

Painful behavior and medicinal cannabis

Comportamento doloroso e cannabis medicinal

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DOI 10.5935/2595-0118.20230006-en

ABSTRACT

BACKGROUND AND OBJECTIVES: Pain is defined as a complex sensory and emotional experience, and it is one of the most common causes for seeking health care, being the chronic pain one of the most prevalent health conditions in the world today, with millions of people debilitated by symptomatic conditions. The discovery of the endocannabinoid system and its organic effects on pain modulation, especially chronic pain, represented an unknown source of possibilities for the production of drugs that, theoretically, would have great potential to improve the quality of life of individuals with chronic pain. Given this, the general objective of this work was to search the literature for studies that investigated the use of medicinal cannabinoids for the treatment of chronic pain and pain behavior.

CONTENTS: This is a narrative review of the literature in which aspects of painful behavior are presented, such as cognitive distortions associated with the experience of pain, and the influence of trauma, stress and psychiatric comorbidities on pain outcomes. The endocannabinoid system influences the modulation of all these points and also the regulation of pain itself.

CONCLUSION: This study provides perspectives on painful behavior and how the endocannabinoid system can interfere with different aspects of pain and with the way the patient perceives pain. Further studies on this issue are extremely important.

Keywords: Cannabis, Chronic pain, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor é definida como uma experiência sensitiva e emocional complexa, e está entre as principais causas de busca por atendimento médico, sendo a dor crônica um dos problemas de saúde mais prevalentes no mundo atual, com milhões de pessoas debilitadas por condições sintomáticas. A descoberta do sistema endocanabinoide e seus efeitos orgânicos na modulação da dor, especialmente a crônica, representou uma fonte desconhecida de possibilidades para a produção de fármacos que, teoricamente, possuiriam grande potencial de melhorar a qualidade de vida de indivíduos portadores de dor crônica. Diante disso, o objetivo geral deste trabalho foi buscar na literatura estudos que investigaram o uso de canabinoides medicinais para o tratamento da dor crônica e do comportamento doloroso.

CONTEÚDO: Trata-se de um estudo de revisão narrativa da literatura em que são apresentados aspectos do comportamento doloroso, como as distorções cognitivas associadas à experiência de dor, e a influência do trauma, do estresse e de comorbidades psiquiátricas nos desfechos de dor. O sistema endocanabinoide tem influência na modulação de todos esses pontos e também na própria regulação da dor.

CONCLUSÃO: Este estudo traz perspectivas sobre o comportamento doloroso e de como o sistema endocanabinoide pode interferir em diversos aspectos da dor e da forma como o paciente percebe a dor. Mais estudos sobre o assunto são de extrema relevância.

Descritores: Cannabis, Dor, Dor crônica.

INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”¹. According to the IASP, “pain is always a personal experience influenced by various degrees of biological, psychological and social factors”². Pain is among the main causes for seeking medical care, and chronic pain (CP) is one of the most prevalent health problems in the world today, with millions of people debilitated by symptomatic conditions³.

The pharmacological therapy for CP proposed by the World Health Organization (WHO) includes the use of analgesics, anti-inflammatory drugs, adjuvant drugs, and opioids, which aim to act in nociceptive and mixed pain⁴. Opioids are considered excellent analgesics; however, their continuous use may present a high risk of tolerance, with the need for increasingly higher doses, which, in fact, increases the risk of adverse effects, use of high doses, and chemical dependence. Thus, seeking new pharmacological alternatives for the treatment of CP is necessary⁵.

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Submitted on June 20, 2022.

Accepted for publication on February 6, 2023.

Conflict of interests: none – Sponsoring sources: none.

HIGHLIGHTS

- Compounds formed in the cannabis secondary metabolism exhibit pharmacological properties of obvious interest.
- Specific errors called cognitive distortions were identified, such as selective abstraction, overgeneralization, personalization, and catastrophizing.
- Association between psychological factors, sleep, central sensitization, pain, and chronic neck, back, limb, and multiregional impairment.

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The discovery of the endocannabinoid system and its organic effects on pain modulation, especially chronic pain, represented an unknown source of possibilities for the production of drugs that, theoretically, would have great potential to improve the quality of life of individuals with CP⁶.

Cannabis flowers are a fundamental raw material for the manufacture of the most diverse extracts known today. Several compounds formed in the secondary metabolism of cannabis have pharmacological properties of evident interest, notably the cannabinoids, especially tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), which, when converted into their neutral forms, tetrahydrocannabinol (THC) and cannabidiol (CBD), have paradoxical pharmacological effects on central nervous system (CNS)⁸. THC is psychoactive with euphoria properties, besides having antiemetic and analgesic effects, while CBD is depressant, with anticonvulsant and anxiolytic properties, with antipsychotic and anti-inflammatory effects⁹. The discovery of the cannabinoid receptors CB1 and CB2 guided the first researches on the subject, CB1 being well distributed in the CNS, which, in the presence of THC, leads to the inhibition of neurotransmitters, and can modulate pain pathways¹⁰. CB2 receptors also participate in the pain response, mainly by modulating dopamine release¹¹.

In fact, scientific research with cannabis provides evidence supporting its medicinal properties, therapeutic use in CP being one of them. Considering the growing incidence of problems associated with chronic pain and the need for the use of alternative therapies, understanding the aspects involved in the use of medicinal cannabis for pain treatment becomes something relevant. Given this, the general objective of this work was to search the literature for studies that addressed behavioral and cognitive aspects associated with CP and the use of medical cannabis.

CONTENTS

Pathological cognitions in pain

One aspect of pathological cognitions that has been extensively investigated in chronic pain is the field of cognitive distortions. The concept of cognitive distortion is borrowed from cognitive models of depression^{12,13} and collectively refers to errors in the logic of interpreting situations. Beck et al. (1967) identified several specific errors called cognitive distortions, such as (1) selective abstraction – focusing on the negative aspects of an experience; (2) overgeneralization – assuming that the negative consequences of an experience apply to similar events in the future; (3) personalization – seeing oneself as personally responsible for negative situations; and (4) catastrophizing – expecting that the worst possible outcome will occur¹³. Catastrophizing, in particular, has been widely studied in chronic pain and it seems to imply not exactly the intensity of pain, but the degree of suffering and physical and mental disability imposed by pain¹⁴.

The association of psychological factors with chronic low back pain was assessed by a cross-sectional study of 472 participants. Of these, 125 participants had severe low back pain. Patients with catastrophizing cognitions had 2.21 (95%

confidence interval = 1.30 – 3.77) greater odds of having severe pain and 2.72 times (CI = 1.75 – 4.23) greater odds of having severe functional limitation than patients without catastrophizing symptoms. Patients with maladaptive beliefs regarding rest were 2.75 (CI = 1.37 – 5.52) times more likely to have severe pain and 1.72 (CI = 1.04 – 2.83) times more likely to have severe functional limitation. Patients with movement phobia were 3.34 (CI = 1.36 – 8.24) times more likely to have severe pain and patients with social isolation were 1.98 (CI = 1.25 – 3.14) times more likely to have severe functional limitation¹⁵.

The endogenous pain modulation assessed in humans by a protocol called Conditioned Pain Modulation (CPM) and catastrophizing were associated with the incidence and severity of acute pain after orthognathic surgery. The weaker the CPM and higher the levels of catastrophizing, higher the incidence and severity of acute postoperative pain¹⁶.

A cross-sectional study of 172 orthopedic patients with foot and ankle CP (64% female, mean age 60.9 years, and mean body mass index – BMI – of 27.6 kg/m²) found a prevalence of depressive symptoms in 48%, central sensitization (CS) in 38%, and pain catastrophizing in 24% of cases. Interestingly, age, gender, and BMI accounted for 12% of the variance in pain scores, while psychological variables accounted for 28.2%. Catastrophizing was the largest independent predictor of pain severity, accounting for 14.4% of the variance, followed by BMI (10.7%) and depressive symptoms (2.3%)¹⁷. In a clinical trial, 78 patients (56 women) with CP had acceptance and commitment therapy (ACT) sessions, and before and after each session blood samples were collected and analyzed for interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) levels. Pain interference and psychological inflexibility improved significantly during treatment, while pain intensity did not change. Psychological flexibility refers to the ability of individuals to engage in activities in spite of pain or distress, and therefore does not measure pain intensity, but rather reflects the interference of pain with daily life activities activities. IL-6 and TNF-alpha levels did not change with the course of treatment. Mean baseline levels of IL-6 and TNF-alpha weighted the improvement in psychological inflexibility during the course of treatment, but did not moderate changes in pain interference or pain intensity. In other words, basal inflammation level may be inversely proportional to greater psychological inflexibility, and probably also to low levels of inflammation would underlie variability in CP behavioral treatment¹⁸. Along this same line, another recent study of individuals with fibromyalgia who participated in a mindfulness-based stress reduction (MBSR) program, and showed that higher levels of pro and anti-inflammatory cytokines (IL-6/IL-10) were associated with lower improvements in psychological inflexibility during treatment¹⁹.

Trauma, stress and psychiatric comorbidities

Symptoms of depression, anxiety, and stress have a significant influence on musculoskeletal pain. Behavioral modification techniques are effective in managing these variables. A systematic review with meta-analysis that included 41 randomized

controlled trials evaluated the effectiveness of telematic behavioral modification techniques (e-BMT) for those psychological variables in patients with musculoskeletal CP. E-BMT achieved relevance, albeit with small effect size for depressive symptoms, and small to moderate effect size for anxiety in this population population, but was not effective for stress symptoms, with moderate level of evidence, perhaps due to the heterogeneity of stress measures, as well as traumatic situations within this population²⁰.

There is substantial evidence, primarily derived from cross-sectional studies, that women who have experienced intimate partner violence (IPV – both physical, sexual, psychological, and through controlling behaviors) have worse physical and mental health than those who have not^{22,23} and that IPV among women is associated with a wide range of health problems, such as head trauma, convulsions, arthritis, migraine, CP, cardiovascular disease, chronic pelvic inflammatory disease, functional gastrointestinal disorders such as irritable bowel syndrome, suicidality, anxiety, and depression^{21,23,24}.

Violence affects health through physical injury, health risk behaviors initiated or escalated by managing emotions, or violence-related stress²⁵, in addition to the overload of activation of the hypothalamic-pituitary-adrenal (HPA) axis from chronic stress that causes physiological reactions (e.g., inflammatory, neuroendocrine, immunological) related to the development of chronic diseases such as depression, post-traumatic stress disorder (PTSD), and CP^{26,27}. Improvement in the mental health of these women generally depends on the reduction or cessation of violence²⁸⁻³⁰, with the greatest level of improvement soon after the violence has ended³¹. However, women may not fully recover their mental health^{22,30,32,33}. In addition, the type and severity of abuse can impact these women's recovery³⁴⁻³⁶.

A longitudinal study in Canada explored over four years the changes in women's mental health after separation from an abusive partner. Results showed that women improved their quality of life after separation, but remained with high levels of depression, PTSD symptoms, and disabling CP over the four-year follow-up. More severe abuse was associated with higher depression, PTSD, and CP scores unrelated to time elapsed after separation. The type and severity of abuse had a strong effect on these health outcomes over time, suggesting the existence of cumulative effects of abuse on health, resulting in long-term problems³⁷.

The association between psychological factors, sleep, central sensitization (CS), pain, and chronic neck, back, limb, and multiregional impairment was assessed in a survey with an online questionnaire applied to 1730 adolescents. CS can be defined as a state of increased responsiveness of nociceptive neurons in CNS, leading to a reduction in the activation threshold of these cells³⁸. In addition, an amplification in pain processing due to an imbalance between inhibitory and facilitatory mechanisms may be present^{39,40}. In this study, CS symptoms increased the chances of pain in the neck, back, and different regions. Depression, anxiety, and stress, as well as lack of physical activity, increased the chances of multi-

regional pain. Fear of moving increased levels of limb pain. A worse quality of sleep was associated with neck and upper limb impairment as well as multiregional pain. Fear of moving and CS symptoms were associated with multiregional pain and impairment⁴¹.

There is substantial evidence that inadequate pain management in children is associated with neurological and behavioral problems, including increased pain sensitivity throughout life⁴². For example, children with sickle cell disease who have a high frequency of vasocclusive episodes are more likely to have a highly painful response during venipuncture⁴³. Children with cancer, sickle cell disease, and other hematologic diseases undergo routine invasive procedures over months or years, and not surprisingly, pain caused by these diagnostic or therapeutic procedures is one of the most commonly reported physical complaints of children with cancer⁴⁴.

Sedation or analgesia can be used for pain control, although the risks of sedation, including hypoxia, outweigh the benefit in routine procedures. Therefore, identifying non-pharmacological interventions for pain management, such as distraction, which shifts the focus of attention from pain to pleasurable objects, images, or videos, may reduce the risks of neurological and behavioral problems^{45,46}.

Audio guided imagery (GI) and a 3D game in which children can be active players or simply watch passively (virtual reality – VR) were compared as distraction strategies in a randomized controlled crossover clinical trial in individuals aged 8 to 25 years (n=50) with hematologic or oncologic diseases and indication for blood or marrow transplantation, not sedated, and who would undergo an invasive procedure such as venipuncture. Those who had high catastrophizing scores reported less nervousness during the procedure with VR than with GI. State anxiety decreased between pre and post-intervention in VR group. Those with high trait anxiety had less pain during GI. In other words, children who had been scarred by stories and beliefs about pain had better response to VR, while those who had high baseline anxiety levels (trait anxiety) had better response with GI. The GI started with diaphragmatic breathing exercises, while VR did not, which may have contributed more to the individuals who already had higher trait anxiety⁴⁷.

CONCLUSION

The behavior and cognitions associated with CP, especially catastrophizing, psychiatric comorbidities, obesity, as well as stress and activation of the HPA axis have substantial influence on the intensity of referred pain and especially on the degree of patient's functional disability.

No single treatment is able to modify so many variables, such as pain itself, depression, anxiety, sleep, HPA axis deactivation, CS, and appetite, as medical cannabis. There are still no studies proving that cannabis modifies cognitions associated with pain, but it is likely that it does, which tends to make it a very useful tool for the management of these patients in clinical practice.

AUTHORS' CONTRIBUTIONS

Eduardo Aliende Perin

Data Collection, Conceptualization, Project Management, Research, Methodology, Writing - Preparation of the Original, Writing - Review and Editing, Software, Supervision, Validation, Visualization

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