‘Standard THC Units’: a proposal to standardise dose across all cannabis products and methods of administration

Tom P Freeman[1,2,3]*, Valentina Lorenzetti[4]

[1]Addiction and Mental Health Group (AIM), Department of Psychology, University of Bath, Bath, BA2 7AY, UK

[2]National Addiction Centre, King’s College London, 4 Windsor Walk, London SE5 8BB, UK

[3]Clinical Psychopharmacology Unit, UCL, 1-19 Torrington Place, London WC1E 7HB, UK

[4]School of Behavioural and Health Sciences, Australian Catholic University, 15 Young St, Fitzroy VIC 3065, Australia

*Address correspondence to:
Tom Freeman
Addiction and Mental Health Group (AIM)
Department of Psychology
University of Bath
Bath BA2 7AY
UK
t.p.freeman@bath.ac.uk

Abstract: 235/250

Main text: 3,236/3,500

Tables: 3

Figures: 2

References: 96

Key words: Cannabidiol, Cannabis, Harm reduction, THC, Safety guidelines, Standard unit

Declarations of interest: No authors report any declarations of interest. TF is funded by a Senior Academic Fellowship from the Society for the Study of Addiction. The funder had no role in the writing of the report or the decision to submit for publication.

Abstract

Background: Cannabis products are becoming increasingly diverse, and they vary considerably in concentrations of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Higher doses of THC can increase the risk of harm from cannabis, while CBD may partially offset some of these effects. Lower Risk Cannabis Use Guidelines currently lack recommendations based on quantity of use, and could be improved by implementing standard units. However, there is currently no consensus on how these should be measured or standardised across different cannabis products or methods of administration.

Argument: Existing proposals for standard cannabis units have been based on specific methods of administration (e.g. joints) and these may not capture other methods including pipes, bongs, blunts, dabbing, vaporizers, vape pens, edibles and liquids. Other proposals (e.g. grams of cannabis) cannot fully account for heterogeneity in cannabis products. Similar to alcohol units, we argue that standard cannabis units should reflect the quantity of active pharmacological constituents. On the basis of experimental and ecological data, public health considerations, and existing policy we propose that a 'Standard THC Unit' should be fixed at 5 milligrams of THC for all cannabis products and methods of administration. If supported by sufficient future evidence, consumption of Standard CBD Units might offer an additional strategy for harm reduction.

Conclusions: Standard THC Units have the potential to be applied across all cannabis products and methods of administration in order to guide consumers and promote safer patterns of use.

Background

Cannabis is used by an estimated 192 million people worldwide (1). This number may rise further as new legal markets in Canada, the USA, Uruguay and elsewhere emerge (2), along with permissive stances towards cannabis in illicit markets (e.g. "cannabis social clubs" in Spain and "coffee shops" in the Netherlands (3)). Cannabis is also gaining increasing acceptance in modern medicine (4). However, there are long-standing concerns about the risks of cannabis use on mental health and cognition (5-7). For example, a relatively consistent finding is that greater levels of cannabis exposure are associated with an increased risk of adverse outcomes such as the development of cannabis use disorders (8, 9). Although there is debate about causality (10-12) the association between cannabis use and risk of psychosis strengthens in some individuals with increasing levels of cannabis exposure (13, 14). These risks could potentially be minimised by promoting safer patterns of use (15, 16).

Canada's current evidence-based (16) Lower Risk Cannabis Use Guidelines (17) include recommendations such as: "If you use, choose low-strength products, such as those with a lower THC content or a higher ratio of CBD to THC" and "Try to limit your use as much as possible". No recommendations are provided based on quantity of cannabis or cannabinoids used. There is currently no consensus on how cannabis use should be measured, which severely limits our ability to provide guidance on cannabis use and its consequences (6, 18-20). The National Institute on Drug Abuse (NIDA) Cannabis Policy Workgroup identified the development of standardised units of dose as its number one cannabis use research priority (21). The workgroup highlighted the importance of accounting for various cannabis products (e.g. herbal, edible, or extract), methods of administration (e.g. smoking, eating, vaping and dabbing), the extent to which people use multiple cannabis products, and that the active components of cannabis include CBD as well as THC (21).

Heterogeneity in quantities of THC and CBD in cannabis products

Cannabis products are extremely heterogeneous with regards to THC and CBD[1], which may have important consequences for their health effects (see Figure 1 and Table 1). Experimental studies of cannabis intoxication have shown that THC produces dose-dependent rewarding effects such as feeling "high" and relaxed, as well as THC dose-dependent adverse effects including psychotic-like symptoms, anxiety and memory impairment (5, 22-24). By contrast, preliminary evidence suggests

[1] Here we refer to 'THC' as the quantity of Δ^9-tetrahydrocannabinol + 0.877*Δ^9-tetrahydrocannabinolic acid, and 'CBD' as the quantity of cannabidiol + 0.877*cannabidiolic acid

that CBD can produce acute effects that are opposite to THC across a range of cognitive tasks (e.g. verbal memory, emotional face processing, response inhibition and visual processing (25)). Co-administration of CBD may partially offset some of the acute negative effects of THC on several cognitive domains and psychopathology symptoms (e.g. verbal memory recall (26, 27), emotional face recognition (28) reward processing (29-31) and psychotic-like symptoms (25, 27)).

Some evidence suggests that long-term exposure to high THC/low CBD cannabis products is associated with increased harms. These include severity and treatment rates for cannabis use disorders (32-36), risk of developing psychosis (37, 38) and relapse following a first episode of psychosis (39). Long-term exposure to CBD, evidenced by toxicological analysis of hair samples, was associated with reduced psychotic-like symptoms (40, 41) and protection from hippocampus volume loss (42, 43).

Not all experimental studies have reported protective effects of CBD (44) and some indicate it may potentiate certain effects of THC (45, 46). Moreover, exposure to CBD in observational studies may be confounded by other factors, such lower levels of THC in varieties of cannabis that produce high levels of CBD (47). 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 (15). Additionally, there may be a role of other cannabinoids such as delta-9-tetrahydrocannabivarin (THCV) (48) and terpenoids such as limonene, myrcene, α-pinene and linalool (49) in moderating the effects of THC.

Heterogeneity in methods of administration of cannabis products

Cannabis products and methods of administration vary widely and are continuing to diversify (50). These include joints, pipes, bongs, blunts, vaporizers, edibles, liquids and others (Table 2). Methods of cannabis use vary within and across countries. For example, a multinational study (51) found that in Canada, joints were the most popular method of use (43%), followed by bongs, pipes and vaporizers (20%, 19% and 13% respectively). In Australia joints were also the preferred route (52%), followed by bongs, pipes and vaporizers (25%, 12% and 6% respectively), while in the United States the most common method was pipes (48%) followed by bongs, joints and vaporizers (19%, 14% and 11% respectively) (51). Dabbing (a method specifically used for cannabis concentrates) has become relatively widely used in new legal markets in the United States, with concentrates representing approximately 12% of all sales in Washington State (52). Edible and liquid cannabis consumption

has also risen in legal markets, representing approximately 10% of sales in Washington State (52). Distinct routes of cannabis use are associated with differences in the duration and the intensity of intoxication. The absorption of cannabinoids is more variable and slow after oral administration than for inhaled administration, which limits the ability to titrate effects based on blood cannabinoid levels (53). Overall, the high and increasing heterogeneity in methods of administration, dosage and related intoxication effects will continue to present challenges for the development of standardised guidelines that outline practical recommendations for safer patterns of use.

Previous arguments for standard cannabis units

We are not the first to discuss the concept of standard cannabis units (Table 3). Existing proposals have been based on the concept of 'Standard Joints' (54, 55), grams (56) and multiple types of administration (55, 57). A key study in Barcelona (54) tested the contents of peoples' joints and equated the 'Standard Joint Unit' to the quantity of THC, price, and weight of cannabis from these joints. CBD was found in joints containing cannabis resin but not herbal cannabis, and was not included in the Standard Joint Unit. Advantages of this approach include its reference to a commonly used method of administration in Europe (51) which may be easily applied in research and clinical settings, and validation against problematic use (58). However, the Standard Joint Unit does not capture other methods of use. Additionally, the extent to which it reflects a standardised dose may be influenced by regional and individual variation in joints (59, 60) and changes in THC concentrations in cannabis over time (61, 62).

Grams of cannabis have been proposed as a standardised measure of quantity (56) but these do not account for variation in THC. For example, based on information from the UK in 2015/2016 (Table 1) a typical gram of cannabis concentrate might contain 26 times more THC than a typical gram of outdoor-grown herbal cannabis (780 milligrams THC compared to 30 milligrams THC). Similarly, a litre of vodka (40% alcohol by volume) would not be considered equivalent to a litre of beer (5% alcohol by volume), as it contains 8 times more alcohol (320 grams compared to 40 grams) and therefore carries an increased risk of harm.

A recent standard cannabis unit proposal addresses both THC and CBD by quantifying their relative ratio (63). Hindocha, Norberg and Tomko classified cannabis into three THC/CBD types: high THC/low CBD (.25g = 1 unit), equal THC/CBD (.5g = 1 unit), or low THC/high CBD (.75g = 1 unit) (63). However, these fixed THC:CBD ratios may not be sensitive to the varying levels of THC and

CBD found in cannabis products. For example, cannabis concentrates and outdoor-grown herbal cannabis in the UK both contain a high level of THC relative to CBD. Therefore, a gram of each of these might be considered equal, despite concentrates containing ~26 times more THC than outdoor-grown herbal cannabis.

The measurement of standard cannabis units is hindered by variation in cannabis products, their THC and CBD content, and different methods of administration. Alcohol research has faced similar issues during the development of standard alcohol units, as there is considerable heterogeneity in the types of drink consumed and the amount of alcohol they contain. Therefore, alcohol units may provide a useful framework to inform the development of objective, standardised cannabis units. Alcohol units are defined by the number of grams of alcohol (e.g. in the UK, 1 unit = 8g alcohol). Although the size of an alcohol unit varies across different countries, the use of a common metric (i.e. grams of alcohol) has allowed standard alcohol units to be applied across a wide range of alcohol products.

A new proposal for Standard THC Units

We argue that for cannabis, as for alcohol, standard units should be based on the quantity of active pharmacological products. The primary psychoactive constituent of cannabis is THC. Therefore, standardised doses of THC should form the basis of 'Standard THC Units' rather than other proxies of cannabis exposure (e.g. grams, joints). It is important to emphasise that dose (milligrams of THC) is different from concentration (% of THC) and the former should be used to inform Standard THC Units. This information could help to guide consumers on the number of standard doses each product contains at the point of sale (Figure 2). Evidence from Canadian respondents suggests that labels listing the number of doses on edible products were more effective at conveying information than those listing THC milligrams alone (64). As with other information on product labels, this information should be as accurate as possible while accounting for variation within a product. Qualitative data from the US suggests that serving size statements on edible products were considered useful as a "baseline" for how much that product might affect the user (65). It was also reported that serving size suggestions would be easier to comprehend if they were made equivalent to the number of "hits" on a joint rather than simply listing the number of milligrams (65). This suggests that there may be value in the concept of a Standard THC Unit and applying it to multiple cannabis products. Labelling of Standard THC Units could be incorporated into existing Lower Risk Cannabis Use Guidelines (17) such that they can provide specific recommendations based on quantity of use. Standard THC Units could be used to

inform specific policies such as minimum unit pricing, which might be especially effective at reducing harmful levels of consumption on the basis of alcohol research (66).

A major challenge for Standard THC Unit implementation is understanding how they can be applied across different products and routes of administration. This is particularly important when considering inhaled and oral administration, which have not been accounted for in previous proposals for standard cannabis units (Table 3). There are important differences in bioavailability and time-concentration profile of inhaled and oral THC. Bioavailability following inhaled THC typically ranges from 10%-35% and is influenced by factors such as the number, duration and spacing of inhalations as well as side stream smoke (67). Oral administration is characterised by significant first pass metabolism in the liver, lower bioavailability (2-14%) (67), a slower onset of absorption, lower peak concentrations and longer elimination when compared to inhaled cannabis, as well as higher 11-nor-9-carboxy-THC concentrations (68). It has been proposed that 1 milligram of THC in oral form might be considered pharmacokinetically equivalent to 5.71 milligrams of THC in inhaled form (69). However, these calculations were not based on the subjective effects of THC. Such effects have a slower onset and longer duration following oral versus inhaled administration (70, 71). However, the peak level of subjective effects has been found to be comparable between these routes (Ohlsson et al., (70); infrequent users in Newmeyer et al. (71)). Peak subjective effects may be an important component of what constitutes a Standard THC Unit (i.e. the maximum level of 'stoned' or 'good drug effect'). Therefore, these findings suggest that the same sized THC unit could be applied across oral, vaporized and smoked routes of administration (71).

We acknowledge that it will not be possible to achieve complete equivalency in the subjective effects of a Standard THC Unit across different routes of administration (as with any conversion across routes). Subjective effects may be influenced by variation in cannabis use behaviours (such as smoking topography (72)) and other factors such as tolerance (71). There are also differences in the health effects of using different methods of cannabis administration (e.g. smoking being most harmful) as recommended by current Lower Risk Cannabis Use Guidelines (16). However, using the same standardised THC unit across different products could have significant advantages in terms of acceptability, feasibility and product labelling. For example, herbal cannabis can be consumed in multiple ways including smoking, vaping and eating and many others methods (Table 2). If the size of Standard THC Unit differed for each of these methods, consumers may it difficult to understand and estimate their unit consumption, especially if they use cannabis in a variety of ways. Labelling multiple unit sizes on a single package might create complex labels that are difficult for consumers to comprehend. This contrasts with the principle that labelling on cannabis products should be clear and

require minimal numeracy to understand (73). Therefore, labelling each cannabis product with a fixed number of Standard THC Units – which apply to all methods of use – could allow standard units to be easily implemented and better understood by consumers.

Another major challenge is establishing how many milligrams of THC should form one Standard THC Unit. Experimental studies have shown that inhaled and oral doses of THC ranging from approximately 2 to 8 milligrams can have intoxicating effects without producing severe adverse responses among infrequent users (22, 74-76). Given that frequent cannabis users can develop tolerance to the effects of THC (77) they may consume higher doses during typical use. However, 8 milligrams vaporized THC was found to produce robust subjective, cognitive and psychotomimetic effects in daily cannabis users (28, 44). This approximate dose range (2 to 8 milligrams) is supported by ecological data from a study in Barcelona (54) which estimated that a Standard Joint Unit should contain 7 milligrams of THC, on the basis of analysis of joints containing herbal cannabis or cannabis resin.

From a public health perspective, it may be considered advantageous to choose a standard THC unit that is lower than the average level of consumption (73). This could encourage people to consume less THC, as reducing the serving size of an alcoholic drink has been found to lower alcohol consumption both in experimental and real-world settings (78). A low dose could also reduce the chances of an excessive and/or unpleasant response to a single THC unit in naïve volunteers. For example, in a study administering 10 milligrams of oral THC people to people with minimal exposure (less than 15 lifetime occasions of use), 33% of the sample experienced a severe reaction such as paranoia (79). Another study of volunteers reporting no cannabis use in the past month found that 12% of the sample vomited after receiving an inhaled dose of 25mg THC (24).

The risk of unintentional or excessive dosing is especially high for edible products, due to the slow onset of effects which limits ability to titrate effects. A study in Colorado found that ingestion was responsible for 74% of all paediatric regional poison centre admissions for cannabis (80). At the time of writing, the maximum quantity of THC that can be sold in a single serving of edible is 5 milligrams in Alaska and Oregon and 10 milligrams in Colorado and Washington (81). Regulations for Canada include a limit of 10 milligrams THC for edibles (per package) and 10 milligrams THC for ingested extracts (per capsule or dispensed amount) (82). On the basis of experimental and ecological data, public health considerations, and existing policy we propose that a Standard THC Unit should be fixed at 5 milligrams of THC for all cannabis products and methods of administration. In terms of edible products, this would allow the same unit size to be applied across different regions within current legislation (half of the maximum serving size in Colorado,

Washington and Canada; the maximum serving size in Alaska and Oregon). The same 5 milligram THC unit could be applied to other products (Figure 1) including pre-rolled joints (Figure 2) to guide consumers on recommended dosage. We argue that a Standard THC Unit of 5 milligrams has the potential to be acceptable as meaningful standard dose, while being low enough to minimise the risk of adverse effects after consuming a single unit. Standard THC Units could be incorporated into Lower Risk Cannabis Use Guidelines (17) to permit quantitative recommendations for safer use.

Remaining challenges

Accounting for CBD may also be important as varying levels of CBD are present in cannabis and may influence its health effects (15). Canada's Lower Risk Cannabis Use Guidelines currently refer to CBD in terms of the CBD:THC ratio (17). However, the evidence for CBD protecting against THC harms is preliminary at present and further research is needed strengthen the evidence and identify dose-response effects (15). If supported by adequate evidence, consumption of CBD units might be recommended in future as a strategy to mitigate the harms of THC unit consumption. Such guidelines might be considered acceptable to people who use cannabis if CBD units could mitigate THC harms without compromising the 'high' they seek, as suggested by some research (15). A recent survey of people residing in US states where recreational cannabis use is legally sold found that CBD content was consistently rated as the one of the most attractive attributes of cannabis products (83). Evaluating the health impact of CBD in cannabis should be a priority given its significant interest to consumers.

Introducing Standard THC Units to public health guidelines may not be feasible in jurisdictions where cannabis use is prohibited. Illicit markets can also create barriers for research on standard units, such as participant recruitment, drug administration and collection of samples. However, if a consensus is reached on which metrics should be used to define Standard THC Units in legal markets, these "ideal criteria" could be used to update and harmonise international research methodology and clinical tools. Moving towards the quantification of active pharmacological products (THC and CBD) could improve our understanding of cannabis use and its consequences. Some researchers are already using milligrams of THC as a metric to estimate long-term THC exposure (84). Dosage of THC and CBD in milligrams can be estimated by combining information on the (i) quantity of cannabis product used, (ii) the type of product used, and (iii) its estimated THC and CBD concentration. Precision may be increased by asking people to physically estimate the amount of cannabis they use with cannabis material (85) or a substitute (85-87). The increasing number of studies quantifying THC and CBD

concentrations in illicit cannabis markets (61, 62, 88-94) and the use of pictorial aids (Figure 1) during substance use assessments (95, 96) may help to improve estimation of THC and CBD exposure in jurisdictions where cannabis use is illegal.

Conclusion

Standardising dosage using fixed quantities of THC could allow the same units to be applied across different cannabis products and routes of administration. Multidisciplinary debates in the international community of researchers, policy makers, clinicians and people who use cannabis will be instrumental for gaining consensus on standard units and their inclusion in lower risk guidelines.

References

1. UNODC. World drug report 2018. In: UNDOC, editor. World drug report series 2018: United Nations Office on Drugs and Crime; 2018.
2. Cerdá M., Wall M., Feng T., Keyes K. M., Sarvet A., Schulenberg J. et al. Association of state recreational marijuana laws with adolescent marijuana use, JAMA pediatrics 2017: 171: 142-149.
3. EMCDDA. Cannabis legislation in Europe: an overview, Publications Office of the European Union, Luxembourg; 2018.
4. Freeman T. P., Hindocha C., Green S. F., Bloomfield M. A. Medicinal use of cannabis based products and cannabinoids, BMJ 2019: 365: l1141.
5. Curran H. V., Freeman T. P., Mokrysz C., Lewis D. A., Morgan C. J., Parsons L. H. Keep off the grass? Cannabis, cognition and addiction, Nature Reviews Neuroscience 2016: 17: 293-306.
6. Volkow N. D., Swanson J. M., Evins A. E., DeLisi L. E., Meier M. H., Gonzalez R. et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review, JAMA psychiatry 2016: 73: 292-297.
7. Bloomfield M. A., Hindocha C., Green S. F., Wall M. B., Lees R., Petrilli K. et al. The neuropsychopharmacology of cannabis: a review of human imaging studies, Pharmacology & therapeutics 2018: 195: 132-161.
8. Blanco C., Hasin D. S., Wall M. M., Flórez-Salamanca L., Hoertel N., Wang S. et al. Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study, JAMA psychiatry 2016: 73: 388-395.
9. Silins E., Horwood L. J., Patton G. C., Fergusson D. M., Olsson C. A., Hutchinson D. M. et al. Young adult sequelae of adolescent cannabis use: an integrative analysis, The Lancet Psychiatry 2014: 1: 286-293.
10. Gage S. H., Jones H. J., Burgess S., Bowden J., Smith G. D., Zammit S. et al. Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study, Psychological medicine 2017: 47: 971-980.
11. Vaucher J., Keating B. J., Lasserre A. M., Gan W., Lyall D. M., Ward J. et al. Cannabis use and risk of schizophrenia: a Mendelian randomization study, Molecular psychiatry 2017.
12. NCAM C. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia, 2018.
13. Moore T. H., Zammit S., Lingford-Hughes A., Barnes T. R., Jones P. B., Burke M. et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review, The Lancet 2007: 370: 319-328.
14. Marconi A., Di Forti M., Lewis C. M., Murray R. M., Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis, Schizophrenia bulletin 2016: 42: 1262-1269.
15. Englund A., Freeman T. P., Murray R. M., McGuire P. Can we make cannabis safer?, The Lancet Psychiatry 2017: 4: 643-648.
16. Fischer B., Russell C., Sabioni P., van den Brink W., Le Foll B., Hall W. et al. Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations, American journal of public health 2017: 107: e1-e12.
17. https://www.camh.ca/-/media/files/pdfs---reports-and-books---research/canadas-lower-risk-guidelines-cannabis-pdf.pdf.
18. Lorenzetti V., Solowij N., Yücel M. The role of cannabinoids in neuroanatomic alterations in cannabis users, Biological psychiatry 2016: 79: e17-e31.
19. Solowij N., Lorenzetti V., Yücel M. Effects of cannabis use on human behavior: A call for standardization of cannabis use metrics, JAMA Psychiatry 2016: 73: 995-996.
20. Temple E. C., Brown R. F., Hine D. W. The 'grass ceiling': limitations in the literature hinder our understanding of cannabis use and its consequences, Addiction 2011: 106: 238-244.
21. NIDA. Recommendations for NIDA's Cannabis Policy Research Agenda. Report from the Cannabis Policy Research Workgroup, 2018.

22. CURRAN V. H., BRIGNELL C., FLETCHER S., MIDDLETON P., HENRY J. Cognitive and subjective dose-response effects of acute oral Δ 9-tetrahydrocannabinol (THC) in infrequent cannabis users, Psychopharmacology 2002: 164: 61-70.
23. D'SOUZA D. C., PERRY E., MACDOUGALL L., AMMERMAN Y., COOPER T., BRALEY G. et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis, Neuropsychopharmacology 2004: 29: 1558.
24. SPINDLE T. R., CONE E. J., SCHLIENZ N. J., MITCHELL J. M., BIGELOW G. E., FLEGEL R. et al. Acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis: a crossover trial, JAMA network open 2018: 1: e184841-e184841.
25. BHATTACHARYYA S., MORRISON P. D., FUSAR-POLI P., MARTIN-SANTOS R., BORGWARDT S., WINTON-BROWN T. et al. Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology, Neuropsychopharmacology 2010: 35: 764.
26. MORGAN C. J., SCHAFER G., FREEMAN T. P., CURRAN H. V. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study, The British Journal of Psychiatry 2010: 197: 285-290.
27. ENGLUND A., MORRISON P. D., NOTTAGE J., HAGUE D., KANE F., BONACCORSO S. et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment, Journal of Psychopharmacology 2013: 27: 19-27.
28. HINDOCHA C., FREEMAN T. P., SCHAFER G., GARDENER C., DAS R. K., MORGAN C. J. et al. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users, European Neuropsychopharmacology 2015: 25: 325-334.
29. FREEMAN T. P., POPE R. A., WALL M. B., BISBY J. A., LUIJTEN M., HINDOCHA C. et al. Cannabis dampens the effects of music in brain regions sensitive to reward and emotion, International Journal of Neuropsychopharmacology 2017: 21: 21-32.
30. LAWN W., FREEMAN T. P., POPE R. A., JOYE A., HARVEY L., HINDOCHA C. et al. Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis 'amotivational'hypotheses, Psychopharmacology 2016: 233: 3537-3552.
31. MORGAN C. J., FREEMAN T. P., SCHAFER G. L., CURRAN H. V. Cannabidiol attenuates the appetitive effects of Δ 9-tetrahydrocannabinol in humans smoking their chosen cannabis, Neuropsychopharmacology 2010: 35: 1879.
32. FREEMAN T., WINSTOCK A. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence, Psychological medicine 2015: 45: 3181-3189.
33. MEIER M. H. Associations between butane hash oil use and cannabis-related problems, Drug & Alcohol Dependence 2017: 179: 25-31.
34. BIDWELL L. C., YORKWILLIAMS S. L., MUELLER R. L., BRYAN A. D., HUTCHISON K. E. Exploring cannabis concentrates on the legal market: User profiles, product strength, and health-related outcomes, Addictive behaviors reports 2018: 8: 102-106.
35. FREEMAN T. P., VAN DER POL P., KUIJPERS W., WISSELINK J., DAS R. K., RIGTER S. et al. Changes in cannabis potency and first-time admissions to drug treatment: a 16-year study in the Netherlands, Psychological Medicine 2018: 48: 2346-2352.
36. ARTERBERRY B. J., PADOVANO H. T., FOSTER K. T., ZUCKER R. A., HICKS B. M. Higher average potency across the United States is associated with progression to first cannabis use disorder symptom, Drug and alcohol dependence 2019: 195: 186-192.
37. DI FORTI M., MARCONI A., CARRA E., FRAIETTA S., TROTTA A., BONOMO M. et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study, The Lancet Psychiatry 2015: 2: 233-238.
38. DI FORTI M., QUATTRONE D., FREEMAN T. P., TRIPOLI G., GAYER-ANDERSON C., QUIGLEY H. et al. The Contribution of Cannabis Use to Variation in the Incidence of Psychotic Disorder across Europe: the EUGEI case-control study, The Lancet Psychiatry 2019.

39. SCHOELER T., PETROS N., DI FORTI M., KLAMERUS E., FOGLIA E., AJNAKINA O. et al. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study, The Lancet Psychiatry 2016: 3: 947-953.
40. MORGAN C. J., CURRAN H. V. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis, The British Journal of Psychiatry 2008: 192: 306-307.
41. MORGAN C., GARDENER C., SCHAFER G., SWAN S., DEMARCHI C., FREEMAN T. et al. Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being, Psychological medicine 2012: 42: 391-400.
42. YÜCEL M., LORENZETTI V., SUO C., ZALESKY A., FORNITO A., TAKAGI M. J. et al. Hippocampal harms, protection and recovery following regular cannabis use, Translational psychiatry 2016: 6: e710.
43. DEMIRAKCA T., SARTORIUS A., ENDE G., MEYER N., WELZEL H., SKOPP G. et al. Diminished gray matter in the hippocampus of cannabis users: possible protective effects of cannabidiol, Drug and alcohol dependence 2011: 114: 242-245.
44. MORGAN C. J., FREEMAN T. P., HINDOCHA C., SCHAFER G., GARDNER C., CURRAN H. V. Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function, Translational psychiatry 2018: 8: 181.
45. SOLOWIJ N., BROYD S., GREENWOOD L.-M., VAN HELL H., MARTELOZZO D., RUEB K. et al. A randomised controlled trial of vaporised Δ 9-tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects, European archives of psychiatry and clinical neuroscience 2019: 269: 17-35.
46. ARKELL T. R., LINTZERIS N., KEVIN R. C., RAMAEKERS J. G., VANDREY R., IRWIN C. et al. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition, Psychopharmacology 2019: 1-12.
47. DE MEIJER E. P., BAGATTA M., CARBONI A., CRUCITTI P., MOLITERNI V. C., RANALLI P. et al. The inheritance of chemical phenotype in Cannabis sativa L, Genetics 2003: 163: 335-346.
48. ENGLUND A., ATAKAN Z., KRALJ A., TUNSTALL N., MURRAY R., MORRISON P. The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: a placebo-controlled, double-blind, crossover pilot trial, Journal of psychopharmacology 2016: 30: 140-151.
49. RUSSO E. B. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects, British journal of pharmacology 2011: 163: 1344-1364.
50. SPINDLE T. R., BONN-MILLER M. O., VANDREY R. Changing Landscape of Cannabis: Novel Products, Formulations, and Methods of Administration, Current Opinion in Psychology 2019.
51. HINDOCHA C., FREEMAN T. P., FERRIS J. A., LYNSKEY M. T., WINSTOCK A. R. No smoke without tobacco: a global overview of cannabis and tobacco routes of administration and their association with intention to quit, Frontiers in psychiatry 2016: 7: 104.
52. CAULKINS J. P., BAO Y., DAVENPORT S., FAHLI I., GUO Y., KINNARD K. et al. Big data on a big new market: Insights from Washington State's legal cannabis market, International Journal of Drug Policy 2018: 57: 86-94.
53. KUMAR R., CHAMBERS W., PERTWEE R. Pharmacological actions and therapeutic uses of cannabis and cannabinoids, Anaesthesia 2001: 56: 1059-1068.
54. CASAJUANA KÖGEL C., BALCELLS-OLIVERO M. M., LÓPEZ-PELAYO H., MIQUEL L., TEIXIDÓ L., COLOM J. et al. The Standard Joint Unit, Drug and Alcohol Dependence 2017: 176: 109-116.
55. ZEISSER C., THOMPSON K., STOCKWELL T., DUFF C., CHOW C., VALLANCE K. et al. A 'standard joint'? The role of quantity in predicting cannabis-related problems, Addiction Research & Theory 2012: 20: 82-92.
56. WETHERILL R. R., HAGER N., GUTHIER E., FRANKLIN T. R. Gram years: a method to standardize and quantify lifetime cannabis consumption, Cannabis and cannabinoid research 2016: 1: 216-217.
57. NORBERG M. M., WRIGHT T., HICKEY K., COPELAND J. A postal intervention for dependent cannabis users, Drug and alcohol review 2012: 31: 320-326.
58. CASAJUANA C., LÓPEZ-PELAYO H., MIQUEL L., BALCELLS-OLIVERÓ M. M., COLOM J., GUAL A. Quantitative Criteria to Screen for Cannabis Use Disorder, European addiction research 2018: 24: 109-117.

59. 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: 1801-1808.
60. FREEMAN T. P., MORGAN C. J., HINDOCHA C., SCHAFER G., DAS R. K., CURRAN H. V. Just say 'know': how do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints?, Addiction 2014: 109: 1686-1694.
61. CHANDRA S., RADWAN M. M., MAJUMDAR C. G., CHURCH J. C., FREEMAN T. P., ELSOHLY M. A. New trends in cannabis potency in USA and Europe during the last decade (2008–2017), European archives of psychiatry and clinical neuroscience 2019: 1-11.
62. FREEMAN T. P., GROSHKOVA T., CUNNINGHAM A., SEDEFOV R., GRIFFITHS P., LYNKSEY M. T. Increasing potency and price of cannabis in Europe, 2006-2016, Addiction 2019.
63. HINDOCHA C., NORBERG M. M., TOMKO R. L. Solving the problem of cannabis quantification, Lancet 2017: 4: 643-648.
64. LEOS-TORO C. Health warnings, cannabis marketing and perceptions among youth and young adults in Canada, 2019.
65. KOSA K. M., GIOMBI K. C., RAINS C. B., CATES S. C. Consumer use and understanding of labelling information on edible marijuana products sold for recreational use in the states of Colorado and Washington, International Journal of Drug Policy 2017: 43: 57-66.
66. HOLMES J., MENG Y., MEIER P. S., BRENNAN A., ANGUS C., CAMPBELL-BURTON A. et al. Effects of minimum unit pricing for alcohol on different income and socioeconomic groups: a modelling study, The Lancet 2014: 383: 1655-1664.
67. GROTENHERMEN F. Pharmacokinetics and pharmacodynamics of cannabinoids, Clinical pharmacokinetics 2003: 42: 327-360.
68. NEWMEYER M. N., SWORTWOOD M. J., BARNES A. J., ABULSEOUD O. A., SCHEIDWEILER K. B., HUESTIS M. A. Free and glucuronide whole blood cannabinoids' pharmacokinetics after controlled smoked, vaporized, and oral cannabis administration in frequent and occasional cannabis users: identification of recent cannabis intake, Clinical chemistry 2016: clinchem. 2016.263475.
69. ORENS A., LIGHT M., ROWBERRY J., MATSEN J., LEWANDOWSKI B. Marijuana Equivalency in Portion and Dosage: An assessment of physical and pharmacokinetic relationships in marijuana production and consumption in Colorado, Colorado Department of Revenue 2015.
70. OHLSSON A., LINDGREN J. E., WAHLEN A., AGURELL S., HOLLISTER L., GILLESPIE H. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking, Clinical Pharmacology & Therapeutics 1980: 28: 409-416.
71. NEWMEYER M. N., SWORTWOOD M. J., ABULSEOUD O. A., HUESTIS M. A. Subjective and physiological effects, and expired carbon monoxide concentrations in frequent and occasional cannabis smokers following smoked, vaporized, and oral cannabis administration, Drug and alcohol dependence 2017: 175: 67-76.
72. VAN DER POL P., LIEBREGTS N., BRUNT T., AMSTERDAM J., GRAAF R., KORF D. J. et al. Cross-sectional and prospective relation of cannabis potency, dosing and smoking behaviour with cannabis dependence: an ecological study, Addiction 2014: 109: 1101-1109.
73. HAMMOND D. Communicating THC levels and 'dose'to consumers: Implications for product labelling and packaging of cannabis products in regulated markets, International Journal of Drug Policy 2019.
74. STROUGO A., ZUURMAN L., ROY C., PINQUIER J., VAN GERVEN J., COHEN A. et al. Modelling of the concentration—effect relationship of THC on central nervous system parameters and heart rate—insight into its mechanisms of action and a tool for clinical research and development of cannabinoids, Journal of Psychopharmacology 2008: 22: 717-726.
75. VAN HELL H. H., BOSSONG M. G., JAGER G., KAHN R. S., RAMSEY N. F. Methods of the pharmacological imaging of the cannabinoid system (PhICS) study: towards understanding the role of the brain endocannabinoid system in human cognition, International Journal of Methods in Psychiatric Research 2011: 20: 10-27.
76. MCDONALD J., SCHLEIFER L., RICHARDS J. B., DE WIT H. Effects of THC on behavioral measures of impulsivity in humans, Neuropsychopharmacology 2003: 28: 1356.

77. D'SOUZA D. C., RANGANATHAN M., BRALEY G., GUEORGUIEVA R., ZIMOLO Z., COOPER T. et al. Blunted psychotomimetic and amnestic effects of Δ-9-tetrahydrocannabinol in frequent users of cannabis, Neuropsychopharmacology 2008: 33: 2505.
78. KERSBERGEN I., OLDHAM M., JONES A., FIELD M., ANGUS C., ROBINSON E. Reducing the standard serving size of alcoholic beverages prompts reductions in alcohol consumption, Addiction 2018.
79. MARTIN-SANTOS R., A CRIPPA J., BATALLA A., BHATTACHARYYA S., ATAKAN Z., BORGWARDT S. et al. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers, Current pharmaceutical design 2012: 18: 4966-4979.
80. WANG G. S., LE LAIT M.-C., DEAKYNE S. J., BRONSTEIN A. C., BAJAJ L., ROOSEVELT G. Unintentional pediatric exposures to marijuana in Colorado, 2009-2015, JAMA pediatrics 2016: 170: e160971-e160971.
81. GOURDET C., GIOMBI K. C., KOSA K., WILEY J., CATES S. How four US states are regulating recreational marijuana edibles, International Journal of Drug Policy 2017: 43: 83-90.
82. HTTPS://WWW.CANADA.CA/EN/HEALTH-CANADA/SERVICES/DRUGS-MEDICATION/CANNABIS/RESOURCES/REGULATIONS-EDIBLE-CANNABIS-EXTRACTS-TOPICALS.HTML.
83. SHI Y., CAO Y., SHANG C., PACULA R. L. The impacts of potency, warning messages, and price on preferences for Cannabis flower products, International Journal of Drug Policy 2019: 74: 1-10.
84. THAYER R. E. Marijuana Use in an Aging Population: Global Brain Structure and Cognitive Function, 2018.
85. HINDOCHA C., FREEMAN T. P., CURRAN H. V. Anatomy of a joint: comparing self-reported and actual dose of cannabis and tobacco in a joint, and how these are influenced by controlled acute administration, Cannabis and cannabinoid research 2017: 2: 217-223.
86. NORBERG M. M., MACKENZIE J., COPELAND J. Quantifying cannabis use with the Timeline Followback approach: A psychometric evaluation, Drug and alcohol dependence 2012: 121: 247-252.
87. TOMKO R. L., BAKER N. L., MCCLURE E. A., SONNE S. C., MCRAE-CLARK A. L., SHERMAN B. J. et al. Incremental validity of estimated cannabis grams as a predictor of problems and cannabinoid biomarkers: Evidence from a clinical trial, Drug and alcohol dependence 2018: 182: 1-7.
88. SWIFT W., WONG A., LI K. M., ARNOLD J. C., MCGREGOR I. S. Analysis of cannabis seizures in NSW, Australia: cannabis potency and cannabinoid profile, PloS one 2013: 8: e70052.
89. DUJOURDY L., BESACIER F. A study of cannabis potency in France over a 25 years period (1992–2016), Forensic science international 2017: 272: 72-80.
90. NIESINK R. J., RIGTER S., KOETER M. W., BRUNT T. M. Potency trends of Δ9-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005–15, Addiction 2015: 110: 1941-1950.
91. ZAMENGO L., FRISON G., BETTIN C., SCIARRONE R. Cannabis potency in the Venice area (Italy): update 2013, Drug testing and analysis 2015: 7: 255-258.
92. POTTER D. J., HAMMOND K., TUFFNELL S., WALKER C., DI FORTI M. Potency of Δ9–tetrahydrocannabinol and other cannabinoids in cannabis in England in 2016: Implications for public health and pharmacology, Drug testing and analysis 2018.
93. STAMBOULI H., EL BOURI A., BOUAYOUN T. Évolution de la teneur en Δ9-THC dans les saisies de résines de cannabis au Maroc de 2005 à 2014, Toxicologie Analytique et Clinique 2016: 28: 146-152.
94. RØMER THOMSEN K., LINDHOLST C., THYLSTRUP B., KVAMME S., REITZEL L. A., WORM-LEONHARD M. et al. Changes in the composition of cannabis from 2000-2017 in Denmark: analysis of confiscated samples of cannabis resin, Experimental and Clinical Psychopharmacology 2019.
95. WILSON J., FREEMAN T. P., MACKIE C. J. Effects of increasing cannabis potency on adolescent health, The Lancet Child & Adolescent Health 2018: http://dx.doi.org/10.1016/S2352-4642(1018)30342-30340.
96. LISDAHL K. M., SHER K. J., CONWAY K. P., GONZALEZ R., EWING S. W. F., NIXON S. J. et al. Adolescent brain cognitive development (ABCD) study: overview of substance use assessment methods, Developmental cognitive neuroscience 2018: 32: 80-96.

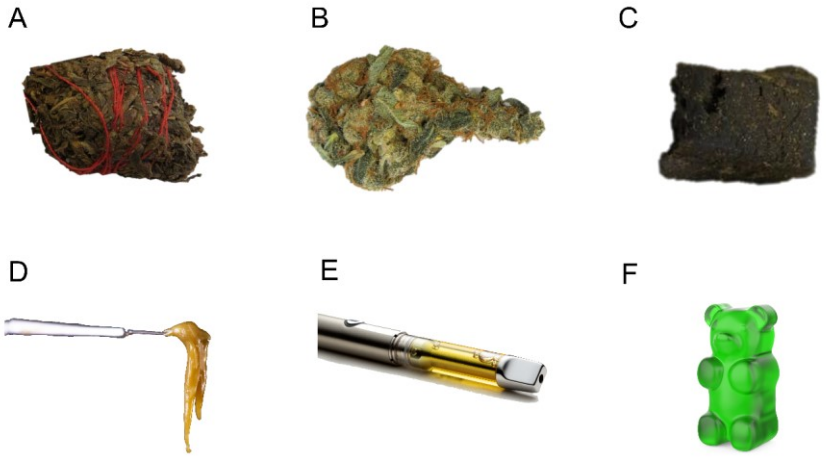

Figure 1: Heterogeneity in cannabis products: (A) Outdoor-grown herbal cannabis or ‘imported herbal cannabis’; (B) Indoor-grown herbal cannabis or ‘sinsemilla’; (C) Cannabis resin or ‘hashish’; (D) Cannabis concentrates used for ‘dabbing’; (E) Vape pen containing cannabinoids; (F) Edible gummy bear containing cannabinoids.

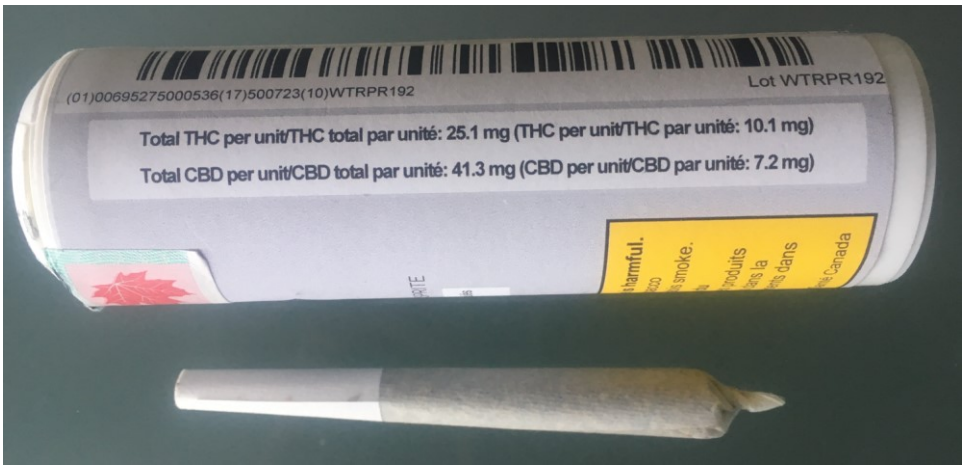

Figure 2: A package containing pre-rolled cannabis joints sold in Canada. Labels include the total quantity of THC (25.1mg) and CBD (41.3mg) per joint. No information is provided on the number of standard doses each joint contains. In order to guide consumers, labels could include additional information such as “Each unit [joint] contains five standard doses of THC”.

Table 1: Heterogeneity in typical concentrations of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) across cannabis products and countries

Country, year	Reference	Outdoor-grown herbal	Indoor-grown herbal	Resin	Concentrates
USA, 2017	(61)	9% THC, <1% CBD	18% THC, <1% CBD	46% THC, <1% CBD	56% THC, <1% CBD
Australia, 2010-12	(88)	15% THC, <1% CBD	19% THC, <1% CBD	-	-
UK, 2015-16	(92)	3% THC, <1% CBD	14% THC, <1% CBD	6% THC, 2% CBD	78% THC, <1% CBD
Netherlands, 2015	(90)	5% THC, <1% CBD	15% THC, <1%CBD	18% THC, 8% CBD	-
France, 2016	(89)	-	-	23% THC, 4% CBD	-
Denmark, 2017	(94)	-	-	23% THC, 6% CBD	-

Table 2: Heterogeneity in methods of administration of cannabis products

Method	Route	Combined with tobacco
Joint	Inhaled, combusted	Yes/No
Pipe	Inhaled, combusted	Yes/No
Blunt	Inhaled, combusted	Yes
Bong	Inhaled, combusted	Yes/No
Dabbing	Inhaled, combusted	Yes/No
Vaporizer	Inhaled, vaporized	Yes/No
Vape pen	Inhaled, vaporized	Yes/No
Edible	Oral	No
Liquid	Oral	No

Table 3: Existing proposals for standard cannabis units/standardised measures of quantity

First author, year	Reference	Standard cannabis unit	Description	Strengths: accounts for	Limitations: does not account for
Wetherill, 2016	(56)	Gram Years	Number of daily grams consumed, multiplied by years of cannabis use	Some different methods of administration	Variation in quantities of THC and CBD
Casajuana-Kögel, 2017	(54)	Standard Joint Unit	1 unit = 1 joint, *or* .25 grams cannabis, *or* 7 milligrams THC, *or* 1 Euro.	The most common method of administration in Europe	Variation in quantities of THC and CBD and other methods of administration
Ziesser, 2012	(55)	Standard Joint	1 standard joint = 0.5 grams cannabis, 10 puffs *or* 5 bong hits, *or* 5 pipe hits	Some different administration methods and/or number of puffs	Variation in quantities of THC and CBD and other methods of administration
Norberg, 2012	(57)	Cannabis Unit	1 unit = 0.25 grams cannabis, *or* 1 paper joint *or* 1 blunt, *or* 2 skinny paper joint/blunt , *or* 3 cones/water pipes/bongs/bucket bongs	Some different sizes of joint and methods of administration	Variation in quantities of THC and CBD and other methods of administration
Hindocha, 2017	(63)	THC/CBD ratios	High THC & low CBD (e.g. 1 unit = .25 gram) Equal THC & CBD (e.g. 1 unit = .50 gram) High CBD & low THC (e.g. 1 unit = .75 gram)	Some variation in THC/CBD ratios	Variation in quantities of THC and CBD