AmericansFor SafeAccess
Advancing Legal Medical Marijuana Therapeutics and Research

Response to *Pre-review: Cannabis plant and resin*
Authored by Americans for Safe Access and International Medical Cannabis Patients Coalition
4 June 2018
40th Meeting of ECDD

Thank you for allowing us to address World Health Organization's Expert Committee on Drug Dependence (ECDD). We are encouraged to see the agenda of the 40th meeting of ECDD dedicated to carrying out pre-reviews of cannabis and cannabis-related substances. Americans for Safe Access (ASA), the leading medical cannabis patient advocacy organization in the United States, represents over 100,000 individuals that are using medical cannabis and the International Medical Cannabis Patient Coalition (IMCPC) represents patients from thirty four countries.

We were in engaged in United Nations General Assembly Special Session on Drugs in 2016 (UNGASS) meetings where the member states reiterated their "strong commitment to improving access to controlled substances for medical and scientific purpose by appropriately addressing existing barriers." We are grateful to have the opportunity to share our experiences and offer the assistance of our international coalition to ECDD. Below you will find our review, suggestions and response to the critical review document entitled *Pre-review: Cannabis plant and resin.*

Section 1 Chemistry
Overall, we agree with the authors section on Chemistry. We suggest using common botanical descriptions, such as using the terms variety, chemical variety, or chemovar, instead of strain as used on page 9. The term strain is appropriate to bacteria and viruses, but is not accepted in Botany. The committee should consider following botanical terminology as described in:

Lewis, M., Russo, E., & Smith, K. (2017). Pharmacological Foundations of Cannabis Chemovars. Planta Medica, 1–10. http://doi.org/10.1055/s-0043-122240

We also suggest that this section address outdoor cultivation, as the committee has only provided a summary of indoor cannabis production. The method of outdoor cultivation is still prevalent and is becoming more common in nations returning to cannabis cultivation. Outdoor cultivation methods are still used to produce cannabis appropriate for use in clinical research,

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such as the various inhalation studies approved by the National Institute of Drug Abuse (NIDA) in the USA.

The section *Risk of contamination and adulteration of street marijuana* gives a detailed overview of the issues facing unregulated markets. We suggest discussing the product safety and labeling studies conducted in laboratories from the Patient Focused Certification (PFC) program in partnership with the International Cannabis and Cannabinoid Institute (ICCI) (www.ICCI.science):

Bonn-Miller, M. O., Loflin, M. J. E., Thomas, B. F., Marcu, J. P., Hyke, T., & Vandrey, R. (2017). Labeling Accuracy of Cannabidiol Extracts Sold Online. Jama, 318(17), 1708–1709. http://doi.org/10.1001/jama.2017.11909

In addition, this section could be enhanced by including a statement emphasizing that standardized cannabis products (i.e., Sativex®, Bedrocan flos, etc.) and synthetic THC as Marinol® have a low street value, and do not pose the same risks as products from the illicit market or produced without proper quality control:

Robson, P. (2011). Abuse potential and psychoactive effects of δ-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. Expert Opinion on Drug Safety, 10(5), 675–685. http://doi.org/10.1517/14740338.2011.575778

Calhoun, S. R., Galloway, G. P., & Smith, D. E. (1998). Abuse potential of dronabinol (Marinol). *J Psychoactive Drugs, 30*(2), 187-196.

Section 2 Pharmacology

This section provides a comprehensive but basic overview of cannabis pharmacology.

In general, we agree with subsection 3, *Abuse Potential,* but this section should be updated with abuse data regarding opioids. Research shows that opioid deaths have decreased in states with medical cannabis laws by as much as 25% and has found a 23% reduction in hospitalizations related to opioid dependence or abuse:

Bachhuber, M. A., Saloner, B., Cunningham, C. O., & Barry, C. L. (2014). Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Internal Medicine, 174(10), 1668–1673. http://doi.org/10.1001/jamainternmed.2014.4005

Surveys of medical cannabis patients have suggested that cannabis is often used to decrease the use of other drugs, most significantly opioid-based painkillers. Sixty-six percent of patients

surveyed reported using cannabis as a substitute for prescription drugs. The most common reasons given for substituting included less adverse side effects (65%), better symptom management (57%), and less withdrawal potential (34%) with cannabis:

Reiman, A. (2009). Cannabis as a substitute for alcohol and other drugs. Harm Reduction Journal, 6, 35–35. http://doi.org/10.1186/1477-7517-6-35

Cannabis enhances the analgesic effects of sub-threshold oxycodone, suggesting synergy, without increases in the abuse liability of cannabis. These findings support the therapeutic use of opioid-cannabinoid combinations for pain:

Cooper, Z. D., Bedi, G., Ramesh, D., Balter, R., Comer, S. D., & Haney, M. (2018). Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability. Neuropsychopharmacology, 1–10. http://doi.org/10.1038/s41386-018-0011-2

Further research has shown that individuals consuming medical cannabis were able to decrease the number of opioids they took and demonstrated cognitive improvement and increased task performance after three months of treatment:

Gruber S., Sagar A., Dahlgren M., Gonenc A., Smith R., Lambros A., Cabrera., Lukas S., The Grass Might Be Greener: Medical Marijuana Patients Exhibit Altered Brain Activity and Improved Executive Function After 3 Months of Treatment, Frontiers in Pharmacology 8, 661-13. https://doi.org/10.3389/fphar.2017.00983

Also of note, patient advocacy groups have also been engaging governments to change laws to support the use of medical cannabis to combat the opioid use epidemic. This white paper provides a good overview of the public health issue:

Americans for Safe Access. (2017, December). Medical Cannabis as a Tool to Combat Pain and Opioid Crisis. Retrieved from www.safeaccessnow.org/opioidblueprint

Additional clarification is warranted regarding *3.1.2 Human Studies.* Standardized products (i.e., Sativex, Marinol, Bedrocan flos, etc.) have demonstrated very low abuse potential and do not pose the same risks as unstandardized products, according to a well-documented review:

Robson, P. (2011). Abuse potential and psychoactive effects of δ-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. Expert Opinion on Drug Safety, 10(5), 675–685. http://doi.org/10.1517/14740338.2011.575778

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Calhoun, S. R., Galloway, G. P., & Smith, D. E. (1998). Abuse potential of dronabinol (Marinol). *J Psychoactive Drugs, 30*(2), 187-196.

The subsections on *Dependence* and *Abuse Potential* could be enhanced with discussion on the use of cannabis and the effects on mental health. The reference provided below provides a review, which considers the potential influences of the use of cannabis on areas of interest to mental health professionals, with foci on adult psychopathology and assessment. The study identified 31 articles relating to the use of cannabis and mental health, and 29 review articles on cannabis use and mental health that did not focus on use for therapeutic purposes. The results reflect the prominence of mental health conditions among the reasons for cannabis use, and the relative dearth of high-quality evidence related to cannabis in this context, thereby highlighting the need for further research into the harms and benefits of medical cannabis relative to other therapeutic options. Preliminary evidence suggests that cannabis may have potential for the treatment of post-traumatic stress disorder (PTSD), and as a substitute for problematic use of other substances. Extrapolation from reviews of non-therapeutic cannabis use suggests that the use of cannabis may be problematic among individuals with psychotic disorders. The clinical implications of cannabis use among individuals with mood disorders are unclear. With regard to assessment, evidence suggests that cannabis use does not increase risk of harm to self or others. Acute cannabis intoxication and recent cannabis use may result in reversible deficits with the potential to influence cognitive assessment, particularly on tests of short-term memory:

Walsh, Z., Gonzalez, R., Crosby, K., Thiessen, M. S., Carroll, C., & Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review. Clinical Psychology Review, 51, 15–29. http://doi.org/10.1016/j.cpr.2016.10.002

Lastly, the section on *Dependence* and *Abuse Potential* should provide a clarification that following dosing and administration guidelines, established from clinical trials and regulatory models, will minimize the risks associated with cannabis:

MacCallum, C. A., & Russo, E. B. (2018). Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine, 49, 12–19. http://doi.org/10.1016/j.ejim.2018.01.004

Section 3 Toxicology

In general, we agree with the author's reporting of cannabis toxicology. A particularly important point from the report is, *"…most of the available evidence of adverse effects involves cannabis use within an illegal, recreational context, where the cannabis that is self-administered is of*

unregulated quality and is administered by smoke inhalation." However, the article could be more balanced, by adding a few additional reports, to reflect more of the available data.

In the subsection *1.6 Fertility and teratogenesis*, the authors could further support their statement regarding, "*Whether the lower birthweights can be specifically attributed to cannabinoids is unclear,"* by discussing or adding additional articles which have findings that contradict some of the assumptions about cannabis fertility. Contrary to the authors statement that, "*There is strong population-based evidence that illicit cannabis smoking during pregnancy reduces the birthweight of offspring"* there is substantial evidence which suggests the opposite once variables, such as socioeconomic status, are controlled:

Russo, E. (2002). Cannabis Treatments in Obstetrics and Gynecology: A Historical Review. Journal of Cannabis Therapeutics, 2(3-4), 5–35. http://doi.org/10.1300/j175v02n03_02

A recent review of available data refutes the risks of low birth weight or teratogenenesis in relation to cannabis:

Torres, C. A., & Hart, C. L. (2016). Prenatal cannabis exposure and cognitive function: a critical review. Paper presented at the College on Problems of Drug Dependency, Palm Springs, CA.

Regarding the sub-section, *1.7 Effects on cognitive function,* we agree with the author's summary of the evidence, "*No relationship could be found between the age of onset of cannabis use and cognitive function. Furthermore, no association between cannabis use and reduced cognitive function could be found in studies with a greater than 72-hour abstinence period, suggesting that the effects of cannabis use on cognition were reversible."*

Regarding the sub-section, *1.8 Mental health,* two recent and thorough review articles provide some information, which may clarify the mental health risks of cannabis. The findings of the references provided below do not support a longitudinal association between cannabis use and incidence of major depression or psychosis:

Feingold, D., Weiser, M., Rehm, J., & Lev-Ran, S. (2015). The association between cannabis use and mood disorders: A longitudinal study. Journal of Affective Disorders, 172, 211–218. http://doi.org/10.1016/j.jad.2014.10.006

Walsh, Z., Gonzalez, R., Crosby, K., Thiessen, M. S., Carroll, C., & Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review. Clinical Psychology Review, 51, 15–29. http://doi.org/10.1016/j.cpr.2016.10.002

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However, we strongly disagree with one statement in subsection *2. Adverse reactions in humans*, *"There are several recent case reports of young children accidentally ingesting cannabis and experiencing respiratory depression…"* Respiratory depression occurs with drugs that have significant interactions in the brain stem. No known cannabinoids are associated with respiratory depression. The others should consider removing this statement or clarifying the statement with a physiological mechanism to support the hypothesis.

Lastly, multiple studies have shown that lifetime use of cannabis is not significantly associated with increased morbidity, brain damage, or cerebral atrophy. The following articles should be discussed within the context of the Toxicology section:

Weiland, B. J., Thayer, R. E., Depue, B. E., Sabbineni, A., Bryan, A. D., & Hutchison, K. E. (2015). Daily marijuana use is not associated with brain morphometric measures in adolescents or adults. Journal of Neuroscience, 35(4), 1505–1512. http://doi.org/10.1523/JNEUROSCI.2946-14.2015

Karst, M., Salim, K., Burstein, S., Conrad, I., Hoy, L., & Schneider, U. (2003). Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. Jama, 290(13), 1757–1762. http://doi.org/10.1001/jama.290.13.1757

Russo, E., Mathre, M. L., Byrne, A., Velin, R., Bach, P. J., Sanchez Ramos, J., & Kirlin, K. A. (2002). Chronic Cannabis Use in the Compassionate Investigational New Drug Program. Journal of Cannabis Therapeutics, 2(1), 3–57. http://doi.org/10.1300/J175v02n01_02

Section 4 Therapeutic applications and extent of therapeutic use and epidemiology of medical use

We agree with the authors, that cannabis and its resin can be effective to treat symptoms related to the following conditions: Appetite stimulation in HIV/AIDS infection, chronic pain, Crohn's disease, diabetic neuropathy, epilepsy, neuropathic pain, migraine and cluster headaches, opioid withdrawal, Parkinson disease, PTSD, psychosis, and sleep disorder. However, it appears this subsection is lacking a lot of the available clinical data. Our recommendations are to re-examine a statement regarding significant differences in a clinical trial, listing multiple sclerosis or spasticity and many other ailments as conditions, and including some brief information which acknowledges the extent of work done with nabiximols (i.e., Sativex).

It appears there was a misinterpretation or error in the Crohn's Disease condition summary on page 8 of Section 4. The committee author's state that the study by Naftali et. al. 2013, demonstrated *"the cannabis smokers group had a significant response on the Crohn Disease*

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Activity Index." While we are in agreement with the committee authors that cannabis could be effective for Crohn's Disease, the study described did not show a statistical difference between treatment and placebo. Naftali et al. state that *"This difference did not reach statistical significance (P= 0.43)",* hence we strongly recommend altering this quote to reflect the statistical analysis between the patient groups.

A few conditions where cannabis has been shown to be effective were not mentioned. We suggest adding information on the following conditions as cannabis and its resin have shown promising or significant results: Hepatitis-C symptoms and its virus, amyotrophic lateral sclerosis, arthritis, Alzheimer's disease, glaucoma, psychiatric disorders (anxiety, depression, and related mood disorders).

Additionally, we recommend listing multiple sclerosis and briefly describing the data, as it is one of the most widely studied and promising conditions for utilizing cannabis-based medicines. Ideally, it could refer readers to the extracts critical review document, after a brief summary is provided acknowledging the 20,000 patient/years of data on the subject and licensing of Sativex in 30 countries.

We found subsection, *3. Marketing authorizations (as a medicinal product)* for herbal cannabis and extracts to be useful and accurate. In this subsection it is important to mention that Sativex, which is a cannabis extract tincture is licensed in 30 countries, or that this will be discussed in another article. As the success of Sativex and the data generated by GW Pharma's clinical studies have influenced the approval of other cannabis-based medicines.

Section 5 Epidemiology

The subsection on Epidemiology presents a balanced and complete overview of the topic. Minor oversights are to be noted though such as data relating to self-medication (under part 2.5.3) in contradiction with data observed in the Netherlands over 13 years, showing a stabilization of use by medical cannabis patients, or with the results of a survey completed by 953 participants from 31countries showing the positive influence of regulated medical access over patterns of use among patients. Important studies about the medical conditions people use cannabis for are missing:

B. de Hoop B, E.R Heerdink & A. Hazekamp, Medicinal Cannabis on Prescription in The Netherlands: Statistics for 2003-2016, Cannabis Cannabinoid Research, 2018.

A. Hazelkamp, M.A. Ware, K.R. Müller-Vahl, D. Abrams and F. Grotenhermen, The Medicinal Use of Cannabis and Cannabinoids-An International Cross-Sectional Survey on Administration Forms. Journal of psychoactive drugs, 2013.

R. Borràs, P. Modamio, C.F. Lastra, & E.L. Mariño, Medicinal use of Cannabis in Spain , Alternative Therapies In Health And Medicine, 2011.

The global analysis of cannabis use should take into account that outside of the United States, cannabis is used with tobacco. European data on cannabis is misleading because the plant material is mixed with a large amount of tobacco, which increases risks of dependence, rates of use, and adverse events. The statistics regarding use and abuse may be over-estimated due to a confounding factor related to concomitant tobacco use; this section mixes together research where tobacco use may be the primary factor, not cannabis.

Regarding subsection *2.5.2 Potency measured from cannabis samples (herbal, resin, extract, tinctures)*, we disagree with the comment on Pg. 28, "*Changes in the legality of cannabis may be one of the causes of increases in THC content."* Increased potency of cannabis is a direct result of prohibition and illegality. Low potency products are now more prevalent than ever because of regulated markets. Similar trends in alcohol potency were documented during prohibition.

Further, the data on potency should have exclusion and inclusion criteria. Most data on cannabis potency was not generated using validated or accepted methods that would comply with international standards for representative sampling, sample preparation, and method of analysis. Very few if any of the potency data would meet standards for labeling. Only data from accredited ISO17025;Cannabis methods (aka Patient Focused Laboratory Certification or equivalent accreditation body) should be used to determine if results are acceptable. Research indicates that cannabis testing has a 70% chance of being inaccurate:

R Vandrey et al., "Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products," *Jama* 313, no. 24 (June 23, 2015): 2491–93, doi:10.1001/jama.2015.6613.

More broadly, tools to measure epidemiology of illicit drugs are subject to numerous bias that ought to be more explicitly stated in the document. Data from self-reports, healthcare statistics, anonymous surveys looking at groups or populations that use cannabis, many not formally engaged
in any health care system or not represented in official census, each carry unique characteristics that require special care to avoid bias. The existence of laws and policies that include mandatory drug treatment as a punishment or as an alternative to penal measures, can also create an important statistical bias:

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WHO Commission on Social Determinants of Health, Women and Gender Equity Knowledge Network. Unequal, Unfair, Ineffective and Inefficient. Gender Inequity in Health: Why it exists and how we can change it. 2007.

G. Maté, Addiction: Childhood Trauma, Stress and the Biology of Addiction. Journal of Restorative Medicine, 2012.

K.J.H. Verweij, B.P. Zietsch, M.T. Lynskey, S.E. Medland, M.C. Neale, N.G. Martin, D.I. Boomsma and J.M. Vink, Genetic and environmental influences on cannabis use initiation and problematic use: a meta-analysis of twin studies. Society for the Study of Addictions, 2010.

Reported data that discriminates use according to gender is lacking an acknowledgment of the social gender conditions that are (a) an important barrier to access to healthcare systems, and (b) a factor of biased declaration to health surveys. These gender conditions vary according to regions and social contexts. Similarly, the access to illicit retail of cannabis is more prone to male than to female, in particular young women, thus virtually inflating the data on problematic use of young males. Also factors of genetic predispositions should be balanced according to what modern research has shown including one study referenced in the report, but which conclusions are only partially cited:

V. Govender and L. Penn-Kekana, Gender biases and discrimination: a review of health care interpersonal interactions. Background paper prepared for the Women and Gender Equity Knowledge Network of the WHO Commission on Social Determinants of Health. 2007.

Additional Resources

ECDD40 Procedural, methodological and terminological bias. For Alternative Approaches to Addiction, Think & do tank. www.faaat.net/cannabis

International Medical Cannabis Patient Coalition (IMCPC)'s UNGASS 2016 Declaration delivered to the UN Commission on Narcotic Drugs in Vienna March 2015: http://bit.ly/1TV0gNi

Cannabis and Cannabis Resin- Critical Review Preparation Document 2016 prepared by the Americans for Safe Access at their National Unity Conference https://www.safeaccessnow.org/critical_review

Testimony from WHO ECDD November 2015 Meetings:

Global Patient Populations Need International Medical Cannabis Policies to Evolve: http://bit.ly/1TV0G6l

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[pdf, 272kb Steph Sherer, Executive Director, Americans for Safe Access]

Cannabis, an irreplaceable botanical medicine of long standing human use http://bit.ly/1TV0vbf [pdf, 50kb Michael Krawitz, Executive Director, Veterans For Medical Cannabis Access: http://bit.ly/1TV0vbf]

The WHO cannabis background document: http://bit.ly/1TV0nID

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