Access to clinically relevant products that reflect current cannabis markets will remain a challenge in countries where use and production are not fully legal and regulated. However, the increasing knowledge and acceptance of potential therapeutic effects may boost the production of medically approved cannabis and cannabis-derived products available to patients and researchers in the near future.

A world-wide research agenda: embracing the mixed effects of cannabis

The NASEM's comprehensive US research agenda translates largely to other nations. However, we would like to stress the need to investigate therapeutic effects systematically and study differential effects of different cannabinoids (THC versus cannabidiol), different cannabis products and different modes of administration. Moreover, we need to know more about the health effects of more finely grained patterns of heavy cannabis use, including differentiation between individuals with and without a CUD, while acknowledging the contribution of comorbid mental health problems. In line with this, we need to develop more reliable subjective and objective assessments of cannabis use. Thirdly, we need to cross geographical boundaries and perform cross-cultural comparisons to study cross-cultural similarities and differences in cannabis-related health effects. This is obviously missing from national reports, but relevant given the recent changes in cannabis policy throughout different states and countries and the potential health impact this could have.

According to the NASEM, existing mixed findings are the result of poor research quality and offer insufficient evidence for either positive or negative health effects; but are we really that bad in conducting cannabis research? The lack of randomized controlled trials, inconsistent terminology and the abundance of observational studies that rely upon self-reports pose a major problem. However, as discussed above, research quality is compromised by inconsistencies in, and poor reliability of, self-report measures, rather than the use of self-reports *per se*. Moreover, high-quality randomized controlled trials and experimental studies have also shown mixed findings, depending, among others, on age, sex, route of administration, pre-existing risk factors and cannabis history (e.g. [3,10,11,16,17,28]. Although the evidence base is underdeveloped for many health outcomes, judging from Table 1, we believe there is already substantial evidence that cannabis can have both positive (e.g. reducing pain, multiple sclerosis symptoms, nausea) and negative (e.g. aggravation of existing respiratory problems, psychosis, motor vehicle accidents, low birth weight, cannabis dependence) effects. The mixed effects of cannabis may therefore contribute significantly to the mixed evidence. The conclusion that cannabis can have both positive and negative effects has been drawn numerous times since the 1980s (e.g. [36–39]). However, after decades of cannabis research, the cannabis debate between good or bad is still ongoing, hindering scientific progress and evidence-based guidance of public health and policy. To further the field, we need to acknowledge the hypothesis of mixed effects on the level of the individual. Beneficial and harmful effects of cannabis may differ between and within individuals, and the existence of positive health effects do not make the harmful effects less severe and vice versa. Given the list of potential harms and benefits, these two aspects of cannabis clearly coexist. Therefore, a shift is called for that goes beyond questions of harms and benefits to that of questions of for whom/what it is harmful and beneficial. Close collaboration between researchers, health care and government is therefore warranted.

Declaration of interests

None.

Keywords Cannabidiol, cannabis, general health, mental health, tetrahydrocannabinol, therapeutic effects.

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References

1. Doherty C., Alec T., Weisel R. *In Debate Over Legalizing Marijuana, Disagreement Over Drug's Dangers*. Washington, DC: Pew Research Center; 2015. Available at: http://www.people-press.org/2015/04/14/in-debate-over-legalizing-marijuana-disagreement-over-drugs-dangers/ (accessed 15 November 2017) (Archived at http://www.webcitation.org/6uzLpst6Y on 15 November 2017).
2. Budney A. J., Hughes J. R. The cannabis withdrawal syndrome. *Curr Opin Psychiatry* 2006; **19**: 233–8.
3. Whiting P. F., Wolff R. F., Deshpande S., Di Nisio M., Duffy S., Hernandez A. V. *et al*. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015; **313**: 2456–73.
4. National Academies of Sciences Engeneering and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: National Academies Press; 2017.
5. Higgins J. P., Altman D. G., Gotzsche P. C., Juni P., Moher D., Oxman A. D. *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
6. Wells G. A., Shea B., O'Connell D., Peterson J., Welch V., Losos M., Tugwell P. The Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 4 December 2017) (Archived at http://www.webcitation.org/6vSZMTm1K on 4 December 2017).
7. World Health Organization (WHO). In: Hall W., Renström M., Poznyak V., editors. *The Health and Social Effects of Nonmedical Cannabis Use*. Geneva: WHO Press; 2016.
8. Fernandez-Serrano M. J., Perez-Garcia M., Verdejo-Garcia A. What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? *Neurosci Biobehav Rev* 2011; **35**: 377–406.
9. Van Duijvenvoorde A. C. K., Peters S., Braams B. R., Crone E. A. What motivates adolescents? Neural responses to rewards and their influence on adolescents' risk taking, learning, and cognitive control. *Neurosci Biobehav Rev* 2016; **70**: 135–47.
10. Broyd S. J., Van Hell H. H., Beale C., Yücel M., Solowij N. Acute and chronic effects of cannabinoids on human cognition—a systematic review. *Biol Psychol* 2016; **79**: 557–67.
11. Batalla A., Bhattacharyya S., Yucel M., Fusar-Poli P., Crippa J. A., Nogue S. *et al*. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. *PLOS ONE* 2013; **8**: e55821.
12. Lorenzetti V., Batalla A., Cousijn J. Cannabis use disorders and altered brain morphology: where is the evidence? *Curr Addict Rep* 2016; **3**: 189–98.
13. Colizzi M., Bhattacharyya S. Does cannabis composition matter? Differential effects of delta-9-tetrahydrocannabinol and cannabidiol on human cognition. *Curr Addict Rep* 2017; **4**: 1–13.
14. Bhattacharyya S., Morrison P. D., Fusar-Poli P., Martin-Santos R., Borgwardt S., Winton-Brown T. *et al*. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* 2010; **35**: 764–74.
15. Zuardi A. W., Shirakawa I., Finkelfarb E., Karniol I. G. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)* 1982; **76**: 245–50.
16. Mokrysz C., Freeman T. P., Korkki S., Griffiths K., Curran H. V. Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males. *Transl Psychiatry* 2016; **6**: e961.
17. Newmeyer M. N., Swortwood M. J., Taylor M. E., Abulseoud O. A., Woodward T. H., Huestis M. A. Evaluation of divided attention psychophysical task performance and effects on pupil sizes following smoked, vaporized and oral cannabis administration. *J Appl Toxicol* 2017; **37**: 922–32.
18. Ketcherside A., Baine J., Filbey F. Sex effects of marijuana on brain structure and function. *Curr Addict Rep* 2016; **3**: 323–31.
19. Prashad S., Milligan A. L., Cousijn J., Filbey F. M. Cross-cultural effects of cannabis use disorder: evidence to support a cultural neuroscience approach. *Curr Addict Rep* 2017; **4**: 1–10.
20. Holm S., Sandberg S., Kolind T., Hesse M. The importance of cannabis culture. *J Subst Use* 2012; **19**: 251–6.
21. Delforterie M., Creemers H., Agrawal A., Lynskey M., Jak S., Van der Ende J. *et al*. Functioning of cannabis abuse and dependence criteria across two different countries: the United States and The Netherlands. *Subst Use Misuse* 2015; **50**: 242–50.
22. Miller P., Plant M. Heavy cannabis use among UK teenagers: an exploration. *Drug Alcohol Depend* 2002; **65**: 235–42.
23. Yucel M., Solowij N., Respondek C., Whittle S., Fornito A., Pantelis C. *et al*. Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* 2008; **65**: 694–701.
24. Stokes P. R., Mehta M. A., Curran H. V., Breen G., Grasby P. M. Can recreational doses of THC produce significant dopamine release in the human striatum? *Neuroimage* 2009; **48**: 186–90.
25. Moreno M., Estevez A. F., Zaldivar F., Montes J. M. G., Gutiérrez-Ferre V. E., Esteban L. *et al*. Impulsivity differences in recreational cannabis users and binge drinkers in a university population. *Drug Alcohol Depend* 2012; **124**: 355–62.
26. Gilman J. M., Kuster J. K., Lee S., Lee M. J., Kim B. W., Makris N. *et al*. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *J Neurosci* 2014; **34**: 5529–38.
27. Humphreys K. L., Eng T., Lee S. S. Stimulant medication and substance use outcomes: a meta-analysis. *JAMA Psychiatry* 2013; **70**: 740–9.

28. Moore T. H. M., Zammit S., Lingford-Hughes A., Barnes T. R. E., Jones P. B., Burke M. *et al.* Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007; **370**: 319–28.
29. Odell M. S., Frei M. Y., Gerostamoulos D., Chu M., Lubman D. I. Residual cannabis levels in blood, urine and oral fluid following heavy cannabis use. *Forensic Sci Int* 2015; **249**: 173–80.
30. Taylor M., Lees R., Henderson G., Lingford-Hughes A., Macleod J., Sullivan J. *et al.* Comparison of cannabinoids in hair with self-reported cannabis consumption in heavy, light and non-cannabis users. *Drug Alcohol Rev* 2017; **36**: 220–6.
31. Buchan B. J., Dennis M. L., Tims F. M., Diamond G. S. Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. *Addiction* 2002; **97**: 98–108.
32. van der Pol P., Liebregts N., De Graaf R., Korf D. J., van den Brink W., van Laar M. Validation of self-reported cannabis dose and potency: an ecological study. *Addiction* 2013; **108**: 1801–8.
33. Subramaniam P., McGlade E., Yurgelun-Todd D. Comorbid cannabis and tobacco use in adolescents and adults. *Curr Addict Rep* 2016; **3**: 182–8.
34. Van der Pol P., Liebregts N., De Graaf R., Ten Have M., Korf D. J., Van den Brink W. *et al.* Mental health differences between frequent cannabis users with and without dependence and the general population. *Addiction* 2013; **108**: 1459–69.
35. Cousijn J. Embracing comorbidity: a way toward understanding the role of motivational and control processes in cannabis use disorders. *Front Psychol* 2015; **6**: 677.
36. Hall W., Solowij N., Lemon J. *The Health and Psychological Consequences of Cannabis Use*. Canberra: Australian Government Publishing Service; 1994.
37. Benson J. A., Watson S. J., Joy J. E., Institute of Medicine *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999.
38. Strang J., Witton J., Hall W. Improving the quality of the cannabis debate: defining the different domains. *BMJ* 2000; **320**: 108–10.
39. Hollister L. E. Health aspects of cannabis. *Pharmacol Rev* 1986; **38**: 1–20.