The health and social effects of non-medical use of cannabis

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Declaration of Conflict of Interest and Acknowledgments

- COI: None

WHO reports on the Health & Social Effects of Cannabis Use

- 1995 – WHO Expert Meeting on Cannabis
- 1997 – Cannabis: a health perspective and research agenda (WHO Programme on Substance Abuse, WHO, 1997)
  - Review and synthesis of the best available evidence on impact of cannabis use and cannabis use disorders on health
  - Address health system responses to cannabis use disorders and associated disorders
  - Identification of priorities for international research.
The health and social effects of nonmedical cannabis use

- Responding to the need for objective and reliable information on health consequences of cannabis use
- Based on the proceedings of the WHO meeting held in 2015
- Does not cover medical use of cannabis and cannabinoids
- Does not cover the issues related to medical use of cannabis, apart from a discussion on the use of CB receptors agonists for management of disorders due to cannabis use (limited to dronabinol, nabiximols, cannabidiol)
- Published in early spring 2016.
Cannabis Plant Profile

- Cannabis preparations are obtained from the female cannabis sativa plant which contains more than 100 cannabinoids.
- $\Delta^9$-THC is the primary active constituent in cannabis being a partial agonist of CB$_1$ receptors.
- The most common preparations are marijuana, hashish, and hash oil.
- Cannabis potency appears to be increasing in a number of jurisdictions around the world:
  - Mode of administration can affect potency and subsequent effects.
  - Use with/without tobacco, concentrated forms such as hash or oils.
  - Use behaviours may be changing with rise of e-cigarette technologies.

Figure 1: Mean potencies (% THC) of imported cannabis resin in Europe (1997–2003) showing the variation between different laboratories/countries. (UK = United Kingdom, NL = Netherlands, D = Germany, CZ = Czech Republic, P = Portugal, A = Austria.)

Source: EMCDDA, 2004
Neurobiology of Cannabinoids: the Endocannabinoid System

- THC and other cannabinoids interact with receptors in the brain that respond to naturally occurring (endogenous) cannabinoids or "endocannabinoids"

- The **endocannabinoid system** is of major physiological importance in regulating the actions of other neurotransmitters implicated in cognition, emotion, and memory.
  - G protein coupled cannabinoid CB₁ and CB₂ receptors,
  - Endogenous compounds known as endocannabinoids that can target these receptors,
  - Enzymes involved in endocannabinoid biosynthesis and metabolism,
  - Processes responsible for cellular endocannabinoid uptake.
CB₁ and CB₂ Receptors

- CB receptors are mostly concentrated within the central nervous system, however, they are also found sparsely in peripheral areas of the body.

- Certain regions of the brain have greater densities of CB₁ and CB₂ receptors.

- CB₁ receptors are primarily found in greater numbers in neural regions involved in memory, cognition, motivation, and motor control.

- CB₂ receptors are primarily found in the body where they seem to play a role in the regulation of the immune system.
Cannabis is the most commonly used psychoactive substance in the world; globally, 181.8M individuals aged 15 to 64 years reported using cannabis in 2013.1

Lifetime prevalence of cannabis use varies considerably
- Use appears to be more common in developed than developing countries

Prevalence of cannabis use among young people in Europe estimated to range between 1.0% to 45.1% (among adolescents and young adults aged 15 to 34)
- Weighted European average of lifetime prevalence of cannabis use: 32.2%.
- 15.4 M (11%) young Europeans have used cannabis in the past 12 months.
Effects on Health

- Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. ²

- Short-term effects on health are those that arise during or shortly after a single occasion of use – depend on the dose, mode of administration, "set and setting"
  - Cannabis intoxication as a common short-term effect on health status

- Long-term effects on health are those that arise from regular cannabis use – especially daily use – over periods of months, years or decades
  - Contributory cause of a number of disorders and health conditions, including cannabis dependence.

- A major challenge exists in establishing causality in associations
  - Need to exclude reverse causation and address confounding variables
  - Biological plausibility, dose-response relationship, specificity and reversibility of association.

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Cannabis Intoxication

- Risk of a fatal cannabis overdose is extremely small relative to opioids and stimulant drug overdoses

- Cannabis users typically smoke dried herb and take deep inhalations holding the smoke in their lungs as long as they can
  - Effects are felt nearly immediately, peak absorption occurs within 9-30 minutes following the start of the episode of use

- Tachycardia is one of the most reliable signs of cannabis intoxication
  - CB₁ and CB₂ are both found in the cardiovascular system

- Adverse effects of cannabis use: panic attacks, paranoia, slowed reaction time, sleep disruption, cannabis-induced psychoses.
Signs and symptoms of cannabis intoxication (ICD-10)

(1) euphoria and disinhibition;
(2) anxiety or agitation;
(3) suspiciousness or paranoid ideation;
(4) temporal slowing (a sense that time is passing very slowly, and/or the person is experiencing a rapid flow of ideas);
(5) impaired judgement;
(6) impaired attention;
(7) impaired reaction time;
(8) auditory, visual, or tactile illusions;
(9) hallucinations with preserved orientation;
(10) depersonalization;
(11) derealization;
(12) interference with personal functioning.
Cannabis Effects on Cognitive Functions

- Long term use of cannabis down-regulates CB₁ receptors in neural regions associated with memory and cognition. THC exposure during puberty amplifies this effect.

- SPECT scan analyses find large decreases in perfusion in comparative studies among long-term cannabis users and non-using controls; these studies also find poorer cognitive performance among long-term users.

- Adults who have smoked cannabis since adolescence have less neuronal connectivity in prefrontal areas that are responsible for executive functioning and inhibitory control in subcortical networks responsible for habits and routines.

- For frequent users, neurocognitive effects can last over 7 days and possibly up to 30 days.

Acute cannabis exposure increases heart rate and blood pressure and can cause orthostatic hypotension.

Cannabis smoking produces acute bronchial dilatation.

Tobacco smoking produces acute bronchial constriction.

Bronchial effects differ around the world depending on the mode of administration.
Cardiovascular Diseases

- Limited studies exist regarding cannabis users and CVD
- Recent case reports suggest that cannabis smoking may increase CVD risk in younger cannabis smokers. Otherwise - low risk of CVD
- Case studies have found associations between cannabis smoking and cerebellar ischemic stroke
  - Cannabis-associated strokes usually occur in chronic or current cannabis users who smoke tobacco
- Reports of cannabis-related myocardial infarctions
- Cannabis smoking may increase CVD risk by increasing carboxyhaemoglobin levels.

Chronic Obstructive Pulmonary Disease

- Studies have **not found an increased risk** of COPD in cannabis-only smokers

- **No impairments in respiratory function** were observed in available longitudinal studies of lung function in regular cannabis smokers

- Though the rate of decline is much slower than in tobacco smokers, cannabis smokers **do lose lung function** more quickly than non-smokers

- Reduced alveolar macrophage activity.
Cancers

- Cannabis smoke is carcinogenic in microbial assays; THC and other cannabinoids *per se* are not carcinogenic

- Upper aerodigestive cancers
  - Pooled analyses have **not found an association** for head and neck cancers

- Respiratory cancers
  - Pooled analyses have **not found an association** between cannabis smoking and lung cancer

- Testicular cancer
  - Cannabinoid receptors are found in the male reproductive system; **an increased risk (OR=1.5)** for high frequency cannabis users as well as those smoking for a decade or more.
### Characteristics of patients in CANABIC trial in primary care in France (Laporte et al, 2017)

<table>
<thead>
<tr>
<th></th>
<th>Employment status, No. (%)</th>
<th>Psychotropic medication use, No. (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Cannabis use</th>
<th>Alcohol use</th>
<th>Tobacco use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Working</td>
<td>82 (58.2)</td>
<td>65 (53.7)</td>
<td>204 (77.9)</td>
<td>240 (91.6)</td>
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<td>No occupation</td>
<td>5 (3.6)</td>
<td>2 (1.7)</td>
<td>110 (78.0)</td>
<td>124 (87.9)</td>
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<tr>
<td></td>
<td>Student</td>
<td>54 (38.3)</td>
<td>54 (44.6)</td>
<td>94 (77.7)</td>
<td>116 (95.7)</td>
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<td></td>
<td>Psychotropic medication use</td>
<td>10 (3.8)</td>
<td>4 (3.3)</td>
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<tr>
<td></td>
<td>Joints per mo, median (IQR)</td>
<td>20 (6-60)</td>
<td>30 (6-80)</td>
<td>20 (5-40)</td>
<td>20 (5-40)</td>
</tr>
<tr>
<td></td>
<td>≥30 joints per mo, No. (%)</td>
<td>121 (46.2)</td>
<td>73 (51.8)</td>
<td>48 (39.7)</td>
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<tr>
<td></td>
<td>Use bongs, No. (%)</td>
<td>39 (14.9)</td>
<td>27 (19.2)</td>
<td>12 (9.9)</td>
<td></td>
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<tr>
<td></td>
<td>Age at first use, mean (SD), y</td>
<td>15.15 (1.9)</td>
<td>15.24 (2.1)</td>
<td>15.04 (1.6)</td>
<td></td>
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<tr>
<td></td>
<td>Alcohol use</td>
<td></td>
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<tr>
<td></td>
<td>Used in past month, No. (%)</td>
<td>204 (77.9)</td>
<td>110 (78.0)</td>
<td>94 (77.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quantity: glasses/wk, median (IQR)</td>
<td>6 (2-10)</td>
<td>5 (2-10)</td>
<td>7.5 (3-14)</td>
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<tr>
<td></td>
<td>Tobacco use</td>
<td></td>
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<tr>
<td></td>
<td>Used in past month, No. (%)</td>
<td>240 (91.6)</td>
<td>124 (87.9)</td>
<td>116 (95.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quantity: cigarettes/wk, median (IQR)</td>
<td>60 (30-82)</td>
<td>60 (35-100)</td>
<td>60 (28-78)</td>
<td></td>
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<tr>
<td></td>
<td>Experimented with other drugs, No. (%)</td>
<td>111 (42.4)</td>
<td>59 (41.8)</td>
<td>52 (43.0)</td>
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</table>
Cannabis users who drive while intoxicated double their risk of a motor vehicle accident

- A causal relationship has been established between cannabis use and traffic injuries

There appears to exist a dose-response relationship between blood THC and culpability in road accidents

Mixed epidemiological study findings exist on cannabis consumption and general injury risk

At present, there is not enough evidence to determine whether acute cannabis use influences the risk of suicidal behaviour
Cannabis Use and Adolescent Health

- Regular cannabis users who initiate cannabis use in adolescence
  - may have lower educational attainment than their non-using peers
  - are more likely to use other illicit drugs
  - appear to experience cognitive impairment and reversibility is unclear
  - adopt a pattern of use that predicts an increased risk of developing dependence and poor psychosocial and mental health outcomes

- Associations persist after controlling for plausible confounders
  - Shared risk factors and reverse causation are still alternative explanations for these associations.
Findings: We recorded clear and consistent associations and dose-response relations between the frequency of adolescent cannabis use and all adverse young adult outcomes. After covariate adjustment, compared with individuals who had never used cannabis, those who were daily users before age 17 years had clear reductions in the odds of high-school completion (adjusted odds ratio 0.37, 95% CI 0.20—0.66) and degree attainment (0.38, 0.22—0.66), and substantially increased odds of later cannabis dependence (17.95, 9.44—34.12), use of other illicit drugs (7.80, 4.46—13.63), and suicide attempt (6.83, 2.04—22.90).
Prenatal cannabis exposure

- Polydrug use is common among pregnant women using psychoactive drugs.
- Prenatal exposure to THC can alter regulation of the mesolimbic dopamine system in children and make the brain's reward system more sensitive to the effects of other drugs.
- Prenatal cannabis exposure is associated with lower birth weight in offspring of mothers smoking cannabis.
- Children exposed to cannabis in utero have higher rates of neurobehavioural and cognitive impairments and demonstrate impaired attention, learning and memory, impulsivity and behavioural problems and a higher likelihood of using cannabis when they mature.
The Global Epidemiology and Contribution of Cannabis Use and Dependence to the Global Burden of Disease: Results from the GBD 2010 Study

Louisa Degenhardt1,2, Alize J. Ferrari3,4, Bianca Calabria1, Wayne D. Hall5,6, Rosana E. Norman4,7, John McGrath8, Abraham D. Flaxman9, Rebecca E. Engell9, Greg D. Freedman9, Harvey A. Whiteford3,4, Theo Vos9

1 National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia, 2 Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia, 3 Queensland Centre for Mental Health Research, Brisbane, Queensland, Australia, 4 School of Population Health, University of Queensland, Brisbane, Queensland, Australia, 5 University of Queensland Centre for Clinical Research, University of Queensland, Brisbane, Queensland, Australia, 6 National Addiction Centre, Kings College London, London, United Kingdom, 7 Queensland Children’s Medical Research Institute, University of Queensland, Brisbane, Queensland, Australia, 8 Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia, 9 Institute for Health Metrics and Evaluation, University of Washington, Seattle, Washington, United States of America

Methods: Systematic reviews of epidemiological data on cannabis dependence (1990-2008) were conducted in line with PRISMA and meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Culling and data extraction followed protocols, with cross-checking and consistency checks. DisMod-MR, the latest version of generic disease modelling system, redesigned as a Bayesian meta-regression tool, imputed prevalence by age, year and sex for 187 countries and 21 regions. The disability weight associated with cannabis dependence was estimated through population surveys and multiplied by prevalence data to calculate the years of life lived with disability (YLDs) and disability-adjusted life years (DALYs). YLDs and DALYs attributed to regular cannabis use as a risk factor for schizophrenia were also estimated.
Dependence potential of different psychoactive substances (Anthony JC et al., 1994)

Estimated Prevalence of Dependence Among Users

- Tobacco: 32%
- Alcohol: 15%
- Cannabis: 9%
- Cocaine: 17%
- Stimulant: 11%
- Analgesics: 8%
- Psychedelics: 5%
- Heroin: 23%
Cannabis Dependence

Substance dependence:
- Impaired control
- Salience
- Physiological features

Humans develop tolerance to THC and cannabis users who seek help often report withdrawal symptoms

Regular cannabis users can develop dependence – approximately 1 in 10 and 1 in 6 in those who start in adolescence

Demand for treatment related to disorders due to cannabis use

Australia (Australian Institute of Health and Welfare, 2008):

- 44% of all treatment presentations to government alcohol and other drug treatment services included cannabis as a drug of concern between 2005 and 2006
  - 23% - primary drug accountable for treatment entry
- Primary substance of concern at age group 15-19 years old followed by alcohol

USA (SAMHSA, 2009):

- Rates of treatment admission for cannabis use disorders relatively stable at 15-16%
Most commonly reported classes of substances in primary diagnoses
(results of the WHO ATLAS survey in 2014)
Country-level DALYs per 100,000 population for cannabis dependence, age-standardised, for 2010

(Degenhardt et al, PloS, 2013)
Comparison of age standardised DALY rates by country with the global mean (Degenhardt et al, PLoS, 2013)
Alcohol-attributable fractions (AAFs) for selected causes of death, disease and injury, 2012 (WHO, 2014)

- For 2012 estimates selected causes if death and disability include:
  - FAS (fetal alcohol syndrome)
  - TB (tuberculosis)
  - Lower respiratory infections
  - HIV/AIDS.
Social & Economic Costs Associated with Cannabis Use

- Comprehensive estimates of societal costs of cannabis use that cover health care costs, legal costs, and productivity losses do not exist.

- Apart from cannabis use disorders, no ICD cannabis-specific disease or injury codes.

- Evidence is clouded by mixed findings in a number of areas pertinent to health.

- Better data on productivity losses and law enforcement costs necessary – currently difficult to obtain.
Significant Knowledge Gaps

- No standard measures currently of quantity of cannabis used by regular users
- THC content remains unknown in most countries
- Lack of research on the extent to which users titrate their dose
- Prevalence figures
- Neurobiology
  - Reversibility of neurobiological changes and cognitive impairments
  - Longitudinal studies combining epidemiological and neuroimaging methods to study the effects of cannabis use on brain function
- Reproductive health and NCD-related health consequences
- Non-communicable disease consequences
- Social and economic impact on communities.

And more...
"Substantial" evidence:

- Cannabis effective for the treatment of
  - chronic pain in adults (cannabis)
  - chemotherapy-induced nausea and vomiting (oral cannabinoids)
  - Multiple sclerosis spasticity symptoms (patient-reported)
- Statistical association between cannabis use and
  - Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking)
  - Increased risk of motor vehicle crashes
  - Lower birth weight of the offspring (maternal cannabis smoking)
  - Development of schizophrenia or other psychoses.
"Moderate" evidence of:

- Statistical association between cannabis use and:
  
  • Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal
  
  • Impairment in the cognitive domains of learning, memory and attention (acute cannabis use)
  
  • Increased symptoms of mania and hypomania in bipolar disorders (regular cannabis use)
  
  • Increased incidence of suicidal ideation, suicide attempts and suicide deaths
  
  • Increased incidence of social anxiety disorder (regular cannabis use)
  
  • Increased risk (small) of depressive disorder.
"Moderate" evidence of:
- Statistical association between cannabis use and:
  - A persistence of problem cannabis use and a history of psychiatric treatment
  - Problem cannabis use and increased severity of posttraumatic stress disorder symptoms
  - The development of substance dependence and/or substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs.
"Moderate" evidence:

- Improves short-term sleep outcomes in sleep disturbance associated with obstructive sleep apnoea syndrome, fibromyalgia, chronic pain, multiple sclerosis (cannabinoids, primarily nabiximols)
- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use.
Psychoactive substance use in the world

- **Alcohol:** ~1.9 billion people aged 15+ (consumed alcoholic beverages in the last 12 months (~35% of the world population aged 15-64) (estimates for 2012; WHO, 2014)
  - 7.2% of men and 1.3% of women aged 15+ - with alcohol use disorders

- **Tobacco:** ~ 1.1 billion people are current tobacco smokers (estimates for 2012, WHO, 2014)

- **Illicit drugs:** ~ 250 million people (~5% of the world population aged 15-64), had used an illicit drug at least once in the previous year (estimates for 2014, UNODC, 2016)
  - "Problematic drug use" (drug use disorders) ~ 29 millions (~0.5% of the world population 15-64 years old).
## Global prevalence, Years Lived with Disability (YLDs) & Disability-Adjusted Life Years (DALYs) of MNS disorders, 2015

<table>
<thead>
<tr>
<th>MNS Disorder</th>
<th>Prevalent cases</th>
<th>YLDs</th>
<th>DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol use disorders</td>
<td>63 million</td>
<td>+ 11%</td>
<td>6 million</td>
</tr>
<tr>
<td>Drug use disorders</td>
<td>46 million</td>
<td>+ 16%</td>
<td>10 million</td>
</tr>
<tr>
<td>Dementia</td>
<td>46 million</td>
<td>+ 38%</td>
<td>7 million</td>
</tr>
</tbody>
</table>

The Committee requested that the Secretariat prepare relevant documentation in accordance with the *Guidance on the WHO review of psychoactive substances for international control* in order to conduct pre-reviews for the following substances:

- Cannabis plant and cannabis resin
- Extracts and tinctures of cannabis
- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Stereoisomers of THC

The purpose of the pre-review is to determine whether current information justifies an Expert Committee critical review.
Contact details and further information

Contact: poznyakv@who.int

Further information at:

http://www.who.int/substance_abuse/

http://www.who.int/medicines/en/

http://www.who.int/mental_health/en/