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Summary

- “Cannabis”, one name for a multitude of uses. An appropriate name for each use would help avoid confusion and conflation, which often lead to incorrect assessment of the plant’s properties.
- The effects of cannabis on health - in particular, the positive effects - are the subject of debate within the scientific community. Meta-analyses of the literature are required in order to reach conclusions concerning the level of evidence associated with each effect, but there is a lack of studies and their quality is often deficient.
- Cannabis is useful for the relief of symptoms such as pain but, as our knowledge currently stands, it has no curative virtues, and, in particular, no anticancer properties as is sometimes wrongly claimed.
- Cannabis use among young people is a source of concern since the health risks are real, at a time when its use has increased substantially in France.

Ms. Huguette Tiegna, MP (National Assembly), Vice-Chairwoman

Depending on the variety, the *Cannabis sativa* plant has numerous properties, from the use of its fibres for paper or rope through to substances with biological - and, in particular, psychoactive - effects, earning its classification as a narcotic by the Single Convention on Narcotic Drugs of 1961.¹

While many countries, including France, have authorised medicines containing cannabis compounds, a smaller number have introduced regulated access to cannabis (raw or processed) for medical purposes² and a few countries have legalised all uses.³ Against this backdrop, France appears to be rather conservative, despite French people being the leading cannabis users in Europe.⁴

In view of these developments in other countries,⁵ accompanied, in France, by demand among patients and health professionals,⁶ the *Agence nationale de sécurité du médicament* (ANSM - French Agency for the Safety of Medicines) set up a specific temporary scientific committee to assess the relevance and feasibility of making cannabis available for medical use.⁷ The positive opinion of this committee recently led to the creation of a second working group concerning the implementation of this trial, scheduled for the start of 2020.

The purpose of the present briefing is to conduct a review of the health benefits and risks of cannabis,

based on current scientific knowledge.

■ Usages and methods of use

- A plant consumed in many different ways...

A single species of *Cannabis sativa* hemp, devoid of the psychotropic substance THC,⁸ is cultivated in France today.⁹ This species is called “industrial hemp” because fibres from the plant’s stalks are used for industrial applications; it can also be consumed in the form of oil, flour or seeds.¹⁰

For plant varieties containing THC, despite being illegal in France, cannabis is smoked mixed with tobacco, in the form of resin¹¹ (*hashish* or *hash*) or flower buds (*herbal cannabis*). The flowers can also be consumed in the form of an infusion and the resin can be incorporated in food preparations.¹²

- ... and for different purposes

Cannabis has long been used for its psychotropic properties, both for medicinal and ritual or religious purposes, since more than a millennium BC.¹³ In Europe, the most common purpose is recreational or festive use for the euphoric properties, the “stoned” feeling or “high” that its use procures.¹⁴ This type of use is practised in groups, by young people, and by more boys than girls.¹⁵ The psychotropic effects are related to the THC: furthermore, the quest to maximise

these effects has led to the development of varieties with increasingly high THC concentrations.¹⁶

The medical use of cannabis has developed outside France, where patients can access raw flowers or cannabis preparations in pharmacies. The future trial in France aims to authorise and regulate this type of use.

The terms “medicinal” and “recreational” omit other uses: “wellness” cannabis corresponds to products without THC but with a high CBD content (cannabidiol, another cannabinoid). The wellness claims are primarily based on the muscle-relaxing properties of CBD, which is non-addictive¹⁷ and has fewer psychoactive effects than THC.¹⁸ Another use, often described as recreational, actually corresponds to a self-medicating use: for example to reduce anxiety and stress and make it easier to sleep.

■ Biological basis of the effects of cannabis

- The existence of an endogenous system receptive to cannabinoids

The cannabinoids in cannabis – or phytocannabinoids – have a biological effect because the human body has cannabinoid receptors; binding of THC or CBD to these receptors triggers cell processes resulting in a biological or behavioural effect. THC receptors CB1 and CB2 were identified and described in the 1990s.¹⁹

Scientists discovered that endogenous molecules exist that are capable of binding to these: endocannabinoids (eCB).²⁰ CB1 and CB2 receptors,²¹ their natural ligands – eCB – and the enzymes that enable the synthesis and degradation of the latter²² form the endocannabinoid system.

CB1 is predominantly present in the central nervous system,²³ but also in the peripheral nervous system,²⁴ whereas CB2 is mainly present in the cells of the immune system.²⁵ The amount of CB1 is higher in developing brains (from embryos to around 25 years of age) than in mature brains.

- Endocannabinoid system functions

The endocannabinoid system is essential on a local level, with eCBs ensuring modulation of synaptic activity,²⁶ but also on larger scales, such as in the growth of axons, these extensions of neurons that enable interneuronal communication.²⁷ The initiation of connections between neuron groups, sometimes distant from the brain, is necessary to increase brain connectivity, one of the processes of brain maturation.²⁸

Disruptions in the endocannabinoid system have been identified in psychiatric disorders such as depression, autism, schizophrenia, addiction, stress and anxiety. While therapeutic projects using substances that interact with CB1, such as Rimonabant, have had to be

halted due to serious adverse effects, the strategies currently under development consist in modulating the degradation or synthesis of eCBs by inhibiting enzymes of the eCB system.²⁹ The eCB system is also involved in pain management.³⁰

- Interaction between cannabis and the eCB system

Since phytocannabinoids can interact with cannabinoid receptors, the effects caused by using cannabis are the result of this interaction. In the brain, THC and CBD have antagonistic effects: THC activates CB1, resulting in psychotropic effects, which are partially diminished by CBD, without this mechanism being fully understood.³¹

Although they have the same biological target, phytocannabinoids do not work in the same way as eCBs: their action is much slower over time³² and is global, whereas eCBs have a local action. These differences in temporality and degree of stimulation disrupt the neuromodulating role of the eCB system.

■ Positive health effects

A very large number of scientific studies have aimed to assess the health benefits and risks of cannabis. However, the lack of clinical trials of adequate quality in humans sometimes makes it impossible to reach a conclusion with respect to the accuracy of a claim.³³

- Scientifically recognised positive effects

Literature reviews such as the one carried out by the American National Academies of Sciences, Engineering and Medicine³⁴ make it possible to associate a level of evidence with each suspected effect. This reveals positive effects of cannabis or cannabinoids to treat chronic pain in adults,³⁵ nausea and vomiting in subjects receiving chemotherapy to treat cancer³⁶ or with AIDS, appetite loss in patients at the end of life, muscular spasticity³⁷ in multiple sclerosis, and in rare types of epilepsy. They also appear to be potentially useful to improve symptoms associated with psychiatric disorders: anxiety, post-traumatic stress disorder and Tourette syndrome.³⁸ The use of cannabis may also have an anti-inflammatory action.

- From medicines containing phytocannabinoids to cannabis for medical use

The regulations were changed in France in 2013 to pave the way for the possibility of treatments using cannabis derivatives.³⁹ Two medicines containing phytocannabinoids currently have a marketing authorisation (MA). Sativex® was authorised in 2014 as a treatment for spasticity due to multiple sclerosis (MS).⁴⁰ Epidyolex® was granted an MA in 2019 for use in the treatment of rare and serious types of epilepsy.⁴¹

The ANSM (French Agency for the Safety of Medicines) plans to make cannabis for medical use available to 3,000 patients for a two-year trial period.⁴² In line with the abovementioned scientific knowledge, the indications are pain refractory to currently accessible therapies, rare types of epilepsy,⁴³ as a supportive treatment in oncology (chemotherapy-related nausea and pain), palliative care and painful spasticity in multiple sclerosis.⁴⁴ The trial will consist in providing raw or slightly processed cannabis⁴⁵ to patients: use by smoking will be prohibited. The treatment will be initiated by a doctor, joining the trial on a voluntary basis, practising in a specialised hospital facility⁴⁶ and having undergone specific training.⁴⁷ The patients will be followed up in order to assess the prescribing and dispensing channels put in place and to monitor the safety and efficacy of the treatment.⁴⁸ A report will be submitted to Parliament at the end of the trial for examination of the mechanism prior to its continuation.

When growing medical cannabis, particular care along with stable, controllable conditions (temperature, humidity, sunshine, etc.) are required so that the cannabinoid contents of the plants are uniform. Pesticides cannot be used. It is therefore grown indoors. A relatively small surface area would be required if medical use were to be continued in the longer term in France: less than 100 ha would cover the needs of 300,000 people.

- The status of medical cannabis

Medical cannabis addresses a strong demand on the part of patients, who perceive a genuine benefit from it, in view of which it does not appear ethical to deny them access to it, as the ethics and cancer committee concluded. Furthermore, medicines containing cannabis will only be accessible for very limited indications in which they have been granted a marketing authorisation. However, in contrast with medicinal products that have been through the marketing authorisation process, medical cannabis has not demonstrated its efficacy by the usual means (placebo-controlled demonstration in randomised trials), nor has it demonstrated a superior efficacy to existing therapies; this would pose a problem if the issue of its reimbursement by the social security system were to be raised, in the event that the trial is continued in the longer term.⁴⁹

Although the curative properties of the plant are currently being studied, particularly in the treatment of addictions⁵⁰ and pancreatic cancer,⁵¹ current knowledge does not justify such uses for cannabis at present.

- Minor components of cannabis

Cannabis contains more than 100 cannabinoids and more than 200 terpenoids⁵² but their effects on health have been the subject of very few studies. A few

researchers support the hypothesis that these minor compounds may act in synergy with THC and/or CBD, hence a better efficacy of cannabis (complete extract) compared to a medicinal product (purified substance): this is the *entourage*⁵³ effect, which is still the subject of debate.

■ Negative health effects

The health risks associated with cannabis use result from the psychoactive effects of THC and disruption of the function of the endocannabinoid system, particularly during brain development phases; these depend on the amount used and the method of use.

- Scientifically recognised negative effects

In a non-medical context, cannabis use is associated, in particular, with a type of testicular cancer,⁵⁴ cardiovascular events, chronic bronchitis, death from poisoning in children, pregnancy complications or low birth weights of offspring. Driving under the influence of cannabis is also dangerous since vigilance is impaired for several hours.⁵⁵

While the psychoactive effects of CBD are less than those of THC, the substance is not innocuous: in particular, it inhibits the hepatic enzyme that breaks down medicines; which can result in interactions between medicinal products.⁵⁶

- Addiction and cannabis

THC can cause addiction to cannabis, with a lower risk of developing dependence, however, than with other substances.⁵⁷ Recent studies suggest that a susceptibility to addiction may be inherited epigenetically when parents are users.⁵⁸

The higher the THC concentration in cannabis, the higher the risk of causing dependence, this effect being limited by the antagonistic action of CBD. However, the varieties developed for recreational use present increasingly high THC contents without any rise in CBD content and are therefore more dangerous.

- Cognitive and psychiatric effects of cannabis

In the developing brain, exposure to cannabis causes structural changes and disrupts the eCB system.⁵⁹ Exposure of young rats to THC causes disturbances in higher cognitive functions that persist in adult rats, even after exposure is stopped.⁶⁰

Clinically, cannabis use is associated with cognitive problems (impaired memory, attention and learning capacities) and psychiatric problems (anxiety,⁶¹ increased manic symptoms in bipolar disorders, increased suicide risk, etc.).⁶²

There is a risk of developing psychotic symptoms, or even accelerating the development of schizophrenia, associated with cannabis use. This risk is higher if the person has a pre-existing susceptibility.⁶³ Moreover,

certain genetic factors appear to potentiate the influence of cannabis.⁶⁴ These effects vary substantially from one person to another, but the idea of not everyone being equal when it comes to addiction and disease is not one that is properly taken on board by adolescents.⁶⁵

The cognitive problems caused by cannabis use during adolescence have repercussions on the individual's life: this use is associated with poor school results,⁶⁶ a dark professional future⁶⁷ and job loss.⁶⁸ In France, consumption has fallen slightly but problem use has increased.⁶⁹

- Dangers associated with synthetic cannabinoids

Synthetic cannabinoids have stronger psychotropic effects than those of THC, since they have a higher affinity for the CB1 receptor. In 2017, these substances had already been responsible for 43 deaths due to acute poisoning in Europe.⁷⁰

- Access to medical cannabis in France

Numerous patients already illegally self-medicate by using cannabis, either by growing it themselves or by buying the product in the street. This practice is dangerous since it is not medically supervised; products with THC and CBD concentrations that are not fully known are used, or they may be "cut" by dealers with substances that are not intended for consumption.

The issue of the influence of authorising medical cannabis, or even overall legalisation, on use among at-risk populations is raised. US states that have authorised medical use have not observed any increase in use among young people.⁷¹ However, use in adults has increased in states that have authorised all uses.⁷²

■ Recommendations

- Academic and industrial research players should be encouraged to organise rigorous clinical trials in order to better determine the relevance of medical cannabis use, identifying its mechanisms of

action. The biological and behavioural consequences resulting from non-medical use also need to be studied. A first measure could consist in facilitating scientists' access to cannabinoids and allowing them to work on complete-spectrum extracts with THC concentrations representative of those of the products bought in the street,⁷³ to enable a better assessment of the health effects of this use.

- The smooth implementation of the medical cannabis trial scheduled in France requires that the ANSM ensure the quality of the products supplied to patients and carry out active pharmacovigilance. Monitoring of research would make it possible to modify the therapeutic indications selected if so justified by evolving knowledge.

- If the trial is continued in the longer term, the ANSM could, in addition to its current functions, be tasked with controlling medical cannabis, from growing of the plant to processing of the flowers, in the same way as the "cannabis agencies" created in other countries, Germany in particular.

- Concurrently with this trial, prevention among pregnant women and young people must be intensified and rethought in order to counter the phenomenon of normalisation of this use. Early prevention⁷⁴ is necessary and the health risks of non-medical cannabis need to be explained. Biology teaching and an introduction to brain function would be the ideal supports.

- Better information for young people concerning psychiatric risks (in general) would help them better identify suppressed problems for which cannabis use is the wrong solution.

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