# Post-truth Cannabis use: back to evidence-based medicine

## Posverdad del consumo de cannabis: de regreso a la medicina basada en la evidencia

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Though post-truth is a widely disseminated concept in the 21st century, already in 1992 the playwright Steve Tesich used this term to refer to American society during his time as "we, as a free people, have freely decided that we want to live in a post-truth world" (Flood, 2016). In 2016, the Oxford Dictionary granted him the word of the year award, together with a clear and concise definition: "Relating to or denoting circumstances in which objective facts are less influential in shaping public opinion than appeals to emotion and personal belief" (*Oxford English Living Dictionaries*, 2017). It seems that the second half of the 20th century brought us evidence-based medicine and that the new century obligates us to defend it. Nowadays, the point is not to use the scientific method for discovering the truth, but rather to exploit science as an instrument for constructing a story. First we create the story and then we look for the evidence to serve as its supporting foundation. In other words, science, in some cases, has fully immersed itself in post-truth. We have some very clear examples, like the relationship between vaccines and autism (Taylor, Swerdfeger & Eslick, 2014; Tomeny, Vargo & El-Toukhy, 2017) but also some less evident ones, like the social discourse concerning cannabis use. It seems irrelevant that there are still many more uncertainties than answers regarding the consequences, both positive and negative, of cannabis use on individuals and society alike; what is most important is to defend an *anti* or *pro* stance.

Over the last 20 years, cannabis use has experienced a major growth in western societies and in our country in particular, from 4.6% cannabis users in the last month among the general population (1997) to 7.3% (2015). In parallel to the increase of regular cannabis use, the perception of risk of regular use has decreased. Whether this is the cause or the consequence is unknown, but over 1/5 of the population thinks that regular cannabis use does not entail a health risk (Delegación del Gobierno para Plan Nacional sobre Drogas, 2015) and society has become more flexible regarding its use and legalisation (Sánchez Caballero, 2014). Likely, the role of post-modern society has had an impact on these changes, in particular among youth (Blasco-Fontecilla, 2018).

### What is known and unknown about harm caused by cannabis?

Its impact on mental health has been clearly established. An excellent review by Robin Murray and his collaborators (2016) establishes the relationship between cannabis use and the onset of psychosis. They disarm theories with scarce scientific evidence, like self-medication or the positive impact of CBD on users and stress the prognostic importance of cannabis use for patients with schizophrenia. Murray does not overlook the importance of differentiating between cannabis types used (synthetic, high-potency, traditional) and their impact on psychopathology. This same review refers to other mental health aspects related

with regular cannabis use, like dependency -1 out of every 10 users, or 17% if onset is during adolescence- or cognitive harm. However, he is more prudent in relating cannabis use with mood and anxiety disorders (Murray, Quigley, Quattrone, Englund & Di Forti, 2016). Nevertheless, a recent meta-analysis provides that the risk of psychosis is related to the intensity of cannabis use (Marconi, Di Forti, Lewis, Murray & Vassos, 2016). Gaps exist as to the relationship between regular cannabis use and mood and anxiety disorders and risk of suicide. Current evidence is insufficient, yet emerging (Marconi et al., 2016). Cognitive harm as a result of cannabis use exists, is dose-dependent and partially reversible upon discontinuation, and is greater if the onset of use occures. Furthermore, there seems to be confirmation that cannabis serves as a gateway to other substances, even as a so-called "reverse gateway"; in other words, that it also serves as a path toward tobacco use (Hall, 2014).

Physical health can also be affected by regular cannabis use. Evidence is most clear regarding cardiovascular health; however, it is less clear regarding lung damage or carcinogenicity. Carcinogenicity of cannabis is not sufficiently documented, but points out the lungs, upper respiratory tract, oesophagus, testicles (non-seminona) and bladder as target organs. One of the main difficulties inherent to these studies is controlling for confounding factors, like tobacco, and in some cases, the absence of prospective studies (Hall, 2014). The cannabinoid hyperemesis syndrome deserves a chapter itself, given that its description dates merely back to 2004 (Allen, de Moore, Heddle & Twartz, 2004) and currently only a series of cases exist on its clinical description (Simonetto, Oxentenko, Herman & Szostek, 2012), a modest study on its prevalence (Bruguera, López-Pelayo, Miquel & Balcells-Oliveró, 2016) and one or another isolated study on its treatment (Pélissier, Claudet, Gandia-Mailly, Benyamina & Franchitto, 2016; Sorensen, DeSanto, Borgelt, Phillips & Monte, 2017). The impact of foetal exposure to cannabis use during pregnancy is not yet fully clear. However, some studies suggest that it would result in low birth weight and greater risk of premature birth. Other possible effects of cannabis use during pregnancy are worse cognitive functioning in adolescence -including intellectual quotient-, behavioural alterations, delinquency, poorer academic performance and mood disorders (Hall, 2014).

Its psychosocial impact, especially in adolescents and young adults, is also backed by a consolidated bibliography. Nevertheless, scientific evidence is contradictory when referring to the risk of academic failure. Although the association is clear, the causality of the same is questionable, as some studies suggest that cannabis use and academic failure share pre-existing risk factors (Lynskey & Hall, 2000). We must not overlook the clear association between traffic accidents and driving under the effects of cannabis; specif-

ically, the risk of accident is double, or even triple, when driving intoxicated. This association has a neurocognitive base in slower reaction time, information processing capacity, eye-hand coordination, motor skill performance, attention and follow-up behaviour (Hall, 2014).

It is important to point out that lack of evidence does not prove inexistent association. Likewise, when a given object of study presents mixed evidence, it is not possible to establish clear cause-effect relationships. Neither can we do so if scientific criteria of causality  namely: internal validity (strength of the correlation, dose-response effect, temporal sequence) and scientific coherence (consistency, biological plausibility, specificity of association and analogy, experimental evidence) are missing (Hill, 1965).

Based on the existing bibliography, the "Lower-Risk Cannabis Use Guidelines" clinical guide proposes, with a certain degree of substantial evidence, the following recommendations: 1) the best way to avoid risks associated with cannabis use is abstinence; 2) preventive messages must stress delaying the age of onset, as adverse risks are fewer with later onset; 3) cannabis users should know the concentration of THC and CBD and try to avoid a high THC concentration (Casajuana, López-Pelayo, Balcells, Colom & Gual, 2018) and prioritise a low THC:CBD ratio, as adverse effects are associated with a high dose of THC -those plants that produce high concentrations of THC generate low concentrations of CBD- (Murray et al., 2016); 4) smoking cannabis, whether alone or mixed with tobacco, should be avoided, and instead other types of consumption (vaporizing or eating) should be chosen; 5) regular or daily use is associated with the majority of the adverse effects; users should strive for occasional consumption (once a week, on weekends, or less frequently); 6) users should try to avoid driving for 6 hours after use -as long as this is not in breach of local legislation in effect- and never drive after drinking alcohol and using cannabis, given the potentiation of acute, negative effects on one's driving capacity. Avoiding driving for a minimum of 6 hours after cannabis use is based on the fact that peak THC plasma concentration occurs at between 5-30 minutes after use, and decreases after 2-4 hours, though intoxication and acute cognitive deterioration may persist for between 3-6 hours. This period could be even longer in the case of high THC levels and/or consumption via oral ingestion. With a lesser degree of supporting evidence, the guide also recommends that: 1) users should avoid synthetic cannabis due to the risk of acute adverse effects. Synthetic cannabis has a high affinity with CB1 receptors, a full agonist, compared with traditional cannabis that is a partial agonist, and diverse complications have been reported, including acute psychosis, kidney failure, myocardial infarction, aggressiveness and brain ischemia. Up to 24 cases of death have been associated with the use of synthetic cannabis (Gurney, Scott, Kacinko, Presley & Logan, 2014; Tournebize, Gibaja

& Kahn, 2017); 2) deep inhalation should be avoided to reduce the risk of lung damage; 3) avoid combining two or more of the abovementioned risk behaviours. Beyond the individual risk associated with one's use pattern, certain demographic groups are at risk for any type of cannabis use: personal or family history of psychosis, pregnant and breastfeeding women, persons with cardiovascular problems. Though without solid supporting evidence but out of prudence, cannabis use should be avoided by those individuals with a personal or family history of other mental disorders (Fischer et al., 2017).

There is evidence that the demand for treatment of cannabis dependence is growing (Mounteney et al., 2016), but despite this, we know that the impact of treatment is limited as low abstinence rates are obtained (Hall, 2017), though reducing cannabis use and improving quality of life are achieved (Gates, Sabioni, Copeland, Le Foll & Gowing, 2016a). All treatments should combine a motivational interview, cognitive-behavioural therapy, and incentives for achieving abstinence (Carney, Myers, Louw & Okwundu, 2016; Denis, Lavie, Fatseas & Auriacombe, 2006; Gates, Sabioni, Copeland, Le Foll & Gowing, 2016b). As regards medication, Gabapentin and N-acetylcysteine are promising, though evidence is still weak (Marshall, Gowing, Ali & Le Foll, 2014).

Finally, legalising cannabis could impact its price (reduction), social perception (normalisation of use), availability (greater accessibility) and potency (increase). This could translate into an increase in long-term use of unknown proportions (Álvarez, Gamella & Parra, 2017; Hall, 2017). In this regard, the experts at ALICERAP (www.alicerap.eu) point out that extreme measures (total prohibition or liberalisation) are not a good strategy, but that regulating cannabis use could be beneficial in terms of public health with the goal of preventing the undesired effects of prohibition, like organised crime and violence, stigma and discrimination against users, substance use in public and users' loss of civil rights, employment, home and personal relationships (Apfel, 2013). However, these hypotheses must be evaluated regularly, especially given that indicators show that the legalisation of cannabis in the USA has resulted in increased use and accidental exposure of minors (Wang et al., 2016) as well as a decreased perception of risk (Schuermeyer et al., 2014; Sobesky & Gorgens, 2016). In this regard, indicators on potency, dose, sales, legal production and harm associated with cannabis (traffic accidents, emergency hospital visits, specialised care for cannabis use disorder, prevalence of use in patients with mental health and justice-related issues) must be considered (Hall, 2017). Finally, public policies based on the *Three Best Buys* (limited access to the substance, limited publicity and price increases through taxation measures or minimum price per consumption unit) (Baccini & Carreras, 2014; Matrai et al., 2014) would make

sense for the purpose of implementing a model similar to that of tobacco use prevention and different from the scarcely efficient and heterogeneous model of alcohol use prevention. This entails not leaving preventive measures in the hand of the emerging cannabis industry through the "responsible use" slogan and assuming, instead, evidence-based prevention strategies.

Despite the foregoing, we must not fall prey to alarm. Cannabis is a much less harmful substance that others, like alcohol or nicotine. For example, Lachenmeier & Rhem (2015) used the Margin of Exposure (MOE) concept to make a comparative evaluation of the risk of several substances. The MOE is the ratio between the toxicity threshold and the estimation of human consumption, calculated on the basis of the average lethal dose in test animals and studies on individuals and populations. The estimated MOE for daily use of THC is more favourable than for the remaining substances, like benzodiazepines, stimulants (cocaine, amphetamines and methamphetamines), MDMA, nicotine, heroine and alcohol (Lachenmeier & Rehm, 2015).

### What is actually known and unknown about the benefits of cannabis?

The use of cannabis in its natural state or as a pharmaceutical formulation (dronabinol) is used for treating several medical conditions. To date, there is insufficient evidence on its efficacy and safty to consider it a therapeutic option for improving appetite, gaining weight or improving mood in patients with HIV/AIDS given that the studies have been conducted over short period of time and with small-sized demographic groups (Lutge, Gray & Siegfried, 2013). Neither does it apparently play a role in treating fibromyalgia (Walitt, Klose, Fitzcharles, Phillips & Häuser, 2016) nor in behavioural alterations of dementia (Krishnan, Cairns & Howard, 2009). There is scarce evidence for its use as an antiemetic for children and youth with oncologic pathologies, for which better alternatives are available with a preferable profile of side effects (Phillips et al., 2016). However, it may be an option for adults with emesis associated with chemotherapy in the case of refractory symptoms. This conclusion could change in the near future with the appearance of new and safer antiemetics (Smith, Azariah, Lavender, Stoner & Bettiol, 2015). Cannabidiol (CBD) could have a positive impact on refractory epilepsy, but it is still too early for this conclusion (Gloss & Vickrey, 2014) and, in addition, the presence of this composition in natural formulations is minimal (Casajuana Kögel et al., 2017), wherefore we cannot recommend its use in this context. Though it seems that cannabis could be efficient for secondary pain in rheumatoid arthritis, its clinical effectiveness has not been sufficiently verified, and some cases describe psychosis and suicidal ideation (Richards, Whittle & Buchbinder, 2012). Neither is the risk-benefit equilibri-

um clear for chronic pain associated with cancer, though it seems to be sufficiently effective (Blake et al., 2017).

A recent analysis of over 10,000 scientific studies by the "US National Academies of Science, Engineering, and Medicine" considered that evidence for medicinal use is only conclusive as regards chronic pain, some symptoms of multiple sclerosis and as a post-chemotherapy antiemetic for adults (Washington, 2017).

Finally, we must bear in mind that the purpose of medicine is to improve quality of life and that in this regard evidence on medicinal cannabis is inconclusive in the best case, when not negative (for example, in patients with HIV) (Goldenberg, Reid, IsHak & Danovitch, 2017).

In any case, it must comply with all safety and evidence-related requirements imposed on any new drug for medicinal use.

### What information is lacking for suitable decision-making?

At a time in which scientific evidence shows that regular cannabis use could have considerable adverse effects, its medicinal use is still limited and legislation ranges from prohibition to liberalisation, we should promote evidence-based regularisation. Tools are lacking for prevention in a regulatory framework that are available, in turn, for alcohol and tobacco. Despite the fact that specific demographic groups under risk have been clearly defined (pregnant women, youth, family or personal history of psychotic disorder, etc.), we lack an operating definition of hazardous consumption based on use patterns (amounts and frequency). However, the conceptual definition posed by the WHO on hazardous use of substances is available as a starting point: "a pattern of substance use that increases the risk of harmful consequences for the user (physical and mental health and social consequences). In contrast to harmful use, hazardous use refers to patterns of use that are of public health significance despite the absence of any current disorder in the individual user" (WHO, 2017). For alcohol use, we can identify hazardous use as that in which a user drinks 28 Standard Drink Units weekly for males, and 17 Standard Drink Units weekly for females. Furthermore, it has resulted in the creation of a fast, reliable and efficient screening tool, the AUDIT-C (Gual, Segura, Contel, Heather & Colom, 2002). For the time being, a definition of this type is not available, given the lack of standardisation in registering cannabis use. Recently, we published a study that standardises use according to the Standard Joint Unit (SJU), for which each SJU is equivalent to 7 mg of THC (Casajuana et al., 2017; Casajuana Kögel et al., 2017). This study should be reproduced in other regions and cultures, and adapted, as has been done with the Standard Drink Unit. The next logical step is to establish a hazardous use pattern, according to amount and frequency, by correlating it with the many dimensions of harm associated with cannabis use. Though this goal is quite ambitious, it is a necessary step for intervention policies to focus on groups of higher risk, even if premature and brief, and as a result, efficient.

Furthermore, we consider it necessary to establish work group networks for purposes of early identification and intervention of hazardous cannabis use, as proposed by Socidrogalcohol through Cannared. The main mission is to train professionals on primary and secondary prevention strategies in cannabis use that have demonstrated sufficient evidence for dissemination.

In conclusion, in our post-truth times, it is more important than ever for professionals (scientists, healthcare workers, teachers, etc.) to count with reliable and updated information on the risks and benefits of regular cannabis use. To this end, it is essential to count with registration tools and operating definitions regarding hazardous cannabis use.

## Conflict of interests

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