#1 - OCTOBER 2021

MEDICINE & DRUGS

FOCUS ON:

CBD, THC AND THEIR RELATED PRODUCTS IN CLINICAL PRACTICE: AN OPPORTUNITY FOR CLARITY

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CANNABIDIOL: PHARMACOLOGICAL ASPECTS

E. Russo

Cannabis plant varieties contain a huge number of active molecules of which Δ^9- tetrahydrocannabinol (Δ^9-THC) is the most famous and characterized. In the 1990's, the discovery of the endo-cannabinoid system represented a landmark in cannabinoid science and since then the number of studies on cannabinoids and the CNS (Central Nervous System) has been growing constantly. Pharmacologically, we need to distinguish three different classes of cannabinoids[1,2]:

1. endocannabinoids (e.g. anandamide) linked to the endocannabinoid system including cannabinoid (CB) receptors and enzymes;
2. synthetic cannabinoids including CB receptors ligands (e.g. agonist, antagonists, partial agonists and inverse agonists);
3. phytocannabinoids, which are a wide variety of terpenophenolic derivatives of which only some are able to bind to CB receptors.

Cannabidiol (CBD), while isolated as early as 1930-40's, was studied starting from the 1960's[3]. CBD is naturally occurring as the (-) enantiomer while it can also be synthesized as a racemic mixture. The (+) enantiomer and its metabolites differ from the (-) enantiomer for their ability to bind to CB receptors at the nanomolar range[4,5].

Further than the debated action on CB receptors, CBD possesses several mechanisms of action which have been described and linked to its efficacy in many disorders[6]. CBD inhibits adenylyl cyclase and voltage gated calcium channels, while activates some potassium channels and mitogen activated protein kinase (MAPK). It has been reported that CBD increases mechanistic target of rapamycin (mTOR) pathway activity[7]; however, this effect is highly debatable considering the recent observation that CBD is effective in Tuberous sclerosis (characterized by hyperactivation of mTOR pathway) patients and animal models[8,9]. CBD is an agonist of the peroxisome proliferator-activated receptors (PPARγ) receptor modulating the expression of pro-inflammatory genes and inflammatory responses[10]. CBD is a GPR55 receptor antagonist, strongly expressed in the nervous (its block reduces neuronal excitation) and immune systems, as well as in other tissues[11]. This receptor shares similarities with cannabinoid receptors (CBRs) and may be a binding site for other cannabinoids[12,13].

CBD also acts on ion channel as an agonist of the TRPV1 receptor[14], which is then desensitized[15]; this effect is linked to calcium currents and neuronal excitation as well as oxidative stress and the biosynthesis of 2-AG[16]. Finally, CBD inhibits T-type voltage-gated calcium channels (VGCCs)[17] and L-type Ca^{2+} VGCCs with an IC_{50} of 0.1 µmol/L in rat myocytes[18]. Furthermore, CBD can block voltage-gated sodium channels (VGSCs) inhibiting hNav1.1-1.7 currents (IC_{50} of 1.9-3.8 µmol/L)[19]. However, the contribution of these latter mechanisms is likely very low and not observable at therapeutic concentrations.

CBD is characterized by high lipophilic properties that allow the compound to easily cross the blood-brain barrier. CBD pharmacokinetics in humans is characterized by high variability[20]. Gastrointestinal absorption after oral administration of CBD is relatively rapid with peak plasma concentrations achieved between 0.5 and 6 hours [21]. After single ascending doses of CBD (1500 to 6000 mg dose range) to healthy volunteers, AUC and C_{max} were achieved at 3-5 h and increased less than proportionally[22]. Fasting CBD oral bioavailability is about 6% due to the very low solubility and presystemic elimination. At odds, CBD administration with a high-fat/high-calorie meal results in an about 4/5-fold increase in AUC and C_{max} with a lower total variability compared with the fasted state. This increase in bioavailability is likely to be potentiated by diversion of the absorbed drug from the portal to the lymphatic system[23]. There is evidence from *in vitro* studies that CBD and its metabolites are > 94% bound to plasma proteins. CBD elimination is characterized by a multiphasic process with half-life values ranging between 14 and 60 h after single and multiple dosing respectively[22]. CBD is predominantly eliminated by metabolism in the liver and the gut and excreted in feces as unchanged drug. CYP2C19 is the major cytochrome P450 enzyme converting CBD to the active metabolite 7-hydroxycannabidiol (7-OH-CBD), which is further metabolized to 7-carboxy-cannabidiol by CYP3A4[24]. UGT enzymes involved in CBD conjugation are the 1A7, 1A9, and 2B7[25]. Furthermore, CBD has a complex interaction with CYP enzymes mostly inhibiting and sometimes inducing their activity, several interactions with other drugs are already known or can be predicted[26]. Finally, CBD shows a high inter-individual pharmacological variability, which is expected to impact on clinical response[22,25,27]. Thus, the identification of genetic variants in genes that encode for protein involved in CBD pharmacodynamics and pharmacokinetics should be a priority to explain, at least in part, the great variability observed in the response to this drug.

CBD and CBD-based products have received a large amount of scientific and public attention over the past 20 years, and pharmaceutical research has led to the authorization of two specific products (one pure CBD and one as a mixture with THC) for the treatment of some specific types of epileptic syndromes and spasticity in MS patients. CBD is currently involved in preclinical and clinical evaluation for the treatment of a variety of CNS disorders, while its mechanism of action has only been partially understood. Overall, this phytocannabinoid is highly promising for the treatment of many CNS diseases, while the study of further cannabinoids is also important as it can add more to clinical practice.

ANALOGIES AND DIFFERENCES BETWEEN INDUSTRIAL DRUGS AND PHARMACY PREPARATIONS

A. D'Arpino, D. Zanon, M. Fortini

Compounding is a necessary component of medical and pharmaceutical practice and provides therapeutic options to patients with medical needs that cannot be addressed by available approved drug products. Compounding differs from pharmaceutical industry drug manufacturing as the amount of drugs prepared and prescriptions dispensed is small compared to approved drugs[28].

POSITION PAPER SIFAP-SIFO[29]

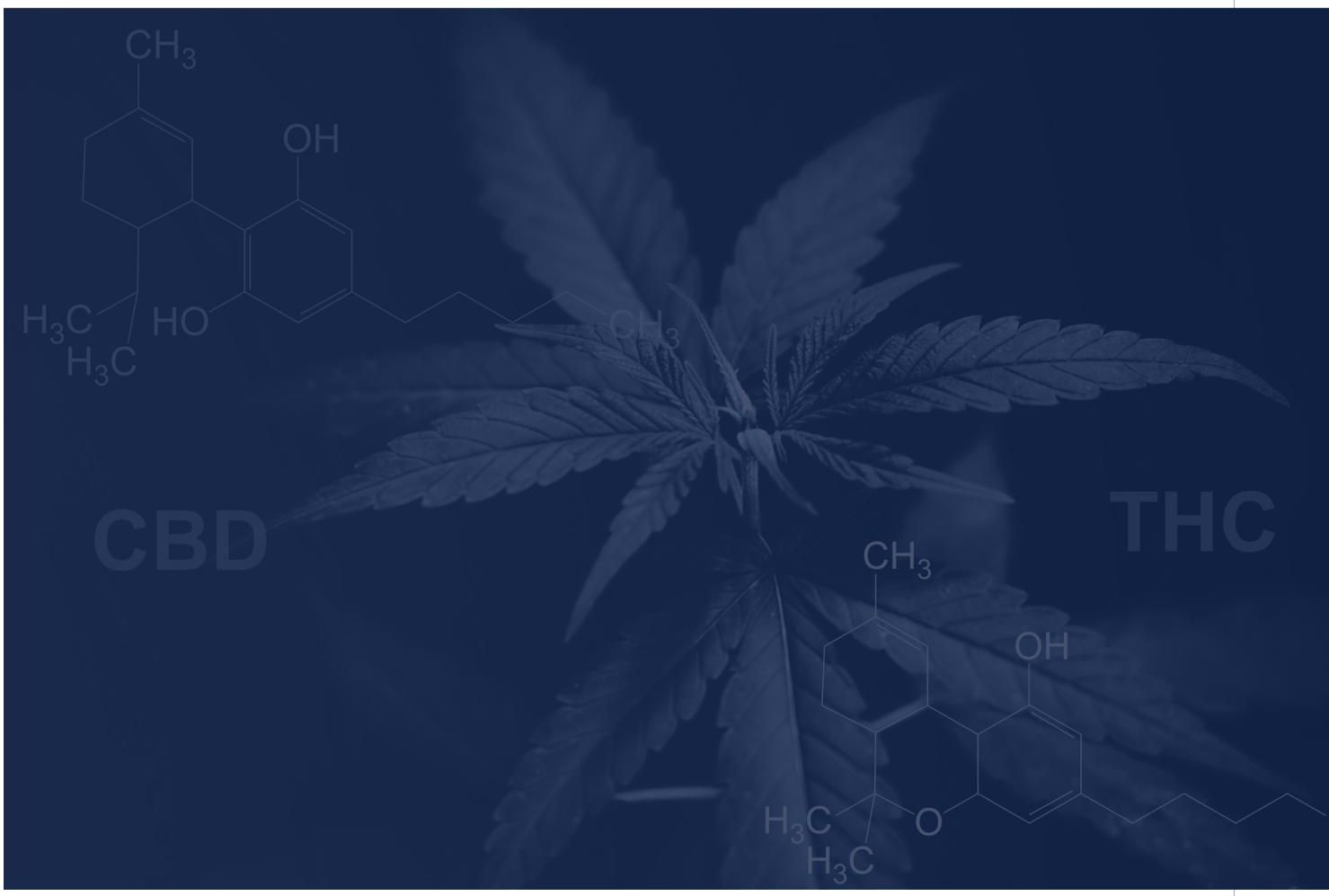
As already reported in the European resolution[30] and then taken up in the SIFAP-SIFO position paper, compounded preparation must respond to a specific need of the patient who does not find in the commercial product a satisfactory response to their therapeutic needs. An example includes different dosing compared to the commercial product or different composition due to a patient's allergy/intolerance to an excipient, or different indications and usage compared to the commercial product.
The same document includes a tool, defined as a decision tree, that allows the pharmacist to assess whether the compound has adjuvant value and, therefore, whether the preparation of the drug itself is necessary.

NBP FUI XII ED.

From a qualitative point of view, the NBPs (*Norme di Buona Preparazione* - Good Preparation Standards) ensure reproducibility and quality of the manufactured product; the substantial difference with industrial drugs is that the efficacy and safety of pharmaceutical preparations are not known, since the need to prescribe them arises from the inadequacy of what is available on the market.

COMMUNITY PHARMACIES AND HOSPITALS

Regarding the preparation of CBD-based compounds in hospital and community pharmacies, oral pharmaceutical formulations, both solid and liquid, are produced in pharmaceutical preparations, also called magistral formula, according to current regulations.
In several cases, when the presence of THC in the prescribed medicine is also required by the physician, oily extracts of cannabis varieties, characterized by different proportions of THC or CBD, are prepared.



CBD IN CLINICAL PRACTICE: DOSING, POLYPHARMACY, AND RELATED CRITICAL ISSUES IN PATIENT MANAGEMENT

N. Specchio, N. Pietrafusa

In 2017 and 2018, the first randomized controlled trials for Epidyolex were published for Dravet syndrome and Lennox-Gastaut syndrome[31,32], and in June 2018, the FDA approved the use of Cannabidiol (CBD) as an adjunctive antiepileptic drug for patients with Lennox-Gastaut syndrome or Dravet syndrome older than two years of age. Epidyolex was also subsequently approved by the EMA in September 2019 for patients older than two years of age with Dravet syndrome and Lennox-Gastaut syndrome, in combination with clobazam. In addition, Epidyolex was approved for the treatment of focal seizures in patients with Tuberous Sclerosis.

CBD has a broad spectrum of action, confirmed by data from randomized, controlled, double-blind clinical trials, and exerted through numerous mechanisms, many of which are still unknown. It also shows a complex pharmacokinetic profile with food-influenced bioavailability, high protein binding, and broad action on hepatic metabolism

DOSAGE

CBD is administered orally as an oil solution. Dosages as high as 25 mg/kg/day have been used in open-label studies, while higher doses up to 50 mg/kg/day have been used in controlled studies. Studies in Lennox-Gastaut syndrome, however, have shown that a significant proportion of patients respond to doses as low as 10 mg/kg/day. Therefore, a “slow start” and “case-by-case escalation” strategy is recommended. A starting dose of 5 mg/kg/day, divided into two doses, would seem appropriate. This dose should be increased to 10 mg/kg/day after one week of treatment. Thereafter, the individual’s response should be carefully observed. The observation time required is strictly dependent on the frequency of baseline seizures prior to CBD administration. If the drug is well tolerated but not sufficiently effective, the dose should be increased slowly in increments of 5 mg/kg/day, if tolerated, to a maximum of 20-25 mg/kg/day[33].

POLYTHERAPY

CBD may exhibit numerous interactions with antiepileptic drugs, both with potent enzyme inducers (such as carbamazepine and phenytoin) and inhibitors (such as stiripentol, felbamate, and valproate); however, the clinical significance of these interactions may not be significant. The best known clinically significant interaction is with clobazam. CBD, through enzymatic inhibition (CYP2C19), can result in an increase (up to five-fold) in its metabolite, N-desmethyl-clobazam[34,35], leading to adverse events (manifesting primarily with sedation)[36], and can occur even at low levels (1 mg/kg/day). In addition, concomitant clobazam may lead to an increase in 7-hydroxy-cannabidiol (7-OH-CBD) (an active metabolite of CBD). Other antiepileptic drugs with a similarly increased effect when co-administered with CBD may include topiramate, rufinamide, zonisamide, and eslicarbazepine. The clinical impact of these interactions should be evaluated on a case-by-case basis, and therapy should be tailored to the specific interactions and concomitant medications. Therapeutic monitoring of baseline medication should be performed prior to CBD administration and subsequently after any increase. If a significant increase in benzodiazepine levels were observed, the dose of clobazam could be reduced (and then monitored), according to an estimate based on linear kinetics. Like CBD, however, stiripentol inhibits the same P450 subtype 2C19 (CYP2C19) and therefore an increase in benzodiazepine level may not occur if the patient is already being treated with stiripentol[1]. CBD has been shown to significantly reduce the frequency of seizures in patients with Dravet Syndrome, Lennox-Gastuat Syndrome, and Tuberous Sclerosis, this reduction has been documented in different randomized controlled clinical trials.

PATIENT MANAGEMENT

Based on the overall data from the controlled studies, frequent, side effects were reported (86% in the CBD groups and 76% in the placebo groups). However, the vast majority of side effects were mild and moderate. These included sleepiness, decreased appetite, pyrexia, and diarrhea, followed by other less frequent adverse events such as vomiting and fatigue. Most side effects occurred within the first two weeks of treatment. More serious side effects were much less common (affecting 19% of CBD groups and 9% of placebo groups). These included, in particular, sleepiness, pyrexia, seizures, skin rashes, lethargy, and elevated transaminases (> three times the upper normal limit). The latter occurred in 16% of patients in the CBD groups and 1% in the placebo groups. In addition, in >79-100% of cases with elevated transaminases, patients were concurrently taking valproate (VPA) therapy, a drug that is already itself hepatotoxic.

Therefore, it is necessary, especially in patients taking valproic acid, to control transaminases at baseline and to monitor them during CBD and VPA treatment.

In controlled studies, 8% of patients showed a significant increase in liver enzymes at 10 mg/kg/day and 16% at 20 mg/kg/day in combination with valproate[31]. This condition led to CBD discontinuation if AST or ALT showed a three-fold increase from baseline in the presence of any symptoms (fever, rash, nausea, abdominal pain, or increased bilirubin) or an eight-fold increase in the absence of such symptoms. In rare cases, an increase in ALT/AST has been observed with 20 mg/kg/day of CBD without concomitant valproate use, but not with lower doses of CBD. The increase in liver enzymes was reversible in about half of the cases without taking any action; in the remaining cases, CBD was discontinued, leading to normalization of AST/ALT[31]. With the exception of clinical trials, a signif-

icant increase in liver enzymes should lead to a dose reduction or eventually a discontinuation of VPA or CBD. A decrease in VPA should be considered first if the patient's history does not indicate a significant benefit with valproate but a favorable effect with the addition of CBD. In all other cases, CBD should be reduced to 10mg/kg or eventually discontinued. A slight increase in ALT/AST may be observed for several weeks before any action is taken.

THERAPEUTIC CANNABIS AND CBD LEGISLATION

A. Casiraghi, P. Minghetti

The potential therapeutic use of Cannabis must deal with the regulation of narcotic drugs; indeed, the main active ingredient, tetrahydrocannabinol (THC), is listed as a narcotic drug all over the world. Only variety of the cannabis plant containing less than 0.2% of the psychoactive cannabinoid THC may be cultivated and used without any restriction. In this case, the hemp plant is not subject to international control according to Articles 2.9 and 28.1 of the UN Single Convention on Narcotic Drugs.

The other main component of Cannabis, which is gaining more and more attention[37], is cannabidiol (CBD), which has no psychotropic effect, and thus it is not considered a narcotic drug

Focusing on Europe, different scenarios relative to the regulation of cannabis medicinal products exist. Many western European countries have approved the medicinal use of cannabis, either as whole cannabis plant or cannabis-based drugs. Only two cannabis-based medicinal products are currently available in Europe: the oromucosal spray Sativex®, based on a mixture of THC and CBD at standardized dosage, and the oral solution Epidyolex®, a strawberry flavored liquid formulation containing CBD. As an alternative, standardized dried flower tops of the medicinal-grade cannabis plant can be used in a magistral formula, namely in a pharmaceutical preparation compounded in a pharmacy, following the Good Compounding Practices, for an individual patient, in accordance with a physician prescription.

Cannabis for medicinal use must have an appropriate pharmaceutical quality, like other starting materials used in medicinal products. Quality standards can be described in the individual monographs of a pharmacopoeia. At present there is no official European Pharmacopoeia (Eur. Ph.) Monograph about Cannabis; in Europe, a Danish official monograph[38] and a German (DAB) monograph entitled "Cannabis Flower Monograph"[39] have been published. The Danish "Cannabisblomst" (Cannabis flos) Monograph contains references to Eur. Ph. tests for Pesticides, Aflatoxines, Heavy Metals, Microbial Contamination and to Eur. Ph. General Monographs. In the DAB monograph, limits of cannabinoid content were introduced for the first time; it is clearly stated that the product must contain not less than 90.0 and not more than 110.0 per cent of cannabinol quantities indicated in the label. This guarantees the availability of an appropriate pharmaceutical quality material, and it has been a progress in the direction of reducing variability of cannabinoid content in raw materials. Nevertheless, for a compounded cannabis medicinal extract this is not enough. The recently published DAB monograph entitled "Cannabis Extract, Standardized (Cannabis extractum normatum)"[4] helps in limiting the variability in cannabinoid content in compounded preparations.

In Italy, narcotic substances with therapeutic effects are controlled by the Ministry of Health and reported in a specific list, called Tabella dei medicinali, included in the Italian Pharmacopeia. This list is organized into five Sections, from A, for substances having major risk of abuse, to E, for substances with minor risk. Cannabis is present in Section B of the narcotic list: in 2007, Δ9-tetrahydrocannabinol, trans-Δ9-tetrahydrocannabinol and nabilone were first introduced in the list[41]; then, the cannabis plant and its dried flower tops were also included[42]. The presence of cannabis and its derivatives in Section B causes prescribers and pharmacists to follow specific formalisms, for the prescription and the distribution of medicinal products containing cannabinoids or preparations compounded by a pharmacist using cannabis dried flower tops, respectively. In case of magistral formula, it can only be given to a patient that possesses a non-repeatable medical prescription to be renewed each time.

Products containing only CBD, a molecule with no psychotropic effects, could fall into the pharmaceutical, cosmetic and food category. Medicinal products obtained after extraction from medicinal grade cannabis containing high level of CBD and a limited THC content have to be considered in Section B and can be marked only in magistral formula. For food use, hemp extracts and derived products containing cannabinoids, therefore also the pure CBD, are considered novel foods as a history of consumption has not been demonstrated. For food use, hemp extracts and derived products containing cannabinoids, therefore also the pure CBD, are considered novel foods as a history of consumption has not been demonstrated and as of now are not being cleared for use by the European Food Safety Authority (EFSA). For other uses, products containing CBD can be marketed without any restriction.

FINANCIAL IMPLICATIONS CONCERNING PRESCRIPTION COMPOUNDING AND INDUSTRIAL PRODUCTS

A. D'Arpino, D. Zanon, M. Fortini

When talking about the cost of a drug, one should consider the generating preclinical and clinical evidence, and developing a suitable formulation to guarantee pharmacokinetic, pharmacodinamic and all relevant quality aspects, including palatability, uniformity of dose, and stability.

When a pharmaceutical product is the result of industrial planning, the initial costs incurred are extremely elevated, and according to the objective, if the drug proves to be effective and safe its price will be determined by the sustained costs, the impact the drug has on the population, its innovation and obviously, the overall number of people who can benefit from this therapy. Based on the aforementioned elements, it is easy to understand that, costs being equal, a drug for a common disease will cost the National Health Service less per package than a drug intended for a rare disease.

Things change, or at least they should, when the drug results from nonprofit trials, or perhaps, from established situations in a hospital setting where the formulation at the origin is a prescription, then compounded in the pharmacy. This is usually a preparation that is confined to its own facility, or as in accordance with Legislative Decree 200/2007, an experimental production in which several centers participate and have access to. Since it is totally different from an industrial production, and it is based on achieved results, the circulation of this new therapy follows the logic of EBM (Evidence Based Medicine), spreading widely in all hospitals that treat that pathology, which authorize their pharmacy laboratories for production. The aim is not to recover the costs incurred, but to treat the patient. The aim is not to recover the costs incurred, but to cure the patient.

This last example is often an advantageous condition for a firm that wants to register a similar drug to the pharmacy preparation for the same indication the latter was studied for. Only under this condition should the cost of the commercial product match, or at least not vary much from, the cost incurred in producing the pharmacy preparation.

With regard to the prescription of CBD-based compounds, the price is calculated according to the updated criteria of the National Tariff for Public Dispensation of Medicinals. *(Ministery of Health, Decree September 22, 2017.)*

It is easy to see how the maximum retail cost to be applied to these preparations is strongly influenced by the cost of purchasing CBD as a raw material and this varies significantly according to quality of the substance. To note, currently there is no National or European Monograph on CBD as active pharmaceutical ingredient.

ON-LINE PRODUCTS – THE IMPORTANCE OF EDUCATING AND INFORMING THE PATIENT

F. Luccini

In recent years the cannabis market has gained worldwide popularity. From recreational and medical marijuana to cannabis-derived products – such as CBD (cannabidiol), a relaxant compound of cannabis – its use is growing globally. Most recently, low-strength cannabis varieties such as hemp (or industrial hemp), rich in CBD, have become very common and sold as herbal cannabis (light cannabis), lotions, extracts, and candies. Although these products have received a remarkable attention, not much is known about the effect of this CBD market, and many concerns have been expressed about the health outcomes of their consumption.

As highlighted by the National Academies of Sciences, Engineering, and Medicine (2017), CBD may not present itself as a threat to human health, but it certainly does in the event of its abuse to treat serious medical conditions. For this reason, in 2018, the Italian National Health Council (CSS) expressed its concern about the safety of products based on cannabis inflorescence and suggested a ban on the commercialization of the product. In their declaration, the CSS lifted worries about the impossibility of tracking individual users, its short- and long-term effects, and particularly for some vulnerable consumers (e.g., patients with pathologies). In fact, because of its relaxing effects, this product can be considered as a substitute for existing medications and encourage self-medication.

Italy can be considered as a case study, as despite its conservative view on cannabis, "cannabis light stores" have unexpectedly emerged because of a gap in the legislation and have received massive political interest. In 2016, the government enforced Law 242/2016, which aimed to remove various restrictions on the cultivation, processing and marketing of industrial hemp. Hemp is not classified as a drug for its use since it is (nearly) free of the psychoactive compound of cannabis (THC). The law, however, has not taken explicit action on the marketing of the cannabis flower, leaving a gap in the legislation. Since it is not expressly banned, herbal cannabis has been liberalized consequently. By May 2017, several startups had tapped into this gray and totally unregulated business and started to market light cannabis as a "tech product," i.e., as a collectible not intended to be smoked or consumed. In addition, the same retailers have also begun selling other CBD products such as oil, extracts, leaves, beverages and food. Before long, cannabis light stores have therefore become a "social phenomenon". A problem of this phenomenon is that some patients might have seen this new product as an opportunity to seek benefit or improve their quality of life, for example, by using a mostly available product that requires no prescription and is perceived to be in regular use. In fact, a study[43] found that the availability of such a product convenient for self-medication had an important impact on sales of drugs dispensed for the treatment of anxiety, psychosis, chronic pain, insomnia, migraine and epilepsy. The study reported that local availability of light cannabis caused a significant and large reduction in dispensed packages of anxiolytics and sedatives, which amounted to about 10%, and a 1-1.5% reduction in the number of prescriptions for antiepileptics, antidepressants, opioids, and antimigrants. These findings are consistent with a hypothesis of self-medication, meaning the adoption of risky behaviors to seek relief and improvement in quality of life. This is a matter of concern since CBD-based products are not subject to any mandatory testing or regulatory framework to establish indication area, daily dosage, route of administration, maximum recommended daily dose, shelf life and stability. Current equivocal regulations for all uses mean that there is considerable variation in the quality and safety of the CBD-based preparations available on the market. Indeed, a recent study[44] that analyzed 14 products on the market found that nine out of the 14 samples tested had concentrations that were notably divergent from the stated amount, and some of the samples contained THC even when the manufacturer claimed the product was THC-free.

The results highlighted the extreme variability of marketed CBD products, supporting the necessity for stricter regulations/controls and the importance of also specifying the amount of THC or any other intoxicating cannabinoid contained.

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