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Article

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Standard Unit for cannabis dose: why is it important to standardize cannabis dosing for drug policy and how can we put it on the public health agenda?

Cannabis is the third most prevalent psychoactive substance used worldwide. An estimated 192 million people used cannabis during the past year (3.9% of the global population aged 15– 64, 2018) (United Nations Office on Drugs and Crime, 2020). Cannabis legislative frameworks are evolving globally. Recently, the United Nations removed cannabis from Schedule IV of the Single Convention but retained it in Schedule I (potential therapeutic but significant public health risk) – more details: https://www.unodc.org/unodc/en/commissions/CND/Mandate_Functions/currentscheduling-recommendations.html.

Recreational cannabis use is increasing across the globe (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2020; Hasin et al., 2015), while the perception of risks associated with cannabis seems to be declining (Barrett & Bradley, 2016; Carliner et al., 2017). Yet, the scientific literature has documented multiple health related harms associated with frequent cannabis use, including respiratory problems, cardiovascular outcomes, and gastrointestinal disorders and detrimental consequences on mental health, cognition and behaviour, the latter increases the risk of injury (Campeny et al., 2020). This changing context will align cannabis use more closely with alcohol, benzodiazepines, prescribed opioids or tobacco than to currently illegal drugs. A transition to diverse approaches to legal, regulated access will present new challenges to implement prevention and harm-reduction strategies to mitigate adverse outcomes associated with cannabis consumption (Kilmer, 2019), as cannabis products become more widely available. Although the quantity per occasion (dosing) has shown to influence cannabis-related outcomes (T. P. Freeman & Lorenzetti, 2019), up to this point cannabis use had been mainly assessed by frequency of use. Based on experiences with other drugs as alcohol or tobacco, frequency alone may lead to a biased estimation of the risks and

harms (e.g., frequency does not capture variations of quantity per day of use in frequent (European Monitoring Centre for Drugs and Drug Addiction, 2013) use). As such, reliable data on cannabis quantity of cannabis use is required to improve assessment for epidemiological and clinical analysis. Consequently we propose that a Standard Cannabis Unit (SCU) based on quantity of 9- Tetrahydrocannabinol (9-THC) should be established. THC has already been proved as the primary psychoactive constituent (Casajuana Kogel et al., 2016). More so, most cannabis use health related harms seem to be associated with quantity of THC, as it has been extensively reported in the literature. For instance, evidence points to a clearly increased risk of developing psychosis symptoms (Di Forti et al., 2019) and also increased risk of psychiatric hospitalization (Schubart et al., 2011). The US National Institute on Drug Abuse along with prominent scientists have called for standard units of dosing for cannabis, similar to those used for alcohol (Volkow, 2020).

In establishing a standardized unit for cannabis dosing, learning from the history of measuring standard units (i.e. alcohol and tobacco) could facilitate public health, research and clinical professionals to navigate through this new context and prevent errors from being repeated. During the 1980s and 1990s, several countries reached a national consensus defining a SD. However, there are large differences between countries in defining the SD (Kalinowski & Humphreys, 2016), due to cultural differences, the fact that some are based on national consensus while others derived from empirical research, making some cross-country comparison, policy analysis and prevention efforts more difficult. However, even if different SD exist, they are all based on the same unit (grams of pure alcohol) and thus can be converted. As a result, the concept of a SD represented an important advance for the alcohol public health field. It provides clinicians, public health specialists, policy makers, and researchers with a useful tool to implement programs ranging from early identification to harm-reduction. Efforts to establish standard units have also been made with other drugs: Morphine Milligram Equivalents (MME) or diazepam equivalents allow standardization of opioid and benzodiazepine dosing respectively. These examples of standard units, similar to the desired SCU, have enabled to

calculate a total dosing in individuals that simultaneously use diverse active principles among the same substance family and also different routes of administration, permitting an estimation of the individual risk of experiencing adverse health consequences. Nonetheless, with cannabis, both the possible routes of administration and continuing changes in potency are not standardized or systematically registered and thus are not taken into account.

A SCU has the potential to become a critical tool for universal prevention, as Standard Drinks (SDs) for alcohol, for example to inform how much cannabis exposure constitutes high risk use for people in the general population, those seeking or receiving treatment, healthcare workers, youth, parents and educators. The development and refining of a SCU can also inform targeted prevention and harm-reduction strategies, through the development of guidelines for low-risk use (Fischer et al., 2017). Additionally, information on patterns of use of SCUs (dosing and frequency) can be used to inform screening and brief interventions, in conjunction with short standardized screening instruments. The use of a SCU in prevention, treatment and public health strategies hold promise to reduce morbidity, mortality and costs related to cannabis use. This is expected based on the benefits of the standard alcohol units (i.e. standard drinks) in the Screening and Brief Intervention (SBI), which was cost-effective and cost-saving for alcohol use (<£150 and <£1,500 in low- and high-income settings, respectively) (Chisholm et al., 2018).

The implementation of cannabis policy aimed at reducing the adverse health impact of cannabis use must be grounded in evidence-based strategies. As the SD has proven to constitute an important vehicle for reducing alcohol-attributable harm through interventions across the spectrum, ranging from prevention and therapy to harm-reduction. Similarly, a SCU could be used in evidence-based interventions that guide and transform health policy.

Importantly, some steps have been made towards achieving an international consensus around what could constitute a SCU. During a workshop with 32 experts (including all the authors of this text) in different disciplines (sociology, psychology, public health, basic and clinical

research, psychiatry) at the Lisbon Addictions Conference 2019, a back-casting foresight method was used to address challenges and achieve consensus in developing a SCU. Participants in back-casting exercises do not predict the future, but rather choose the desirable future and work backwards to define the steps needed to achieve that goal. During this exercise, several characteristics of a SCU (divided into three domains to facilitate discussion and reaching consensus) were identified and agreed upon: 1) core values: easy-to-use, universal, focused on THC, accurate, and accessible; 2) key challenges: sudden changes in patterns of use, heterogeneity of cannabis compounds (diversity in content/composition (e.g. quantities/proportions of THC, CBD, other cannabinoids, etc.) as well as in administration routes, variations over time in THC concentrations, and of laws that regulate the legal status of recreational and medical cannabis use; and, 3) facilitators: previous experience with standardized measurements, funding opportunities, multi-stakeholder support, high prevalence of cannabis users, and widespread changes in legislation. Among all the challenges to be faced, diversity of cannabis compounds has to be taken into account: levels of CBD are present in cannabis and might influence its health effects. But, as some of the authors have already discussed in previous papers (T. P. Freeman & Lorenzetti, 2019), up to this point the effects of CBD have not been consistent throughout all studies and outcomes (A. M. Freeman et al., 2019). So far not all experimental studies have reported protective effects of CBD (Morgan et al., 2018), and some even indicate that it may potentiate certain effects of THC (Arkell et al., 2019). Additionally, there may be a role of other cannabinoids such as Δ^9 -tetrahydrocannabivarin (THCV) (Englund et al., 2016) and terpenoids (Russo, 2011) in moderating the effects of THC. Therefore, evidence into the potential role of CBD as a harm reduction strategy is still progressing, and further evidence is needed to establish how different doses of CBD might influence the effects of THC. All in all, we consider that a SCU should still be based on dose of THC.

Another challenge important to consider are the recent changes in cannabis potency. The changes in potency in recent years have been well-documented internationally (T. P. Freeman et al., 2020), and high potency is associated with increased psychosis risk (Di Forti et al., 2019) and first-time cannabis admissions to drug treatment (T. P. Freeman et al., 2018). More data on THC levels per joint in different settings and countries are needed. Easily and rapidly

reproducible methods of analysis are required in order to adapt a future SCU (based on milligrams of THC) to changes in potency that can impact dosing (Fischer et al., 2017). Previous research in Spain (a naturalistic study with joints provided by real users) found the Standard Joint Unit (SJU) to be 7mg of THC for the population 18 years or older (Casajuana Kögel et al., 2017), but empirical data from other countries are less consistent. However, the impact on changes in the levels of cannabis potency on use behavior or – more specifically – on dosing, remains a challenge to tackle for standardizing the SCU. Another issue is that cannabis is not exclusively used in joints (e.g., bongs, pipes, edibles and drinks). Therefore, as some of the authors previously proposed, a complementary strategy might be to apply a fixed standard unit of THC (based on a narrative review of the literature 5mg THC per unit was proposed) to all manufactured cannabis products (T. P. Freeman & Lorenzetti, 2019).

Previously described Standard THC Unit and Standard Joint Unit could be complementary concepts. Standard Joint Unit (SJU), accounts for the most frequent route of administration in Europe (Hindocha et al., 2016) and might be useful both for legal and illegal markets when the route of administration is smoked. On the other hand, a Standard THC Unit might be useful in legal markets and in contexts where more diverse routes of administration are available, such as the USA (Hindocha et al., 2016). A convergence between both suggested standard units is expected and desirable, but more empirical data from field studies are needed to confirm this.

In conclusion, the implementation of a SCU in the years to come is feasible after overcoming several surmountable barriers and harnessing contextual facilitators. The authors agreed that the establishment of a SCU is possible on the basis on the following key steps: 1) the building of a task force to define, develop and advocate for an evidence-based SCU; 2) reviewing and expanding available national-level data on cannabis use and related risks; and 3) examining how the SCU relates to the concept of ‘risky use’ of cannabis.

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