Gaps in our knowledge and future research on the endocannabinoid system and the painful phenomenon

As lacunas do nosso conhecimento e as pesquisas futuras sobre o sistema endocanabinoide e o fenômeno doloroso

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ABSTRACT

JUSTIFICATIVA E OBJETIVOS: O presente artigo teve como objetivo debater e apontar as principais lacunas e gargalos na pesquisa clínica nacional e internacional relativas aos compostos canabinoides de uso medicinal e suas respectivas relevâncias nas práticas relacionadas ao controle da dor. Outros objetivos foram estabelecer padrões e regulamentos para testar a qualidade, eficácia e segurança de cultivo e fabricação de produtos de cannabis (semelhantes aos padrões biofarmacêuticos) antes de prescrever ou comercializar, e investigar abordagens a fim de estabelecer orientações robustas para dirigir sob influência de canabinoides.
CONTEÚDO: Uma pesquisa com os termos "canabinoides" e "*pain*" no domínio do www.clinicaltrials.gov, plataforma internacional de dados de registro de ensaios de pesquisa clínica, cita apenas dois estudos brasileiros, sobre fibromialgia e cefaleia crônica. A busca do termo "canabinoide" na Plataforma Brasil retornou apenas nove menções de estudos relacionados ao tema dor, sendo a maioria relatos de casos ou estudos observacionais, sem intervenção ativa, ou sem grupo controle.
CONCLUSÃO: Ainda há poucos estudos clínicos, randomizados e controlados avaliando doses eficazes, vias e intervalo de administração, interação farmacológica com opioides ou entre os diversos canabinoides, interação com analgésicos adjuvantes, lesões potenciais no contexto do uso a longo prazo e fatores individuais que predisponham ao uso indiscriminado dos canabinoides.
Descritores: Cannabis, Dor, Pesquisa sobre Serviços de Saúde.

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HIGHLIGHTS
- Recognize the adverse effects of cannabinoids
- Highlight scientific evidence
- Encourage high quality studies

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RESUMO

BACKGROUND AND OBJECTIVES: This article aimed to discuss and point out the main gaps and bottlenecks in national and international clinical research regarding medicinal cannabinoid compounds and their respective relevance to pain management practices. Other objectives were to establish standards and regulations for testing the quality, efficacy, and safety of cultivation and manufacturing of cannabis products (similar to biopharmaceutical standards) before prescribing or marketing, and to investigate approaches in order to establish robust guidelines for cannabinoid-influenced driving.
CONTENTS: A search with the terms "cannabinoids" and "pain" in the domain www.clinicaltrials.gov, international data platform for registration of clinical research trials, found only two Brazilian studies, on fibromyalgia and chronic headache. The search for the term "cannabinoid" in *Plataforma Brasil* returned only nine mentions of studies related to pain, most of them being case reports or observational studies, without active intervention or control group.
CONCLUSION: There are still few clinical, randomized, controlled trials evaluating effective doses, routes and interval of administration, pharmacological interaction with opioids or among the various cannabinoids, interaction with adjunct analgesics, potential injury in the context of long-term use, and individual factors that predispose to indiscriminate cannabinoid use.
Keywords: Cannabis, Pain, Research on Health Services.

INTRODUCTION

The global use of cannabinoids for medicinal and non-medical purposes is accelerating at a remarkable pace. By 2026, the market capitalization of cannabinoids is predicted to reach the figure of approximately US$ 97 billion, which will far surpass the largest pharmaceutical company in the world[1]. According to data from the Brazilian Cannabinoid Industry Association (BRCANN), the import of these drugs currently moves R$ 250 million per year. In the next five years, the expectation is that the sector will move R$ 700 million. Cannabis-based products will be marketed in pharmacies in the national retail network[2]. In 2017, a project for the creation of Cannabinoid Research Center was elaborated, a partnership between *Universidade de São Paulo* (USP) research laboratories and the industry, and whose group of researchers expressively represents the national and international knowledge on the subject[3].

However, the scientific production of researchers from Medical School of Ribeirão Preto - USP (*Faculdade de Medicina de Ribeirão Preto* – (FMRP-USP) is focused mainly on studies with cannabidiol (CBD) and its use in neurology and treatment of psychoaffective disorders[4]. Professor Carlini, creator of the Brazilian Center for Information on Psychotropic Drugs (*Centro Brasileiro de Informações sobre Drogas Psicotrópicas* - CEBRID) and precursor of research on the subject in the country, stressed the importance of national production of research on the subject and even the creation of a Brazilian medical cannabis agency.

However, a search for the term "cannabinoid" in *Plataforma Brasil*, a national and unified database of research involving humans for the entire CEP/CONEP (Brazilian Research Ethics Committees Integration - *Comitês de Ética em Pesquisa/Comissão Nacional de Ética em Pesquisa*) system, returned only nine mentions of studies on cannabinoids related to pain, with diverse methodological designs, most being case reports or observational studies, without active drug intervention, or without pairing with a control group. A search with the terms "cannabinoids" and "pain" in the domain www.clinicaltrials.gov, international data platform for registration of clinical research trials, found only two Brazilian studies (NCT04989413, NCT05283161) related to the treatment of fibromyalgia and chronic headache in pre-recruitment phase, both in collaboration with the pharmaceutical industry.

The present article aimed to point out and discuss the main gaps and bottlenecks in national and international clinical research concerning medicinal cannabinoid compounds and their respective relevance in practices related to pain control.

CONTENTS

Cannabinoid-related research

Research in cannabinoids field basically involves three distinct areas: phytocannabinoids, endogenous cannabinoids (anandamide and 2-araquidonoilglycerol, 2-AG), with their respective synthesis and metabolism enzymes and their respective effects on cannabinoid receptors 1 and 2 (CB1 and CB2), and, finally, analogues of endogenous endocannabinoids. Preclinical and clinical research has advanced greatly in recent years, and new knowledge in all three domains will not only shed light on a large number of physiological processes, but will also serve as a starting point for the development of new drugs[5].

Cannabinoids are endogenous or exogenous compounds that have activity at cannabinoid receptors. Three types of cannabinoids can be described: phytocannabinoids (plant-derived such as nabiximol), endocannabinoids (endogenous compounds such as anandamide and 2-araquidonoylglycerol - 2-AG), and synthetic cannabinoids (dronabinol and nabilone). Cannabis plants contains about 60 to 100 types of cannabinoids. The main cannabinoids found in cannabis plants are delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN). The most important and best studied endogenous cannabinoids (ECs) are anandamide (AEA) and 2-araquidonoilglycerol (2-AG), which can be found in various tissues.

In addition to the classical ECs, virodamine (VIR), noladine ether (NE) and N-araquidonoil dopamine (NADA) presumably act as ECs[6]. Noladine ether is a potent and selective agonist of the cannabinoid CB1 receptor, which can cause hypothermia, intestinal immobility, and mild antinociception[7]. Despite being considered ECs, these substances are still detected in minute quantities and can hardly be evidenced in biological tissues, particularly in the human species. Therefore, much of the controversy regarding medicinal use of cannabinoids lies in the discrepancies between preclinical and clinical studies.

The American Society of Anesthesiologists (ASA) recently endorsed two bills that seek to expand CBD and marijuana research: H.R. 601, the Medicinal Cannabis Research Act of 2019, and S. 2032, the Cannabidiol and Marijuana Research Expansion Act[8]. ASA commissioned the Caravan® survey, containing five questions and conducted online August 5-7, 2019, with the participation of 1,005 adults, including 503 men and 502 women, aged 18 and older. The survey revealed some troubling data: when respondents who said they have used or would consider using marijuana or cannabinoids were asked why, the majority (62%) said they believe cannabinoids are safer than opioids, and (57%) said they believe cannabinoids have fewer adverse effects than other drugs. In this regard, ASA members expressed concern that pain patients do not know that marijuana and cannabinoids may not be safer than other drugs, such as anti-inflammatory drugs, for example, and that they can have adverse effects - from excessive drowsiness to liver damage - and, more importantly, that on U.S. soil these products are not regulated or monitored for quality[9].

According to National Health Surveillance Agency (ANVISA) regulations (RDC 327/2019), Brazilian compounding pharmacies could not work with medical cannabis. For the agency, only non-manufacturing drugstores could commercialize the product. This impasse creates not only a legal gap that increases the risks to safety and quality of the products made available to patients, but also places limits on the possibility of formal clinical registries for patients undergoing medical cannabis use in clinical trials, observational trials, and comparative databases.

Other data from the American survey reinforce this perception. Among all those surveyed (including those who said they would never use marijuana or cannabinoids), only 57% believe in the need for additional research; 34% would dismiss the need to discuss the use of these products with their doctor; 58% believe there are fewer adverse effects than other drugs; 48% think they know what they are getting; and finally, 40% of them believe that CBD sold in supermarkets, truck stops, health food stores, or medical marijuana dispensaries, is FDA approved[9]. The younger the individual, the greater this perception. Certainly, such perceptions reinforce patients' disinterest and disengagement in participating in future clinical trials.

Barriers and limitations on cannabinoid compound research

There are specific regulatory barriers, including the classification of cannabis as a substance of abuse, that limit research on cannabis and cannabinoids[10]. Authorization by regulatory agencies in various countries regarding the use of cannabinoid-derived drugs and cannabinoids is quite heterogeneous[11]. Currently, the Anti-Drug Law prohibits, in all Brazilian territory, the planting, cultivation, harvesting, and exploitation

of plants and substrates from which drugs can be extracted or produced, with the exception of those plants used exclusively for religious ritualistic purposes, and in the case of medicinal and scientific purposes.

It can be difficult for researchers to gain access to the quantity, quality, and type of products needed to address specific research questions about health effects of cannabis use. A diverse network of funders to support cannabis and cannabinoid research projects aimed at examining not only the potential therapeutic effects, but also exploring the harmful health effects of cannabis use, is extremely important. In a country with progressively restricted resources for clinical and experimental research, funding through partnerships with industry becomes attractive, but always involving sponsors with occasional conflict of interests.

To develop more consistent evidence of the effects of cannabis use on short- and long-term outcomes, improvements in techniques and standardization of research methodology (especially in controlled clinical trials and observational studies) are needed. Unfortunately, most randomized, blinded clinical trials have numerous methodological limitations. Certainly the main one is limited casuistic, which affects the achievement of statistical significance to allow extrapolation of conclusions beyond the study populations.

Even if the best levels of evidence are considered, such as randomized clinical trials (RCTs), systematic reviews or meta-analyses, few studies cover casuistics above one hundred individuals. Moreover, even RCTs encounter methodological difficulties in blinding the control group. Like other psychoactive substances, cannabis presents a challenge in blinding subjects due to its intrinsic psychoactivity. The placebo arm of trials evaluating both smoked and vaporized cannabis usually consists of inactive marijuana. Although the inactive form may visually and taste similar to cannabis, many participants can distinguish between the intervention and the placebo - presumably because the psychoactive properties of cannabis are not present in placebo[12].

Real-World Evidence (RWE)

RWE is defined as evidence derived from health data from non-interventional studies, medical records, electronic health records, and insurance data, as opposed to the highly controlled setting of RCT. RWE has broader inclusion criteria, taking into account factors such as non-standard dose, and is not limited by disease scope, thus improving ecological validity. However, some studies have concluded that there is little difference between the results obtained through RCT and observational studies.

RWE usually has longer patient follow-up and consequently can detect rare but important adverse effects that are not detected in RCT. RWE can improve the efficiency of clinical trials by generating hypotheses, refining eligibility criteria, and exploring drug development tools. Registries can be used to form an infrastructure for conducting a clinical trial, reducing costs and maintaining the high quality of evidence.

More recently, there has been a focus on gathering evidence from clinical registries and national databases in many countries, with evidence generated from patient-reported outcome measures and long-term pharmacovigilance. RWE may bring more clarity on questions that remain unanswered in RCTs. A recent study used anonymous surveys of fibromyalgia patients who consumed cannabis flowers. In addition to reporting positive outcomes on depression and pain, the study also reported negative aspects of cannabis consumption, for example, driving under the influence of cannabis in 72% of patients[13]. Databases for this purpose have been created in several countries, such as the UK, Canada, Australia, Denmark, Italy, Germany, the USA and Ireland, just for the purpose of feeding specific data on this subject[14].

The president of the International Association for the Study of Pain (IASP) has established a task force on cannabis and cannabinoid analgesia, with the goal of systematically examining and summarizing the evidence on: (1) analgesic pharmacology of cannabinoids and preclinical evidence of their antinociceptive efficacy in animal models of persistent pathological or injury-related pain, (2) the clinical efficacy of cannabis, cannabinoids, and cannabis-based medicines (CBMs) for pain management, (3) injuries related to long-term use of cannabinoids, as well as (4) social issues and policy implications related to the use of cannabinoids, cannabis, and CBMs for pain management[15].

Analgesic pharmacology of cannabinoids and preclinical evidence of their antinociceptive efficacy in animal models of persistent pathological or injury-related pain

A systematic review revealed an overall poorly defined risk of bias and low prevalence of methodological quality criteria. Such criteria included blinded outcome assessment, random selection, animal exclusions and predetermined animal exclusion criteria, allocation concealment, and sample size calculations[16]. The task force listed several points of preclinical research priorities:

- Neurobiology of endocannabinoid signaling in relation to pathological pain processing and search for additional potential analgesic targets of the endocannabinoid system.
- Cannabinoid receptor signaling and the role of allosteric modulation and biased agonism of cannabinoid receptors.
- Better alignment between compounds tested in clinical trials and those tested preclinically, to allow for a better comprehension of the endocannabinoid system's translational pharmacology, for analgesia.
- Investigating the pharmacology of cannabinoids other than THC, including CBD and other phytocannabinoids.
- Detailed characterization of cannabinoids' pharmacokinetic properties and determination of the pharmacokinetic-pharmacodynamic (PK-PD) relationship between plasma concentrations, effect site concentrations and antinociception in the context of specific preclinical models.
- Optimization of drug modalities and formulations to achieve consistent exposure at the site of action.
- Research of the additional analgesic potential of cannabinoid receptors and targets outside the central nervous system (CNS) to avoid unwanted central adverse effects.

• Physiological interactions between endogenous cannabinoid and opioid systems in pain modulation.
• Role of the endocannabinoid system and cannabinoids in modulating the affective-motivational and cognitive dimensions of pain processing and pain experience.
• Enhanced external validity of animal models and outcome measures used to determine the antinociceptive effects (particularly long-term effects) of cannabinoid and endocannabinoid system modulators.
• Improving rigor and transparency of pre-clinical trial design, conduct, analysis, and reporting.

Clinical trials of analgesic efficacy

A systematic review of the literature on the analgesic efficacy of cannabis, cannabinoids, and CBM was conducted, including studies in people with acute or chronic pain (excluding experimental pain) and in individuals receiving cannabinoid products of any kind, natural or synthetic, by any route of administration. The review in question found 36 studies qualified for inclusion (representing a total of 7,217 participants). Most studies focused on cancer pain, acute pain, multiple sclerosis pain, and neuropathic pain, with only a few studies on musculoskeletal and abdominal pain. Of these, eight studies tested individual cannabinoids or endocannabinoid system modulators, six tested cannabis, and 22 tested CBM.

The authors of aforementioned review rated all studies as having an uncertain or high risk of bias. Using GRADE criteria, all results were judged as low or very low quality evidence for all types of cannabis, cannabinoids and CBMs studied so far, regardless of the type of pain[17]. In light of this analysis, the task force recommended planning future clinical trials based on the following principles:

• Trials of cannabinoids should include pain intensity and, in the context of chronic pain, also assessment of the effects on sleep, quality of life, function, and on affective-motivational and cognitive dimensions of the pain experience, particularly those most important from the patient's perspective.
• Dosing and titration (if applicable) methods should be explicit; placebo and active comparators should be encouraged, as should studies examining cannabis, cannabinoids, or MBCs administered as monotherapy and in conjunction with other analgesics.
• Analysis of the patient's demographic, phenotypic, and genotypic characteristics that are pertinent to a possible personalized response to treatment.
• Research of the relationships between plasma concentrations and cannabinoid targets and their respective pharmacodynamic effects for both efficacy and toxicity endpoints.
• High quality trials studying cannabidiol (CBD) in specific pain conditions.
• High quality trials studying the cannabinoids, endocannabinoid system modulators, and CBMs that show the most promise in preclinical studies.
• Designs of experimental pain studies with cannabinoids that would translate into relevant and clinically meaningful analgesia.
• Research of interactions between opioid-based and cannabinoid-based interventions for (1) analgesic efficacy, (2) adverse effect profile, e.g. abuse liability or respiratory depression, and (3) change or inhibition of symptoms during opioid reduction or withdrawal.
• Determining the optimal therapeutic proportions of cannabinoids (e.g. THC-CBD) in specific pain conditions, for example in strategies that attempt to separate analgesia from adverse effects.
• High quality trials with inhaled or vaporized cannabinoids, with adequate sample size, sufficient duration, detailed pharmacokinetic analysis, and stringent controls.
• High quality population health studies based on "real world" data on the benefits and harms of cannabis, cannabinoids and CBMs in large numbers of people with pain.
• Unified quantification of higher or lower phytocannabinoid content for cannabis preparations evaluated in clinical trials.
• Determining the effects of regulatory restrictions on clinical cannabinoid research.

Systematic reviews of cannabis-related injuries, cannabinoids, and drugs based on cannabis

An overall analysis of systematic reviews on the injuries of cannabis and cannabinoids in chronic pain and other conditions was performed. A total of 72 reviews addressed cannabis (smoked, vaporized, or ingested) and seven reviews addressed cannabinoids individually; therefore, most of the safety data pertain to the use of cannabis, rather than single cannabinoid compounds. Overall, 76 of 79 included reviews received a "critically low" score and three received a "low" AMSTAR-2 score. Although adverse events were higher in the nabiximol and THC treatment groups compared to control, individual RCTs did not consistently report harms or adverse events, possibly underestimating adverse effects[18]. It is worth mentioning the lack of data on specific harms in pain studies, with most reviews evaluating the safety of cannabis in mixed populations, outside of the pain setting itself. The following are the top priorities listed by the task force for this type of review:

• To identify potential injuries in the context of long-term use of cannabis, cannabinoids, and CBMs for the treatment of chronic pain: (1) Cognitive effects in different age groups; (2) Neurodevelopmental effects in infants, children, and adolescents, including neuronal development, effects on learning, learning impediments, and academic performance; (3) Mental health disorders, with emphasis on psychosis and depression; (4) Neurological effects; (5) Cannabis use disorders; (6) Pulmonary effects; (7) Effects on pregnancy and lactation; (8) Effects on driving and operating machinery; (9) Cardiovascular effects; (10) Carcinogenicity, with emphasis on genitourinary cancers.
• The role of a cannabinoid compound, dose, route, exposure (pharmacokinetics) and duration of use on specific short- and long-term adverse effects.
• Pharmacological interactions, particularly with drugs with narrow therapeutic windows (e.g., anticoagulants, immunosuppressants, opioids, or intravenous general anesthetics).

• Individual factors (e.g., demographic, psychological, genetic, comorbidity, and concomitant drug use) that confer susceptibility versus resilience to the adverse effects of cannabinoids.
• Injuries related to the use of cannabis and synthetic cannabinoids for medical purposes under medical supervision compared to those associated with use in the absence of specialized medical supervision.
• Population-based research methods to track the self-prescribed use of cannabis, specific to pain management, and to track the potential benefits and harms of this mode of use.
• Improve approaches for assessing and reporting the harms of cannabis, cannabinoids, and CBMs in RCTs on pain, with appropriate duration and post-exposure, for long-term adverse event follow-up.

Systematic reviews on the use of cannabinoids for pain

A review was designed to assess the quality, scope, and results of the many existing systematic reviews on the efficacy of cannabis, cannabinoids, and CBMs for pain relief[19]. A total of 106 articles were selected, of which 57 were included, containing 15 distinct pain conditions, most of which were published from 2010 onwards. None of the reviews examined the effects of a specific cannabinoid, at a specific dose, using a specific route of administration, for a specific pain condition, reporting a specific analgesic outcome.

Confidence in the results, using AMSTAR-2 definitions, was generally low: critically low (39 reviews), low (8), moderate (5), and high (2). Less than 10% of reviews used relevant criteria for pain assessment. Effect estimates were highly variable, with extreme examples of data clustering, and could not guarantee a basis for decision making. The IASP task force suggested the following priorities for future systematic reviews:

• Systematic reviews should meet the Cochrane definition of systematic reviews and provide sufficient detail to be of moderate or high confidence according to AMSTAR-2.
• Studies should be pre-registered, outlining objectives, primary and secondary endpoints, and data analysis strategy.
• Double-blind, randomized trials should be adequately conducted in people with a defined pain condition and initial pain self-rated as moderate or severe.
• The potential for small study bias, imputation methods, and potential risk of publication bias should be examined.
• The review's perspective should be stated in advance; choose efficacy or effectiveness outcomes relevant to that perspective.
• A meta-analysis should be performed at the individual level whenever possible.

Social issues and policy implications of widespread use of cannabinoids for pain

The use of cannabis without adequate regulation of manufacture and supply, along with ready access to unregulated and often illicit markets for highly concentrated products, can result in great social risks and harms[20]. The cultivation of cannabis plants and subsequent extraction or formulation processes present complexities and legal challenges due to wide legal variability and local health processes.

The growth and composition of cannabis, including its phytocannabinoid content, is subject to a wide range of influences. To better control these parameters, especially to cannabis intended for medicinal use, indoor cultivation is usually favored over outdoor cultivation. In the absence of universally accepted regulations, some countries have determined their own criteria, resulting in a divergent global regulatory landscape for cannabis cultivation that is far below standards compatible with the pharmaceutical manufacture of medicines for human use.

The marketing of cannabis products used as medicines (as opposed to regulated CBMs) is generally unregulated since agencies such as Food and Drug Administration (FDA) or European Medicines Agency (EMA) don't use the standards established for other pharmaceutical products, leading to reduced oversight of health claims made for cannabis products for medicinal or recreational use for adults. In some countries, there is a rapid growth of "specialized cannabis clinics" in which patients, often with complex medical comorbidities, are treated predominantly with cannabis-based therapy, without a comprehensive treatment approach.

Furthermore, in contrast to pharmacies where drugs are dispensed by trained and licensed professionals, most cannabis dispensaries provide drugs and medical advice by non-medical staff. The IASP task force has defined the following priorities for sociopolitical issues on the widespread use of cannabis in the context of pain[15]:

• Establish standards and regulations to test quality, efficacy, and safety of cultivation and manufacturing of cannabis products (similar to biopharmaceutical standards) before prescribing or marketing.
• Research into marketing and advertising of cannabis products. Investigate the consequences (use and effects) of banning benefit claims not supported by robust data. Ban advertising to children and adolescents.
• Research approaches to establish robust guidelines for driving under the influence of cannabinoids.
• Establish education programs for vulnerable populations; leverage patient partners to improve outreach.
• Engagement with physicians and patient partners to establish education programs for healthcare professionals to provide reliable information to patients, including developing countries and countries where English is not the primary language.
• Research broader social harms (e.g., addiction, psychosis, or cognitive effects) in the context of pain management.
• Research approaches to encourage or compel the cannabis industry to fund high quality cannabis research to support efficacy claims and improve product standards and patient safety while minimizing and managing conflicts of interests.

CONCLUSION

Several questions still need to be answered by clinical research on cannabinoids. There are still few controlled, randomized, clinical studies evaluating effective doses, routes and interval of administration, pharmacological interaction with opioids or among

the various cannabinoids, interaction with adjuvant analgesics, potential injury in the context of long-term use, and individual factors predisposing to indiscriminate use of cannabinoids. As for research in Brazil, there is little availability of financial resources for research on pain, especially when it comes to clinical studies with drugs. Therefore, few studies are developed in the clinical area.

Some peculiarities of Brazil are worth mentioning: it is a continental-sized country, whose population is miscegenated and quite diverse. Data obtained from other countries are not always applicable to the country. It is necessary to create databases in health services, learn to use the industry database, and create specific complementary legislation for cannabinoid research based on national data. Such information is needed to argue for government regulation of drugs.

AUTHORS' CONTRIBUTIONS

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