REVIEW ARTICLE

Phytocannabinoids and the individualization of treatment. Why is there no level of evidence?

Fitocanabinoides e a individualização do tratamento. Por que não há nível de evidências?

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ABSTRACT

BACKGROUND AND OBJECTIVES: The individualization of treatment has been recognized as essential in medical practice, especially due to the demand for different therapeutic approaches for similar situations. However, the complex and variable nature of the phytocannabinoids present in the cannabis plant presents challenges for the application of traditional models for testing the efficacy and safety of new drugs. The objective of the present study was to highlight the particularities of cannabis, including genetic variety, cultivation and production, which make it difficult to comply with traditional drug registration protocols, and the importance of individualizing treatment in the use of cannabis for the control of pain.
CONTENTS: Traditional models for testing the efficacy and safety of new drugs are based on a rigid methodology, divided into development and post-market phases. However, the complexity of the cannabis plant, with hundreds of actives that can vary according to the genetic variety, cultivation and production process, makes the application of these models difficult. In addition, international rules do not allow the registration of patents on cannabis products, due to the consideration that they are natural products and the extraction methods are already used in the industry for other plant actives. The individualization of treatment is fundamental in the use of cannabis for pain control, given the complexity of the plant and the limitations of traditional models of testing and drug registration.
CONCLUSION: The particularities of cannabis, such as genetic variability and the impossibility of registering patents, make compliance with current protocols difficult. However, the individualization of treatment allows adapting therapies to the needs of each patient, considering effectiveness and tolerance of side effects. Therefore, there is a need to rethink research and registry models to allow for a more flexible and personalized approach in the field of cannabis medicines.
Keywords: Cannabinoids receptors, Cannabis, Evidence-based pharmaceutical practice, History, Medical marijuana, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A individualização do tratamento tem sido reconhecida como essencial na prática médica, especialmente devido à demanda por diferentes abordagens terapêuticas para situações semelhantes. No entanto, a natureza complexa e variável dos fitocanabinoides presentes na cannabis apresenta desafios para a aplicação dos modelos tradicionais de testes de eficácia e segurança de novos fármacos. O objetivo deste estudo foi destacar as particularidades da cannabis, incluindo a variedade genética, o cultivo e a produção, que dificultam a conformidade com os protocolos tradicionais de registro de medicamentos, e bem como a importância da individualização do tratamento na utilização da cannabis para o controle da dor.
CONTEÚDO: Os modelos tradicionais de testes de eficácia e segurança de novos fármacos são baseados em uma metodologia rígida, dividida em fases de desenvolvimento e pós-mercado. No entanto, a complexidade da planta de cannabis, com centenas de ativos que podem variar de acordo com a variedade genética, o cultivo e o processo de produção, torna difícil a aplicação desses modelos. Além disso, as regras internacionais não permitem o registro de patentes de produtos canábicos, devido à consideração de que são produtos naturais e os métodos de extração já são utilizados na indústria para outros ativos vegetais. A individualização do tratamento é fundamental na utilização da cannabis para o controle da dor, dada a complexidade da planta e as limitações dos modelos tradicionais de testes e registro de fármacos.
CONCLUSÃO: As particularidades da cannabis, como a variabilidade genética e a impossibilidade de registro de patentes, dificultam a conformidade com os protocolos atuais. No entanto, a individualização do tratamento permite adaptar as terapias às necessidades de cada paciente, considerando a efetividade e a tolerância aos efeitos colaterais. Portanto, é necessário repensar os modelos de pesquisa e registro para permitir uma abordagem mais flexível e personalizada no campo dos fármacos canábicos.
Descritores: Cannabis, Dor, História, Maconha medicinal, Prática Farmacêutica baseada em evidências, Receptores de canabinoides.

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HIGHLIGHTS
• Biological imposition of individualization of pain management according to pharmacogenetics characteristics.
• Legal and regulatory restrictions on the development of studies with *Cannabis sativa*.
• Infinite possibilities of concentrations and ratios of actives in each cannabis product according to plant variety, cultivation method and extraction method.
• Lack of robust clinical trials due to impossibility of financial return through patent exploitation of natural products.

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INTRODUCTION

Individualization of pain treatment has long been recognized as fundamental to good medical practice, and it is becoming a necessity to achieve the highest percentage of positive outcomes while minimizing risks and costs for patients[1-3].

The need for individualization of pain treatment, as with most, if not all diseases, is imposed. It would be much easier if, for each clinical condition, there was a standardized and effective solution in all cases, however, this does not represent reality. This is due to a mosaic of personal characteristics such as genetic profile, quantity and quality of the converting enzymes, and environmental-behavioral issues. This set of variables makes the rigid standardization of treatments, without the flexibility for individual adjustments, something inefficient in the real world[1,4-6].

A ludicrous example: what is the chance that a patient with typical neuropathic pain (NP) caused by diabetic neuropathy would be able to control his symptoms, if there were supposedly a law saying that, for all patients with NP, only 150 mg/day of pregabalin associated with 150 mg tramadol and amitriptyline 12.5 mg per day could be prescribed, on a unique and exclusive basis[7]? Anyone who has treated patients with NP knows that some may respond satisfactorily to this approach, but many will undoubtedly not perceive significant relief. Not to mention that adverse effects will make it impossible to continue using these drugs. This is how individualization is imposed[8,10].

On the other hand, with so many therapeutic options available, how to choose what to do for patients? How to keep up to date with what is being done around the world, without leaving aside the ethical rectitude of not prescribing a new drug just because it is the trend of the moment[11-13]?

Among the possibilities of answers to these questions, it is important to highlight the search for reading quality and relevant scientific publications, the use of *guidelines* proposed by consensus of specialists with real-world clinical experiences that contemplate various treatment possibilities according to the individual needs of each case, with openness to the new therapeutic options[14,15].

Those who already have a few decades of medical practice tend to look back at how pain was handled in the past, not infrequently feeling some degree of anguish and even embarrassment. How was one able to treat chronic pain with so few pharmacological options and limited knowledge about pain physiology[16]?

On the other hand, despite all the advances in recent decades in relation to therapeutic options, dissemination of knowledge about the pathophysiology of pain, understanding the mechanisms of action of drugs, interventional techniques and new tools currently available, there are still many patients with refractory pain despite all the efforts, introduction and modifications of conduct[17,18].

This refractory factor is not necessarily related only to the inability to reduce pain intensity, but often occurs because of unavoidable adverse effects or the patient's financial impossibility to maintain their treatment, which is something very common in countries like Brazil[19-21].

Going back in time, long before contemporary medical-scientific methodology, mankind was already suffering from various diseases and painful conditions. From the very beginning, one dealt empirically with the means that were available in nature; and this has been documented since ancient Egypt[22].

Like other plants, *Cannabis sativa* has been used throughout history for the relief of pain and other neurological symptoms such as convulsions and muscle spasms. It has been employed for thousands of years on different continents and in different cultures; and the reason it has remained in use for so long is that it is an effective tool for relieving various symptoms that have always afflicted mankind[22,23].

Only in the last decades alternative therapies with proven efficacy and safety within Cartesian scientific methodology have emerged and occupied space. For this reason, traditionally used substances and conducts have been ignored and even criminalized. This was happening under the correct argument of greater security for the population of scientifically tested substances and technologies and to avoid charlatanism, which saw no boundaries and was very present until the first half of the 20th century[24-26].

However, despite all the scientific rigor, several drugs and medical procedures initially considered to be safe and effective were released and then withdrawn from the market after problems with their use were verified on a scale[25].

Likewise, despite all the advances made, the available therapeutic options are far from meeting the demands of all patients, keeping many people in constant pain and a high burden of suffering[17,18]. In the search for alternatives for pain control and motivated by reports of patients who perceived relief from their symptoms with cannabis, physicians in several countries in the northern hemisphere have for two decades followed patients officially using cannabis as a drug for different types of pain and other symptoms of various medical conditions[27,28].

Cannabis treatments that began empirically, based exclusively on its history of relative safety and effectiveness in controlling various symptoms throughout history, in recent years have become increasingly grounded in pharmacological knowledge of the interaction of its active ingredients in humans[27-30].

Varieties of cannabis

Like any plant, *Cannabis sativa* has several varieties, which differ not only in external aspects, their shape and appearance, but also in their chemical composition. Depending on the genetic variety, environmental, water and nutritional conditions during its growth and maturation, this plant will produce different amounts and proportions of its active ingredients[31-33].

Depending on the variety and quality of the plant raw material, and depending on the extraction method used, cannabis extracts will be produced with different active ingredients and numerous possibilities of concentrations and ratios. According to the chemical composition of the extract, the dose, and the individual characteristics of the patient, different effects and results can clearly be perceived in the same person[33-35].

The therapeutic actions of cannabis are credited to the effects of three classes of active ingredients present in the plant: phytocannabinoids, terpenes and flavonoids. Of these three, only the phytocannabinoids are practically exclusive to some varieties of *Cannabis sativa*; therefore, phytocannabinoids are the active ingredients that make this plant unique and special[36,37].

When one thinks of the traditional models for efficacy and safety testing of a new drug, a rigid methodology classically divided into phases one, two, three and post-market comes to mind. These studies take up a lot of time and huge amounts of money, often exceeding the billion-dollar mark. Although expensive and time-consuming, most of the time, these studies are directed at showing the efficacy and safety of a single active ingredient for some particular disease or set of symptoms[38].

These studies have the purpose of helping the population in medical issues, but also aim at the production or confirmation that a certain active has clinical applicability, transforming it into a product to be commercially explored by the pharmaceutical industry[39].

Introduction of artificial intelligence

The introduction of research tools using artificial intelligence (AI) has become a reality in recent years. With the entry of AI, researchers believe they will be able to speed up the process of developing new drugs and reduce some of the astronomical costs of all the phases currently required by regulatory agencies such as the National Health Surveillance Agency (ANVISA). However, there is still a long way to go to say that AI is a revolution in the research and development of new technologies[39,40].

In relation to cannabis, two particularities get in the way of this traditional logic. Firstly, cannabis is a plant with hundreds of active ingredients that can vary drastically depending on the genetic variety, cultivation and production process. Under the traditional method, a study would only be valid for a product with a specific chemical composition and a specific clinical situation. This would require the repetition of time-consuming and extremely expensive studies for each of the numerous possibilities of cannabis extracts[22,31-35,38,39,41].

Secondly, since the active ingredients of cannabis come from nature and its extraction methods are already established in the industry for the extraction of active ingredients from other plants, international rules do not allow the registration of patents for cannabis products, because they are considered natural products. The impediment to obtaining these patents makes it difficult or even impossible to obtain a financial return to fund the research phases of these products, which are normally covered by the income obtained from the 15-year exclusive license for marketing patented drugs[42,43].

For these reasons, clinical studies with cannabis and its derivatives are not able to meet the current methodological standards to be considered of high scientific relevance. On the other hand, it is unquestionable that the use of active ingredients derived from nature, especially those with already established popular use, will be the target of numerous scientific studies in the upcoming decades[43,44].

If, on the one hand, scientific evidence of quality regarding the clinical applicability of cannabis is still lacking, for some time now there has been access to a vast body of highly relevant publications focused on the interaction of phytocannabinoids, especially in relation to cannabidiol (CBD), cannabigerol (CBG) and tetrahydrocannabinol (THC) on receptors acting in mechanisms similar to the drugs already established to control chronic pain[45-48].

Articles from basic science show that these phytocannabinoids act on receptors inside and outside the endocannabinoid system. These interactions interfere with the release of several well-known endogenous substances, such as prostaglandins, GABA, glutamate, serotonin, noradrenaline and dopamine. Phytocannabinoids also have direct action on the receptor (TRPV1), disrupting the ascendancy of the pain impulse by closing calcium channels; similarly to lidocaine and capsaicin[45-47,49,50].

Among the most commonly used phytocannabinoids, cannabidiol (CBD) and tetrahydrocannabinol (THC) stand out as the most relevant assets in pain control. Both have very similar actions on various receptors, such as CB1, CB2, GPR55, 5-HTA, opioid receptors, GABA-A, and PPARγ. The great difference between them is in the way they interact on the CB1 receptor. This different actions on CB1 makes CBD not cause dissociative psychoactive effects[45-47,50-52].

Depending on individual sensitivity and the dose used, THC acts with greater or lesser intensity as an agonist of the CB1 receptor, leading to alterations in the reward and aversion systems, which are mediated directly by the dopamine and GABA neurotransmitters. To this mechanism, the psychoactive effects of THC is credited[53].

As already mentioned, the psychoactive effect of THC can be of greater or lesser intensity, most often causing feelings of relaxation, pleasure, and well-being. The psychoactivity of THC can also interfere with the emotional aspects of pain and suffering imposed by objective and subjective issues of pain consequences. When well tolerated, the psychoactive effects of THC can play an important role in the acceptance and improvement of quality of life; regardless of its effectiveness in reducing pain[53,54].

Because there is no possibility of psychoactivity with CBD, many health practitioners initially recommend using cannabis products with CBD as the dominant phytocannabinoid, titrating the dosage progressively until improvement in symptoms is observed. Those who do not perceive relief at dosages greater than 50 mg or more of CBD per day are the ones who should gradually add THC to their prescription[52].

This recommendation is not based on the greater effectiveness of CBD, but on its greater safety compared to THC. Following this logic, since it is possible to obtain improvement of symptoms with CBD for patient safety, it does not make sense to start with products with a higher amount of THC, leaving this phytocannabinoid as a second option, i.e., in cases where CBD does not help[45-47,50-54].

It is increasingly becoming undisputed, despite the difficulties of scientific documentation within traditional metrics, the therapeutic potential of cannabis and its derivatives in controlling pain in patients who respond satisfactorily to one or more of its actives, being especially useful for those individuals who have obtained frustrating responses with conventional treatments[55-62].

CONCLUSION

Not unlike other drugs traditionally used in pain management, the use of *Cannabis sativa* and its derivatives for pain control

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reaffirms the need for individualization of treatment based on therapeutic response due to its effectiveness and tolerance to side effects of the active ingredients prescribed.

AUTHORS' CONTRIBUTIONS

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Data Collection, Conceptualization, Project Management, Methodology, Writing – Preparation of the original, Writing – Review and Editing
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