

Perspectives for Medicinal Cannabis in Argentina. Advances in Clinical Trials in the World and Its Use for Chronical Pain Treatments

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ABSTRACT

Cannabis is used around the world for medicinal, religious and recreational purposes. In 2018, the Argentine Republic approved new legislation, adapting to the provisions of the WORLD HEALTH ORGANIZATION. Law No. 27,350 regulates medical and scientific research on the medicinal, therapeutic and / or palliative use of the Cannabis plant and its derivatives. At the time of this publication, 5 projects were approved for the production of plant material and scientific studies. This work aims to show the results of the latest studies published in the world, on the effectiveness of treatment with medicinal cannabis or cannabinoids, in voluntary patients with chronic pain.

Keywords: Cannabis; Medicinal Use; Pharmaceutical Challenges; Clinical Trials

Introduction

What is pain? We all intuitively understand what it means. But when trying to quantify, giving it values and intensities, the subjectivity of each individual comes into play [1]. Pain is one of the prevalent pathologies worldwide and acquires special importance, due to the health expenditure it generates [2]. However, that pain is one of the prevalent pathologies in society around the globe, is an indicator of a much deeper question that requires another type of analysis. Usually, the medical doctor uses a scale of values between 1 to 10 as a way to standardize what is not standardized [3]. The subjectivity with which we perceive the intensity of chronic pain induces in the human being a state of despair, which influences all his healing processes. Chronic pain makes the human being susceptible to contracting diseases, due to the decrease in the cells of the immune system. Depression and stress, produced by prolonged states of discomfort and pain, decrease defenses due to increased synthesis of adrenaline and cortisol [4].

Persistent nociception induces depressive behavior. And its relationship is made by the enzyme that synthesizes the tryptophan amino acid [5]. Chronic pain affects the general condition of the patient and increases the circulation of catecholamines in the blood. The excess of circulating catecholamines, reduce the concentration of leukocytes, cells that defend against possible infections, increasing the risk of contracting diseases. A study made in mice evaluated the consequences of stress on the quality and quantity of long-term immune memory. The animals were subjected to stress through an aggressive event. Later they were inoculated with herpes simplex virus (HSV). The mice in the stressed group showed a suppression of the Acs response and a decrease in the memory of IL-4 and IL-10 synthesis. The mice in the control group, which had not been exposed to the stressor, showed non-impact on the immune responses and immune memory [6].

This also creates a vicious cycle that only prolongs pain and the feeling of discomfort. Studies prove that states of intense pain are maintained and become chronic due to pro-inflammatory central immune signaling. Recent findings involve the innate immune system, known as Toll-like receptors. Toll receptors are involved in the activation of these pro-inflammatory events that activate pain pathways through molecular patterns associated with pathogens or hazards [7]. As a sensory or emotional experience, pain is at least a cause of discomfort. It can be associated with both tissue injury and potential damage. Beyond the scales, pain is considered to exist as long as the patient expresses that he or she feels pain. It is in any case a subjective concept and exists whenever a patient says that something hurts [8]. It is a prevalent pathology and that acquires special relevance among the labor population due to its socioeconomic implications [9]. A brief comment aside, are deserve for the analgesics and the chronic consumption that leads patients to opiate addiction and in many cases to death [10].

The U.S. Centers for Disease Control and Prevention revealed that overuse of opiates during the coronavirus pandemic killed nearly 70,000 Americans in 2020, with an agency provisional tally showing that 93,331 deaths were recorded in 2020, a record and an increase of 29.4% over the previous year [11]. So is modern pharmacology the only way to counteract the consequences on a biological, mental and emotional level that chronic pain produces? For several years there has been a growing interest in the general population for alternative therapies that go beyond treating a symptom, hiding it behind a pill with more side effects than solutions [12]. In 2018, the Argentine Republic approved new legislation, adapting to the provisions of the WORLD HEALTH ORGANIZATION. Law No. 27,350 regulates medical and scientific research on the medicinal, therapeutic and / or palliative use of the Cannabis plant and its derivatives. At the time of this publication, 5 projects were approved for the production of plant material and scientific studies.

An option for the treatment of chronic pain and a palliative for associated mental and emotional conditions are phytocannabinoids. So far, 108 phytocannabinoids have been identified from the Cannabis Sativa and Indica plant [13]. Cannabidiol (CBD) and Δ^9 -tetrahydrocannabivarin (THCV) are reported as being of great clinical interest. Δ^9 -tetrahydrocannabinol (THC) is the phytocannabinoid with the highest affinity for endocannabinoid receptors in the brain. The cannabis plant uses very similar enzymes for the synthesis of THC and CBD, so both are C₂₁ terpenophenols with pentyl alkyl tails [14]. Minewile THC of C₁₉₄ propyl tail is a structural analog. The natural options captured the interest of the population that seeks the resolution of their diseases, from a holistic perspective of health and general well-being. Conscious movement, as the reversion to an ancient therapy that aligns body,

mind and spirit, requires a paradigm shift and an expansion of therapeutic options [15].

The notorious appearance of patients who choose the alternative of cannabis treatment as a solution to their ailments is an indicator of acceptance [16]. Palliative treatments in diseases such as chronic pain, degenerative diseases, cancer, epilepsy and some of those classified as mental, such as depression, are just some of the options offered by this medicinal plant [17-20]. This work aims to update and contextualize the latest published information on clinical data, with well-founded protocols considering subjectivity. Without the intention of defining, which is the ideal classification, it is true that pain is a subjective appreciation, which involves electrical thresholds, emotional perceptions, context, duration, mental state, the individual personality characteristics, who manifests it, among many other variables. It is also true that cannabinoid treatment is still prescribed, only in case of failure of other analgesics previously, that is to say that the pain becomes chronic, while we look for an efficient palliative. According to a metadata study published in September 2021 by Wang, et al [21], which sought to establish a risk-benefit ratio in the prescription of cannabinoids and medicinal cannabis for the treatment of chronic pain.

For the review they used better known scientific databases. The selected clinical trials consisted of those in which the administration was following double-blind models. Trials where medicinal cannabis or cannabinoids were administered for a time equal to or greater than thirty days, against other analgesics commonly used in the treatment of chronic pain. A total of 32 clinical trials were scrutinized, 29 of which used placebo vs cannabinoids or medical cannabis in the double-blind study. Data from 5174 adult patients, who were administered the drug or placebo orally in 30 of the reviewed studies. Only two clinical studies were reviewed and applied topically. The authors of the metadata review found that the trials carried out evidence moderate to low analgesia in most of the sample cases studied. However, it was also reported that a smaller group of people experienced a significant improvement in analgesia, pain relief, better sleep quality, and general well-being. Some limitations of this study mentioned by the authors were:

- 1) No long-term effects were measured. We found no eligible trials of chronic pain treatment with medical cannabis that exceeded 5 months and 5 days.
- 2) Only a third of the trials chosen for this study, included in their cohort patients who consumed or are currently consuming the substance. Volunteers who have consumed other types of substances were also ruled out, also volunteers with mental illnesses in 75% of the cases, while the remaining 25% do not report whether the volunteers with mental illnesses fall within the cut-off line. Therefore, our conclusions do not reach or may not be transferable to this group of the population.

3) Third, the high variability between the trials, the subjectivity of the volunteers, the effects, the reduced numbers of volunteers, contribute to making some subgroups more visible than others, minimizing important subgroup effects.

Although the possibility of the use of cannabis as a therapeutic agent in the treatment of pain is very attractive and opens a plethora of possibilities, other studies also agree with Wang's work. Haleem & Wright 2020 [22] analyzed the effect of a medical cannabis treatment for pain in older adults. For this, they selected 34 studies published between 2000 and 2020. Of the selected studies, 30 were randomized clinical trials (RCTs). They concluded that cannabis-based drugs are effective in refractory multiple sclerosis therapy. In case of cancer pain in advanced stages, it was found that relief is not enough. Encouraging results were found regarding its use for the control of chronic rheumatic pain. Adverse effects attributed to a low THC concentration in the samples were reported.

Conclusion

Training is essential for pharmacist, the role of the chemist in the synthesis of cannabinoids and the accompaniment during the treatment of the doctor. In this way, users of Cannabis and its derivatives make informed and safe use. This review only aims to navigate a sea of unanswered questions and others that, although answered, need more evidence to shore them up. Further research is requested on the intensive care setting of medical cannabis and the relative implications. Pharmacists must explore metabolic pathways of action and detoxification. Chronic toxicity studies to know the long-term effect of consumption are also a pending debt that can be resolved with the application of the new law in our country [5]. Fundamentally, more studies are necessary, which consider a larger population. According to a report by the United Nations Office on Drugs and Crime, 77 countries have reported an increase in cannabis use during the pandemic. In surveys of health personnel, the people surveyed, stated that 42% of them use cannabis.

This represented a marked increase during the pandemic. These data lead us to rethink the design of clinical trial protocols, since almost half of the population is excluded. In order to reliably establish whether medical cannabis or cannabinoids really represent an advantage over commercial pain relievers, further research is necessary. A promising future is predicted with the approval of the first studies with cannabis in the Argentine Republic.

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Conflicts of Interest

Authors declare there is no conflict of interest.

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