

# Practical aspects of the use of medicinal cannabis in chronic pain

## *Aspectos práticos do uso da cannabis medicinal em dor crônica*

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### ABSTRACT

**BACKGROUND AND OBJECTIVES:** Evidence has revealed an important role in the use of medical cannabis, and the interaction of the endocannabinoid system with other drugs for the treatment of chronic neuropathic and nociplastic pain. The objective of this review is to bring an update on published data on doses and care with the use of cannabinoids that demonstrate the interaction in the pathophysiology of chronic pain and its treatment.

**CONTENTS:** A research-based review was carried out in the MEDLINE, PUBMED database using the keywords “cannabis and pain”, “endocannabinoid”; “neuropathic pain”; “nociplastic pain”; “drug interactions”.

**CONCLUSION:** Drug interaction with cannabinoids requires further scientific knowledge and doses are individual, which makes it difficult to create a protocol for treatment.

**Keywords:** Cannabis and pain, Endocannabinoid, Neuropathic pain, Nociplastic pain and drug interactions.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** As evidências têm revelado um papel importante sobre o uso da cannabis medicinal e da interação do sistema endocanabinoide com outros fármacos para o tratamento de dor crônica neuropática e nociplástica. O objetivo deste estudo foi prover atualização sobre os dados publicados quanto a doses e cuidados com o uso dos canabinoides que mostrem interação na fisiopatologia da dor crônica e seu tratamento.

**CONTEÚDO:** Foi realizada uma revisão baseada em pesquisa na base de dados Medline, Pubmed com uso dos unitermos “cannabis e dor”, “endocannabinoid”, “neuropathic pain”, “nociplastic pain” e “drug interactions”.

**CONCLUSÃO:** A interação farmacológica com os canabinoides requer aprofundamento do conhecimento científico e as doses são individuais, o que dificulta a criação de um protocolo para tratamento.

**Descritores:** Cannabis, Dor, Dor crônica.

### INTRODUCTION

Medical cannabis is a new type of drug and, according to the current regulatory situation in Brazil, is called “cannabis-based products”. Like any new phytomedicine, its integration into clinical practice is still done with caution by medical prescribers since the individuality of clinical responses and possible pharmacological interactions are known. Another important aspect to be considered in prescribing is the presence of several active and synergistic components, which may have different clinical effects<sup>1,2</sup>.

THC is responsible for most of the pharmacological and adverse effects of cannabis, including its psychoactive effect through its signaling pathway via CB1 and CB2 receptors. In its clinical use, its analgesic, antispasmodic, antiemetic, appetite-stimulating and intestinal motility-lowering activities stand out<sup>2,3</sup>.

Cannabidiol or CBD, is one of the phytocannabinoids that does not have the similar psychotropic effect as THC. It acts through different mechanisms, with indirect action on CB1 and CB2 receptors and direct effects on other targets such as transient receptor potential (TRP) channels, peroxisome proliferator-activated receptor, among others. The main clinical effects of CBD are analgesia, anticonvulsant, anti-inflammatory, antipsychotic and anxiolytic effects<sup>3</sup>.

Therefore, to simplify and organize the process of product choice, initial dose, titration and patient follow-up, the practical aspects involving the prescription of cannabis-based drugs will be described, focusing on the treatment of chronic pain according to relevant scientific articles<sup>4</sup>.

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### HIGHLIGHTS

- Every day, cannabinoids for the treatment of chronic pain is establishing itself as an adjuvant treatment; knowing how to administer it depends on an accurate diagnosis of the painful signs and symptoms.
- Use of phytocannabinoids for painful symptoms is often non-specific, it does not follow a fixed protocol.
- Adverse effects with the use of phytocannabinoids are more common than one might think, and the more we learn about treatments and doses, the longer the list of pharmacological interactions gets.

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In general, it is necessary to understand if there is a clinical indication for each patient specifically. If the indication is confirmed, one should investigate whether there are any relative contraindications, pharmacological interactions, whether previously used as an adult or medicinal use and/or other precautions that one should take when choosing the ideal cannabinoid<sup>4</sup>.

Then, it is determined which ideal cannabinoid, or its combinations, should be chosen, which class of products is more indicated, that is, a full spectrum product, an isolate, or another known as broad spectrum, always thinking about the composition of the product and the proportion between the cannabinoids. Finally, the initial dose to be prescribed and the product to be indicated are chosen.<sup>3,4</sup>

To determine whether there is an indication, one should consider the complaint of primary or secondary chronic pain, remembering that we are talking about a second line of treatment. If the complaint is acute pain, cannabinoids are unlikely to be part of the prescription as there are first line drugs, although there is ongoing research into a treatment arm for acute pain<sup>2,5</sup>.

In addition to the main complaint of chronic pain, the clinical history, physical examination, laboratory tests and imaging should also explore other comorbidities that may be directly or indirectly associated with the main complaint. For example, the existence of inflammatory diseases, sleep or mood disorders, cognitive difficulties, among others. Patients with chronic pain usually present strong emotional components associated with symptoms such as catastrophism and very important pathophysiological changes, both in the ascending and descending pathways of pain. Pain represents for the patient what he loses in quality of life, in the ability to interact with the world. Therefore, treatments with multifactorial drugs, such as cannabinoids with the endocannabinoid system, are very favorable for patients with chronic pain<sup>6</sup>.

Cannabinoids can be used for various types of patient complaints, such as chronic neuropathic pain, chronic nociplastic pain, mixed pain, tolerability to some drugs, sleep disorders, other indications (epilepsy, anxiety, neurodegenerative diseases, autoimmune diseases, etc).

The treatment of patients with chronic pain can be an important therapeutic challenge for the physician. Cannabinoids enter this context for multifactorial patients. A recent article published in

the journal *Pain*, one of the leading references in pain publications in the world, showed that CBD has more than 65 therapeutic targets. Cannabinoids act on all pain pathways, in areas responsible for pain transmission, modulation or perception<sup>2,7</sup>. The choice of specific cannabinoid for symptoms requiring treatment is summarized in Table 1.

Although CBD is chosen as the initial treatment, delta-9-tetrahydrocannabinol (THC) has been shown to be effective in some cases of difficult pain control, especially when pain is associated with muscle spasticity, such as in multiple sclerosis or patients who have suffered brain-cortical lesions, with loss of motor functions of the limbs, leading to spasticity<sup>8</sup>.

The cannabinoid that has the most important analgesic potential is delta-9-THC. This active ingredient binds directly to the anandamide (endogenous cannabinoid) receptors of the endocannabinoid system, re-modulating the release of neurotransmitters into the synaptic cleft. This mechanism is also responsible for the known adverse effects of indiscriminate THC use. These adverse effects are dose-dependent. Therefore, one can minimize these unwanted symptoms by titrating the doses, i.e., starting with low doses and increasing the daily doses slowly and progressively<sup>9</sup>.

Other available cannabinoids also have analgesic activity, with less impact on attention, motor control and other adverse symptoms typical of THC. These other cannabinoids such as delta-8-THC, cannabiol (CBN) and cannabigerol (CBG) show analgesic effect as they are intrinsically related to delta-9-THC. CBG is considered to be the origin of all cannabinoids, including THC, and exhibits some of the characteristics of its most famous metabolite. CBN is a product of the degradation of delta-9-THC by time or elevated temperature. Therefore, it can be assessed at the time of prescription whether CBN or CBG-based products should be considered in place of THC to achieve the desired analgesic effect<sup>7,8</sup>.

CBD also shows an analgesic effect, but of lesser intensity than THC. Most likely, CBD analgesia is achieved by its anti-inflammatory action in synergy with the small amounts of THC (<0.3%) present in full spectrum products, together with the other active components of the plant (terpenes, flavonoids, phytosterols and others), which is called the entourage effect<sup>9</sup>.

**Table 1.** Main indications of THC, CBD, and their combinations, according to the main symptoms and the desired therapeutic effect.

	Full spectrum	Broad spectrum CDB	Broad spectrum THC	Purified or iodized CBD	Purified or iodized THC	Synthetic CBD	Synthetic THC	CBD predominant	THC predominant
CBD	*	*		*		*		* 20	* 1
THC	*		*		*		*	* 1	* 20
Other Cannabinoids	*	*	*					*	*
Terpenes	*	*	*					*	*
Flavonoids	*	*	*					*	*
Sugars	*	*	*					*	*
Entourage Effect	*	*	*					*	*

It is known that a 4 to 6 times higher amount of the isolated active component is needed to obtain the same therapeutic effect when using a complete extract of the plant. The entourage effect was well demonstrated by a work on the active ingredients of cannabis<sup>3,7,9</sup>.

In patients with neuropathic pain, there is more published clinical evidence. In these patients, in general, CBD is used in higher concentrations compared to THC, increasing the dose of cannabinoids slowly. Scientific evidence shows that the presence of THC, even at low doses, can bring better results in patients with neuropathies induced by human immunodeficiency virus, chemotherapy, or diabetes<sup>5,10</sup>.

### Nomenclature for cannabinoid-based products

The practical importance of the nomenclature is due to the way it refers to each type of product, based on the concentration of the cannabinoids and the type of purification to which the product has been subjected, removing specific cannabinoids or else leaving only one of these components (isolated product)<sup>10</sup>.

Broad spectrum products also contain all the components of the plant, with the exception of THC. The product undergoes a purification process to remove one of the cannabinoids, also called isolates and are used in very specific situations and therefore we will not have the entourage effect<sup>10,11</sup>.

### Entourage effect

When we use whole plant extracts containing major cannabinoids such as CBD and THC with the secondary cannabinoids, flavonoids, terpenes, sugars, and other components of the plant, the effects are potentiated and is called the entourage effect.

This justifies the superior results of full-spectrum products compared to single products. By using products of known and certified origin, full or broad spectrum, the desired pharmacological effects can be achieved at a lower dose and with fewer adverse effects.<sup>12</sup>.

### Contraindications

Contraindications are almost all THC-related and are dose-dependent.

There are groups of people in whom caution should be exercised in the use of medical cannabis:

- people under 25 years of age have relative contraindication, as there are indications that high daily doses of THC may interfere with cognitive development that occurs up to this age;
- if the patient's history identifies an adult substance use disorder;
- in mental health disorders such as schizophrenia and psychoses that are not under control, THC is contraindicated as it can trigger crises at higher doses;
- unstable heart disease: one of the adverse effects of THC is increased heart rate and therefore in patients with unstable heart disease the use of medical cannabis should be avoided;
- inhaled use is contraindicated in patients with unstable respiratory disease. Remembering that inhalation or even vaporization is prohibited in Brazil and should never be indicated by the doctor, although it is known that in other countries there are vaporizers approved for medicinal use;

- in pregnancy and lactation there is no safety data to support the use of medical cannabis. There are reports of newborns of mothers who were chronically using smoked cannabis, who came to term with lower weight than the population average;
- increased liver enzymes may occur with the use of CBD in patients who have some previous liver dysfunction. Therefore, it is important to identify patients with a previous history of hepatotoxicity and to request a liver function laboratory profile before starting CBD treatment and every 3 months thereafter.<sup>11,12</sup>.

### Determining dose in clinical practice

The pharmaceutical forms available in Brazil for administration of cannabinoid-based products are oils, tinctures, gel capsule, creams, suppositories, and recently topical patch. Oils, such as MCT (medium chain triglycerides), coconut oil and olive oil, are the most widely used vehicles and have the advantage of facilitating the titration of products in the early stages of treatment, facilitating the number of milligrams through the number of drops to be used at each time and day. Products of known and certified origin always carry the information that how many milligrams of each cannabinoid, has a drop or in 1 mL. This information is vital for prescribing and calculating the titration<sup>12</sup>.

Guidance on treatment with cannabinoids:

- Determining which pathologies and symptoms we want to treat. Is there an indication?
- Are there any possible contraindications or pharmacological interactions?
- Which cannabinoid should be favored (CBD or THC) or the use of a balanced product?
- What is the best type of product to use (full, broad, or isolated)?
- Choose the concentration of each cannabinoid and choose the product.
- Prescriptions are white non-carbonated with the necessary information that ANVISA requires, blue or yellow depending on the product.
- Determine what the clinical goals and "patient goals" are for the treatment and what the expected outcomes are so that it is possible to determine the success or failure of the intervention, as well as manage patient expectations<sup>13</sup>.

When starting and titrating medical cannabis, do not change or add other drugs.

If other drugs have their doses changed or new drugs are introduced, it will be impossible to determine if the patient is experiencing adverse effects from the change in the previous drug or if the adverse effects are due to the introduction of cannabis. Stabilize the dose of cannabis before changing other drugs in use. One should remember to start with the lowest dose and move slowly - "Start Low - Go Slow"<sup>13</sup>.

This should be customized for various conditions. If the patient reports a poor prior experience, it is likely that they are a slow metabolizer of THC and therefore you should be careful with the initial dose and titration, or even consider the use of CBG. Make treatment goals very clear to the patient, and document<sup>14</sup>.

If adverse effects occur, they are mitigated by slow titration of cannabis over a period of two to four weeks and by using products with a higher proportion of CBD to THC. CBD modifies the bioavailability curve of THC, making it lower and longer in relation to time, and in this way minimizes the adverse effects of THC. The optimal dose usually remains stable and does not require increasing doses over time. If tolerance occurs, review whether the patient is confusing euphoria with symptom control. If tolerant to the physiological effects of cannabis, suggesting a short “drug holiday” of 48h is usually sufficient to improve their response to treatment<sup>15</sup>.

There is little published work on how to dose and administer medicinal cannabis products. An extensive paper was published, with a good review focusing on THC, and suggested starting doses and dose escalation of this cannabinoid, with little reference to CBD<sup>7,15</sup>.

Each patient may have a distinctive endocannabinoid receptor expression profile, and the hepatic metabolism of cannabinoids varies individually. These particularities make it essential to find the individualized dose for each patient<sup>16</sup>.

According to the latest consensus on medical cannabis treatment made in 2018 by scholars from several countries, three different types of titration protocols organized by types of patients and their conditions have emerged:

1. routine protocol: adult patients, non-polypharmacy, with no experience or previous positive experience with cannabinoids.
2. conservative protocol: elderly and frail patients, or with poor previous experience with cannabinoids or using polypharmacy.
3. rapid protocol: patients with previous positive experience with cannabis and requiring higher doses of cannabinoids<sup>16</sup>.

The patient may report improvement of symptoms or other conditions that positively affect their quality of life. For example, “the pain is still here, but I can manage better and do household chores”. It is at this point that the dose is stabilized, and this patient is kept under observation and follow-up<sup>10,11</sup>.

Remember that oils containing cannabinoids take about 1 to 2 hours to take effect and remain in the metabolism for 6 to 8 hours. One should always be aware of the dose of THC, which, even low, may eventually cause some undesirable side effect<sup>16</sup>.

In the expert consensus, it was agreed that when the patient reaches the dose of 40 mg per day of full spectrum CBD and the treatment goals have not been achieved, one should consider adding a second product that contains a higher amount of THC than the first product<sup>16,17</sup>.

Another practical aspect, rarely mentioned in the literature but observed in clinical practice, is the administration of cannabis-based products together with fatty foods. Being lipophilic, cannabinoids have their absorption optimized when administered together with foods of this nature and significantly increase their bioavailability, from 6% (without fatty foods) to 30% (with fatty foods), and the number of doses per day depends on the coverage we want to give to each patient.

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always be aware of the dose of THC, which, even if low, may eventually cause some undesirable adverse effect<sup>16</sup>.

It is worth noting that the consensus dose administration was developed for use in adult patients. The indication for pediatric use should consider the risks and benefits to be gained from cannabinoid therapy. There is no clinical evidence that doses used medicinally may adversely affect the development of cognition<sup>9,16</sup>. In clinical practice, one may differ from these protocols when one already has experience with prescribing medical cannabis. For example, instead of starting THC when the patient reaches 40 mg of CBD without success, one can follow full or broad spectrum CBD titration up to 80 mg to 100 mg before starting THC. This level of CBD is called the sweet spot, where most patients already show some clinical response. If the patient does not report improvement with this dose of CBD, THC should be started<sup>16</sup>.

The adverse effects of THC are diminished when CBD is used in combination<sup>16</sup>.

### Drug interactions

The treatment of patients with chronic pain using cannabinoids must comply with pharmacological principles considering possible pharmacological interactions, the laws in force in the country, as they can interact and modify the bioavailability of anti-convulsants, antidepressants, opioids and many others.<sup>16,17</sup>

The rational use of cannabis-based drugs, the staggered increase in dose, the correct choice of active compound, are the main bases of safe treatment. There are few data on pharmacological interaction with medical cannabis. However, we know that its metabolism takes place in the liver via cytochrome CYP450, the same metabolic pathway used by many other drugs. Most pharmacological interactions are associated with the concomitant use of CNS depressants (alcohol, sedative-hypnotics). There are no specific studies of pharmacological interactions with cannabis but observations in studies with other primary and secondary objectives. Interactions can increase and even decrease the amount of circulating drugs. This is very important for the clinical management of patients with other drugs in use. CYP450 inducers such as rifampicin decrease the maximum concentration and area under the curve of THC and CBD, while CYP450 inhibitors such as ketoconazole increase this ratio<sup>18</sup>.

Theoretically, by competing for the same metabolizing pathway, THC may decrease serum concentrations of:

- clozapine,
- haloperidol,
- duloxetine,
- cyclobenzaprine,
- olanzapine,
- cyclosporine,
- theophylline.

CBD can increase serum concentrations of:

- haloperidol,
- antipsychotics,
- benzodiazepines,

- tricyclic antidepressants,
- calcium channel blockers,
- atorvastatin and simvastatin,
- beta-blockers,
- anti-histamines,
- antiretroviral drugs,
- opioids,
- clobazam,
- macrolides,
- sildenafil,
- cyclosporine,
- tamoxifen,
- varfarin.

Most pharmacological interactions are associated with the concomitant use of CNS depressants such as alcohol and benzodiazepines. Of all the drugs, only pimozide is absolutely contraindicated for concomitant use with medical cannabis, due to its increased risk of QT interval widening on the electrocardiogram<sup>17</sup>.

Following the disclosure of these observations, it has become clinical practice to request liver function tests (OGTT, GPT, bilirubin, gamma glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, total protein, and prothrombin time) for all patients reporting previous or active liver disease. Follow-up is based on the original profile and repeat tests every three months. If any of the parameters are showing changes, CBD use should be stopped, and the causes investigated.

Cancer pain is a symptom difficult to control with cannabinoids alone, which are used as adjuvants, as they potentiate the effects of opioids<sup>8</sup>, and consequently, the opportunity to reduce the dose of opioids<sup>18</sup>.

In patients with cancer pain and other symptoms, the trend is to start adjuvant treatment with full spectrum CBD with low doses of THC. Evaluate the clinical conditions and response of these patients not only in pain but also in anorexia, anxiety, insomnia and in the perception of the disease, which may benefit from intervention with cannabinoids<sup>18,19</sup>.

### Safety – considerations

There are no cannabinoid receptors in the brainstem. This is important because this is where the neuronal center of cardiorespiratory control is located. Because cannabis does not cause depression of the respiratory centers, there are no reports of death from cannabis use.

The same cannot be said for opioids, whose receptors are abundant in this area of the brain and are known to cause respiratory depression and death<sup>19</sup>.

One way to assess the safety of medical cannabis use is through its toxicity, comparing the ratio between the lethal dose and the pharmacological (or effective) dose. Thus, the greater the difference between the effective dose and the lethal dose, the safer is the substance<sup>20</sup>.

The most toxic adult-use drugs, such as GHB (gamma-hydroxybutyrate) and heroin, have this ratio between effective and lethal doses of less than 10. The largest grouping of psychoactive

substances has a lethal dose that is 10 to 20 times the effective dose: this includes cocaine, MDMA (ecstasy) and alcohol. As there are no known deaths reported in relation to ingestion or inhalation related to cannabis, its lethal dose remains unknown (or only possible in theory until some study comes along proving otherwise), making it a relatively risk-free substance in terms of toxicity<sup>20,21</sup>.

### Patient monitoring in clinical practice

After starting treatment, it is suggested that patients should be closely monitored to check for possible changes in clinical condition and possible occurrence of any adverse effects arising from the use of cannabinoids or even pharmacological interactions, within 15 days of starting treatment. At this time, in the vast majority of cases and the beneficial effects may already be being felt, if necessary, some dose adjustment, dose distribution during the hours of the day or even guiding the patient to follow with titration should be made<sup>21</sup>.

After the first return visit, follow-up can be spaced out according to the doctor-patient needs. It should be remembered that this follow-up is only a general guideline, as each patient will require specific follow-up according to their disease, degree of involvement and need for contact with the medical team.<sup>20</sup>

It is also important during follow-up to know whether the drug is being taken correctly. For this, it is always asked how many drops or milliliters the patient is taking in each period and how much is left to finish the bottle. This allows us to understand if the patient is overexposing himself or herself or even underdosing compared to the prescription. Cannabis abuse disorder can be identified, and attempts made to correct the doses. If adverse effects of THC are identified, the dose of this component can be reduced or the dose of CBD increased<sup>21</sup>.

### CONCLUSION

Medical cannabis can be considered a new and safe therapeutic class, as the difference between the pharmacological dose and the lethal dose is >1000 times (e.g. alcohol is 10x).

In Brazil, only products in the pharmaceutical forms of oil, gel capsules or topicals are available; inhalation is not allowed. The use of cannabinoids can also relieve anxiety, improve sleep quality, and potentiate the effects of other analgesics, but they are not first-line treatments. Orally, the onset of action is between 1 and 3 hours and the effect is maintained for 6 to 8 hours. This is important when prescribing to decide at what time and how often to titrate the doses during the day.

Adverse effects and relative contraindications related to THC are dose-dependent and adverse effects of THC can be minimized with increasing concomitant administration of CBD and that the main indications are treatment of chronic neuropathic and nociceptive pain, sleep disorders, anxiety, depression, symptoms of neurodegenerative diseases, seizures, and palliative patients.

Relative contraindications are mainly for people under 25 for THC, substance abuse disorders, mental health disorders such as

schizophrenia and psychoses that are not under control, unstable heart disease, pregnancy, and lactation, that CBD can increase the level of liver enzymes in patients who have some previous liver dysfunction. Contrary to what many patients imagine, it is not necessary to feel euphoric effects in order to have the medicinal effects.

## AUTHORS' CONTRIBUTIONS

### Wellington Briques

Data Collection, Writing - Preparation of the original.

### Carla Leal Pereira

Conceptualization, Project Management, Research, Writing - Review and Editing, Supervision.

### Paulo Sergio Feliz

Data Collection, Research, Writing - Review and Editing, Visualization.

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