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Place of therapeutic cannabis in France and safety data: a literature review

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Abstract

Objectives: To date, very few cannabis-based specialities are authorised on the French market despite a growing demand from patients and health professionals. The objective of this study is to review the tolerance profile and the French legislative status of the two main cannabinoids used for therapeutic purposes: tetrahydrocannabinol (THC) associated with psychoactive effects and non-psychoactive cannabidiol (CBD).

Methods: This review is based on relevant articles retrieved by a search in Google Scholar and PubMed databases and on an assessment of the legal texts and summaries of product characteristics available in France.

Results: Evidence for the tolerability of CBD during chronic use is reassuring, but a significant risk of drug interactions exists. THC use appears to be associated with a higher proportion of

serious adverse effects, including neuropsychological and cardiovascular effects. Inhaled cannabis appears to be associated with greater toxicity than the oral route. These data are presented together with the pharmacokinetic and pharmacodynamic data of THC and CBD.

Conclusion: The literature reports several frequent but rarely serious adverse effects of CBD during chronic use as well as a significant risk of drug interactions. THC use seems to be associated with a higher proportion of serious adverse effects compared to CBD, particularly at the neuropsychological and cardiovascular levels. Health professionals should be up to date on the particularities of therapeutic cannabis in terms of efficacy, safety and drug interactions.

Keywords: tetrahydrocannabinol, cannabidiol, therapeutic cannabis, experimentation, adverse drug reaction

Résumé

Objectif: Très peu de spécialités à base de cannabis sont autorisées sur le marché français. L'objectif de cette étude est de réaliser une revue de la littérature sur le profil de tolérance et le statut législatif français des deux principaux cannabinoïdes utilisés à des fins thérapeutiques : le tétrahydrocannabinol (THC) associé à des effets psychoactifs et le cannabidiol (CBD) non psychoactif.

Méthodes: Cette revue est basée sur des articles pertinents retrouvés dans les bases de données Google Scholar et PubMed et sur une évaluation des textes législatifs au regard des produits disponibles en France.

Résultats: Les données de tolérance du CBD lors d'un usage chronique sont rassurantes, mais un risque important d'interactions médicamenteuses existe. La consommation de THC semble

être associée à une proportion plus élevée d'effets indésirables graves, incluant des effets neuropsychologiques et cardiovasculaires. Le cannabis inhalé semble être associé à une plus grande toxicité que la voie orale. Ces données sont présentées parallèlement aux données pharmacocinétiques et pharmacodynamiques du THC et du CBD.

Conclusion: La littérature rapporte plusieurs effets indésirables fréquents mais rarement graves du CBD lors d'une utilisation chronique ainsi qu'un risque important d'interactions médicamenteuses. La consommation de THC semble être associée à une proportion plus élevée d'effets indésirables graves par rapport au CBD, notamment au niveau neuropsychologique et cardiovasculaire. Les professionnels de santé doivent être au courant des particularités du cannabis thérapeutique en termes d'efficacité, de tolérance et d'interactions médicamenteuses.

Keywords: tetrahydrocannabinol, cannabidiol, cannabis thérapeutique, expérimentation, effet indésirable

HIGHLIGHTS

- To date, very few cannabis-based specialities are authorized on the French market despite a growing demand from patients and health professionals.
- Evidence for the tolerability of CBD during chronic use is reassuring, but a significant risk of drug interactions exists.
- THC use appears to be associated with a higher proportion of serious adverse effects, including neuropsychological and cardiovascular effects.
- Inhaled cannabis appears to be associated with greater toxicity than the oral route.

POINTS ESSENTIELS

- A ce jour, très peu de spécialités à base de cannabis ont l'autorisation de mise sur le marché en France, malgré une demande croissante des patients et des professionnels de santé
- Les données de tolérance du CBD lors d'un usage chronique sont rassurantes, mais un risque important d'interactions médicamenteuses existe
- La consommation de THC semble être associée à une proportion plus élevée d'effets indésirables graves, incluant des effets neuropsychologiques et cardiovasculaires.
- Le cannabis inhalé semble être associé à une plus grande toxicité que la voie orale.

1. INTRODUCTION

Therapeutic cannabis is at the heart of the medical news in Europe, and in particular in France. In view of the converging data in the literature showing the interest of cannabis in the treatment of certain pathologies, it could enrich a sometimes limited therapeutic arsenal (1,2). At present, in addition to the question of the feasibility of making it available in France, the question of the place of therapeutic cannabis needs to be supported by an objective, evidence-based benefit-risk ratio, which has so far been poorly defined.

In this context, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) has launched an experiment since 26 March 2021 to assess the relevance and feasibility of the implementation of medical cannabis in France. This experimentation extends

over 24 months from the date of inclusion, and plans to include 3,000 patients in specific clinical situations for which the ANSM considers the use of cannabis for medical purposes relevant. The five therapeutic indications selected concern (i) neuropathic pain refractory to accessible therapies (medicinal or not), (ii) certain forms of severe and pharmaco-resistant epilepsy, (iii) certain rebellious symptoms in oncology linked to cancer or its treatments, (iv) certain palliative situations and (v) painful spasticity in multiple sclerosis or other central nervous system pathologies (1). The inclusion of a patient is done according to certain criteria and in voluntary reference structures authorised by the ANSM, by the sole decision of the doctor and the patient's consent. The pharmaceutical forms made available include oily solutions for oral use and flowering tops of cannabis to be vaporised for inhalation, dispensed on secure prescription. These medicines are available in different ratios of the two active ingredients Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), and distinguish between THC-dominant, THC:CBD-balanced and CBD-dominant presentations.

To date, the question of adverse effects of cannabis has arisen in the context of its use for therapeutic purposes, particularly in view of the data available on its toxicity during recreational use (3). The objective of this work is to conduct a literature review on medical cannabis toxicity data. Google Scholar and PubMed databases were used to search for relevant peer-reviewed articles published in English between 1970 and 2021 using the following search terms: cannabis, cannabinoids, phytocannabinoids, cannabidiol, medical, toxicity, chronic, long term, acute, toxic effects, safety, exposure, pharmacology, pharmacokinetics, pharmacodynamics, endocannabinoid system. Studies providing relevant information on the toxicity data of medical cannabis were included for analysis.

2. THERAPEUTIC CANNABIS

2.1. What are we talking about?

In France, according to the order of 30 December 2021, the cultivation, import, export and industrial and commercial use of only those varieties of *Cannabis sativa L.* with a THC content of no more than 0.3% (as opposed to 0.2% before that date) and which are listed in the Common Catalogue of Varieties of Agricultural Plant Species or in the Official Catalogue of Species and Varieties of Plants Grown in France, are authorised (4). Otherwise, they fall within the scope of criminal anti-drug policy.

Therapeutic cannabis, or medical cannabis, refers to the use of the species *Cannabis sativa L.*, a herbaceous plant native to Central Asia, of the family Cannabinaceae, for purely medical purposes. This plant contains more than 540 natural compounds, grouped into the families of phytocannabinoids, terpenes and phenolic compounds (5). For medical purposes, it is mainly the phytocannabinoids that are reported as potentially relevant. Indeed, *Cannabis sativa L.* contains over 100 different phytocannabinoids, including THC and CBD (5). These phytocannabinoids can be classified into several subclasses, including THC analogues, Δ^9 -tetrahydrocannabivarin analogues, CBD analogues and cannabinol analogues (5).

Most of the other compounds present in the *Cannabis sativa L.* plant are still poorly understood, especially in terms of their psychotropic and somatic effects. THC is the main active substance in cannabis and is responsible for the main symptoms of acute intoxication due to its psychotropic activity (Figure 1). In contrast, CBD is the main non-psychoactive component, which is why the potency of cannabis is usually based on the THC content of the product (Figure 1) (6). These two molecules are currently the two main substances of interest in therapeutics, justifying the growing number of scientific publications referring to them in recent years.

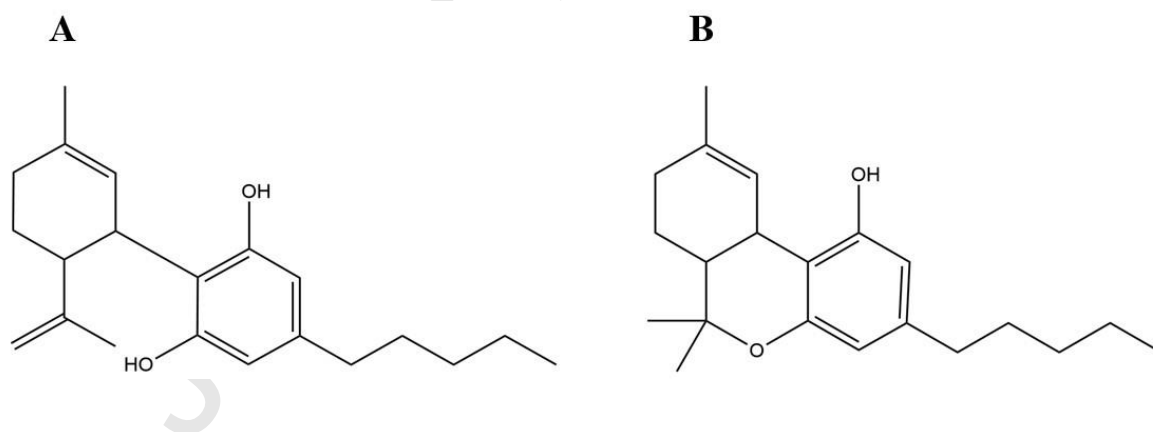


Figure 1: Chemical structure of (A) cannabidiol, and (B) tetrahydrocannabinol.

Figure 1: Structure chimique du (A) cannabidiol, et du (B) tetrahydrocannabinol.

2.2 How is it consumed?

Cannabis, as a product used for recreational purposes, is most often smoked and thus consumed by inhalation. This route of administration is associated with well-known pulmonary toxicity, which can be limited by the use of alternative routes of administration (7). In the context of the use of cannabis for medicinal purposes, the oral route (*per os*) is often preferred, although administration by inhalation (mostly vaporised), by intravenous route, or by topical application to the skin or mucous membranes is also described (2,6,8). The most frequently found dosage forms are oily forms (oil capsules or oils for oral administration), although some states or countries allow access to dried flowers or whole cannabis plants (2).

2.3. Medications available in France

In France, only three medicines containing cannabis-derived molecules have obtained a Marketing Authorisation (MA) or an Authorisation for Compulsory Access (9–11) : Sativex®, Epidyolex® or Marinol® (Table 1).

Sativex® (nabiximols) is a mixture of two cannabis extracts with a marketing authorization in France since 2014 for the treatment of symptoms related to moderate to severe spasticity due to multiple sclerosis (MS) in adults who have not sufficiently responded to other antispasticity treatments and who are responders to initial treatment (10). Created in 1998 by GW Pharmaceuticals, it comes in the form of a mouth spray delivering 100 µL of a 1:1 THC:CBD ratio with each spray (10). Currently, this product is available in more than 30 countries. In France, however, it has not been marketed due to an "absence of agreement between the government and the laboratory on the selling price, according to the laboratory Almirall" marketing the product (12).

Epidyolex®, also produced by GW Pharmaceuticals, is a drinkable solution of CBD at a concentration of 100 mg/mL (9). In 2018, this product obtained a Temporary Use Authorisation in France and was available in pharmacies for internal use as an adjuvant to clobazam, in the treatment of convulsions insufficiently controlled by current treatments in Lennox-Gastaut syndrome and Dravet syndrome. Since 19 September 2019, Epidyolex® has obtained marketing authorisation for this same indication in patients aged 2 years and over (9).

Lastly, Marinol® is marketed by the company Alkem in the form of soft capsules containing 2.5 mg of dronabinol, synthetic THC (11). Between 2003 and 2022, this speciality was available on hospital prescription within the framework of an ATU in three indications, namely neuropathic pain after failure of all treatments, nausea and vomiting in the context of cancer chemotherapy, and anorexia in patients suffering from the human immunodeficiency virus (13). To date, only the indication of neuropathic pain has been approved for compassionate access (14).

Apart from Marinol® and Epidyolex®, only the "medicinal cannabis experimentation" range of medicines is currently available with a secure prescription within the framework of the French experimentation on therapeutic cannabis, for which a 100% reimbursement is applied.

Table 1: Therapeutic indications for medical cannabis treatment in France.

Tableau 1 : Indications thérapeutiques des traitements par le cannabis médical en France.

| | |
|---------------------------------|--|
| National experimentation | Neuropathic pain refractory to available therapies (drug and non-drug) |
| | Certain forms of severe and drug-resistant epilepsy |
| | Some intractable symptoms in oncology related to cancer or its treatment |
| | Palliative situations |
| | Painful spasticity in multiple sclerosis or other central nervous system diseases |
| Sativex® | Treatment of symptoms associated with moderate to severe spasticity due to multiple sclerosis (MS) in adult patients who have had an inadequate response to other antispasticity therapies and in whom clinically significant improvement in these symptoms has been demonstrated during initial treatment |
| Epidyolex® | In combination with clobazam in the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in patients 2 years of age and older. |
| | Adjuvant treatment of epileptic seizures associated with Tuberous sclerosis (BTS) in patients 2 years of age and older. |
| Marinol® | Central and peripheral neuropathic pain after failure of first or second line treatments. |

3. THE ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) is a large neuromodulatory network involved in the development of the central nervous system (CNS). It plays a major role in the development of many cognitive and physiological processes (15). Its composition is relatively complex, but

endogenous cannabinoid compounds, cannabinoid receptors and enzymes that are responsible for the synthesis and degradation of endocannabinoids are found (15,16).

Endocannabinoids are endogenous substances found in animals and humans that play an important role in mammalian reproduction, neonatal growth, but also in most biological systems (16). Of the five endocannabinoid molecules currently known, anandamide and 2-arachidonylglycerol (2-AG) are the most studied (17) (Figure 2A). For example, 2-arachidonylglycerol (2-AG) is the most abundant endocannabinoid in the brain and is recognised as a complete cannabinoid receptor antagonist. Upon post-synaptic activation, 2-AG is released immediately after its synthesis and activates pre-synaptic cannabinoid 1 receptors, thereby exerting a feedback control on the release of neurotransmitters (16,18).

Cannabinoid receptors, divided into 3 main types (cannabinoid 1 [CB1R or CB1], CB2 and CB3), are expressed throughout the body, although there are preferential locations (16) (Figure 2B). They play a crucial role in many biological phenomena, including the regulation of the functioning of the cardiovascular system, in which CB1 and CB2 receptors influence myocardial contractility, heart rate and blood pressure. Interestingly, these receptors can have antagonistic roles. Stimulation of CB1 receptors leads to a decrease in cardiomyocyte contractility, while stimulation of CB2 receptors increases the contractile force of these cells. (16).

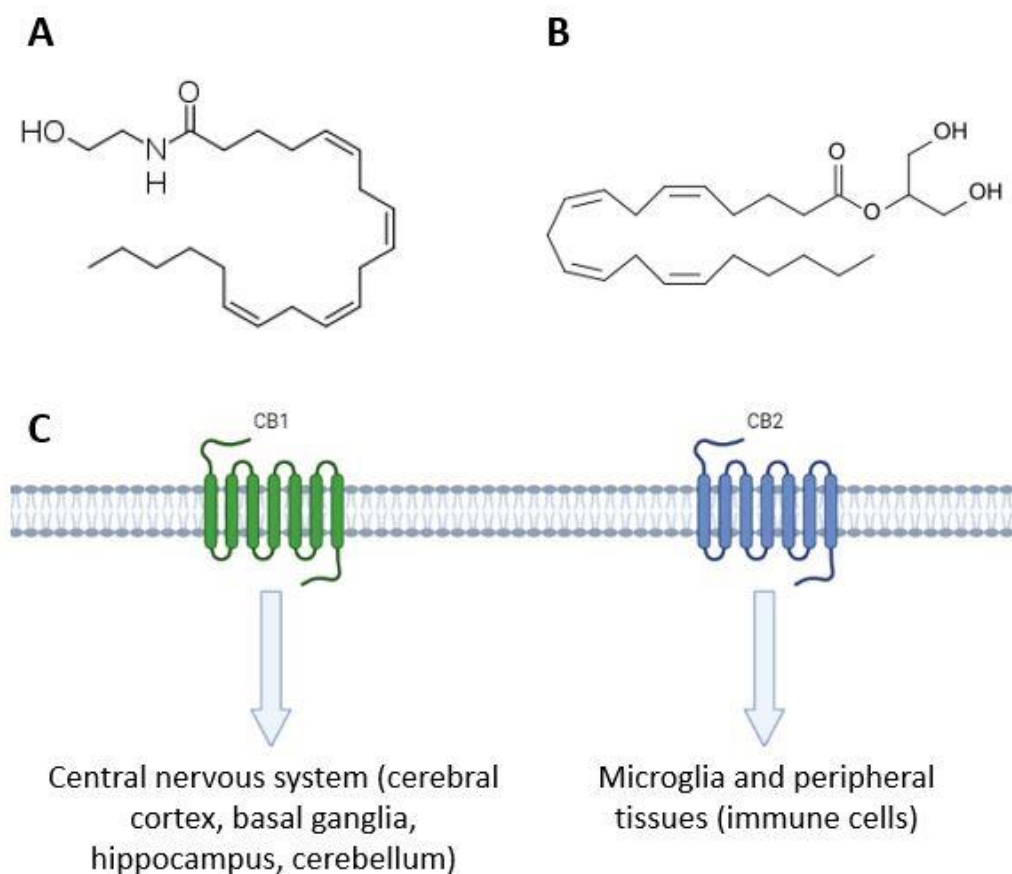


Figure 2: Structure of the endocannabinoids (A) anandamide and (B) 2-arachidonylglycerol (C) Preferential location of CB1 and CB2 cannabinoid receptors.

Figure 2 : Structure des endocannabinoïdes (A) anandamide et (B) 2-arachidonylglycérol (C) Localisation préférentielle des récepteurs cannabinoïdes CB1 et CB2.

Unlike the term "endocannabinoid", the term "cannabinoids" refers to compounds found in cannabis plants, some of which may interact with the endocannabinoid system.

4. PHARMACOLOGY OF THERAPEUTIC CANNABIS

4.3. Pharmacokinetic data

4.1.1 Pharmacokinetics of THC

Absorption. After inhalation, THC is detectable in plasma only a few seconds after the first puff of a cannabis cigarette. The peak plasma concentration is measured 3-10 minutes after the start of the first puff. Systemic bioavailability is generally between 10 and 35%, and is higher in regular users. This bioavailability varies according to several parameters such as the depth of inhalation, the number of puffs, and the concentration of THC present in the smoke (19).

When used orally, the absorption of THC is slow and irregular. Peak plasma concentration is measured after 60-120 minutes, and in some cases up to 4-6 hours. THC is generally degraded by the acidic pH of the stomach and in the intestine, and undergoes a first-pass hepatic effect, resulting in a bioavailability of about 4-12%. With oily formulations, the bioavailability of THC can be increased to between 10 and 20%. (20). In sublingual form, the absorption would be faster (19).

Distribution. The tissue distribution of THC and its metabolites is governed by its physicochemical properties. About 90% of THC in blood is distributed in plasma and about 10% in red blood cells. Also, 95-99% of plasma THC is bound to plasma proteins, mainly lipoproteins, and slightly less to albumin. The lipophilicity of THC gives it a particular affinity for fatty tissue, which then constitutes a reserve organ, especially during chronic use. THC rapidly penetrates highly vascularised tissues such as the liver, heart, lungs, jejunum, kidneys, spleen, and pituitary gland, resulting in a rapid decrease in plasma THC concentration (Figure 3) (19,21).

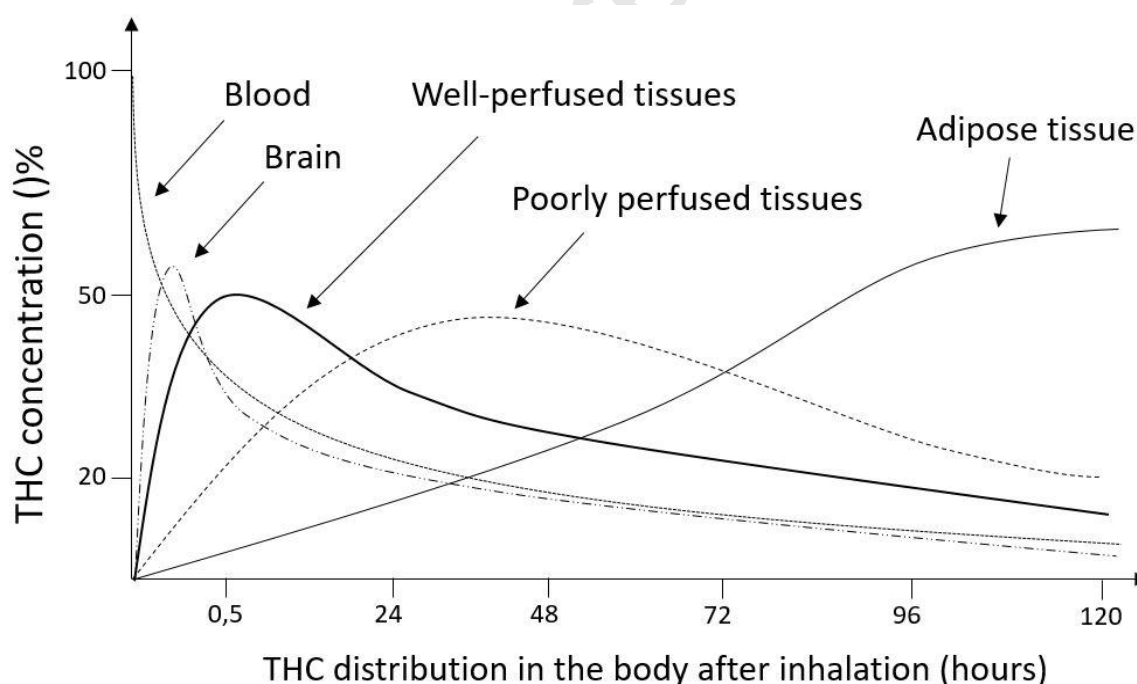


Figure 3: Representation of THC pharmacokinetics after inhalation.
Figure 3 : Représentation de la pharmacocinétique du THC après inhalation

Metabolisation. The metabolism of THC occurs mainly in the liver by microsomal hydroxylation and oxidation, catalysed by enzymes of the complex cytochrome P450 (CYP) isoenzyme system, particularly the CYP2C (CYP2C9, CYP2C19) and CYP3A (CYP3A4) subfamily. Over 100 metabolites are currently identified. Although the liver is the main organ of metabolism, the heart and lungs have also been described as being able to metabolise THC. The main metabolites formed are monohydroxylated compounds. In humans, C11 is the main site of metabolism, yielding 11-OH-THC by hydroxylation. The latter is also oxidised, producing THC-COOH, which in turn can be glucuronidised to 11-demethyl-9-carboxy-THC glucuronide (Figure 4). Note that it is the long conjugated chains of 11-OH-THC that constitute the storage forms of THC in adipose tissue. The limiting step in THC blood clearance is controlled by hepatic blood flow (19).

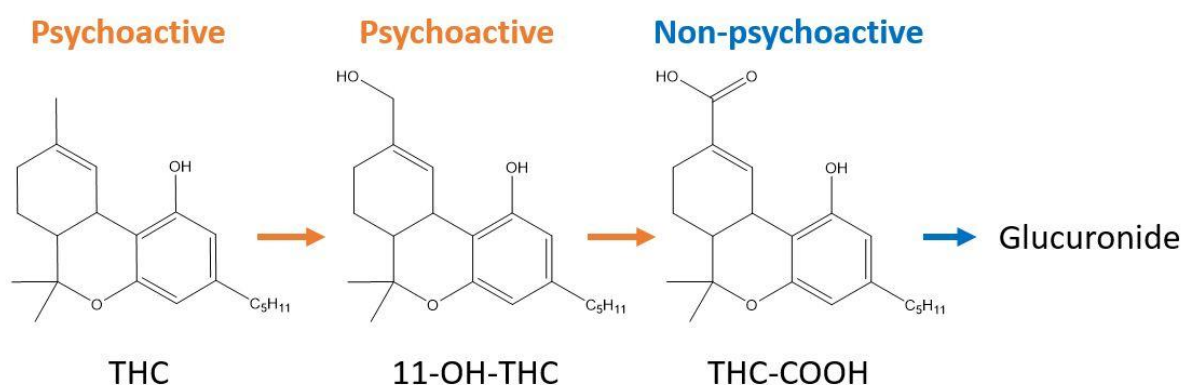


Figure 4: Metabolism of tetrahydrocannabinol (THC) to 11-OH-THC, THC-COOH and glucuronide.

Figure 4 : Métabolisme du tétrahydrocannabinol (THC) en 11-OH-THC, THC-COOH et glucuronide

Excretion. After administration by inhalation, THC is detectable between 7 and 12 hours in plasma. The plasma half-life is difficult to determine precisely since the plasma/fat balance is slowly reached, and varies greatly between individuals. Interestingly, however, THC-COOH is detectable several days after smoking a large amount of cannabis due to its systemic redistribution from fatty tissue (19). THC is excreted within a few days, mainly as acidic metabolites (about 20-35% in urine and 65-80% in faeces), and less than 5% of an oral dose of THC is eliminated in the faeces without modification (19).

4.1.1 Pharmacokinetics of CBD

The average systemic bioavailability of inhaled CBD is about 31% and its plasma profile is broadly similar to that of THC. After oral administration of CBD, the plasma concentration profile is equivalent to half the amount of THC (e.g. 40 mg CBD is equivalent to 20 mg THC). The metabolism of CBD is also similar to THC, producing mainly 7-OH-CBD by hepatic hydroxylation via CYP450. The excretion rate of metabolites in urine is about 16% within 72 hours. In contrast to THC, a high percentage of unchanged CBD is however excreted in the faeces (>5%) (19).

4.2. Pharmacodynamics data

In general, cannabinoids activate the same signaling pathways as endocannabinoids (endogenous) at the neuronal level, also sharing their mechanisms of action (22).

4.2.1. Pharmacodynamics of THC

THC is an agonist at the two cannabinoid receptors CB1 and CB2. Although the effects attributed to these two Gi/o-coupled transmembrane receptors were initially related to a decrease in cyclic adenosine monophosphate (cAMP) levels and intracellular potassium influx, it is now described that multiple signaling pathways are involved in their effects, such as regulation of the MAPK pathway, modulation of ion channels, or modulation of intracellular calcium concentrations (17,23) (Figure 5). The action of cannabinoids is also linked to an interaction with other receptor systems, such as opioid receptors, TRPV receptors, 5-HT₃ serotonin receptors or NMDA glutamate receptors (23).

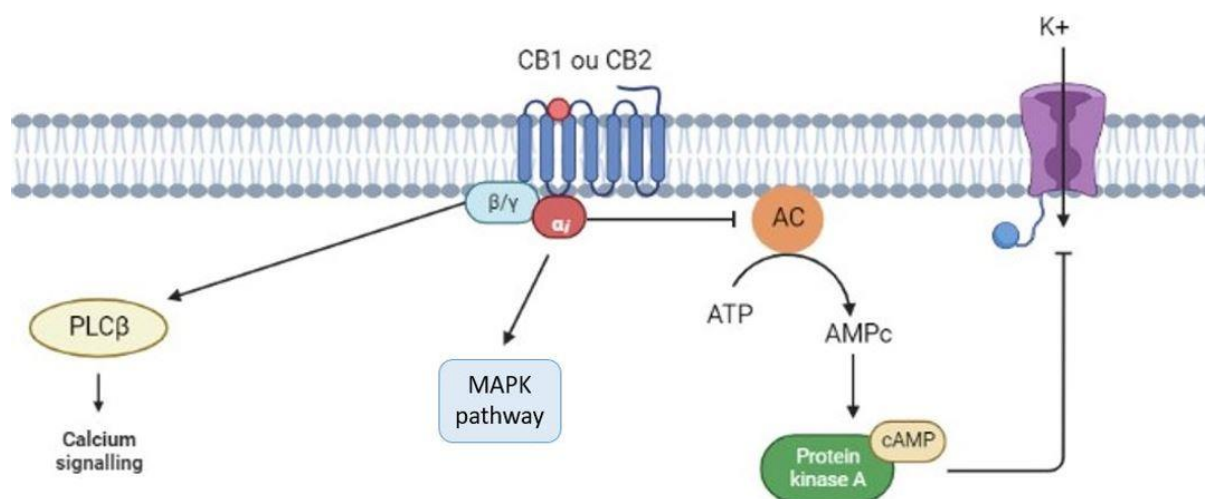


Figure 5: Major signal transduction pathways of cannabinoid receptor activation. AC : Adenylate cyclase; ATP : Adenosine triphosphate; AMPc : Cyclic adenosine monophosphate; CB1 et CB2 : Cannabinoid receptor type 1 and 2; MAPK : Mitogen-activated protein kinases ; PLCβ : Phospholipase Cβ ; PKA : Protein kinase A.

Figure 5 : Principales voies de transduction du signal de l'activation des récepteurs cannabinoïdes. AC : Adenylate cyclase; ATP : Adenosine triphosphate; AMPc : Cyclic adenosine monophosphate; CB1 et CB2 : Cannabinoid receptor type 1 and 2; MAPK : Mitogen-activated protein kinases ; PLCβ : Phospholipase Cβ ; PKA : Protein kinase A.

The CB1 receptor is predominantly present in the CNS, particularly in the hippocampus, basal ganglia (striatum, substantia nigra, globus pallidus), cerebral cortex, amygdala and cerebellum. Through activation of pre-synaptic CB1 receptors, THC causes inhibition of neurotransmission and leads to psychoactive effects such as impairments in learning, memory, spatial orientation and attention in the case of acute cannabis intoxication (2,23). The CB2 receptor is expressed in microglia cells and in the periphery. In particular, the localisation of CB2 receptors within the immune system implies that some of the immunosuppressive effects induced by cannabinoids are mediated by this receptor (23).

Cannabis, through its interaction with the endocannabinoid system, thus generates effects such as significant cognitive and psychomotor disturbances (associated with THC concentrations exceeding 5 ng/mL). In healthy patients, THC administration can produce psychotic symptoms, altered perception, cognitive impairment and increased anxiety. Also, THC may cause tachycardia, probably due to its direct agonist action on CB1 receptors in the heart tissue (24).

Lastly, cannabis with a high THC content is associated with significant dependence, especially when compared to low THC cannabis use (24). A tolerance phenomenon has also been shown, whereby THC reduces the density and/or efficiency of CB1 (25). ~~It should be noted that the lethal dose 50 (LD50) of THC consumed orally is between 800 and 1900 mg/kg in rats, making lethal intoxication very unlikely when extrapolating these data to humans.~~

4.2.2. Pharmacodynamics of CBD

The mechanisms of action of CBD are not fully elucidated, but different sources agree on its non-psychoactive properties. It appears to act as a negative allosteric modulator of the CB1 receptor, thus blocking or limiting certain effects of THC, particularly at the neuropsychological and cardiovascular levels, and allowing better tolerance of cannabis (26,27). It also acts as an inverse agonist of CB2 receptors, partially explaining its anti-inflammatory activity (28).

Recent studies show that CBD has interesting benefits for medical use, supported by its anxiolytic, anti-inflammatory, neuroprotective, anti-emetic, and anti-psychotic properties (24). ~~Thus, apart from these effects on cannabinoid receptors, several other targets of CBD have been identified. Its interaction with TRPV receptors (and in particular TRPV1) has been associated with neuroprotective and anti-convulsant effects (29,30), anti-psychotic effects (31), and immunomodulatory effects (32). Through its 5-HT1A receptor agonist properties, CBD has shown *in vivo* panicolytic (33), antidepressant (34), and anti-aggression effects (35), as well as a reduction in autonomic stress responses (36) in rodents. Lastly, recent data in the literature suggest the existence of many other pharmacological targets, including adenosine, the G-coupled protein (GPR) 55 receptor, GPR18, GPR119, proliferator-activated receptor alpha and glycine receptors (28,37).~~

5. TOLERANCE DATA ON THE CHRONIC USE OF THERAPEUTIC CANNABIS

The understanding of the efficacy and tolerance profile of therapeutic cannabis seems to have been limited by decades of prohibition in many countries. The acute toxicity of CBD and THC being well detailed in the literature (38–40), only the chronic toxicity of these 2 compounds is addressed here. In this context, any repeated exposure to cannabis or its compounds for at least

10 days was considered (sub)chronic and included for analysis. The main chronic toxicity data reported in humans are summarised in Table 2.

5.2. Neuropsychic data

Neuropsychological toxicity is one of the most worrying signals regarding chronic non-medical cannabis use (41,42). Indeed, repeated use of cannabis is associated with elevated anxiety symptoms and panic disorders. In people diagnosed with bipolar disorder, cannabis may trigger or reinforce manic symptoms (41). Also, diagnoses of major depressive episode and depressive symptoms are relatively high among cannabis users (41). Chronic cannabis use is also associated with an increased risk of developing a psychiatric condition such as schizophrenia (41). Lastly, recent studies have shown structural and functional brain abnormalities in heavy cannabis users, with smaller amygdala and hippocampus compared to non-users (41).

The data in the literature on the neurological toxicity of CBD are more reassuring. Indeed, a study by Mincis and colleagues (1973) shows that oral administration of 10 mg of CBD for 21 days does not induce any neurological changes (43). Also, Cunha and colleagues (1980) showed that oral administration of CBD at higher doses in healthy patients (3 mg/kg body weight for 30 days, corresponding to subchronic exposure), or in epileptic patients (200-300 mg daily for 135 days, corresponding to chronic exposure), was well tolerated and showed no signs of toxicity or serious adverse effects on neurological and physical examination (44). In terms of chronic exposure, Rosenkrantz et al (1981) also showed that a 90-day exposure to CBD orally at doses around 200 mg/kg (estimated to be 1/100th of the oral LD50) in rhesus monkeys did not induce clinical changes in neurological, cardiovascular, or weight gain (45). However, an increase in the mass of certain organs (liver, kidneys, heart), as well as a slight difference in the weight of the gonads between the sexes was observed. In the context of a single exposure to doses of CBD around the LD50 in intravenous (150 to 300 mg/kg), these same authors reported the appearance of tremors associated with CNS inhibition (sedation, prostration, bradypnoea), convulsions and bradycardia (45).

Interestingly, Hartley al. (2019) showed that the effect inhalation from cannabis joints on vigilance and driving performance was more marked and lasted for longer in occasional consumers than in chronic consumers, whereas the opposite occurred in the pharmacokinetic parameters, with THC being present in blood at higher concentration and for a longer period in

chronic consumers than in occasional consumers. According to researchers, these results suggest a nonrelationship between whole blood concentration of THC and psychoactive effect of this substance, and thus a partial tolerance to these effects with more frequent exposure (46).

These data should also be compared with the summaries of characteristics of cannabis products marketed in France which also include neurological or psychiatric adverse effects. Thus, Sativex® users reported dizziness and fatigue as very common (> 10% of patients) while attention disorders, irritability/aggressiveness, amnesia, balance disorders, dysarthria, dysgeusia, lethargy, memory impairment, drowsiness, blurred vision and falls are reported as common (between 1 and 10% of patients) (47).

In Epidyolex® summary of product characteristics, lethargy and epilepsy seizure were reported as very common (> 10% of patients) while somnolence, fatigue, attention disorders and irritability/aggressiveness were reported as common (between 1 and 10% of patients) (48).

Lastly, Marinol® users reported anxiety/nervousness, ataxia, depersonalisation, euphoria, hallucinations, paranoid reactions, amnesia, confusion, dizziness and somnolence in over 1% of cases (49).

5.3. Cardiovascular disorders

Cannabis has multiple effects on the cardiovascular system. First of all, smoked cannabis leads to the production of cardiotoxic compounds similar to tobacco. It also causes stimulation of the sympathetic nervous system and inhibits the parasympathetic nervous system, thereby increasing heart rate, myocardial oxygen demand, blood pressure, platelet activation, and is associated with endothelial dysfunction and oxidative stress (50). In contrast, CBD alone is associated with a decrease in blood pressure and heart rate, improves vasodilation in a model of endothelial dysfunction and reduces inflammation and vascular hyperpermeability in diabetic mouse models (50–52). These data are supported in particular by a recent meta-analysis reporting that cannabinoid consumption is associated with the occurrence of tachycardia and hypotension, particularly orthostatic (53).

In parallel, cannabis use (smoked or inhaled) is associated with greater carboxyhaemoglobin formation compared to smoked tobacco use, potentially increasing endothelial dysfunction, lipoprotein oxidation and disrupting oxygen binding to haemoglobin (54). In addition, the

effects of long-term high levels of carboxyhaemoglobin are associated with various cardiac events such as cardiomyopathy, angina, myocardial infarction, arrhythmias, heart failure, pulmonary oedema and sudden death (55). To date, there is little high-level evidence for a causal relationship between long-term cannabis use and cardiovascular risk, particularly as most of the available data are observational and short-term in nature (26). There is even less data on the use of cannabis for medical purposes.

In Sativex® summary of product characteristics, hypertension, palpitations and tachycardia are reported as uncommon (less than 1% of patients) while hypotension have been reported in less than 1% of cases using Marinol® (47,49).

5.4. Lung data

A review of the literature by Beaulieu et al (2005) reports that animals exposed to varying doses of cannabis smoke for 12 to 30 months show significant airway damage and a high incidence of acute and chronic pneumonia compared to non-smokers (sham smoke) (56). Other studies in humans report that cannabis use by inhalation is associated with symptoms of chronic bronchitis and airway inflammation, particularly with heavy use (57). However, there is conflicting evidence of an association between cannabis use and the development of chronic obstructive pulmonary disease (58,59). It should be noted that the changes in respiratory functions associated with chronically smoked cannabis are difficult to dissociate from those caused by tobacco alone because of consumption habits that include tobacco (60).

The issue of lung damage associated with e-cigarettes (electronic cigarettes) or vaping is also of current interest. Indeed, a study by Blagev and colleagues confirms the results of other reports in which patients exposed to vaping (of e-tetrahydrocannabinol, e-nicotine or both) showed constitutional, gastrointestinal and respiratory symptoms (lung damage) (61). The incriminating agent is in fact vitamin E acetate and not cannabinoids. Indeed, a study by Landman and colleagues shows that vitamin E acetate was identified in the bronchoalveolar lavage fluid samples of 29 patients with "Vaping Associated Lung Injury" (VALI) (62). These 29 patients are from the 2172 cases of VAP reported to the US Centers for Disease Control and Prevention as of November 13, 2019. As a reminder, vitamin E acetate is used as an excipient in e-tetrahydrocannabinol (THC for vaping).

In 2006, an American meta-analysis of 19 studies reported that the presence of tar and the way cannabis is used (depth of inhalation and longer smoke retention) increased the risk of tumour formation (63). In 2013, a cohort study that followed 49,321 Swedish men over 40 years exposed to tobacco and cannabis showed a two-fold increase in the cancer risk of developing lung cancer for "heavy" cannabis users, defined as having used cannabis more than 50 times in their lifetime (64). In this context, the combination of tobacco and cannabis use could increase the risk of developing cancer.

In Epidyolex® summary of product characteristics, coughing is reported as common, while no common adverse reactions appear to affect the respiratory tract for Marinol® and Sativex® (47–49).

5.5. Digestive system

A study by Ewing and colleagues reported that 10-day (sub-acute) exposure to CBD doses above 50 mg/kg in mice was well tolerated after a single administration (65). In contrast, repeated administration of CBD would present a risk of hepatotoxicity, notably described by hepatic cytoplasmic swelling, increased liver/body weight ratio, and elevated aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) and total bilirubin. These results support those of other clinical trials in which 5-20% of patients showed an increase in liver enzymes during chronic administration of CBD at doses of 20 mg/kg body weight (65).

Consistently, the Epidiolex® product monograph states that CBD may cause dose-dependent elevations of liver transaminases without reference to frequency. These elevations usually occur within two months of initiation of treatment, although cases have been observed up to 18 months after initiation of treatment, particularly in patients taking valproate (48).

In the Marinol® product monograph, it is also mentioned that THC can cause liver enzyme elevations, with clinical trial data reporting this adverse effect in $\leq 1\%$ of cases (49).

Lastly, intestinal disorders including diarrhea, nausea and vomiting were reported as a frequent to very frequent adverse effect (from 1% to $> 10\%$ of patients) for the 3 cannabis specialities marketed in France (47–49).

5.6. Kidney data

To date, no data appear to have shown organic renal toxicity from chronically consumed therapeutic cannabis. However, rare cases of renal infarction have been described due to renal artery stenosis (66).

5.7. Genotoxicity and reproductive toxicity

Chronic use of cannabis has been described as impairing reproductive functions. Indeed, in animals, chronic use of cannabis containing cannabinoid agonists (such as THC) has been shown to reduce testosterone secretion, impair sperm production and motility, and interfere with the ovulatory cycle (41,67).

Another study by Cavalho and colleagues indicates that chronic exposure to CBD is associated with changes in the male reproductive system, suggesting chronic reproductive toxicity (68). Indeed, the results show that administration of CBD at doses of 15 to 30 mg/kg body weight for 34 consecutive days (subchronic exposure), followed by a 35-day recovery period, caused significant changes in the testes of adult male mice. In particular, an increase or decrease in the frequency of spermatogenesis stages and a decrease in testosterone levels at the highest dose (30 mg/kg body weight) were reported (68).

5.8. Data in pregnant or breastfeeding women

Interestingly, a passage of THC into the mother's milk is also described in monkeys, where about 0.2% of the THC ingested by the mother is found in her milk. In addition, chronic administration to the mother leads to accumulation of THC in fatty tissues, resulting in an ingestion of about 0.01-0.1 mg THC per day by the infant (19).

There is little data on the use of therapeutic cannabis in pregnant or breastfeeding women. To date, the Teratogen Reference Centre has not reported any malformative effects associated with cannabis use in the first trimester, although THC does cross the placental barrier. However, regular heavy cannabis use (6 or more times per week) is associated with preterm birth,

intrauterine growth retardation and withdrawal syndromes in the newborn, although the specific role of tobacco smoked with cannabis is difficult to distinguish from that of cannabis alone. Finally, deficits in attention, hyperactivity and disturbances in some behavioural tests and executive functions have been observed in children aged 10 to 16 years whose mothers used cannabis regularly and extensively during their pregnancies (69).

5.9. Drug interaction data

Recently, the risk of drug interactions involving cannabis use has been described, leading to caution when co-prescribing drugs with a narrow therapeutic range (70). These interactions are thought to be mediated by CBD, a potent substrate and inhibitor of cytochromes P450 CYP3A4 and CYP2C19. Leino et al (2019) described an overdose of tacrolimus when combined with purified pharmaceutical CBD (71). Also, a case of clobazam overdose has been described during CBD administration in the context of drug-resistant epilepsy (72). Although there are still few data on clinically significant drug interactions caused by medicinal cannabis, close monitoring is recommended, especially in elderly, renal or hepatically impaired patients for whom a CBD prescription is being considered (70).

5.10. Purity and dosage of CBD in products available for sale to the public.

As CBD-containing products are widely marketed over the counter (mostly in the form of dietary supplements), the question of purity and dosage of these products has inevitably emerged alongside its use. Thus, some studies have reported the presence of toxic contaminants such as heavy metals, pesticides and solvents in these products (73). In addition, a study analysing 84 CBD products sold online found that 42% of the products contained more CBD than stated on the label, 26% were under-dosed, while only 31% contained the stated amount, showing concerning variations in dosage (74). Lastly, Lachenmeier et al. (2019) showed through the analysis of 293 food products from the German market (mainly CBD oils) that 28 products (10%) contained Δ 9-THC above the lowest observed adverse effect level (2.5 mg/day) suggesting that the adverse effects of some commercial CBD products might be based on a low-dose effect of Δ 9-THC (75).

6. SECURITY RISK

In addition to the problems of somatic toxicity, the question of the security risk after the use of cannabis for medical purposes must also be taken into account. Although acute and infrequent cannabis use usually leads to cognitive and psychomotor impairment, this is not always the case for chronic heavy use (76). Indeed, the psychoactive effects of cannabis are likely to modify cognitive performance and therefore driving ability, but with inter-individual variability according to consumption habits. In particular, Alvarez et al. (2021) showed that chronic inhalation cannabis users had 2.41 higher bioavailability than occasional users, resulting in higher THC C_{max} and AUC for the same dose. However, the positivity of the oral fluid test depends on the presence of THC in the mouth, which comes from smoking and not from distribution from the blood. Consequently, occasional users are more likely to screen positive than chronic consumers for a similar blood concentration (77). In contrast, driving simulations after CBD use in 17 healthy adults show that acute, oral CBD treatment does not appear to induce feelings of intoxication and is unlikely to impair cognitive function or driving performance (78).

Tableau 2 : Tolerance data in chronic use of therapeutic cannabis in humans. THC : tetrahydrocannabinol ; CBD : cannabidiol. + : supported adverse effects in the literature; +/- : doubt on adverse effects data in the literature; - : reassuring data in the literature; NA : no/few data in the literature.

Tableau 2 : Données de tolérance de consommation chronique de cannabis thérapeutique chez l'homme. THC : tétrahydrocannabinol ; CBD : cannabidiol. + : effets indésirables avérés dans la littérature ; +/- : doute sur les données d'effets indésirables dans la littérature ; - : données rassurantes dans la littérature ; NA : pas/peu de données dans la littérature.

| Tolerance data | Whole plant (<i>Cannabis sativa</i> <i>L.</i>) | THC | CBD | References |
|---|--|-----|-----|---------------|
| Neuropsychic effects | | | | |
| <i>anxiety, panic disorder, major depressive episodes, psychotic symptoms, attention disorders, amnesia</i> | + | + | - | (41–45,47–49) |
| <i>Fatigue, somnolence, irritability</i> | + | + | + | (47–49) |
| Cardiovascular system | | | | |
| <i>Hypertension, platelet activation, endothelial dysfunction</i> | ++ (if smoked by combustion) | NA | NA | (26,47–55) |
| <i>Hypotension (+/- orthostatic), tachycardia</i> | + | + | + | |
| <i>Cardiomyopathies, angina, myocardial infarction, arrhythmias, heart failure,</i> | NA | NA | NA | |

| | | | | |
|---|-----------------------------|-----|-----|---------------|
| <i>pulmonary oedema, sudden death</i> | | | | |
| Lung system | | | | |
| <i>Symptoms of chronic bronchitis, inflammation of the airways</i> | + (if smoked by combustion) | NA | NA | (56–58,58,60) |
| <i>Chronic obstructive pulmonary disease</i> | +/- | NA | NA | |
| <i>Lung cancer</i> | + (if smoked by combustion) | NA | NA | |
| Gastro-intestinal system | | | | |
| <i>Elevated transaminases</i> | NA | + | + | (48,49) |
| <i>Diarrhea, nausea, vomiting</i> | + | + | + | (47–49) |
| Kidney | | | | |
| <i>Kidney damage</i> | - | - | - | |
| Genotoxicity/reproductive toxicity | | | | |
| <i>Decreased testosterone secretion, decreased sperm production and motility</i> | +/- | +/- | +/- | (41,68) |
| Pregnant and breastfeeding women | | | | |
| <i>Preterm births, intrauterine growth retardation, newborn withdrawal syndrome</i> | + | NA | NA | (19,69) |
| <i>Attention deficits, hyperactivity, and disturbances in certain behavioural tests and performance functions</i> | + | NA | NA | |
| Drug interactions | | | | |
| <i>Enzyme inhibitory effect on CYP3A4 and 2C19</i> | +/- | - | + | (70–72) |

7. CONCLUSION

Therapeutic cannabis in France is still mostly at the experimental stage. **The literature reports several frequent but rarely serious adverse effects of CBD during chronic use as well as a significant risk of drug interactions.** ~~However,~~ THC use seems to be associated with a higher proportion of serious adverse effects **compared to CBD**, particularly at the neuropsychological and cardiovascular levels. Cannabis smoked by combustion appears to be associated with greater toxicity than the oral route. Little data are available on its use by pregnant or breastfeeding women, leading to caution in this population. **As the studies found in the literature are mostly carried out on a small number of individuals,** ~~Ultimately,~~ the clinico-biological data relating to the current experimentation should be able to provide elements for a more detailed assessment of the benefit-risk ratio of therapeutic cannabis in France in each of the indications selected, depending on the specific characteristics of the patients.

CONFLICTS OF INTEREST

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