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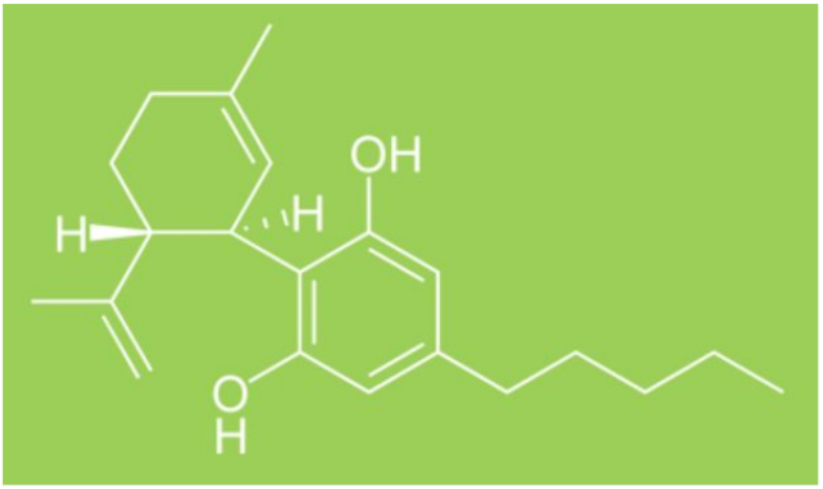

"CBD chemical structure"

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Comments on Cannabidiol

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Summary

The Food and Drug Administration (FDA) is requesting interested persons to submit comments concerning **abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes** on availability for medical use of 17 drug substances. These comments will be considered in preparing a response from the United States to the World Health Organization (WHO) regarding the abuse liability and diversion of these drugs. WHO will use this information to consider whether to recommend that certain international restrictions be placed on these drugs. This notice requesting comments is required by the Controlled Substances Act (the CSA).

1. Medical usefulness

Evaluating safety and efficacy, the two key parameters which are the basis for evaluating the clinical pharmacology of a medicine, safety and efficacy, shall provide justification of the medical usefulness of cannabidiol (CBD). CBD is a cannabinoid separated by extraction and purification from botanical material, usually flowers and leaves, of the cannabis plant.

1.1. Safety and efficacy profile

There is a large body of evidence which supports both the safe and effective nature of the compound, particularly human clinical trials. While epilepsy is the most notable and well known disorder for which CBD has shown to be safe and effective; it has also been demonstrated in the treatment of psychosis, anxiety and a whole host of neurodegenerative disorders.

1.1.1. Epilepsy

Examining the safety profile: no major toxicity, genotoxicity, or mutagenicity was observed in Pentylenetetrazole in Vivo Seizure Model (epilepsy animal model)[1]. Additionally, a rotarod assay reported no effect on motor function caused by CBD [2], unlike other approved anti-epileptic medication which cause strong motor side effects.

Clinical evidence justifying the safety of cannabidiol has been around for 27 years. In a clinical study examining the effects of the chronic administration of CBD (up to 3 mg/kg daily of CBD), the subjects showed no signs of any toxicity [3]. Around 11 years later another significant result was displayed in a study evaluating the effectiveness of CBD in Huntington's disease. When administered at a daily dose of about 700mg/day for six weeks, no toxicity was reported in the subject group of patients [4].

With a thoroughly proven safety profile, there is a large body of evidence demonstrating the effectiveness of CBD in a wide array of diseases. In the case of drug resistant epileptic

disorders, it has been widely acknowledged by specialists colleges worldwide that it is effective [5]. In a recent double-blind, placebo-controlled Phase 3 clinical trial, CBD was administered at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. Results from the study demonstrated that CBD significantly reduced the frequency of total seizures [6].

1.1.2. Psychosis and schizophrenia

In double-blinded and randomized clinical trial, CBD was evaluated against amisulpride (an antipsychotic drug) for it's potential in treating psychotic symptoms in patients with schizophrenia. Patients who were administered CBD showed significant clinical improvement without any significant side effects. Unlike amisulpride, which is known to cause motor disturbances, weight gain and sexual dysfunction [7].

1.1.3. Anxiety disorders

CBD has also shown to be effective in the treatment of an array of anxiety disorders, particularly social anxiety disorder (SAD). In a simulation public speaking test (SPST) conducted on healthy control (HC) patients and treatment-naïve SAD patients, CBD significantly reduced anxiety, cognitive impairment and discomfort in their speech performance, and significantly decreased alert in their anticipatory speech [8].

In a pavlovian fear-conditioning paradigm, assessing the effects of CBD on fear extinction and consolidation, CBD showed to enhance the consolidation of extinction learning; showing the potential to be an extinction-based therapy for anxiety disorders [9]. Furthermore, in a functional magnetic resonance imaging (fMRI) CBD attenuated the blood oxygenation level-dependent signal in the amygdala and the anterior and posterior cingulate cortex, while the subjects were exposed to fearful stimuli [10]. The neurocircuitry of these brain regions is particularly relevant for anxiety disorders, often experiencing overactivation in anxiety disorders [11]. Results from the study showed how CBD could be effective in reducing autonomic arousal and subjective anxiety.

1.1.4. Neuroprotection and antioxidant effects

The neuroprotective and antioxidant potential of CBD has been widely established, and proven. So much so that US Patent 6630507 titled, "Cannabinoids as antioxidants and neuroprotectants" was granted by the United States Patent and Trademark Office (USPTO) was granted on 7th February 2001. As suggested by Claim 1 of this patent, CBD can be a method of diseases caused and prolonged by oxidative stress. Diseases such as neurodegenerative diseases, Alzheimer's disease and Parkinson's disease could benefit greatly with incorporating CBD in the treatment regime.

1.1.5. Other

A number of diseases which are implicated from endocannabinoid dysregulation, theorized as chronic endocannabinoid deficiency (CECD). Clinical data has confirmed that underlying

endocannabinoid deficiencies can cause chronic migraine, fibromyalgia, irritable bowel syndrome and a growing list of other medical conditions [12]. Given that CBD has the ability to enhance intrinsic anandamide (an endocannabinoid) signaling, leading to symptom improvement in psychosis, it makes a case for it's use in treating these conditions [7]. Particularly because the safety profile in undoubtedly proven, the use of CBD should be preferred over other possible candidates e.g. new chemical entities, for minimal harm and maximum therapeutic impact in healthcare settings.

2. Abuse potential

CBD, unlike Δ^9-Tetrahydrocannabinol (THC), does not stimulate the CB1 receptor in the brain [13], and it does not cause any psychoactive effect. In fact it is a non-psychoactive cannabinoid, it does not cause a sense of euphoria, and has no instant rewarding capability to induce a state of addiction. Psychoactive substances bring about changes in consciousness and mood, and this can often be rewarding and pleasant for the user. Moreover when compared to the psychoactive compound to THC in a functional magnetic resonance imaging (fMRI) study, CBD had an opposite effect on the brain (in terms of the brain areas which were activated) [14]. Therefore, there is evidence to suggest CBD can counteract the effects of dysregulated dopaminergic transmission induced by other drugs, such as amphetamine [15].

Given the lack of evidence supporting the abuse risk of CBD, it does not fit any of the definitions set by the United Nations for scheduled substances. Henceforth it would not be appropriate to define CBD as a scheduled substance, and placing greater restrictions on the use of the substance.

2.1. Opioid epidemic and other addiction

Rather being subject of abuse, CBD has the potential to treat the opioid, cocaine, and psychostimulant addiction - with successful preclinical and clinical evidence to suggest so [16]. The opioid epidemic currently bears an enormous cost to society, with more than 59,000 deaths reported from drug overdose in 2016 in the United States [17]. Opioid addiction is a major factor, and the ease of their prescription is a major public health concern. Opioids are most commonly prescribed for pain, without much consideration of the potential for inducing addiction . The total economic burden of prescription opioid overdose, abuse, and dependence to the USA is estimated at over $78.5 billion. [18] Widespread case reports suggest that those using CBD products were able to decrease the use of other prescription medications, including opioids, to treat symptoms such as insomnia, depression, anxiety and joint pain [19]. Switching to CBD medicines which have no abuse potential, or any significant toxicities, can reduce significant public health risks such as prescription drug abuse.

3. Actual abuse

No cases of abuse have been reported for CBD. In a study assessing a wide range of doses of CBD (200, 400, 800 mg), there were no subjective ratings of drug effect found when compared to a placebo [20]. More specifically, other measures that were taken such as street value estimates, ratings of high, feeling good drug effect, desire to take again, showed no significant differences between CBD and the placebo.

Besides from having low abuse potential, and no cases of actual abuse, as mentioned above CBD makes a case for the treatment of other addiction disorders. CBD was subject to a randomised double blind placebo clinical trial to study its use in smokers who wished to stop smoking. In subjects treated with CBD, it was able to reduce the number of cigarettes smoked as well as reduce cravings for smoking [21].

Other treatment options for smoking, such as varenicline, often cause mood disturbances by interfering with nicotine induced reward systems in the brain [22]. CBD on the other hand, can reduce cravings and at the same time have little effect on mood. There is also a body of evidence to suggest that it may have antidepressant properties [23], potentially affecting a key symptom influencing reward seeking behaviour.

4. Trafficking

As CBD has varying restriction levels from country to country, it has resulted in thriving legal markets for the substance in some and undercover illegal markets in others. In countries where it is legal and easy to access such as: Canada, Israel, Italy and Switzerland; high purity CBD products are being manufactured. These products contain CBD within specified active range and have minimal impurities such as pesticides, residual solvents, heavy metals or other substances that may be derived from the manufacturing process.

As pure CBD is not scheduled as per the UN single Convention on Narcotic Drugs, the trade of CBD between countries where it is unscheduled occurs as any other chemical material would do. Trafficking often occurs for personal reasons as patients go to countries or purchase online from countries, where it is easy to source legally and bring back (or ship) to countries, where there are high restrictions placed on the product. These patients have no other options and are often on their last resort of medication in the form of CBD. These people should not be subjected to breaking national laws to seek their medication or their children [24].

4.1. Europe

In the European countries CBD is not scheduled and currently lies into a grey area for what concerns its pharmaceutical use / applications. CBD is considered a chemical entity in its pure form (CAS # 13956-29-1) and has been added to the European Commission database for information on cosmetic substances and ingredients (CosIng) because of its strong antioxidant qualities and proven anti seborrheic, skin conditioning and skin protecting effects [25]. This has enabled the use of CBD in the cosmetic industry, and developing another substantial contribution of the compound to the worldwide economy.

4.2. Australia

In other countries, such as Australia, CBD is highly restricted and is very expensive to attain, as it is a scheduled substance [26]. Many patients who require CBD on a daily basis, such as those suffering from epilepsy or neuromuscular diseases, often have to turn to the black market as a source of CBD, which is being produced in substandard manufacturing environments. In fact, currently CBD products such as oils or pills are imported illegally from Europe and traded in Australia by several suppliers (which basically turn into smugglers, facing years of jail). Doctors are not willing to take responsibility by CBD because medical indemnity insurance does not cover if something happens meaning that doctors are liable if patients sue them.

4.3. USA

In the United States, all cannabis products are lumped into schedule 1, under the United States Controlled Substances Act. The DEA considers CBD illegal because it talks about this substance only in relation to cannabis plant extracts. In their definition all extracts (including hemp extracts) may contain trace amounts of other cannabinoids (including THC) making it illegal [27]. However, upon demonstrating that these extracts do not contain any traces of THC or other cannabinoids, such product would fall within the new drug code 7350. Moreover the DEA statement contradicts an amendment made to the Agricultural Act of 2014 (Farm Bill) [28], which allows growers to cultivate, process, and market hemp products, which contain CBD and traces of other cannabinoids but very low levels of THC (usually below 0.2% w/w).

As the hemp industry is expanding, and cannabis has been legalized in up to 30 states either for recreational or medical use, a massive cultivation and manufacture industry has been developed in individual states for the production of CBD.[29] What has not been developed in parallel are the quality standards that are required for CBD products, specifically federal guidelines specifying purity and minimal contaminant requirements.[30]

While there might be some businesses which adopt international quality standards, it is not unanimously enforced and audited as it should be. CBD trafficking occurs across state borders, mainly to those states where it is illegal. Similarly to the situation in Australia, it is often patients who have to break the law transporting CBD products across borders between legal and illegal states as they require CBD on a daily basis. This situation is seen by many as hypocritical and putting families of unwell relatives in a precarious situation, risking many legal circumstances if caught "trafficking illegal substances" as per DEA regulations.

5. Impact of scheduling changes

The undoubted medical evidence supporting the use of CBD, coupled with its safety profile, makes it not suitable to schedule CBD as a controlled substance. In fact, the DEA uses drug scheduling as a rating system to determine which drugs have a higher potential for abuse [31]. Since cannabidiol have no demonstrated potential for abuse it is an absurdity that it is considered Schedule 1 because cannabis it is listed as such. Cannabis itself should not be listed as a like heroin, ecstasy and other hallucinogens, since Schedule 1 controlled substances are claimed by the DEA and FDA as substances with no defined medicinal purposes and have the highest potential for abuse. Cannabinoids drugs have clinical uses as demonstrated with Sativex,which is an approved drug manufactured by GW pharmaceuticals for spasms in Multiple Sclerosis patients and Epidiolex, which is currently under clinical testing for Dravet syndrome and other drug-resistant epilepsy showing high degree of safety and effectiveness in improving quality of life of patients.

5.1. Economic and social impact

Keeping CBD under the same Schedule would result in a number of people breaking international laws to access a life saving medicine, as the scheduling of CBD would increase the administrative cost associated with its trafficking, as ultimately make CBD very cost prohibitive (such is the case in Australia). Therefore suffering from debilitating diseases would have to turn to the black market for CBD, and potentially compromise their health and their lives with products which have not quality assurance.

In Europe, great economic interest surround the area and many more manufacturers started producing a wide range of products. Despite the fact that these products aren't yet classified nor as food supplements or pharmaceuticals, in most of the countries of the EU, CBD products are sold freely in a grey area. The increasing number of manufacturers and the general availability of these products more and more present in shop shelves and online shops, are driving the price CBD down but still do not provide any assurance of its quality and any reimbursement by local healthcare systems.

5.2. Hemp and cannabis

CBD can be derived from industrial hemp, which are strains of cannabis with less than 1% THC, and these crops have no illicit value as they contain very low levels of THC - the key factor for cannabis to attain value in the black market. *Hemp and cannabis are the same plant and they are mainly diversified by the THC content, leading to their separate legal definition.* Many strains of industrial hemp have significant percentages of CBD, providing another source of revenue for cultivators of hemp. There are stringent due diligence requirements for hemp growers to maintain low levels of THC in their crops, in countries where licenses for growing industrial hemp is permitted. This compliance ensures there is no diversion of industrial hemp into the illegal market.

The current definition of cannabis is therefore very restrictive on the potential uses of low THC cannabis crop, which is usually called hemp. The definition of cannabis in the scheduled list should therefore be adapted to cannabis plants (or hemp plants) with more than X% THC, where the range of X should be 0.01-1% per weight of the flowering tops. This will improve access to CBD for medical reasons, barring it is grown with Good Agricultural and Collection Practices (GACP), and its derivatives are manufactured in Good Manufacturing Practices (GMP). This will enable low THC cannabis to have greater flexibility in it's use, effectively turning it into a cash crop like cotton, rice and wheat.

6. Conclusion

The current scheduling should be adjusted to remove restrictions on the trade of CBD. This would allow the majority of the CBD trade to happen through legal means, managed by quality supply chain management companies, similar to the flow of other medicinal compounds.

A worldwide consensus to deschedule CBD as a narcotic drug would decrease legal implications for sufferers of debilitating diseases. Refocusing prosecution attempts on other more harmful substances, which have higher abuse potential, would a better use of public resources.

6.1. General Opinion: Proposed Solution

The trade of CBD from countries where it is legal, and being produced in recognized Good Manufacturing Practice (GMP) facilities, should be conducted with minimal bureaucracy; analogous to a substance with similar safety, efficacy and lack of abuse profile. This will keep the cost of the CBD affordable, and henceforth decreasing the illegal trade of the compound. Allowing importation and exportation of CBD will ease the trade and provide the right quality standards to be applied to these products.

The lack of abuse potential and toxicity profile, coupled with the battery of evidence suggesting its medical usefulness, does not justify CBD being listed as a schedule substance. More emphasis should be placed on reducing the barriers globally for CBD, would in return reduce illicit trafficking. This would turn an illegal industry into a legal one, where quality control can be monitored oif CBD and professional logistic services and supply chain management companies can be tasked for it's tracked transport across the world.

Our suggestion is to deschedule cannabidiol (CBD) and improve its availability in any forms as long as quality measures and good practice principles (GxP) are applied.

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