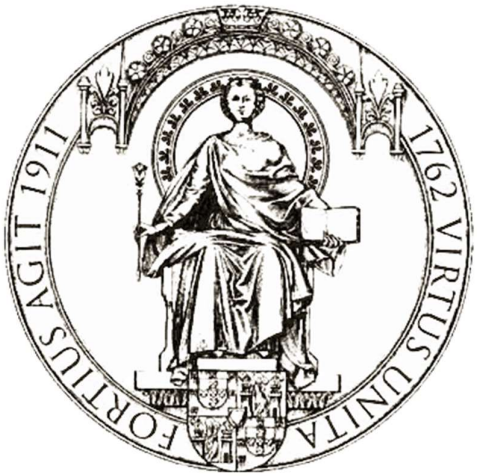
U.PORTO

FACULDADE DE MEDICINA DENTÁRIA
UNIVERSIDADE DO PORTO

Análise da medicação e possibilidade de interações medicamentosas numa amostra de doentes com dor crónica devido a disfunção temporomandibular

Analysis of medication and the possibility of drug interactions in a sample of patients with chronic pain due to temporomandibular disorders



Julio Ruiz Marrara

Maria Helena Raposo Fernandes, *orientadora*

César Bataglion, *coorientador*

Porto, 2019.

Agradecimentos

Agradeço aos meus pais, José Marrara Junior e Eliana Ruiz Marrara, os quais apoiaram-me até chegar ao final deste ciclo de estudos com seu exemplo, esforço e sacrifício.

Agradeço à minha madrinha, Tânia Ruiz, quem apadrinhou meus estudos e permitiu-me, por meio de seu sacrifício, dedicação e orientação, lograr a conquista deste título.

Agradeço à Professora Laís Valencise Magri que foi fundamental em todo o desenvolvimento deste trabalho, pelo esforço e exemplo.

Agradeço à Melissa Melchior, grande colaboradora e importante integrante nesta pesquisa.

Index

Resumo…….IV

Abstract……V

Introduction…….……. 1

Materials and Methods ……... 14

Results …… 15

Discussion …….. 18

Conclusion ……..……. 20

References…….…….. 21

Attachments …… 24

Resumo

Introdução – A dor crônica é um fator de grande impacto na qualidade de vida de um individuo, e pode ter consequencias negativas para a saude geral e para o seu bem estar social e psicologico. O processo de envolve varios mecanismos, permitindo diferentes estratégias de tratamento. O tratamento farmacológico é utilizado na maioria das situações, mas pode ser combinado com tratamentos coadjuvantes não farmacológicos.

Objetivos – Analisar eventuais relações entre o desempenho dos doentes em testes cognitivos e de variáveis de dor, presença de comorbilidades e uso de medicação.

Metodologia – A recolha de informação foi efetuada a partir de revisão bibliográfica no meio de pesquisa PubMed e dos resultados obtidos num estudo clínico em doentes com dor crónica devido a disfunção temporomandibular que foi realizado na Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo. A amostra é composta por 33 voluntários com diagnóstico de dor crónica devido a disfunção temporomandibular (*Diagnostic Criteria for Temporomandibular Disorders*), com idade entre 15 e 66 anos, sem distinção de género. A avaliação destes indivíduos incluiu os seguintes parâmetros: aplicação de questionários (sociodemográfico, Escala de Pensamentos Catastróficos sobre Dor, *Pain Vigilance and Awareness Questionnaire*, *Central Sensitization Inventory),* avaliação de variáveis de dor (intensidade, tempo de dor, presença de dor referida, presença de dor em regiões extratrigeminais, número total de sítios orofaciais com dor à palpação, catastrofização, hipervigilância à dor e sensibilização central), presença de comorbilidades, utilização de medicações e capacidades cognitivas (MoCA, Montreal Cognitive Assessment).

Resultados – Por meio de análises descritivas, observou-se nos boxplots uma tendência à valores reduzidos no teste de capacidade cognitiva e maiores resultados nos testes de catastrofização e hipervigilância nos pacientes que relatam maior sensação de dor.

Conclusão – Com esses resultados, é possível concluir que a presença de déficit leve da capacidade cognitiva observada em alguns grupos de pacientes com DTM dolorosa está provavelmente mais associada ao estímulo nociceptivo crônico e à sensibilização do sistema nervoso central, do que o uso de algum tipo específico de fármaco, como a hipótese feita inicialmente neste estudo. Além disso, os pacientes expostos a níveis mais altos de dor são mais catastróficos e hipervigilantes, ou apresentam níveis mais elevados de dor, por apresentarem um perfil mais catastrófico e hipervigilante. Assim, um estímulo nociceptivo crônico pode gerar uma sensibilização central, que poderia causar um leve déficit da capacidade cognitiva em alguns grupos de pacientes com DTM dolorosa.

Palavras chave: dor crónica, farmacologia, opioides, mindfulness, meditação capacidade cognitiva, catastrofização da dor, sensibilização central, disfunção temporomandibular.

Abstract

Introduction - Chronic pain is a major impact factor on the quality of life of an individual and can be negative consequences for a general state and for their social and psychological well-being. The process of developing several mechanisms, using different treatment strategies. Pharmacological treatment is used in most situations but can be combined with non-pharmacological treatments.

Objectives - To analyze risks between the performance of patients in cognitive and pain variables tests, the presence of comorbidities and the use of medication.

Methodology - Data collection was performed based on a bibliographical review in the middle of the research and, in part, the temporomandibular dysfunction that was installed in the Faculty of Dentistry of Ribeirão Preto, University of São Paulo. The indication is made by 33 patients with chronic pain due to temporomandibular dysfunction (diagnostic criteria for temporomandibular disorders), aged 15-66 years, without gender distinction. The assessment of data types includes the following: questionnaire applications, pain awareness and central awareness questionnaire, central sensitization inventory, assessment of pain variables, time intensity, presence of pain, presence of diseases in extratrigeminal regions , presence of the comorbidities, use of cognitive measures and capabilities (MoCA, Montreal Cognitive Assessment).

Results - Analyze descriptions, observed in the boxplots one of their reduced capacities without test of cognitive ability and results in the tests of catastrophizing and hypervigilance in the patients that relate greater amount of pain.

Conclusion – With those results, it is possible to conclude that the presence of a mild deficit of the cognitive capacity observed in some clusters of painful TMD patients is probably more associated with the chronic nociceptive stimulus and a sensibilization of the central neural system, than the use of some specific kind of drug, as hypothesized initially in this study . Also, patients exposed to higher levels of pain are more catastrophic and hypervigilant, or they have higher levels of pain because they had a more catastrophic and hypervigilant profile. So, a chronic nociceptive stimulus can generate a central sensitization, which could cause a mild deficit of the cognitive capacity in some clusters of painful TMD patients.

Key words: chronic pain, pharmacology, opioids, mindfulness, meditation, cognitive behavior, pain catastrophic, central sensibilization, temporomandibular disorders

Introduction

Definition

The International Association for the Study of Pain (IASP) defined Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.

Chronic or persistent pain had been defined by the IASP as 'pain without apparent biological value that has persisted beyond normal tissue healing time', usually a pain that lasts more than 3 months, or more the period when an acute insult would have been expected to heal.(1)

Chronic pain is one of the most prevalent health problems in the world, with millions of people debilitated by conditions such as back pain, headache and arthritis.(2) The overall prevalence of chronic pain in Europe is estimated at 18%. (1) In 2012, 25.3 million adults in the United States experienced chronic pain (3)

Chronical pain patients may describe sleep disturbance, fatigue and mood disorder, those symptoms having potential major effects on the patients quality of life through a Cycle of distress and disability, that leads to high levels of anxiety, depression, poor general physical health, social and occupational dysfunction, unemployment and family stress. Further, it can lead to significant medical, social and economic consequences, and related issues such as low productivity and large health care costs. The atual model of chronic pain is based on a biopsychosocial perspective, in

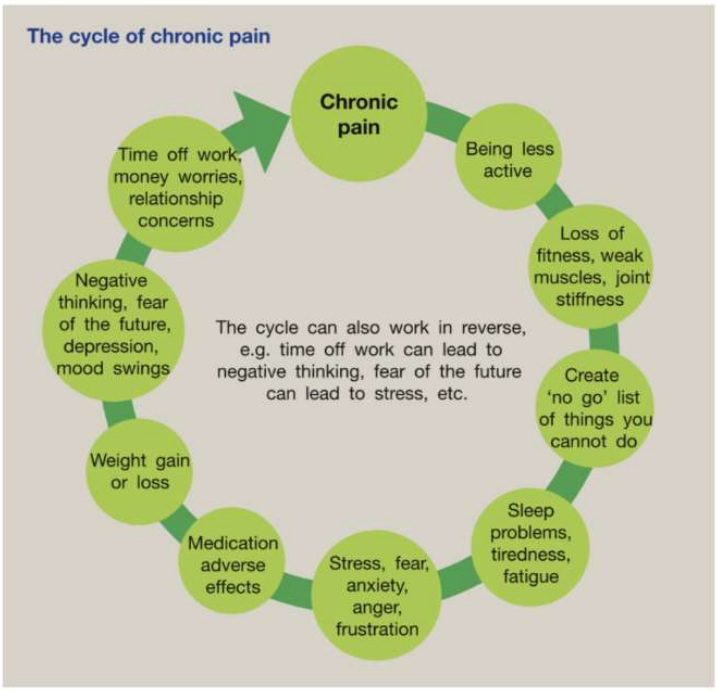


Figure 1. The cycle of chronic pain. (1)

which depression, pain related fear and catastrophising have a prominent role, Figure 1. (1,4,5)

Reported studies show that there is a close association between emotions and pain, with a variety of theories, some of those trying to describe the bidirectional associations between

increased negative emotions and increased pain, meanwile others viewing emotional distress and physical pain as two manifestations of the same fundamental mechanisms, Figure 2. (3)

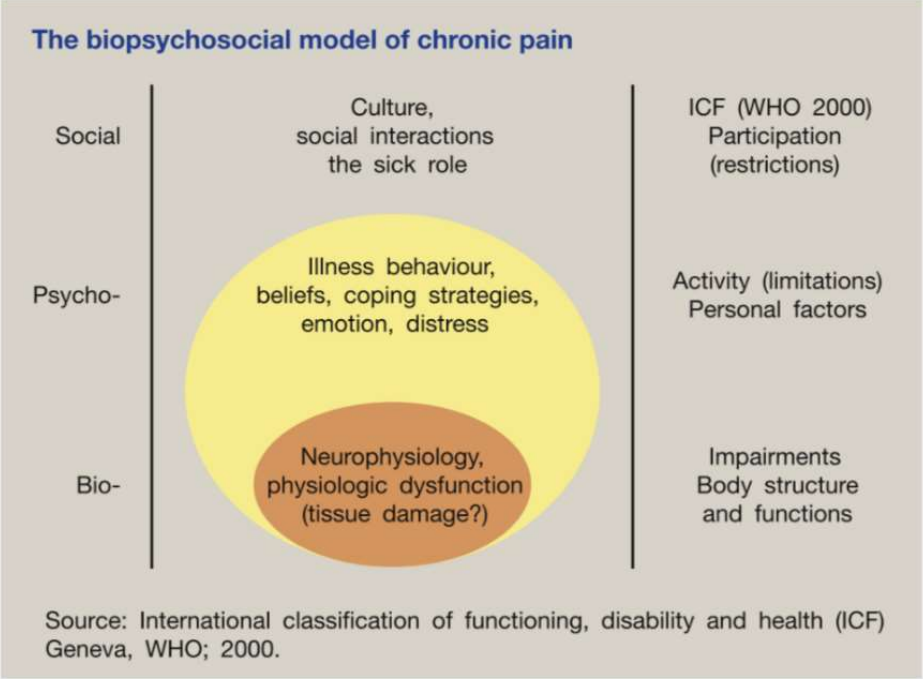


Figure 2. The biopsychosocial model of chronic pain. (1)

Moreover, depression, anxiety and stress, that caracterized Psychological distress, has been shown to mediate the association between pain severity and disability. (3)

Furthermore, some studies suggested a possible cyclical association between difficulties with emotion regulation and opioid-related outcomes, opioid misuse predicted less positive affective response to positive stimuli in an experimental heart rate variability task compared to non-misusers, this affective response pattern was asssociated with craving for opioids.(3)

Diagnosis and assessment of chronic pain

In the diagnosis of chronic pain, a detailed patient assessment is essential in order to discard any underlying medical disorder. To evaluate the functional impact of the pain several scoring systems are available, i.e. the visual analogue scale, the Brief Pain Inventory and the McGill Pain Questionnaire. Other pain evaluation tools can be also used. (1)

The features of chronic pain, i.e. its high prevalence and refractory nature, together with the deleterious consequences of medication dependence has fostered new treatment strategies which include adjunctive therapy or alternatives to pharmacologic treatment.

In spite of the limited knowledge of the mechanisms underlying chronic craniofacial pain, it is recognized from clinical and preclinical studies that alterations in afferent brain inputs, brain structure as well as modulatory pathways play a role in chronic pain(6)

Many studies have shown that the emotional state has an enormous influence on pain perception. A negative emotional state increases pain, whereas a positive state lowers pain. (2,3,7–11)

Not just emotion imparts a value system to sensory processing, but attention too, allowing the central nervous system to mold sensory experience into a subjective landscape. There is a differential pain modulation by mood and attention, with mood modifying preferentially pain unpleasantness and attention affecting mainly pain intensity. (6)

Besides the subjetivity of the pain by the individual perception and emotional-psichological interaction, there are two phisiological phenomena that need also to be considerated: Conditioned pain modulation and Central sensibilization.

Conditioned pain modulation (CPM)

Conditioned pain modulation (CPM) or Diffuse Noxious Inhibitory Controls (DNIC) is a phenomenon known as "pain inhibits pain". A variety of studies strongly suggest that CPM is reduced in patients with chronic pain, e.g., TMD, fibromyalgia and migraine. These observations show that CPM is handicapped in patients with TMD pain particularly at sites with chronic pain but not at pain-free sites; additionally, the features of the clinical pain do not affect CPM. (12)

Central sensibilization

Central sensitization is reflected as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, aftersensations, and enhanced temporal summation. Clinical cohort studies revealed changes in pain sensitivity having an important contribution of central sensitization to the pain phenotype in conditions of fibromyalgia, osteoarthritis, musculoskeletal disorders with generalized pain hypersensitivity, headache, TMD, dental pain, neuropathic pain, visceral pain hypersensitivity disorders and postsurgical pain. Advances in the genetic and environmental contributing factors and the establishment of reliable biomarkers of central sensitization will be a step forward in treatment strategies in the prevention and reduction of this as will form of pain plasticity (13). Preclinical studies on stimulus-response relations in the spinal cord revealed that the afferent activity induced by peripheral injury triggers a long-lasting increase in the excitability of spinal cord neurons, affecting significantly the gain of the somatosensory system. The observed central facilitation is reflected as a reduced threshold (allodynia), an increased responsiveness and longer aftereffects to noxious stimuli (hyperalgesia), as well as a receptive field expansion that allowed input from non-injured tissue to produce pain (secondary hyperalgesia).

These basic science studies suggest the possibility that the experimented pain might not reflect the presence of a peripheral noxious stimulus. This is of upmost relevance as central sensitization introduces another dimension, in which the CNS has the potential to change, distort or amplify pain, increasing its degree, duration, and spatial extent in a way that no longer reflects the specific features of the peripheral noxious stimuli, but instead the particular functional states of CNC circuits. In his way, conceptually, pain has become "centralized" instead of being exclusively peripherally driven. Thus, central sensitization reflects an uncoupling of the specific stimulus response relationship that defines nociceptive pain. It is now clear that a noxious stimulus while sufficient is not necessary to produce pain. Depending on the modulation of the "pain pathway", neurons might be activated by low threshold, innocuous inputs. Consequently, pain might be equivalent to an illusory perception, i.e. with the same features of that triggered by a real noxious stimulation but occurring in the absence of such a harmful stimulus. The pain is real but not triggered by a noxious stimulus. Thus, it is not a nociceptive pain but a state of induced pain hypersensitivity, presenting similar "symptom" profile to that observed in several clinical conditions.(13)

Regarding chronic craniofacial pain conditions, it involves both peripheral and central amplification of nociceptive signals which may sustain pain. Repeated episodes of pain and sustained nociceptive drive might alter the balance of central modulation favoring facilitation, also promoting amplification and contributing to sustained chronic pain.(6)

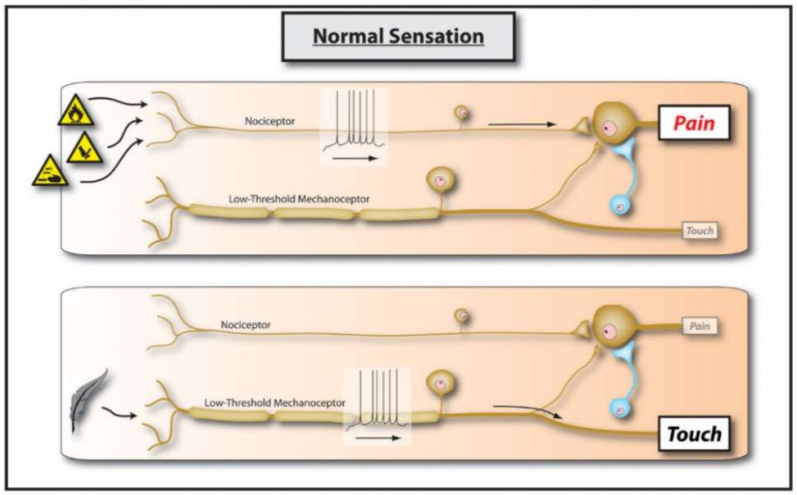


Figure 3

Normal sensation. The somatosensory system is organized such that the highly specialized primary sensory neurons that encode low intensity stimuli only activate those central pathways that lead to innocuous sensations, while high intensity stimuli that activate nociceptors only activate the central pathways that lead to pain and the two parallel pathways do not functionally intersect. This is mediated by the strong synaptic inputs between the particular sensory inputs and pathways and inhibitory neurons that focus activity to these dedicated circuits. (6)

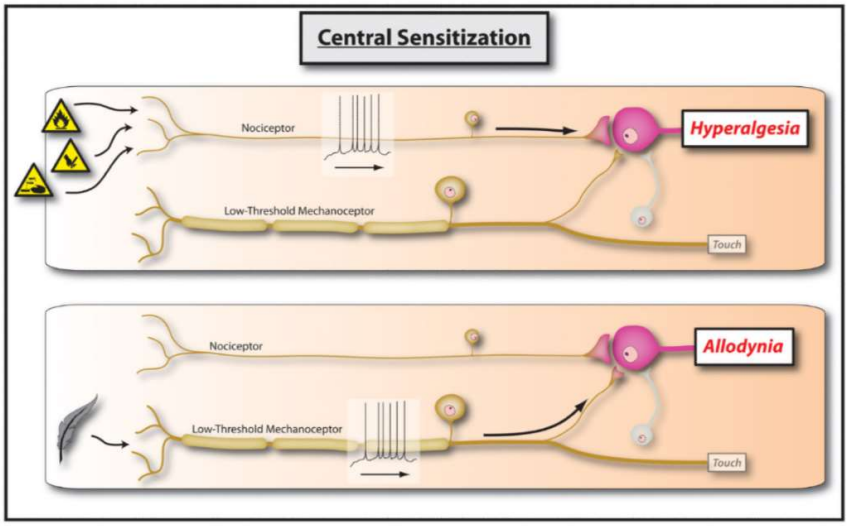


Figure 4

Central sensitization. With the induction of central sensitization in somatosensory pathways with increases in synaptic efficacy and reductions in inhibition, a central amplification occurs enhancing the pain response to noxious stimuli in amplitude, duration and spatial extent, while the strengthening of normally ineffective synapses recruits subliminal inputs such that inputs in low threshold sensory inputs can now activate the pain circuit. The two parallel sensory pathways converge. (6)

Temporomandibular disorders (TMD)

The knowledge of the mechanisms underlying chronic craniofacial pain and TMD remain limited. TMD appears to be associated with increased generalized pain sensitivity after isometric contraction of the orofacial muscles. Women suffering from myofascial TMD display widespread bilateral, mechanical and thermal pain sensitivity, compared to age matched controls, suggesting extensive central sensitization. Additionally, these patients reported increased referred pain elicited from the more frequent trigger points, compared to controls. (14)

For pain associated to periradicular inflammation (periradicular periodontitis), a major feature appears to be mechanical allodynia. Reduced threshold also occurs in contalateral non inflamed teeth, which reflects central sensibilization. (12,15)

Evidence for central sensitization might also be noticed after a third molar extraction, for at least a week. This is reflected by enhanced response to repetitive intraoral pinprick and electrical stimulation aftersensations and extraoral hyperalgesia. (12,15)

Comorbidities

In general, nociceptive pain arises from noxious stimuli, inflammatory pain is produced by tissue injury and/or immune cell activation, and neuropathic pain is associated to a nervous system lesion. Further, pain conditions are also experienced in the absence of such stimuli. A variety of syndromes presents pain hypersensitivity in the absence of noticeable etiological factors, which might effectively reflect a primary dysfunction of the nervous system. Examples include temporomandibular joint disease, tension-type headache, fibromyalgia and irritable bowel syndrome, all having central sensitization as a specific contribution. Even, it can be hypothesized that the primary defect in some of these syndromes is an enhanced capacity to produce or maintain central sensitization. (13) In this way, knowing the contribution of central sensitization to many "unexplained" clinical pain conditions provides the underlying mechanisms, assisting in the identification of therapeutic targets.

In light of this, increased co-occurrence of comorbidity is highly expected. Several studies support this view. In a study involving 4,000 twins addressing comorbidity of chronic fatigue, low back pain, irritable bowel syndrome, chronic tension type headache, temporomandibular joint disease, major depression, panic attacks and post-traumatic stress disorder, comorbidity associations exceeded those expected by chance, and the main conclusion appears to be that these conditions share a common etiology (16). Other epidemiological study on comorbidity involving 44,000 individuals (including twins) suffering from chronic widespread pain, reported co-occurrence with chronic fatigue, joint pain, depressive symptoms and irritable bowel syndrome, suggesting that associations between chronic widespread pain and its comorbidities may include genetic factors (17). Comorbidity has been reported also for back pain and temporomandibular disorders (18), and migraine and temporomandibular disorders (19).

This is a most relevant issue, as knowing and understanding comorbidity patterns would assist clinicians care for challenging patients.

The management of chronic pain

Goals

Management of chronic pain aims at controlling the pain to optimize patient function through a multidisciplinary approach. This may include a variety of pharmacological and non-pharmacological, physical, interventional and surgical approaches culminating in attendance at a functional and holistic restorative program. (1)

Like other chronic disease, patients must bear in mind that the treatment aims to control pain rather than curing. Patients need also to understand the involved biopsychosocial aspects to cope with the needed multimodal approach in the pain management control. (1)

Pain catastrophising

One important contribute to emotion dysregulatioon in pacients with chronic pain is Pain catastrophising.

The definition of Pain catastrophising is an exaggerated negative orientation toward pain stimuli and pain experience. Pain catastrophising is the most prominent predictor of social functioning, vitality, mental health and general health. (4)

Catastrophising and fear of movement appear to have a important role in the transition of acute to chronic pain. A negative correlation between pain catastrophising and the effect of a radiofrequency lesion of the dorsal root ganglion has been reported in a population with cervical brachialgia.(4) The authors hypothesised that a decrease on the level of catastrophising applying a psychological treatment approach would mediate a positive effect on the treatment outcome. (4)

Further, in this study sample, catastrophising scores were significantly higher infemales, and this might be the reason for their lower quality of life.(4)

The important role of pain catastrophising as a predictor of the psychological burden of illness may imply that an initial approach based in cognitive behavioural treatment, followed by pharmacological treatment can be more effective or even drug medication is no longer needed. It can be hypothesized that a treatment focused on decreasing the level of catastrophising, may increase the effect of medical treatment.(4)

Pharmacological approaches

Generality

Management of chronic and acute pain might involve the following drug types: opioids analgesics, nonopioid analgesics (mostly nonsteroidal anti-inflammatories, NSAIDs) antidepressants, anticonvulsants, cannabinoids, botulinum toxin, topical agents, and intrathecal drugs (20). These drugs can act directly in the pain stimuli or, indirectly, changing mood or resilience to pain.

Pharmacological therapy aims to control pain improving the patient's quality of life, while minimizing unwanted adverse effects. Current pharmacological agents provide some patients with a 50% improvement in overall pain. The classification of the pain condition and symptoms as nociceptive/inflammatory, neuropathic or a combination of these will assist in the establishment of the proper pharmacological treatment. Thus, NSAIDs are of great value in inflammatory pain, although mostly ineffective to control neuropathic pain.

In general, fixed dosing schedules or slow-release analgesic preparations are used to manage chronic pain. Non-opioids or adjuvant drugs are favored and, additionally, non-pharmacological approaches are used to manage flare-ups or incident pain (predictable activity related exacerbations). A long analgesic therapy should be based upon achieving functional

goals as well as reducing pain symptomatology. Treatment of nociceptive pain traditionally follows the World Health Organization (WHO) ladder, beginning with paracetamol, and progressing with non-steroidal anti-inflammatories and weak opioid, but neuropathic pain responds better to antidepressant and anticonvulsant drugs. Progression from weak to strong opioids (morphine, tramadol or oxycodone) often occurs. (1)

Addressing directly the noxious stimulus

- NSAIDs, opioids

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandin (PGs), affecting varying degrees of pain modulation and also anti-inflammatory effects, which are responsible for their therapeutic use. However, PGs exert a key role in a number of homeostatic events, thus its decreased synthesis is associated to a number of adverse effects.

Opioids are agonists of the opioid receptors. Stimulation of the mu opioid receptor causes analgesia, respiratory depression, sedation and constipation. Action on kappa and delta receptors also contributes to their clinical effects.

A variety of studies together to a recent meta-analysis have consistently reported that the addition of an NSAID to a pain management regimen can have an opioid-sparing effect of between 20% and 35%. (20)

The increased awareness of the undertreatment of chronic pain noticed in the last decade paralleled an increase in opioid prescribing (21). Concomitantly, the number of deaths by opioid overdose increased fourfold, as well as admissions for the treatment of opioid dependence. Further, the adverse effects associated with chronic opioid therapy include respiratory depression, constipation, impaired cognitive ability, immune suppression, opioid-related endocrinopathies, tolerance and dependence. (20)

In addition to paracetamol, NSAIDs and COX-2 inhibitors are mostly used to control moderate-severe pain states. Significant adverse effects include gastrointestinal (GI) bleeding and renal injury, and assessment of the risk / benefit ratio is needed. Even short-term use can cause fatal GI bleeding. The COX-2 inhibitors are more protective for the GI tract but appear to increase the risks of thrombus formation. In nociceptive plain, the addition a low dose of opioids is the next step, mostly buprenorphine and tramadol. This approach appears to provide some benefit in osteoarthritis, but the associated adverse effects (nausea, dizziness, constipation) may limit its utility, especially in the elderly. Long term use of these opioids is uncertain, as most of the reported studies are based on outcomes at 12 weeks. Long-term opioid therapy is frequently discontinued due to adverse effects or insufficient pain relief.

Neuropathic pain is characterized by having positive and negative sensory symptoms (Table 1). Neuropathic pain is a term used to cover a group of diseases or injuries to the peripheral or central nervous system that exhibits a degree of similarity between pain descriptors. A proper clinical and diagnostic assessment of a particular neuropathic pain condition is needed for a targeted and successful treatment. Further, a careful explanation of the condition, together with

the management of its psychological impact, is essential to maximize the effectiveness of the pharmacological therapy. Monotherapy accounts only for partial pain relief, and just in 40-60% of patients, thus the norm is the combination therapy. More effective opioids (e.g. morphine) are normally advised as second- or third-line treatment. Short-term benefits are reported by several randomized controlled clinical trials. Efficacy on long-term use lacks evidence, and the adverse effects of prolonged opioid use are substantial. (22)

- Benzodiazepines

Benzodiazepines can be useful in a variety of chronic pain settings, namely those with associated comorbid and debilitating psychiatric conditions. These include mostly anxiety disorders and panic disorder and panic attacks. Due to the long-term adverse effects of benzodiazepines, the weigh risk vs benefit of any therapy should be considered, especially when opioids are used in combination with other medications.(23)

Addressing indirectly the noxious stimulus

- Antidepressants, anticonvulsivants

Tricyclic antidepressants (TCAs, nortriptyline, amitriptyline, duloxetine) and the anticonvulsionants gabapentin and pregabalin are first-line therapies in the management of chronic pain associated to peripheral neuropathic pain. These drugs act on the central nervous system, normalizing enhanced neural activity. The efficacy of these drugs in the management of neuropathic pain emphasizes the relevance of the central component of this type of pain and, thus, a key target for its control. (13)

The gabapentinoids (gabapentin, pregabalin) have a role in the neuromodulation of the pain signal transmission and in central sensitization. These effects appear relevant and these drugs may act as opioid-sparing medication. Pregabalin is normally favored over gabapentin due its linear pharmacokinetics, allowing more predicable dosage schedules. Additionally, pregabalin has anxiolytic effects, a useful effect in this clinical setting. Most frequent adverse include somnolence, dizziness and some impact on cognition. (22) These drugs have a high safety profile and effectiveness in the control of neuropathic pain, and are considered first-line therapy by the International Association for the Study of Pain Neuropathic Pain Special Interest Group.(20)

In a similar way, tricyclic antidepressants are useful in neuropathic pain. (1) The analgesic effect occurs in small doses, lower than those used in the treatment of depression conditions and with a faster onset. In addition, changes in depression or mood state appear not to influence the analgesic effect. These drugs inhibit the reuptake of noradrenalin and serotonin, increasing the activation of descending inhibitory pathways in the midbrain and spinal cord (by decreasing

the neuronal influx of $Ca2^{+}$ or Na^{+}). TCAs appear also to interact with some receptors with a role in pain mechanisms, namely histamine, cholinergic, and N-methyl-D-aspartate receptors. More frequent adverse effects are anticholinergic effects (dry mouth), postural hypotension, sedation (this side effect is minimized by taking the drug at bedtime) and alteration in cardiac conduction. With TCAs, there is also the risk of serotonin syndrome with the concomitant use of other serotonin reuptake inhibitors. Overdose of TCAs may be fatal. (20)

- Cannabinoids

Cannabinoids act in CB1 and CB2 receptors, which have distinct locations and functions. Mostly, CB1 receptors are expressed in the brain, spinal cord and primary sensory nerve terminals, and their activation decreases pain transmission at several levels at both central and peripheral nervous system. CB2 receptors exist in microglia, monocytes, macrophages, and B/T lymphocytes, and their stimulation appears to decrease the release of inflammatory cell mediators, plasma extravasation and afferent terminal sensitization. Efficacy of cannabinoids in neuropathic pain has been shown in several placebo-controlled randomized studies. Integration of this information into medical practice is still not clear.(20)

- Botulinum toxin

Botulinum toxins, produced by the anaerobic bacterium Clostridium botulinum, act on cholinergic nerve terminals, inhibiting the presynaptic release of acetylcholine . Botulinum toxin presents few adverse effects. Nevertheless, unwanted spread of the toxin from its application site to distant parts of the body may occur, resulting in botulism-like symptoms. Most of these events occurred with the use of high-dose botulinum toxin in children with cerebral palsy-associated spasticity, but similar cases have been described in adults. (20)

- Intrathecal drug therapy

Indications for intrathecal drug delivery include (1) cancer pain in patients with life expectancy longer than 3 months and ineffective pain relief or intolerable adverse effects from systemic therapy, and (2) noncancer pain with clear evidence of pathology, and inadequate pain relief or unbearable adverse effects from systemic therapy . The most common complications result from catheter malfunction, e.g. obstruction, as is happen with catheter tip granuloma formation, or catheter fracture.(20)

- Surgical and interventional management

Interventional strategies are useful in certain conditions. (1) Under image guidance, epidural injections of corticosteroids are effective for radicular pain secondary to nerve injury in some situations. Interventional therapy is also often used in trigeminal neuralgia in several approaches, i.e. Gasserian gangliolysis via thermal (radiofrequency), osmotic (glycerol injection) or mechanical compression (balloon catheter) therapy under fluoroscopy. Craniotomy to achieve microvascular decompression may decrease pain in conditions of arterial or venous compression of the trigeminal nerve. Radiotherapy has also been tested (in the form of gamma knife therapy). Further, injection of local anaesthetics (under image guidance) may be used by diagnostic means in some musculoskeletal pain situations, e.g. facet joint syndrome. (20)

Non-pharmacologic treatments

Generality

A growing interest has been directed to mind-body oriented therapies (2). Meditation, yoga and cognitive behavioral therapy is gaining an increased role in pain control.

Pain is a complex experience with interrelated sensory and emotional events and, as such, presents a wide inter-individual variability and also varies within the same individual depending on the context and meaning of objective and subjective settings. (2). Pain perception is greatly affected by cognitive and emotional factors. Negative expectations have clear deleterious effects in pain control. On the other hand, positive expectations greatly contribute to pain relief through a placebo effect. (2)

A myriad of processes affect the activity of afferent pain pathways, which include the attentional state, positive and negative emotions, empathy and placebo administration. Also, psychological factors activate intrinsic modulatory systems in the brain, namely those involved in the opioid pain control. To further complicate this scenario, chronic pain also affects these pathways, reflected by anatomical and functional alterations, which may result in pain worsening and an altered cognition. (2)

Physical therapy

A combination physical approach of physiotherapy, pilates, massage and appropriate exercise programs are useful in managing nociceptive chronic musculoskeletal pain, particularly in the context of setting goals. (1)

Meditation and Mindfulness

There is evidence that approaches as meditation contribute to decrease pain and further have powerful protective effects on brain grey matter and connectivity within pain modulatory circuits (2,24–28)

Mindfulness meditation appears to have positive effects in cognitive control and emotion regulation. Endogenous opioid pathways appear to mediate the analgesic effect and also the growing resilience to external suggestion with increasing practice. It has been reported that pain and unpleasantness scores were greatly reduced after natural mindfulness meditation and after placebo, but this was not observed after naloxone administration. Additionally, the same study showed a positive correlation between the pain scores following naloxone vs placebo and participants' mindfulness meditation experience. Thus, investing in a long-term practice of meditation in chronic pain patients may have potential therapeutic effects. (29)

Mindfulness meditation is believed to readjust the mind in the present and increase awareness of the external environment and internal sensations, allowing the individual to step back and reshape the experiences. This is achieved by paying attention to the present moment with openness, curiosity and acceptance.

Clinical benefits of mindfulness have been described in several settings including substance abuse tobacco cessation, stress reduction, and chronic pain. Controlled trials in pain patients suggest positive outcomes on pain symptoms, pain acceptance, mood disturbance, anxiety, depression pain-related drug use, quality of life, and functional status. (5)

Acupuncture - Stimulatory analgesia

The use of the neuromodulation in the control of chronic pain has its support in the gate theory of pain signal transmission (Figure 5).3 This can take a simple form, like acupuncture. Trans-cutaneous electrical nerve stimulation (TENS) may activate the gate in a similar manner. (1)

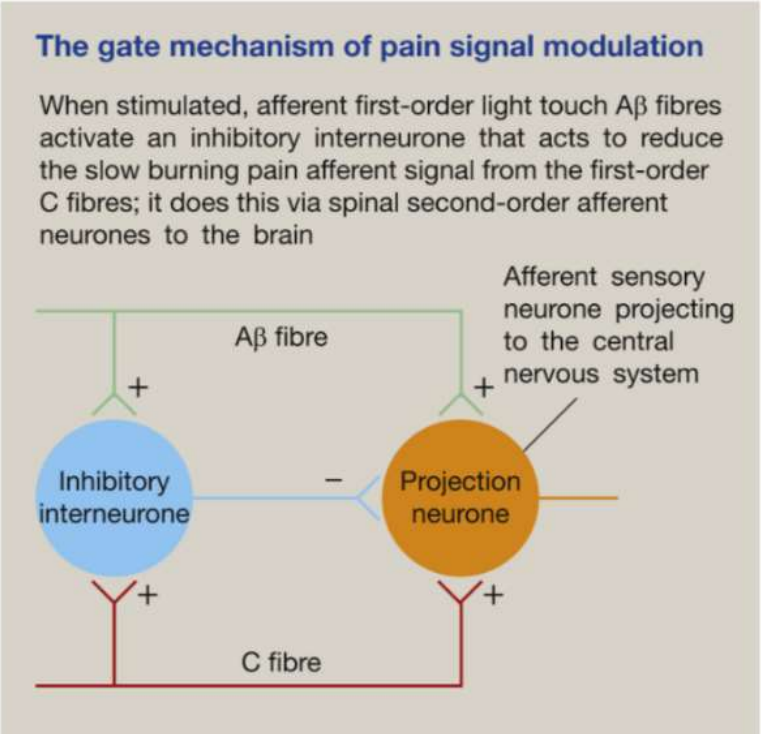


Figure 4 Stimulatory analgesia (1)

Low-Level Laser Therapy

There are many studies reporting the use of the low-level laser therapy (LLLT) as a therapeutic option for the painful TMD treatment. When compared with a placebo laser treatment, the active LLLT maintain analgesia longer than placebo (follow-up 30 days). LLLT placebo has also been shown to be effective in pain management in patients with painful TMD, with improvement results similar to active LLLT, although it is important to consider that in LLLT the placebo is amplified compared to other therapies because it is technological equipment with high publicity in the health area. (30,31)

Studies in animal models have demonstrated that laser light is able to reduce proinflammatory substances in the TMJ of rats with persistent inflammation. The analgesic effects of LLLT are associated with different endogenous mechanisms, such as the release of opioids; increase in ATP production; reduction in the production of prostaglandins, mainly COX-2; a decrease in lymphocyte metabolism and secretion of histamine, kinins, and cytokines. In addition to the release of endorphins and enkephalins, these neurotransmitters are released with LLLT, leading to the modulation of nociceptors and the modification of the conduction of nerve impulses and membrane permeability of the neurons. (30,31)

Materials and methods

The information was collected from the results obtained in a clinical study in patients with chronic pain due to the temporomandibular dysfunction that is being performed at the Faculty of Dentistry of Ribeirão Preto, University of São Paulo, and whose objective is to analyze possible relationships between the performance of patients in cognitive tests and oral stereognosis and pain variables, the presence of comorbidities and the use of medication. The sample consisted of 33 volunteers diagnosed with chronic pain due to temporomandibular disorders (Diagnostic Criteria for Temporomandibular Disorders) between 15 and 66 years of age, regardless of gender. The evaluation of these individuals includes the following parameters: questionnaires (sociodemographic, PCS - Pain Catastrophic Scale, PVAQ - Pain Vigilance and Awareness Questionnaire and CSI - Central Sensitization Inventory), evaluation of pain variables (intensity, duration of pain, presence of referred pain, presence of pain in extratrigeminal regions, total number of orofacial sites with pain to palpation, catastrophic, hypervigilance to pain and central sensitization), presence of comorbidities, use of medications, evaluation of oral stereognosis and cognitive abilities (MoCA - Montreal Cognitive Assessment). This study is approved by the Ethics Committee of the School of Dentistry of Ribeirão Preto, University of São Paulo (attached document).

Results

The group of 32 females with painful TMD, with ages ranging from 15 to 66 years, was analyzed in the School of Dentistry of Ribeirão Preto, University of São Paulo, . The following protocols were applied: MOCA, PVAQ, CSI and PCS to assess the cognitive capacities, hypervigilance, central sensibilization and pain catastrophizing evaluation respectively.

Using the IBM SPSS Statistics 25, through descriptive analysis and analysis of boxsplots, no straight connection was observed between the administration of drugs that act in the Central Nervous System and the deficit of the cognitive capacities or some increase in the hypervigilance, central sensibilization and pain catastrophizing (Boxsplots I, II, III and IV).

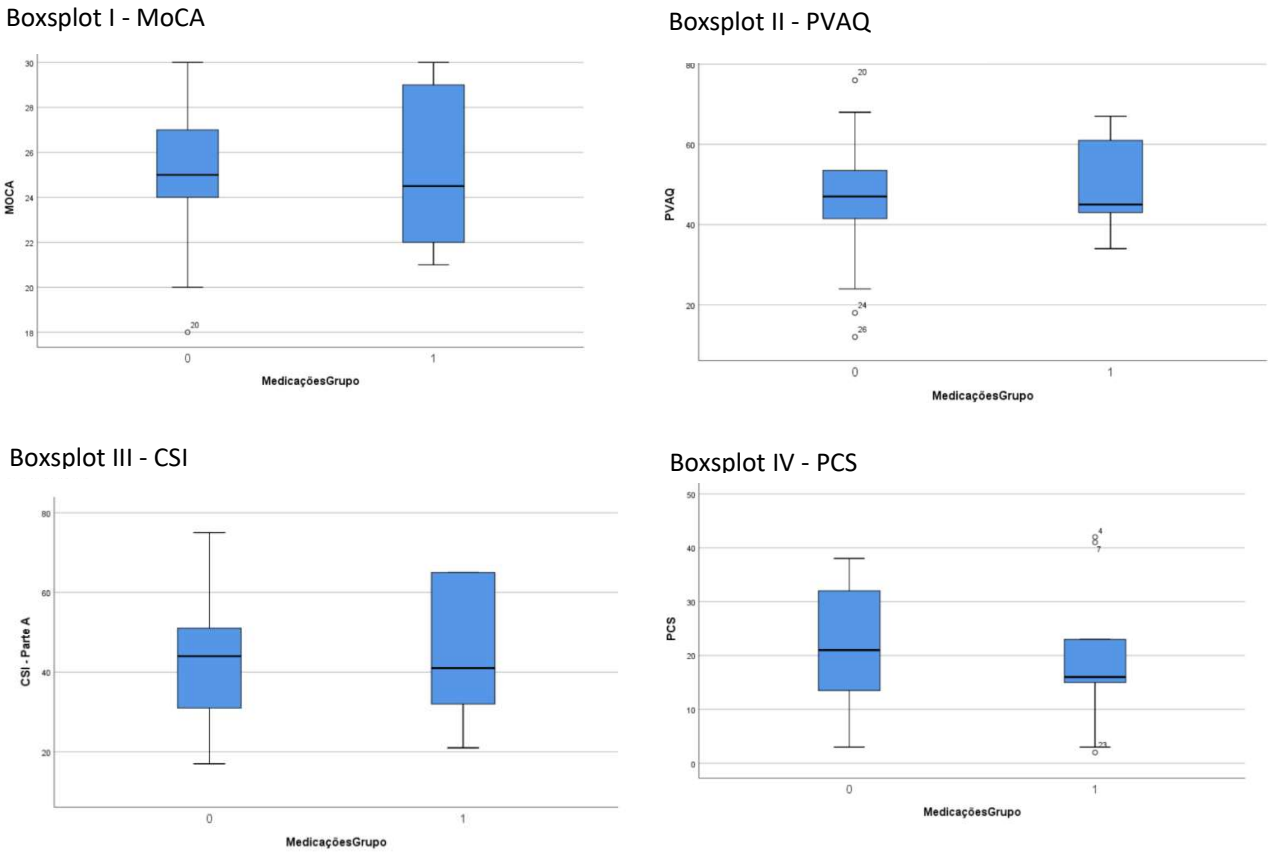


*Figure 5. Central drug administration and MoCA (Montreal Cognitive Assessment),PVAQ (Pain Vigilance and Awareness Questionnaire), CSI (Central Sensibilization Inventory) and PCS (*Pain *Catastrophizing Scale). In the Boxsplots I, II, III and IV: 1 represents the group of patients that uses drugs with action in the Central Nervous System, and 0 those who use other drug groups or are not treated with any drug medication.*

However, it was found a considerable tendency in the results of the protocols influenced by the presence of headache and/or migraine. Patients with those painful comorbidities had worst results in the MOCA scores, indicating a possibility of a mild deficit of the cognitive capacity, and high scores in PVAQ, CSI and PCS, that point to a high level of hypervigilance, central sensibilization and pain catastrophizing respectively. (Boxsplots V,VI, VII, VIII)

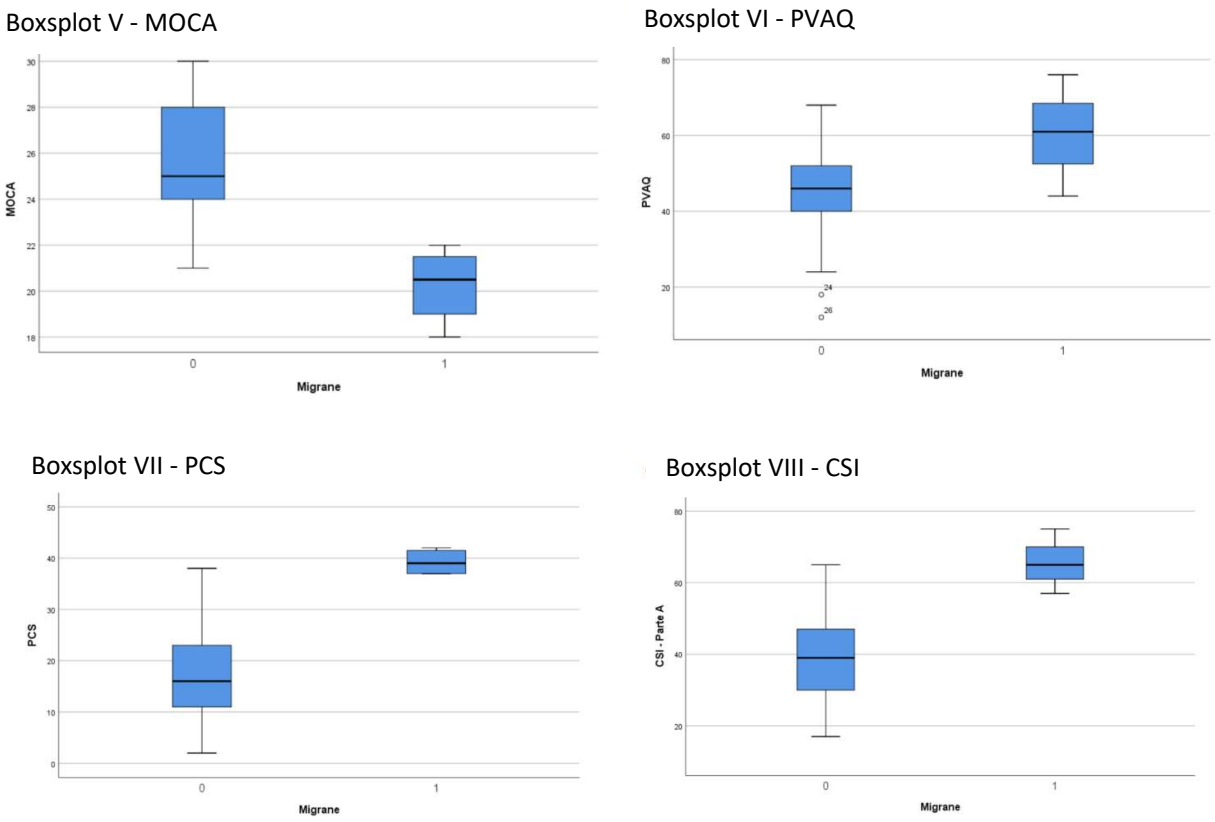
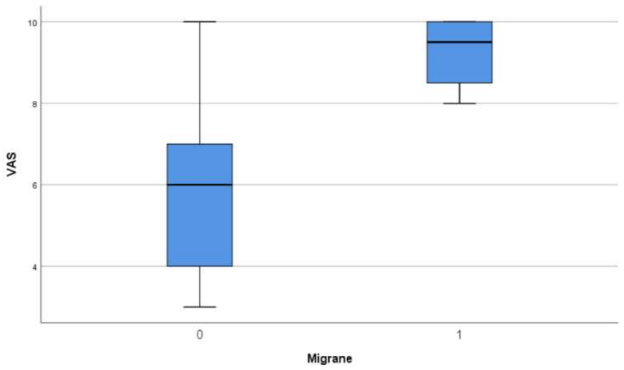


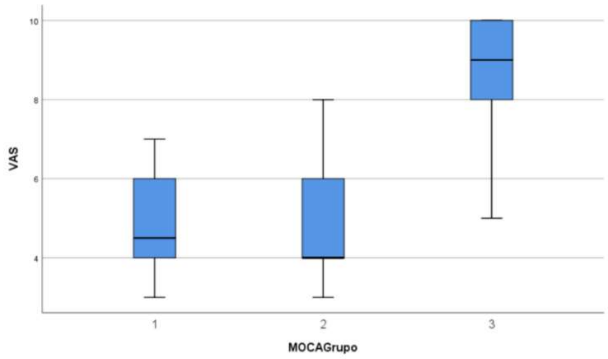
Figure 6 - In the Boxsplot V, VI, VII and VIII: 1 represents the group of patients that report Migraine and/or Headache as comorbidities, and 0 those who do not.

Further, in the Visual Analogue Scale (VAS, pain intensity), it was observed that patients who had the decreased scores in MOCA (under 22 points) and patients who had headache and/or migraine as comorbidities had the highest score in VAS (higher pain perceived pain intensity). Also, there is a tendency to increase the score in PVAQ and PCS the higher the VAS score in the studied sample. (Boxsplot IX, X, XI, XII)



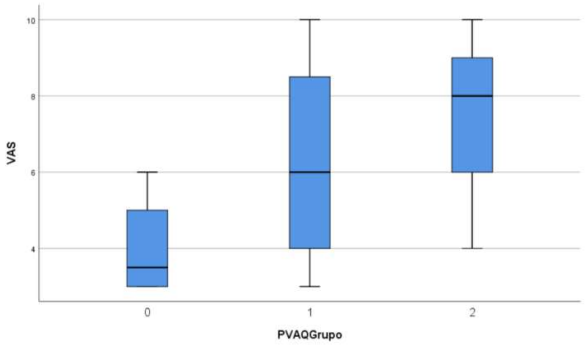
Boxsplot IX

Patient with migraine and/or headache present a strong tendency to to have higher scores in VAS. Group of patients that report Migraine and/or Headache as comorbidities (1), and those who do not report (0).



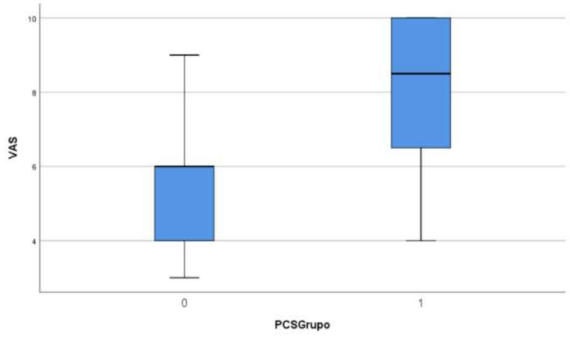
Boxsplot X – Patients were classified by the MOCA score, 26 or more (1), from 23 to 25 (2) and 22 or less (3).

Patient with lower MOCA score present a strong tendency to to have higher scores in VAS



Boxsplot XI - Patients were classified by the PVAQ score, until 40 (0), from 41 to 55 (1) and 56 or more (2).

Patient with higher PVAQ score present a strong tendency to to have higher scores in VAS



Boxsplot XII- Patients were classified by the PCS score, until 40 (0), from 41 or more (1).

Patient with higher PCS score present a strong tendency to to have higher scores in VAS

Discussion

These results suggest a straight relation between the personal perception of pain, through the VAS examination, and this tendency is related to higher scores in emotionally shocked patients. The higher score in the VAS examination influence the cognitive capacities of the patients.

Pain catastrophic, hypervigilance and, even the personal perception of the pain, are related to the emotional state of the patient.

Difficulties with emotion control have been shown to be associated with pain complaints. There are diferent strategies to regulate the emotions. Those strategies can be classified as

- adaptive (e.g., nonjudgment of emotions, reappraisal, acceptance) and
- maladaptive (e.g., expressive suppression, experiential avoidance, rumination) emotion regulation strategies.

Generaly, the maladaptive strategy of avoidance is related to substance abuse. Poor emotion regulation may confer greater risk of opioid medication misuse among chronic pain patients.(3)

Acording to Lutz et al. 2018 "This increased risk would be consistent with more general theories of substance abuse, such as the self-medication hypothesis, which posits that individuals abuse substances as a way to cope with negative psychological states in the face of impairment in regulating those negative emotions." Response that can become dangerous if applied to chronic pain and opioids use. (3)

Substance abuse is a form of avoidance and it allows individuals to fairly immediately change their affective and physiological states without addressing the specific issues. (3)

Fear-avoidance models assume that pain catastrophising promotes fear of movement and/or (re)injury, it leads to avoidance behaviour, disuse, disability and depression. (4)

The emotion dysregulation associated with chronic pain can contribute to the maladaptive response of avoidance, which provides additional negative affect cues associated with negative reinforcement, for example, any kind of discomfort or pain becomes a cue to use opioids. (3)

That maladaptive response can produce a physical dependence with opioid medication that can occur after a small number of uses. The chronic use can result in hyperalgesia.(3)

A most revelant aspect is that some studies strongly suggest that emotion dysregulation might be associated with a higher risk of opioid misuse, but the reverse also occurs, i.e. opioid misuse would difficult emotion control. (3)

However, there is some evidence pointing that the body can adapt to stress or a stress environment trying to keep the balance. Psychological stress and stress-produced hormones affect the immune system and, conversely, a poor immune status influence CNS structure and function via humoral and cellular pathways. Homeostasis is achieved by these bidirectional neuroimmune pathways. Sustained or severe disruption of this equilibrium results in disease. Scant attention has been paid to the role played by the adaptive component in responding to and affecting mood states. It is known that chronic psychological stress affects lymphocyte numbers and function via sympathetic and steroid hormone effector pathways. Studies in mice

showed that psychological stress primes the adaptive immune system to confer stress resiliency to naive mice when it receives blood from a mice exposed to psychological stress.(12) That adaptation could explain the human immunological system adaptation to stress. However, human emotions and how they influence the CNS, the immunological system and the neuronal stimuli are not clearly understood.

For those reasons it is important to use non-invasive and non-pharmacological complementary techniques and treatments, such as LLLT, acupuncture, physical therapy, meditation and Mindfulness. These treatments have shown very positive results in the management of pain, not only in the clinic, but also in the academic areas.

Thus, these treatments for the management of emotions should be more explored, studied and practiced and, also, more studies should be carried out from a broader perspective analyzing the individual as a bio-psychic organism and all the consequences of it.

Conclusion

With those results, it is possible to conclude that the presence of a mild deficit of the cognitive capacity observed in some clusters of painful TMD patients is probably more associated with the chronic nociceptive stimulus and a sensibilization of the central neural system, than the use of some specific kind of drug, as hypothesized initially in this study . Also, patients exposed to higher levels of pain are more catastrophic and hypervigilant, or they have higher levels of pain because they had a more catastrophic and hypervigilant profile. So, a chronic nociceptive stimulus can generate a central sensitization, which could cause a mild deficit of the cognitive capacity in some clusters of painful TMD patients.

References

1. Blackburn JP. The diagnosis and management of chronic pain. Med (United Kingdom) [Internet]. 46(12):786–91. Available from: https://doi.org/10.1016/j.mpmed.2018.09.001

2. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci. 2013;14(7):502–11.

3. Lutz J, Gross RT, Vargovich AM. Difficulties in emotion regulation and chronic pain-related disability and opioid misuse. Addict Behav [Internet]. 87(July):200–5. Available from: https://doi.org/10.1016/j.addbeh.2018.07.018

4. Lamé IE, Peters ML, Vlaeyen JWS, Kleef M V., Patijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. Eur J Pain. 2005;9(1):15–24.

5. Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, et al. Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. Ann Behav Med. 2017;51(2):199–213.

6. Chichorro JG, Porreca F, Sessle B. Mechanisms of craniofacial pain. Cephalalgia. 2017;37(7):613–26.

7. Villemure C, Bushnell MC. Mood Influences Supraspinal Pain Processing Separately from Attention. J Neurosci. 2009;29(3):705–15.

8. Young KS, van der Velden AM, Craske MG, Pallesen KJ, Fjorback L, Roepstorff A, et al. The impact of mindfulness-based interventions on brain activity: A systematic review of functional magnetic resonance imaging studies. Neurosci Biobehav Rev. 2018;84(February 2017):424–33.

9. C. H. Mind-body therapies use in chronic pain management. Aust Fam Physician. 2013;

10. Harrison R, Zeidan F, Kitsaras G, Ozcelik D, Salomons T V. Trait Mindfulness Is Associated With Lower Pain Reactivity and Connectivity of the Default Mode Network. J Pain [Internet]. 00(00). Available from: https://doi.org/10.1016/j.jpain.2018.10.011

11. Greeson J, Eisenlohr-Moul T. Mindfulness-Based Stress Reduction for Chronic Pain [Internet]. Second Edi. Mindfulness-Based Treatment Approaches. Elsevier Inc.; 2014. 269–292 p. Available from: http://dx.doi.org/10.1016/B978-0-12-416031-6.00012-8

12. Oono Y, Wang K, Baad-Hansen L, Futarmal S, Kohase H, Svensson P, et al. Conditioned pain modulation in temporomandibular disorders (TMD) pain patients. Exp Brain Res. 2014;232(10):3111–9.

13. Clifford JW. Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2012;152:1–31.

14. Karina do Monte-Silva K, Schestatsky P, Bonilla P, Caparelli-Daquer E, Hazime FA, Chipchase LS, et al. Latin American and Caribbean consensus on noninvasive central nervous system neuromodulation for chronic pain management (LAC2-NIN-CP). PAIN Reports. 2019;4(1):e692.

15. Campi LB, Jordani PC, Tenan HL, Camparis CM, Gonçalves DAG. Painful temporomandibular disorders and central sensitization: implications for management—a pilot study. Int J Oral Maxillofac Surg. 2017;46(1):104–10.

16. Schur EA, Afari N, Furberg H, Olarte M, Goldberg J, Sullivan PF, et al. Feeling bad in more ways than one: Comorbidity patterns of medically unexplained and psychiatric conditions. J Gen Intern Med. 2007;22(6):818–21.

17. Kato K, Sullivan PF, Evengård B, Pedersen NL. Chronic Widespread Pain and Its Comorbidities. Arch Intern Med. 2006;166(15):1649.

18. Wiesinger B, Malker H, Englund E, Wänman A. Back pain in relation to musculoskeletal disorders in the jaw-face: A matched case-control study. Pain. 2007;131(3):311–9.

19. Gonçalves DAG, Bigal ME, Jales LCF, Camparis CM, Speciali JG. Headache and Symptoms of Temporomandibular Disorder: An Epidemiological Study. Headache J Head Face Pain. 2009;50(2):231–41.

20. Beal BR, Wallace MS. An Overview of Pharmacologic Management of Chronic Pain. Med Clin North Am [Internet]. 2016;100(1):65–79. Available from: http://dx.doi.org/10.1016/j.mcna.2015.08.006

21. Brachman RA, Lehmann ML, Maric D, Herkenham M. Lymphocytes from Chronically Stressed Mice Confer Antidepressant-Like Effects to Naive Mice. J Neurosci. 2015;35(4):1530–8.

22. Gronow D. The place of pharmacological treatment in chronic pain. Anaesth Intensive Care Med [Internet]. 14(12):528–32. Available from: http://dx.doi.org/10.1016/j.mpaic.2010.10.015

23. Cheatle MD, Shmuts R. The Risk and Benefit of Benzodiazepine Use in Patients with Chronic Pain. Pain Med (United States). 2015;16(2):219–21.

24. Hölzel BK, Carmodyc J, Vangel M, Congletona C, Yerramsettia SM, Gard T, et al. Meditation pratice leads to increases in regional brain gray matter density. Psychiatry Res. 2012;191(1):36–43.

25. Grant JA, Courtemanche J, Duerden EG, Duncan GH, Rainville P. Cortical Thickness and Pain Sensitivity in Zen Meditators. Emotion. 2010;10(1):43–53.

26. Mackey AP, Whitaker KJ, Bunge SA. Experience-dependent plasticity in white matter microstructure: reasoning training alters structural connectivity. Front Neuroanat. 2012;6(August):1–9.

27. Lutz A, Mcfarlin DR, Perlman DM, Salomons T V, Davidson RJ. Experience of painful stimuli in expert meditators. Neuroimage. 2013;64:538–46.

28. Lazar SW, Yerramsetti SM, Congleton C, Gard T, Hölzel BK, Vangel M, et al. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res Neuroimaging [Internet]. 2010;191(1):36–43. Available from: http://dx.doi.org/10.1016/j.pscychresns.2010.08.006

29. Sharon H, Maron-Katz A, Ben Simon E, Flusser Y, Hendler T, Tarrasch R, et al. Mindfulness Meditation Modulates Pain Through Endogenous Opioids. Am J Med [Internet]. 2016;129(7):755–8. Available from:

http://dx.doi.org/10.1016/j.amjmed.2016.03.002

30. Magri LV, Carvalho VA, Rodrigues FCC, Bataglion C, Leite-Panissi CRA. Non-specific effects and clusters of women with painful TMD responders and non-responders to LLLT: double-blind randomized clinical trial. Lasers Med Sci. 2018;33(2):385–92.

31. Magri LV, Carvalho VA, Rodrigues FCC, Bataglion C, Leite-Panissi CRA. Effectiveness of low-level laser therapy on pain intensity, pressure pain threshold, and SF-MPQ indexes of women with myofascial pain. Lasers Med Sci [Internet]. 2017;32(2):419–28. Available from: http://dx.doi.org/10.1007/s10103-016-2138-x

Attachments

Attachment 01 – Declaração de autoria do trabalho apresentado

Attachment 02 – Parecer da Orientadora para entrega definitiva do trabalho

Attachment 03– Parecer do Coorientador para entrega definitiva do trabalho

Attachment 04– Aprovação na Comissão de Ética

U.PORTO

FACULDADE DE MEDICINA DENTÁRIA
UNIVERSIDADE DO PORTO

DECLARAÇÃO

Monografia de Investigação

Declaro que o presente trabalho, no âmbito de Monografia de Investigação, integrado no Mestrado Integrado em Medicina Dentária, da Faculdade de Medicina Dentária da Universidade do Porto, é da minha autoria e todas as fontes foram devidamente referenciadas.

Porto, 23 de maio de 2019.

(Júlio Ruiz Marrara)

U.PORTO
FACULDADE DE MEDICINA DENTÁRIA
UNIVERSIDADE DO PORTO

PARECER

Orientador

Informo que o Trabalho de Monografia desenvolvido pelo estudante Julio Ruiz Marrara com o título "Analysis of medication and the possibility of drug interactions in a sample of patients with chronic pain due to temporomandibular dysfunction."

Está de acordo com as regras estipuladas na Faculdade de Medicina Dentária da Universidade do Porto, foi por mim conferido e encontra-se em condições de ser apresentado em provas públicas.

Porto, 23 de maio de 2019.

Maria Helena R. Fernandes

(Maria Helena Raposo Fernandes)

U.PORTO

FACULDADE DE MEDICINA DENTÁRIA
UNIVERSIDADE DO PORTO

PARECER

Coorientador

Informo que o Trabalho de Monografia desenvolvido pelo estudante Julio Ruiz Marrara com o título "Analysis of medication and the possibility of drug interactions in a sample of patients with chronic pain due to temporomandibular dysfunction."

Está de acordo com as regras estipuladas na Faculdade de Medicina Dentária da Universidade do Porto, foi por mim conferido e encontra-se em condições de ser apresentado em provas públicas.

Ribeirão Preto, 23 de maio de 2019.

(Cesar Bataglion)

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: DESEMPENHO EM TESTES COGNITIVOS E DE ESTEREOGNOSIA ORAL DE SUJEITOS COM DTM DOLOROSA CRÔNICA EM FUNÇÃO DE VARIÁVEIS DE DOR, PRESENÇA DE COMORBIDADES E USO DE MEDICAÇÕES.

Pesquisador: Laís Valencise Magri

Área Temática:

Versão: 1

CAAE: 03383218.7.0000.5419

Instituição Proponente: Universidade de Sao Paulo

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.091.541

Apresentação do Projeto:

Estudos recentes demonstraram prejuízos no desempenho em testes cognitivos de pacientes com dor crônica, uma vez que o

funcionamento do cérebro é alterado na permanência de estímulos nociceptivos. Objetivo: Analisar a estereognosia oral e habilidades cognitivas de sujeitos com DTM dolorosa crônica em comparação à sujeitos controles, a fim de verificar se há prejuízos destes aspectos em função de variáveis de dor, presença de comorbidades e utilização de medicações para manejo de dor crônica.

Objetivo da Pesquisa:

Este projeto terá como objetivo analisar a estereognosia oral e habilidades cognitivas de sujeitos com DTM dolorosa crônica em comparação à

sujeitos controles, a fim de verificar se há prejuízos destes aspectos em função de variáveis de dor (intensidade, tempo de dor, presença de dor

referida, presença de dor em regiões extratrigeminais, número total de sítios orofaciais com dolorimento à palpação, catastrofização, hipervigilância à dor e sensibilização central), presença de comorbidades e utilização de medicações para manejo de dor

crônica.

Endereço: Avenida do Café s/nº
Bairro: Monte Alegre **CEP:** 14.040-904
UF: SP **Município:** RIBEIRAO PRETO
Telefone: (16)3315-0493 **Fax:** (16)3315-4102 **E-mail:** cep@forp.usp.br

Avaliação dos Riscos e Benefícios:

Riscos:

O risco durante o processo de coleta pode ser associado a possibilidade do sujeito engasgar com as balas que serão oferecidas, o que será minimizado ao se questionar os sujeitos quanto ao histórico de engasgos frequentes e dificuldades de deglutição (disfagia) sendo este um dos critérios de exclusão dos sujeitos da pesquisa, além de orientá-los quanto à atenção e cuidado ao explorar as balas dentro da boca.

Benefícios:

O desenvolvimento deste projeto permitirá o conhecimento sobre a capacidade de sujeitos com DTM em reconhecer as características do que se tem dentro da boca (estereognosia) e se esta capacidade pode estar relacionada a diferentes características estruturais e psicossociais, como intensidade e tempo de dor, número de sítios de dor, presença de dor referida, uso de próteses, perdas dentárias, entre outros, o que contribuirá

com o entendimento sobre as necessidades específicas de reabilitação funcional do sistema estomatognático em diferentes situações.

Comentários e Considerações sobre a Pesquisa:

O projeto está corretamente enquadrado na área temática e a metodologia proposta é adequada. Os antecedentes científicos justificam a execução da mesma. Possui cronograma de execução detalhado, todos os documentos estão anexados, o TCLE está claro e correto. A temática proposta é original e importante para a área da saúde humana. O projeto está bem estruturado, com revisão bibliográfica adequada, pertinente ao tema e atualizada. Os pesquisadores apresentam formação acadêmica adequada para desenvolver o projeto.

Considerações sobre os Termos de apresentação obrigatória:

Adequados.

Recomendações:

Aprovado.

Conclusões ou Pendências e Lista de Inadequações:

Projeto de pesquisa aprovado.

Considerações Finais a critério do CEP:

Projeto aprovado conforme deliberado na 222ª Reunião Ordinária do CEP/FORP de 17/12/2018.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1260359.pdf	20/11/2018 19:35:05		Aceito
Outros	declaracao_participacao.pdf	20/11/2018 19:34:39	Laís Valencise Magri	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	tcle.pdf	20/11/2018 19:33:51	Laís Valencise Magri	Aceito
Declaração de Instituição e Infraestrutura	infraestrutura.pdf	20/11/2018 19:33:27	Laís Valencise Magri	Aceito
Folha de Rosto	folha_de_rosto.pdf	20/11/2018 19:32:25	Laís Valencise Magri	Aceito
Outros	DCTMD_parte2.pdf	19/11/2018 15:32:05	Laís Valencise Magri	Aceito
Outros	DCTMD_parte1.pdf	19/11/2018 15:31:45	Laís Valencise Magri	Aceito
Outros	PVAQ.docx	19/11/2018 15:29:17	Laís Valencise Magri	Aceito
Outros	MOCA.pdf	19/11/2018 14:59:37	Laís Valencise Magri	Aceito
Outros	EPCD.pdf	19/11/2018 14:58:52	Laís Valencise Magri	Aceito
Outros	CSI_Brazilian_Portuguese.pdf	19/11/2018 14:55:18	Laís Valencise Magri	Aceito
Projeto Detalhado / Brochura Investigador	projeto.docx	19/11/2018 14:54:34	Laís Valencise Magri	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

RIBEIRAO PRETO, 18 de Dezembro de 2018

Assinado por:
Simone Cecilio Hallak Regalo
(Coordenador(a))

Endereço: Avenida do Café s/nº
Bairro: Monte Alegre **CEP:** 14.040-904
UF: SP **Município:** RIBEIRAO PRETO
Telefone: (16)3315-0493 **Fax:** (16)3315-4102 **E-mail:** cep@forp.usp.br