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Cannabis Tolerance: A Scope Review

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ABSTRACT

Cannabis is a widely consumed drug, so studying the effects of its chronic consumption becomes relevant. Regarding chronic consumption, the phenomenon of tolerance has been described in several drugs, including cannabis. Currently, multiple studies have addressed this phenomenon, with high heterogeneity in terms of methodology, evidence, and results. We aim to describe and analyze the literature on cannabis tolerance evaluated in physiological, cognitive, behavioral, and subjective responses, incorporating a critical perspective to account for some gaps and controversies in its study. Cannabis tolerance shows a disparity between the effects produced after a first administration compared to its chronic use. Each of them incorporates heterogeneity of cannabinoids, doses, and routes of administration. Also, there is diversity in the regularity and temporal extension of consumption and its effects at the different response levels. Even when the heterogeneity of measurements allows for incorporating different perspectives, this results in poor standardization and a lack of rigor in what is understood as cannabis tolerance. Furthermore, there is no consideration of the stimuli present at drug administration, which have been relevant in the understanding of tolerance to other drugs as a learning process. Cannabis tolerance should be further studied, incorporating rigorous definitions and measurements that allow the phenomenon to be addressed in a global and standardized manner.

Keywords
tolerance, associative tolerance, chronic consumption, THC, CBD

RESUMEN

El cannabis es una droga ampliamente consumida, por lo que el estudio de los efectos de su consumo crónico adquiere relevancia. Respecto al consumo crónico, se ha descrito el fenómeno de la tolerancia en varias drogas, entre ellas el cannabis. En la actualidad, múltiples estudios han abordado este fenómeno, con una alta heterogeneidad en cuanto a metodologíaí, evidencia y resultados. Nuestro objetivo es describir y analizar la literatura sobre tolerancia al cannabis evaluada en respuestas fisiológicas, cognitivas, conductuales y subjetivas, incorporando una perspectiva crítica para dar cuenta de algunas lagunas y controversias en su estudio. La tolerancia al cannabis muestra una disparidad entre los efectos producidos tras una primera administración frente a su consumo crónico. Cada uno de ellos incorpora heterogeneidad de cannabinoides, dosis y vías de administración. También existe diversidad en la regularidad y extensión temporal del consumo, así como en sus efectos en los diferentes niveles de respuesta. Aun cuando la heterogeneidad de las mediciones permite incorporar diferentes perspectivas, ello redunda en una escasa estandarización y falta de rigor en lo que se entiende por tolerancia al cannabis. Además, no se tienen en cuenta los estímulos presentes en el momento de la administración de la droga, que han sido relevantes en la comprensión de la tolerancia a otras drogas como un proceso de aprendizaje. La tolerancia al cannabis debe ser estudiada en mayor profundidad, incorporando definiciones y mediciones rigurosas que permitan abordar el fenómeno de forma global y estandarizada.

Palabras clave
tolerancia, tolerancia asociativa, consumo crónico, THC, CBD

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Tolerancia al cannabis: una revisión de alcance

Introduction

Cannabis is currently one of the most widely consumed drugs worldwide (United Nations Office on Drugs and Crime, 2022), and many countries have even legalized its medical or recreational use, generating a remarkable interest in its research.

Cannabis is composed of multiple cannabinoids, such as THC (Δ9-tetrahydrocannabinol) and CBD (cannabidiol) as the most remarkable (Castaño-Pérez et al., 2017; ElSohly et al., 2017). Its effects have been defined as psychoactive, which may affect several neurophysiological processes that are modulated by the endocannabinoid system (González at al., 2005), such as pain regulation, memory and attentional processes, anxiety, paranoia, hypotension, among others (e.g., Castaño-Pérez et al., 2017; Miller et al., 2018; Parsons & Hurd, 2015; Rutkowska et al., 2006).

Most of the studies about the effects produced by cannabis have focused mainly on the exploration of physiological variables and pharmacodynamics, particularly on the acute consequences that are produced after a brief period following drug administration, including motor coordination affectation (Crean et al., 2011), catalepsy, hypothermia (Hayakawa et al., 2008), sedation (Lucas et al., 2018), and increased blood pressure (Kayser et al., 2020). Also, there is evidence that cannabis produces some neuroprotective (Castillo et al., 2010), anti-inflammatories, analgesics, antioxidants (Hayakawa et al., 2010), anticonvulsants and anxiolytics effects (Castaño-Pérez et al., 2017; Crippa et al., 2011), among others.

Beyond the short-term effects of the drug, growing scientific evidence has shown the consequences of prolonged cannabis use both in human and non-human animals. In this regard, one of the phenomena present in the literature is drug *tolerance*, described as a condition that results from the persistent use of a drug, characterized by a marked decrease in its effects after repeated exposures to the same dose, or as the need to increase the dose of a drug to achieve effects similar to those produced initially by a lower dose (American Psychological Association, 2022; Ritchie & Roser, 2019). Some authors call this phenomenon chronic tolerance (e.g., Berger et al., 2004; San Martín et al., 2017), as such a process is developed by chronic consumption of the substance. On the contrary, acute tolerance has been defined as the decrease in the response to a substance or drug during a single exposure, that is, an organic mechanism of recovery of homeostasis that occurs to cope with the effects produced by the drug (Comley & Dry, 2020; San Martín et al., 2017). This phenomenon has been evidenced with drugs such as alcohol, opioids,

and nicotine, among others (Bespalov et al., 2016; González et al., 2019; Siegel et al., 2000).

Knowledge of the effects of prolonged cannabis use may be relevant, especially considering the discussion around the potential medical use of this drug. Although there is no clear consensus within the scientific community about the safety of its potential medical use (Amato et al., 2017; Black et al., 2019; Castaño-Pérez et al., 2017; Fitzcharles et al., 2016; Mücke et al., 2016; Wang et al., 2008), there are studies that support its therapeutic use for chronic pain (Gruber et al., 2021; Romero-Sandoval et al., 2018), epilepsies resistant to conventional treatments, reduction of nausea and vomiting associated with chemotherapy (Freeman et al., 2019), sleep disorders (Whiting et al., 2015), and the reduction of symptoms associated with obsessive-compulsive disorder (Mauzay, 2021).

To date, the phenomenon of tolerance has been described using several different drugs and methodologies (Gonzalez et al., 2019; Lefkof et al., 2022; Sal et al., 2021), involving different perspectives, tests, and measurements, resulting in a multiplicity of evidence about what is understood as tolerance. Thus, the objective of this review was to describe and analyze the current state of studies regarding cannabis tolerance, incorporating a critical perspective that allows us to account for some literature gaps and controversies, with emphasis on behavioral and physiological effects of cannabis. The literature search included empirical studies, narrative reviews, systematic reviews, meta-analyses, and gray literature associated with keywords such as "tolerance", "dependence", "cannabis", and "marijuana" (Web of Science and PubMed databases were used).

Methodological Heterogeneity of Cannabis Tolerance Studies

Although there is a growing body of literature, studies on cannabis tolerance currently show a large variety of methodological differences. This heterogeneity is expressed in the different drug preparations (i.e., substances), routes of administration, and doses used, just to name a few, which may also vary according to the species to which the subjects studied belong. A description of this methodological heterogeneity is shown in Table 1.

Table 1

Methodological heterogeneity in cannabis tolerance studies

	Species	Study	Preparations	Administration Routes	Doses
Humans		D'Souza et al. (2008)	Δ-9-THC	Intravenous	2.5 or 5 mg
		Gorelick et al. (2013)	Oral synthetic THC (dronabinol)	Oral (20 mg capsules)	40 mg on Day 1, 100 mg on Days 2–4 and 120 mg on Days 5 and 6
		Mason et al. (2021); Ramaekers et al. (2016)	Δ-9-THC	Vaporized	300 μg/kg
		Uliel-Sibony et al. (2021)	Cannabis oil extract (CBD/THC ratio of 20:1)	Oral	Mean CBD dose was 11.3 (4–38) mg/kg/day
Non Human Animals	Mice	Hayakawa et al. (2007)	Δ9-THC	Intraperitoneal	3, 10 mg/kg
			CBD	Intraperitoneal	1, 3 mg/kg
		Henderson-Redmond et al. (2020)	Δ9-THC	Intraperitoneal	30 mg/kg (acute and chronic tolerance)
			CP55,940	Intraperitoneal	0.3 mg/kg (chronic tolerance)
			WIN55,212-2	Intraperitoneal	10 mg/kg (chronic tolerance)
		Henderson-Redmond et al. (2021)	Δ-9-THC	Intraperitoneal	6 and/or 10 mg/kg
		McKinney et al. (2008)	Δ-9-THC	Subcutaneous	10 mg/kg, or escalating doses of 10 to 20 to 30 or 10 to 30 to 60 mg/kg
		Parks et al. (2020)	Δ-9-THC	Intraperitoneal	10 mg/kg THC
	Rat	Gomez et al.	WIN55-212-2	Intravenous	0.2-0.8 mg/kg

	(2021)			
	Greene et al. (2018)	CBD	Intraperitoneal	10 mg/kg
		Δ-9-THC	Intraperitoneal	3.6 mg/kg females; 9.3 mg/kg males
	Hill et al. (2004)	HU-210	Intraperitoneal	150 µg/kg
	Nguyen et al. (2018)	Δ-9-THC	Vaporized	200 mg/ml
	Nguyen et al. (2020)	Δ-9-THC	Vaporized	100 mg/ml
	Wakley et al. (2014)	Δ-9-THC	Intraperitoneal	5.4 mg/kg in females; 7.6 mg/kg in males
Rhesus monkey	Ginsburg et al. (2014)	Δ-9-THC	Intravenous	0.1 mg/kg (intermittent treatment)
		Δ-9-THC	Subcutaneous	1 mg/kg (chronic treatment)
	McMahon (2011)	Δ-9-THC	Intravenous and subcutaneous	0.032-10 mg/kg
		CP 55940	Intravenous and subcutaneous	0.001-0.32 mg/kg
		WIN 55212-2	Intravenous and subcutaneous	0.01-3.2 mg/kg
	Wilkerson et al. (2019)	Δ9-THC	Subcutaneous	1 mg/kg/12 h
		Δ9-THC	Intravenous	0.1 mg/kg
	Winsauer et al. (2011)	Δ9-THC	Intramuscular	0.32 mg/kg

Note. Species are grouped first by Humans and then by non-humans, from top to bottom. Columns contain, from left to right, study reference, drug preparation, administration route and doses. This is not a systematic literature review, so the data presented in this table are only examples of the substances, doses, and routes of administration used in cannabis tolerance studies.

Why would it be important to consider this heterogeneity? Precisely because of the impact that these parameters may have on the results or what is considered "cannabis tolerance". For example, administration route can affect the development of tolerance. Hayakawa et al. (2007) administered 14 daily intraperitoneal injections of 10 mg/kg THC

and evidenced tolerance to neuroprotective and hypothermic effects of the drug, while injections of 3 mg/kg CBD did not produce tolerance effects, demonstrating that even when exposure to both cannabinoids was equally prolonged, the development of tolerance was differential to each one. However, Uliel-Sibony et al. (2021) evaluated the effectiveness of a CBD-enriched oil for the treatment of refractory epilepsy at a daily concentration of 11.3 mg/kg. While 54% of the patients reduced their convulsions were reduced by 50% or more during treatment, 25% of the patients evaluated developed tolerance to the substance after 7 months of exposure. Thus, it is possible to appreciate that, even though the substances evaluated were the same between the two studies, the modification of doses, routes of administration, and number of exposures produce variable results regarding the development of tolerance.

In contrast, if the same cannabinoids, doses, routes of administration, and species are considered, it is possible to find some similarities in the results. In three different studies implemented by Hayakawa et al. (2007), Henderson-Redmond et al. (2021), and Parks et al. (2020), doses of 10 mg/kg THC administered intraperitoneally in mice were used. The results of all three studies show the development of tolerance to various effects. Hayakawa et al. (2007) showed that the subjects developed tolerance to the neuroprotective and hypothermic effects; Henderson-Redmond et al. (2021), meanwhile, argue that both females and males acquired tolerance to the anti-allodynic effects; while Parks et al. (2020) show the development of rapid tolerance to the hypothermic and antinociceptive effects produced by the substance.

Nevertheless, the wide variability described above should also be taken into consideration in the study of cannabis tolerance, since it can make it difficult to establish standardized measurements, making the interpretation of results more difficult.

Tests, Measurements, and Results in Cannabis Studies

Regularity and Temporal Extent of Cannabis Exposure

In terms of timing, some studies indicate that development of tolerance to the effects of this substance may take days (e.g., Bass & Martin, 2000; Parks et al., 2020) or weeks (e.g., Hampson et al., 2003), depending on preparation and substance used. In human studies, the regularity and history of use are relevant, and the distinction between non-users, moderate/occasional users, and chronic users is common, however, there is no clear consensus regarding their classification. Babor (1975) considers moderate users to

be those who use marijuana more than 5 times per month, but less than once per day; while chronic users have at least 2 years of daily marijuana use. D'Souza et al. (2008) describe frequent users as those participants who had a positive toxicological test for cannabis, and at least 10 exposures to the substance in the last month. In contrast, Ramaekers et al. (2009) considered "heavy users" to be those participants who consumed cannabis more than 4 days per week during the year before the study, while occasional users were defined as those who had a single weekly consumption, or less.

The difference in the **"**heavy user" definition would have implications for some results reached by studies using chronic users as experimental subjects because, as reported in the literature, frequent or chronic cannabis users are less sensitive to the effects of the drug in cognitive and psychomotor domains, compared to occasional or non-users (e.g., Colizzi & Bhattacharyya, 2018; Ramaekers et al., 2011).

Regarding the temporal extent of tolerance effects, studies such as Winsauer et al. (2011) have found that tolerance developed to the disruptive effects of THC on a behavioral task was maintained for 7 to 12 months. Bass & Martin (2000) argue that tolerance to antinociceptive effects lasted about 7.5 days after sustained THC administration for 6.5 days, while at 11.5 days after cessation of treatment, subjects showed no tolerance. For their part, Tai et al. (2015), provide evidence that the hypothermic effects of tolerance prolong their duration up to 14 days after the last dose.

These results highlight the need to consider the time it takes for the tolerance phenomenon to develop and its temporal extension to establish regularities on which to interpret the results obtained.

Diversity of Effects: Physiological, Cognitive, Behavioral, and Subjective

Just as there is methodological heterogeneity in the study of cannabis tolerance, it is also possible to find a wide variety of effects, tests, and measurements. Such is the case of physiological effects, including the development of tolerance to the antinociceptive (Nguyen et al., 2018), diuretic (Chopda et al., 2016), hypothermic (Singh et al., 2011), and even neuroprotective effects (Hayakawa et al., 2008).

Other domains that have been widely related to cannabis tolerance have been cognitive and behavioral. In this regard, a systematic review by Colizzi and Bhattacharyya (2018) emphasizes that cognitive function is one of the most likely to be tolerant after chronic exposure to the drug. Ramaekers et al. (2011) demonstrated that

chronic cannabis users develop tolerance to the effects of THC in neurocognitive tests, shown by their performance in the critical monitoring tasks, the "stop-signal task" and the "Tower of London" test, which are sensitive to the effects of THC when used in non-regular users. Withey et al. (2021) showed a similar effect on cognitive performance in a novel visual stimulus discrimination learning task. Moreover, as indicated by Colizzi and Bhattacharyya (2018), the emergence of tolerance could explain the failure of some studies to clarify the acute effects of cannabis on the cognitive performance of frequent users (e.g., Hart et al., 2001, 2010), by not considering this phenomenon as a substantial part of the explanation of why chronic users do not differ in their performance with control or infrequent user groups in some of the cognitive tasks studied.

Regarding the effects of cannabis on motor coordination, Da Silva et al. (2001) report the development of rapid tolerance to THC in a rotarod test. Hill et al. (2004) administered synthetic cannabinoids (HU-210) chronically to rats in an associative paradigm, using an open field test. Here, two different procedures were used: in one, rats were exposed to drug administrations in a particular physical context, and the placebo was delivered in a different physical context (i.e., CS+); while in the other, randomized contexts were used during drug and placebo administration (i.e., CS-). The results showed that rats associated with CS+ developed tolerance significantly faster than rats in the non-associative group (CS-). However, such differences were not found when the CS+ group received drugs in the non-habitual administration context, demonstrating that this enhancement of tolerance development by contextual cues does not necessarily imply dependence on such cues.

One of the measures used in human studies is subjective reports. Mason et al. (2021) in a comparative study of the effects of THC in occasional v/s chronic users, added the subjective rating of feeling “stoned”, measured through a scale that included scores from 0 (not at all stoned) to 10 (extremely stoned). The authors demonstrated that occasional users showed increases in both the subjective state of feeling stoned and other pharmacodynamic tests, while chronic users did not show significant changes in any of them, which could be due to the alteration that these latter subjects have in the reward circuitry resulting from neuroadaptations developed after chronic use of the drug, showing a pharmacodynamic tolerance to cannabis. In contrast, Babor et al. (1975) examined the subjective state of moderate v/s regular users who consumed THC cigarettes for 21 days at a frequency and dose of their choice, using a scale with categories such as "stoned" or "straight". As a result, moderate users rated themselves as slightly

more stoned than regular users. However, these differences were not significant, even though some participants increased their consumption doses over the days, which would indicate a lack of tolerance development.

Overall, these results show that the subjective effects exhibit some variability, which could be a product of both the personal assessment that each subject has of his or her condition, as well as of the administration parameters of each study.

Discussion: Gaps and Controversies

The literature on cannabis tolerance is characterized by a diversity of parameters, tests, measurements, and results. Although this heterogeneity makes it possible to cover a wide spectrum of perspectives, tolerance may not be a unified phenomenon, since it is dependent on the characteristics of each study.

The definition of tolerance is a problem in the literature. Tolerance is defined as the first administration of the drug (e.g., Da Silva et al., 2001; Parks et al., 2020), to the most used definition that incorporates the chronicity of usage (e.g., D'Souza et al., 2008; McMahon, 2011; Nguyen et al., 2018). There is even a wide range of studies that do not provide a definition or specific parameters of what they consider as tolerance beyond the decrease in effects resulting from the chronicity of consumption (e.g., Henderson-Redmond et al., 2020; Nowlan & Cohen, 1977; Winsauer et al., 2011), an issue that should be of concern to researchers in the area. In addition, the processes involved in each of these perspectives require different measurements. In acute or rapid tolerance, the measurements consider a comparison between the first and second or third administration, not requiring continuous and extended monitoring of consumption (Henderson-Redmond et al., 2020; Uran et al., 1980). In chronic tolerance, it can help to elucidate the effects expressed by prolonged or chronic consumption (Mason et al., 2021; Ramaekers et al., 2011), which is why studies should take into consideration the periodicity of consumption.

Another controversial point is the definition of chronic or regular users. A well-defined tolerance concept could explain why regular users manage to have the same effects as control groups or infrequent users, even when they have considerable experience with the drug (Colizzi & Bhattacharyya, 2018). Similarly, there are studies such as those by Ramaekers et al. (2009) and Verrico et al. (2020) that incorporate the comparison between control groups and groups with high consumption experience, and whose results in neurocognitive and memory tests show that chronic consumers have a

decreased initial response to the substance under study compared to non-consumers. However, neither study considers these phenomena as tolerance, which could be just a few of the many cases in the cannabis literature that account for tolerance, even if they do not consider it as such.

Another point of analysis is that the use of subjective variables as a source of information can only be considered as a measure of correlation with other observable variables, such as heart rate, pulse rate, brain activity, and sustained attention tests (Babor et al., 1975; Mason et al., 2021; Nowlan & Cohen, 1977), which could be indicative of how deficient such an indicator can be when applied on its own.

Additionally, part of the variables excluded or that have minimal presence in the cannabis tolerance literature are contextual variables, despite being a fundamental element during the development of tolerance to other drugs (González et al., 2019; Siegel, 1975, 1977, 2005, 2008, 2011, 2016; Siegel et al., 2000), finding in the present review only one study (Hill et al., 2004) that incorporated the association "physical context"-"drug administration context" as an intervening element in the process.

A psychological approach that has been successful in explaining tolerance to drugs such as morphine and ethanol is the Compensatory Responses Model (Siegel, 1975, 2001, 2005, 2008, 2011, 2016; Siegel et al., 2000). From a Pavlovian analysis of tolerance, the stimuli, contexts, and situations present at the time of exposure to a drug serve as conditioned stimuli [CS], whereas the pharmacodynamic effects of the drug function as unconditioned stimuli [US]. When the effects of exposure to a substance disrupt the homeostasis of the organism, it responds with opposing unconditioned responses [UR] that compensate for the effects of the drug (explaining the expression of acute tolerance). After an association is formed between consumption cues [CS] and drug effects [US], the cues begin to elicit responses that mimic the unconditioned responses [CR], helping to decrease the dysregulation caused by the drug and promoting the development of chronic tolerance, which seems to be at least in part associative in nature.

Certainly, this psychological model gives a preponderant role to contextual associations in the development of tolerance, emphasizing learning processes that go beyond the purely physiological or pharmacodynamic effects, allowing a more global understanding of the phenomenon. In this regard, San Martín et al. (2017) warn that one of the difficulties in the representation of tolerance is the lack of consideration of the contextual specificity at the base of the phenomenon. The authors emphasize the importance of considering tolerance as a learning process that encompasses

pharmacodynamic components, but also their relationships with the environmental variables present during drug exposure. The associative model could explain how cues present during drug administration may be get associated with the effects of the drug on the organism, eliciting compensatory responses to regulate homeostasis, and explaining - for example - the reason the responses of some chronic users do not differ substantially from those expressed by control groups.

Future research on cannabis tolerance should incorporate the associative learning approach to provide a richer understanding of this phenomenon. This approach has proven valuable for explaining chronic tolerance (e.g., Betancourt et al., 2008; González et al., 2019; Siegel, 2005), and would be useful in expanding the evidence on the effects of this drug.

As an ending point, continued development of tolerance measurements is crucial for both understanding long-term cannabis effects (Castaño-Pérez et al., 2017) and optimizing clinical applications (Freeman et al., 2019). Prolonged therapeutic use necessitates considering potential tolerance, which should be assessed through comprehensive physiological, behavioral, and cognitive measures.

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