How experimental cannabinoid studies will inform the standardized THC unit

The tetrahydrocannabinol (THC) unit may facilitate significant advances in cannabis research and guidance for safe use. This must be supported by further experimental studies to provide accurate information on the effects of THC at different doses and administration routes, as well as the impact of CBD.

We read with great interest the article by Freeman & Lorenzetti, which raises a very important topic in cannabis research. While there have been a number of suggestions in the past for standardized cannabis units, there is still a lack of consensus on how a unit should be defined [1–3]. As noted by Freeman & Lorenzetti, current public health directives designed to limit high-risk cannabis use, such as Canada’s Lower Risk Cannabis Use Guidelines, lack numerical dose recommendations [4]. With the rapidly expanding range of cannabis-based products available on some legal markets, defining standard cannabis units has become necessary to provide clearer guidelines for users to reduce harms. Freeman & Lorenzetti suggest that standard cannabis units should be based on the quantity of the intoxicating component, tetrahydrocannabinol (THC), and conclude that a dose of 5 mg should be the benchmark for a standard unit. This would allow for consistent labeling and safety guidelines for all cannabis products, resulting in a greater clarity for consumers, clinicians and researchers. Freeman & Lorenzetti also outline some of the difficulties faced in defining a measure of cannabis, such as variations in other psychoactive compounds, namely cannabidiol (CBD), and the starkly different pharmacokinetic profiles of the drug across routes of administration.

Experimental research should inform the design of a standard THC unit and subsequently guide both recreational users and clinicians as to expected effects. We believe that the THC unit should be related to the subjective effects of THC in novice or infrequent users. Such users are more likely to experience untoward effects due to lack of experience with the drug and the absence of tolerance [5,6]. We would suggest that the THC unit should be related to the minimum dose of THC required to produce levels of intoxication significantly different from placebo. This requires experimental placebo-controlled studies using precise doses of THC in a controlled environment. For example, Kleinloog et al. [7] collated results of 10 of their studies to compare doses of THC with placebo, using visual analogue scales (VASs) to measure subjective effects in infrequent cannabis users. In this article they reported that 2 mg of THC significantly differed from placebo in 58% of volunteers. Once a THC unit is established, further experimental studies can similarly be used to produce clear information on the likelihood of positive (e.g. euphoria, laughter) and negative effects (e.g. nausea, anxiety, paranoia) at multiples of units. They could also inform users of what the expected effects are depending on characteristics such as age, gender, body mass index and tolerance [5,8,9].

There should also be further consideration into whether THC units can be standardized across different routes of administration, as there are major differences in the pharmacokinetic profiles of inhaled and orally ingested THC [10]. Inhaled THC reaches peak plasma levels within minutes, while oral THC reaches peak plasma levels after 2 hours and effects start manifesting after an hour (depending on fasting status) [11]. Standardizing units across multiple routes of administration could result in accidental over-intoxication and increase the likelihood of adverse events. It is also unclear whether tolerance extends across routes of administration, and experimental studies could compare the subjective effects of oral and inhaled THC within individuals with tolerance to only one route of administration.

Lastly, as suggested by Freeman & Lorenzetti [4], the ability of CBD to mitigate the negative effects of THC are unclear. There have been contrasting results in the acute setting [12,13], with some indication of benefit in the longer term for regular cannabis users [14]. As evidence is currently scarce, more experimental studies are needed to clarify the potential benefits of CBD, both acutely and in longer-term use, before establishing a CBD unit.

We believe the THC unit, as proposed by Freeman & Lorenzetti, lays the foundations for progress which, if supported by further experimental studies, has the potential to lead to significant advances in cannabis research as well as in clinical and recreational settings. Such studies can provide accurate information on effects of THC at different doses and administration routes, as well as the impact of CBD. With current global trends towards decriminalization and legalization, it is increasingly important for clear, informative guidelines to encourage safer use. We believe the THC unit will make a substantial contribution to informing such guidelines and future research.

Declaration of interests
None.
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