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*Commentary*

## Cannabis Medicine Offers Hope for Severe Paediatric Epilepsies

Giuseppe Di Giovanni\*<sup>1</sup>

<sup>1</sup>*Neurophysiology Laboratory, Department of Physiology and Biochemistry University of Malta, Msida, Malta*

Science does not need to take a position on legalizing the recreational use of cannabis, this is more a political issue or a personal choice. Cannabis, as the other drugs of abuse, produces several detrimental effects on brain function but differently from alcohol, nicotine, cocaine, heroin and ecstasy (just to cite the most commune abused ones) these are mostly present with acute intoxication and disappear after termination of drug intake.

Consequently, there is no scientific reason for which we have some legal drugs of abuse such as alcohol and tobacco sold by governments and others labelled as illegal and banned by society. This is, of course, a flawed situation but one that illustrates a major paradox in international laws on drugs. Despite being illegal, cannabis is (ab)used by about 87.6 million European adults (23.7% of adults) (EMCDDA, 2017). Cannabis is also the most commonly used illicit drug among the Maltese adult population aged 18–65 years. According to the 2013 general population study, around 4.3% of those aged 18–65 years reported having used cannabis during their lifetime (EMCDDA, 2017).

One of the most controversial issues in science but also in the media regards the link between marijuana and schizophrenia. It has been shown that marijuana significantly increases the risk of developing a psychotic disorder later in life, particularly among those individuals who use it at an early age, who frequently use high-potency cannabis or ‘skunk’ and who have a genetic predisposition to psychosis (Aas et al., 2018; Evins, Green, Kane & Murray, 2013). On the other hand, adult-onset cannabis use may not be associated with the same level of risk (Donoghue et al., 2014).

The link between smoking marijuana and schizophrenia is much more complicated than we thought, and as with other scientific issues, we do not have a certain response. Firstly, the aetiology of schizophrenia is very complex. In addition, not just cannabis, but also abuse of nicotine (cigarettes smoking) (Gurillo, Jauhar,

Murray & MacCabe, 2015), alcohol (Jordaan & Emsley, 2014), hallucinogens, sedatives and other substances has also been found to significantly increase the risk of developing schizophrenia (Gururajan, Manning, Klug & van den Buuse, 2012). Therefore, one potential source of overestimating this link is neglecting the effect of a poly-drug abuse when correcting the epidemiological data analyses. For example, a recent large longitudinal Danish study on 3,133,968 individuals (Nielsen, Toftdahl, Nordentoft & Hjorthoj, 2017) that took into consideration the effect of a poly-drug abuse showed a lower association compared with previous studies, with cannabis and alcohol abuse increases the risk of developing schizophrenia later in life by five and three times, respectively.

Caution should be taken when using these epidemiological data though since we really do not know if these findings indicate a causal relationship. Indeed, they might just simply indicate that those who have a predisposition to develop schizophrenia later on in life are more likely to use cannabis and indeed we know that they are more likely to suffer comorbid substance use disorders than the general population. If there is a causal role between cannabis and schizophrenia, recent results suggest that this may have been overestimated. The lack of data regarding an increase in schizophrenia incidence in countries where marijuana is legal tend to suggest this possible scenario.

Nevertheless, extreme caution has to be taken regarding the (ab)use of all drugs of addiction, including marijuana. Marijuana should definitely be forbidden to adolescents. People with a family history of schizophrenia should avoid cannabis but schizophrenia is not just caused by marijuana. Events that might have the potential to cause stress can also play a part, because genes and the environment are interconnected. Thus, people who are at risk should try to avoid substances that might damage their mental well-being. These sub-

\*Correspondence to: Giuseppe Di Giovanni ([giuseppe.digiovanni@um.edu.mt](mailto:giuseppe.digiovanni@um.edu.mt))

stances include marijuana or any other drug of abuse, including those that can be legally bought at any shops.

Nevertheless, I believe that marijuana and research on cannabinoids may give rise to the discovery of new potential treatments for many disorders, especially epilepsy. This idea is also shared by many neuroscientists including Dr Mechoulam (personal communication, see Fig. 1) who discovered THC in the '60s (Mechoulam & Gaoni, 1965).



**Figure 1:** Left, Raphael Mechoulam (Hebrew University, Israel), right, Giuseppe Di Giovanni (University of Malta, Malta) at the MNS2017 in Malta. On the background on the left, Prof. Giacomo Rizzolatti (University of Parma, Italy).

Different lines of my research in Malta are focused on the effect of cannabinoids on different types of neuropsychiatric disorders, such as drugs of addiction, anxiety and epilepsy. I do not use the chemical found in marijuana called delta-9 tetrahydrocannabinol ( $\Delta^9$ -THC), which induces marijuana's psychotropic effects, but a synthetic analogue named WIN 55,212-2, that is many times more powerful than  $\Delta^9$ -THC. As far as focal epilepsy is concerned, we have found that in temporal lobe epilepsy, synthetic cannabinoids are even more effective than the epileptic drug phenytoin. The only problem with this treatment is that the dose of cannabinoid impairs the hippocampus, an important part of the brain, and thus blocks the process that is needed for learning and memory. We have bypassed these side effects by using a new compound that blocks the breakdown of the natural cannabinoids our brain normally makes the fatty acid amide hydrolase (FAAH) inhibitor URB597. The new drug boosts the amount of self-produced marijuana in epileptics' brains. The new compound is less effective in stopping epilepsy but is longer-lasting without major side effects (Colangeli et al., 2017). We are currently following this line of intervention, trying other drugs that increase the levels of

our own cannabinoids when and where they are needed to avoid any possible side effects. This research could potentially treat millions of epilepsy patients safely.

We are also investigating status epilepticus, a life-threatening condition in which one epileptic fit follows the other without the sufferer recovering consciousness. We found that synthetic cannabinoids only had a modest effect on the development of this type of seizures. Surprisingly, when serotonin was activated, their effectiveness multiplied, stopping the fits. We have discovered an important interaction between cannabinoids and 5-HT, at the moment we are investigating various possibilities and we believe that the outcome could be important for further understanding of the pathological mechanisms and for new treatments (unpublished observations).

Finally, although cannabis has been used for a century to treat convulsive and focal epilepsy, no evidence instead exists of a role for the CB system in human absence epilepsy, a non-convulsive type of paediatric epilepsy (Crunelli & Leresche, 2002). Indeed, very few studies have investigated the involvement of the CB system in absence seizures, and their results are highly contrasting. Thanks to an RIDT grant I have started to investigate the role of the eCBs in this type of epilepsy and the results are very promising.

The governments attitude toward marijuana research is finally changing. Strikingly, only a few days ago, on June 25<sup>th</sup> 2018, the U.S. Food and Drug Administration today approved Epidiolex (cannabidiol, CBD) oral solution by GW Research Ltd. for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome (see FDA News Release at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm611046.htm>).

Therefore, marijuana and marijuana research should not be demonized but encouraged and supported, it may save millions of lives!

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