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Topical Capsaicin in Peripheral Neuropathic Pain: Efficacy and Quality of Life

Márcia Ribeiro Valentão Pitrez Santos

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Topical Capsaicin in Peripheral Neuropathic Pain: Efficacy and Quality of Life

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Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Márcia Ribeiro Valentão Pitrez Santos

Aluna do 6º ano profissionalizante de Mestrado Integrado em Medicina

Afiliação: Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço: Rua de Jorge Viterbo Ferreira, n.º 228, 4050-313 Porto

Endereço eletrónico: marciapitrez@gmail.com

Orientador: Professora Doutora Dalila Maria Rodrigues Gonçalves Veiga Mora

Assistente hospitalar de Anestesiologia do Centro Hospitalar Universitário de Santo António

Professora Auxiliar Convidada do Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto

Afiliação: Serviço de Anestesiologia do Centro Hospitalar Universitário de Santo António

Endereço: Largo Prof. Abel Salazar, 4099-001 Porto

Coorientador: Professor Dr. José Manuel Romão

Assistente hospitalar graduado sénior de Anestesiologia do Centro Hospitalar Universitário de Santo António

Professor Associado Convidado do Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto

Afiliação: Serviço de Anestesiologia do Centro Hospitalar Universitário de Santo António e Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço: Largo Prof. Abel Salazar, 4099-001 Porto

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Assinado por: **Márcia Ribeiro Valentão Pitrez Santos**
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Márcia Pitrez Santos

Professora Doutora Dalila Veiga

Professor Dr. José Romão

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Resumo

Introdução: A dor neuropática periférica (DNP) é uma patologia desafiante de tratar com um impacto significativo na qualidade de vida dos doentes. O tratamento tópico com o adesivo de capsaicina 8% tem se revelado nas últimas décadas uma alternativa aos fármacos de administração oral no tratamento da DNP apresentando menos efeitos secundários e eficácia promissora.

Objetivos: Avaliar a eficácia da aplicação tópica de capsaicina em doentes com DNP e o seu impacto na qualidade de vida com base no uso de capsaicina no Centro Hospitalar e Universitário de Santo António (CHUdSA).

Métodos: O estudo incluiu 100 doentes com DNP localizada de mau controlo analgésico e sem melhorias com tratamentos prévios que realizaram pelo menos 1 tratamento com adesivo de capsaicina 8%. Foi avaliada a eficácia em função do alívio da dor, número de tratamentos necessários, segurança e impacto na qualidade de vida através de um conjunto de questionários.

Resultados: Relativamente à etiologia da DNP, 67.6% (N=46) dos doentes apresenta dor pós-cirúrgica ou induzida por trauma e 64.7% (N=44) reporta dor nos membros inferiores. Após o tratamento, 30.9% (N=21) dos doentes afirma ter melhorado um pouco, 22.1% (N=15) melhorado muito e 13.2% (N=9) melhorado imenso. Numa escala de 1 a 10, na semana anterior ao contacto telefónico, a mediana da intensidade da dor foi 6 e a mediana da interferência na qualidade de vida foi 7. A maioria dos doentes refere limitações na mobilidade e atividades diárias, bem como dor moderada.

Conclusão: O adesivo de capsaicina 8% é eficaz no tratamento da DNP, pelo menos a curto prazo. Aplicações repetidas podem ser importantes para garantir analgesia a longo prazo. A baixa concentração sistémica e os poucos efeitos adversos levam a que o tratamento seja geralmente bem tolerado. Devido ao seu efeito analgésico, a capsaicina pode melhorar a qualidade de vida dos doentes com DNP.

Palavras-chave: Capsaicina, dor neuropática, eficácia do tratamento, segurança, qualidade de vida

Abstract

Introduction: Peripheral neuropathic pain (PNP) is one of the most challenging diseases to treat with a significant negative impact on the patients' health-related quality of life (HRQoL). Capsaicin 8% patch has arisen in the last decades as an alternative to oral drugs in the treatment of PNP with fewer side effects and promising results in efficacy.

Objectives: This work aims to evaluate the effectiveness of the topical application of capsaicin in PNP and its impact on patients' HRQoL based on the use of capsaicin in Centro Hospitalar e Universitário de Santo António (CHUdSA).

Methods: This study included 100 patients with localized PNP with poor pain control and without improvement with previous treatments that were treated at least once with an 8% capsaicin patch to access its effectiveness on pain relief, number of treatments needed, safety and their impact on HRQoL through a set of questionnaires.

Results: Regarding the aetiology of PNP, 67.6% (N=46) have post-surgery or trauma induced PNP with 64.7% (N=44) of patients reporting pain in the lower limb. After the treatment, 30.9% (N=21) felt minimally improved, 22.1% (N=15) felt much improved and 13.2% (N=9) felt very much improved. On a scale from 1 to 10, in the week prior to the survey, the median intensity of pain was 6 and the median interference in quality of life was 7. The majority of patients report limitations in mobility and daily activities and moderate pain.

Conclusion: Capsaicin 8% patch is effective in PNP treatment at least in the short term. Repeated applications may be important for long-term analgesia. The low systemic dose and few side effects mean that the treatment is generally well tolerated by patients. Due to the analgesic effect, capsaicin can improve the quality of life of patients with PNP.

Keywords: Capsaicin, neuropathic pain, treatment effectiveness, safety, quality of life

List of Abbreviations

BPI - Brief Pain Inventory
CINP – Chemotherapy-Induced Peripheral Neuropathy
CNS – Central Nervous System
DN4 – Douleur Neuropathique en 4 Questions
DNP - Diabetic Polyneuropathy
ENFD - Epidermal Nerve Fibre Density
EQ-5D-3L - EuroQol Questionnaire, 5 dimensions, 3 levels
HIV – Human Immunodeficiency Vírus
HRQoL - Health-related Quality of Life
PGIC - Patient Global Improvement Change Scale
PNP - Peripheral Neuropathic Pain
SNRI - Serotonin Noradrenaline-Reuptake Inhibitors
TCA - Tricyclic Antidepressants
TRPV1 - Transient Receptor Potential Vanilloid 1

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Introduction

Neuropathic pain is defined by the International Association for the Pain Study as "*pain caused by a lesion or disease of the somatosensory nervous system*".[1] The somatosensory system includes both the peripheral neurons and the central nervous system (CNS). The affected fibres in the peripheral nervous system are mainly the small unmyelinated C fibres and the myelinated A fibres, predominantly the Aβ and Aδ fibres.[2, 3] The damage to these fibres provokes loss of function and paradoxically an increase in pain sensitivity and spontaneous pain – peripheral neuropathic pain (PNP).[1] Although the pathophysiology is not fully understood, this paradoxical effect of peripheral neuropathy is due to a dysfunction of transmission of sensory signals from the periphery to central neurons.[3, 4] Imbalance between excitatory and inhibitory signalling, ion channel alterations and altered modulation of pain stimuli in the CNS seem to be the mechanisms responsible for PNP by maintaining a state of hyperexcitability.[3-5] Besides, remains of an injured afferent nerve can generate ectopic activity causing pain in a numb region.[3-5]

Chronic PNP is defined as pain due to injury of the peripheral sensory fibres that is persistent or recurrent lasting 3 or plus months.[1] The transition to chronic pain is likely due to a series of alterations, occurring from the periphery to the brain cortex over time.[3, 4] This disease has several different aetiologies such as diabetes mellitus or other metabolic dysfunctions, peripheral nerve injury, painful polyneuropathy, postherpetic neuralgia or other infectious diseases (HIV), painful radiculopathy after chemotherapy, immune dysfunctions (Guillian-Barré Syndrome), inflammatory disorders (trigeminal neuralgia), inherited neuropathies and other specified and unspecified causes.[1, 3, 5-7] It has an estimated prevalence of 6.9% to 10% worldwide.[1, 3, 8, 9] In general, this condition is more frequent in the elderly (>60 years) and women rather than in men.[3, 6, 10] Also, the lumbar and lower limbs and neck and upper limbs are the most affected locations.[3, 6] It is expected to increase in the future due to higher rates of conditions that affect the small fibres such as diabetes mellitus, chemotherapy with higher survival rates and overall ageing of the global population.[3]

PNP is experienced differently from patient to patient, even the ones with the same underlying pathology.[1, 7] It can be described as different sensations like burning, pricking, shooting, pins and needles, freezing pain and squeezing. It is often present electric-shock-like pain either isolated or associated with ongoing pain. Pain may be spontaneous or evoked when it surges in response to a painful stimulus (hyperalgesia) or a usually non-painful stimulus (allodynia).[1, 3-7] Pain can be associated with other positive symptoms like abnormal sensations either unpleasant (dysesthesia) or pleasant (paresthesia).[1-3, 7] Also, there are often negative symptoms such as decreased or loss of sensation.[1-3]

Regarding the health-related quality of life (HRQoL) in patients with chronic PNP, there is a strong negative impact on patients' lifes with great suffering and disability.[1, 3, 5, 8, 11, 12] HRQoL is considerably poorer in individuals with chronic neuropathic pain than in those without pain and even when compared to patients with chronic pain of nonneuropathic characteristics.[8, 13-15] On one side, spinal neurons have projections to the thalamus and cortex and parallel pathways to the limbic areas, that in PNP are altered. This contributes to high pain, anxiety, depression and sleep problems described in the majority of patients with chronic PNP.[3, 4] On the other side, the symptoms tend to persist and respond less to medication becoming chronic, compromising patients' physical and mental health.[3, 15, 16] For these reasons, PNP has a detrimental effect on HRQoL.

Treatment of PNP consists of symptom management once the aetiology is usually not treatable. The current pharmacotherapy for PNP is systemic medications in monotherapy like gabapentinoids (pregabalin, gabapentin), tricyclic antidepressants (amitriptyline), serotonin noradrenaline-reuptake inhibitors (duloxetine).[4, 12, 17-20] The most frequent second-line option is the association of gabapentinoids and TCAs or SNRIs.[17, 20] Strong opioids are not recommended for chronic PNP as a first-line therapy.[3, 4, 19, 21]

However, these drugs have limited efficacy in this pathology contributing only to modest pain relief but have potentially serious common side effects like somnolence and cognitive impairment.[3, 4, 12, 19, 20] Besides, the majority of patients with PNP are older and frequently poli-medicated.[3, 4, 19, 20] For these reasons, there has been an increase in the use of topical treatments like local anaesthetics (lidocaine 5% patch) and capsaicin (8% patch), currently second or third-line treatments for PNP.[17-21]

Capsaicin is an alkylamine (trans-8-methyl-N-vanillyl-6-none amid) of natural origin present in chilli peppers and other plants of the capsicum plant family.[18, 22] This molecule is a highly selective agonist of transient receptor potential vanilloid 1 (TRPV1) and induces analgesia thru the defunctionalization of TRPV-1-expressing nociceptors. TRPV-1 is a non-selective ion channel receptor complex, present on skin nociceptive afferents, mostly in C fibres and some Aδ, particularly the ones responsible for painful or noxious sensations.[18, 22-26] TRPV1 has been proven a key molecule in peripheral hyperexcitability responsible for neuropathic pain. When activated, TRVP1 allows the influx of sodium and calcium that originate the electrical impulse.[12, 18, 23, 24, 27]

Capsaicin is available in two different formulations according to its concentration: low-concentration skin cream (0.025%-0.1% capsaicin) or high-concentration skin patch (8% capsaicin, 179mg).[18, 22, 28] Low doses of capsaicin induce desensitization of nociceptors reversible in hours owing to inactivation and inhibition of TRVP1 without causing structural changes. On the other hand, high doses of capsaicin induce defunctionalization for weeks that include loss of membrane

potential and retraction of epidermal nerve fibre endings.[18, 22] Overall, this long-lasting effect is caused by structural ablation of TRPV1-expressing afferent terminals generally leading to a reduction of epidermal nerve fibre density (ENFD).[12, 18, 22-24, 26, 29] It is important to note that is not obligatory to have nerve fiber degeneration to attain analgesia. The intrinsic effect of capsaicin on TRPV1 receptors can be enough to cause alteration in nociception.[30, 31] On the other side, reduction of ENFD does not necessarily guarantee decreased reaction to mechanical stimuli nor analgesia for PNP.[18] The impaired nociceptor functionality is responsible for reduced warmth detection, flare response and laser-evoked heat pain, without affecting tactile sensitivity or cold pain.[32, 33]

Besides its action in impulse transmission, capsaicin causes depletion of substance P, a neuropeptide involved in nociceptive transmission and inflammation, however, its effect is not sufficient to produce analgesia on its own.[18, 22] Also, capsaicin induces TRPV1+ neurons to release somatostatin responsible for analgesia. This mechanism is thought to contribute to the reduction of neuropathic pain at least in the initial period.[18, 20, 22, 34]

A recent study proposes that the associated analgesia mechanism of capsaicin is due to the accelerated regeneration of peptidergic fibers and restoration of function rather than the destruction of these fibers. A disease-modifying effect of capsaicin on these fibers already occurs 4 weeks after treatment and repeated application of capsaicin might enhance the regenerative properties of peptidergic fibers, which might explain sustained and long-lasting pain relief.[35]

Capsaicin is well absorbed in the skin with minimal systemic concentration minimizing the probability of systemic adverse effects and does not interfere with the metabolism of other drugs because it avoids first-pass metabolism.[11, 18, 26, 28, 36-39] Capsaicin adverse effects are few and mild. It has been reported a small transitory increase in blood pressure and local reactions such as burning pain, erythema and pruritus.[12, 18, 22, 23] Nevertheless, the low dose and transient side effects allow for treatment with capsaicin 8% patch to be well tolerated in repeated applications.[11, 26, 36, 38-41]

Multiple studies demonstrated that capsaicin 8% adhesive bandage is effective in controlling pain intensity for several weeks at a time and reducing the painful area in patients with PNP from various aetiologies, even in slower responders. Furthermore, the majority of patients reported an improvement in their quality of life.[11, 28, 36-38, 40-43]

This treatment has been performed at Centro Hospitalar e Universitário de Santo António (CHUdSA) since 2012, relying exclusively on hospital application and currently one of the first-line therapeutics for PNP. This dissertation aims to evaluate the effectiveness of the topical application of capsaicin in peripheral neuropathic pain and its impact on patients' quality of life based on published literature and the use of capsaicin in CHUdSA.

Methods

A retrospective study was elaborated at Centro Hospitalar Universitário de Santo António (CHUdSA) with approval by the Ethics Committee and the Department of Education, Training and Research and the Responsible for Clinical Information Access (Ref. 2022.203). This study included 100 patients with localized PNP with poor pain control and without improvement with previous treatments that were treated at least once with an 8% capsaicin patch in this hospital. Of these, 9 were excluded due to death and 23 did not respond to the telephone interview. Informed patient consentient was obtained previously.

The following information was consulted in the medical files and/or inquired about through the telephone survey:

- Age and gender
- Telephone number
- Diagnostic
- Duration of pain
- Number of treatments administrated in CHUdSA
- Location of pain
- Pain characteristics through the application of the validated Portuguese version of the "Neuropathic Pain Questionnaire" (DN4) (adapted)
- Pain response to treatment immediately after the treatment through the application of the validated Portuguese version of the "Patient Global Improvement Change Scale" (PGIC).
- Pain evaluation and interference in quality of life through the application of the validated Portuguese versions of "Brief Pain Inventory" (BPI) (adapted) and "EuroQol Questionnaire, 5 dimensions, 3 levels" (EQ-5D-3L).

Table I presents the description of the categories considered for the analysis of the variables under study.

Pain Assessment

The DN4 questionnaire was originally developed and applied in France with the purpose of screening for neuropathic pain. Nowadays is used worldwide and is validated for the Portuguese population. It includes 10 items related to pain characteristics, from which 3 are descriptive terms for pain quality (burning sensation, painful cold sensation, electric shocks sensation), 4 refer to abnormal sensations associated with the pain (tingling, pricking, numbness, itching) and the rest (touch hypoesthesia, prick hypoesthesia, touch allodynia) is evaluated in the physical examination of the painful area. In this study, were used only the first 7 items.[44] For the

statistical analysis, a positive answer to any item is coded as a value of 1 and a negative item is coded as a value of 0.

To assess pain responsiveness to the capsaicin treatment was used the PGIC questionnaire. Literature defends that PGIC significantly correlates with pain severity, pain interference in quality of life and treatment efficacy.[45] It consists of a 7-point score from "very much improved" to "very much worse" according to the patient's perception of pain changes after the treatment, however, it does not indicate in what aspect has the pain changed. This questionnaire has been validated by IASP.[45]

The BPI questionnaire includes 15 items to evaluate the existence of pain, severity, localization, functional interference, and efficacy of therapeutic strategies, in the last week. In this study, was applied an adapted version contemplating the following variables: pain severity scale with four items (maximum, minimum, mean and in the moment) using a scale from 1 to 10, pain interference scale with 7 items (general activities, mood, mobility, work, personal relations, sleep, and life pleasure) using a scale from 1 to 10, and 2 items to assess the efficacy of current pharmacological treatment. This questionnaire has been validated by IASP given its reproducibility and sensitivity in pain diagnosis, follow-up, and characterization. It also was translated, adapted and validated for the Portuguese population.[44] For statistics purposes, the severity of pain was evaluated using the median of the 4 four items and the pain interference was also evaluated using the median of the 7 items.

Health-Related Quality of Life

Regarding the evaluation of the HRQoL in this set of patients was applied the EQ-5D-3L questionnaire. This instrument is used to evaluate the quality of life related to health status thru a system composed of five dimensions (mobility, personal hygiene, daily activities, pain/malaise, anxiety/depression) with three levels each (no problems, few problems, extreme problems) according to patient's perception. It has been validated for the Portuguese population.[46]

Statistical analysis was performed using IBM SPSS Statistics®, version 28.0.1.0.

Results

Of the 68 individuals who responded to the telephone survey, 77.9% (N=53) are female and 22.1% (N=15) are male. (Table II) The age gap in this group is from 30 to 79 years old with an average of 61.4 years. (Table III) Our non-response rate was of 22,1% (n=32).

Regarding the aetiology of PNP, 67.6% (N=46) have post-surgery or trauma induced PNP. Other/non-determined aetiologies correspond to 19.1% (N=13) of the patients. 4.4% (N=3)

patients refer post-herpetic neuralgia, 1.5% (N=1) have diabetic polyneuropathy and 1.5% (N=1) have pain in the residual limb after amputation. (Table IV)

The most frequent location for PNP in this group is the lower limb, 64.7% (N=44), followed by the superior limb, 16.2% (N=11), and the lumbar region, 10.3% (N=7). Other locations include the pelvic region, 8.8% (N=6), thoracic region, 8.8% (N=6), cervical region, 5.9% (N=4), abdomen, 5.9% (N=4), face, 4.4 (N=3) and cranium, 1,5% (N=1). (Fig. 1)

In the DN4 questionnaire, 72.3% (N=47) of the individuals refer to pins and needles, 72.3% (N=47) to numbness, 70.8% (N=46) to tingling and 26.2% (N=17) to itching. The most frequent quality attributed to pain was burning, 58.5% (N=38), next was electric shocks, 41.5% (N=27), and 27.7% (N=18) referred to painful cold. (Fig. 2)

The duration of pain until the first treatment varies from 2 to 588 months, with an average of 71.36 months and a median of 30 months. 25% of patients have a duration of pain inferior to 12 months, but 75% have a duration over 61.5 months. (Fig.3) The median of the number of treatments is two, with an interval of values between 1 and 7. (Fig. 4)

After the treatment, 33.8% (N= 23) of the patients did not feel improvements. On the other hand, 30.9% (N=21) felt minimally improved, 22.1 (N=15) felt much improved and 13.2 (N=9) felt very much improved. (Fig. 5) 70.6% (N=12) of patients with only one treatment reported no changes. No patient with 4 to 6 treatments reported no change in pain. (Table V) In post-surgical or traumatic pain and pain of unspecified aetiology, 67.4% (N=31) and 76.9% (N=10), respectively, report at least some improvement in pain. (Table VI)

In the week prior to the telephone survey, 9% (N=6) of the patients did not experience pain. On a scale of 0 to 10, 25% of the patients affirm an intensity under 3, 50% of patients report pain between 3 and 8, with a median of 6, and 25% over 8. (Fig. 6) Regarding pain interference the week before the survey, 14.9% (N=10) affirm no interference. On a scale of 0 to 10, 25% report an interference under 3, 50% between 3 and 8, and 25% over 8 with a median of 7. (Fig. 7)

Only 2% (N=1) of the patients affirm the complete efficacy of the analgesics the week before the study. 35.6% (N=18) report more or less pain relief with medication, 29.4% (N=15) report a lot of efficacy, 21.6% (N=11) have little relief, and 11.8% (N=6) affirm no relief with medication. (Fig. 8)

The majority of patients, 72.5% (N=37) report always feeling pain, even with medication. 9.8% (N=5) affirm that is very frequent to have pain after medication, 9.8% (N=5) report that rarely have pain after taking analgesics, 3.9% (N=2) say sometimes have pain after analgesics and only 3.9% (N=2) never have pain after taking medication. (Fig. 9)

In the EQ-5D-3L questionnaire, 69.1% (N=47) of the patients reported having problems walking, 29.4% (N=20) have no mobility problems and 1.5% (N=1) are incapable of walking. (Fig.

10) In personal hygiene, 57.4% (N=39) affirm no limitations, 38.2% (N=26) have limitations and 4.4% (n=3) are incapable of doing their hygiene by themselves. (Fig. 11) Regarding daily activities, 76.9% (N=32) reported some problems, 19.1% (N=13) have no problems and 4.4% (N=3) are incapable of doing their daily activities. (Fig. 12) The majority, 66.2% (N=45), affirm moderate pain or discomfort, 23.5% (N=16) affirm extreme pain or discomfort and 10.3% (N=7) report no pain or discomfort. (Fig. 13) At last, 41.2% (N=28) feel extremely depressed or anxious, 30.9% (N=21) do not feel anxious or depressed and 27.9% (N=19) feel moderately anxious or depressed. (Fig. 14)

Discussion

This study aims to evaluate the effectiveness of the topical application of capsaicin in peripheral neuropathic pain and its impact on patients' quality of life. In this set of patients, a total of 66.2% reported pain improvement in the short term after treatment with capsaicin 8% patch. More specifically, 30.9% report a mild improvement, 22.1% very much improved and 13.2% affirm great improvement. No patient reported a worsening in pain after the capsaicin 8% patch treatment. When discussing these results, it is important to have in mind that PGIC is a personal perception. The absence of an impression of change does not mean there were not any changes, for example in the area of pain instead of intensity.[28, 30, 37-39, 42] Moreover, some patients were submitted to treatment almost 10 years ago, meaning that is important to consider a possible memory bias.

Although we acknowledge that we present a small sample for some aetiologies, it is important to note that 67.6% of the patients have post-surgery or trauma pain. Of this, 32.6% report no change in pain after treatment, but 67.4% have improvement in pain. Postsurgical pain is one of the most common causes of neuropathic pain.[43, 47] It is expected to continue to increase its frequency as the number of surgeries performed increases.[37] However, the evidence for capsaicin treatment in chronic postsurgical neuropathic pain was scarce[43], until recently when various studies found a significant pain intensity reduction with capsaicin 8% patch treatment in this group of patients.[37, 43, 48-50] Our study is in line with the previously published results.

As for the long-term response, in the week prior to the telephone survey, six patients reported no pain. However, the median of pain intensity was 6 and half of the patients referred to pain in an interval between 3 and 8. This means they maintain mild to moderate pain, although claiming improvement right after the treatment. This may suggest that the analgesic effect is stronger in the first weeks after treatment and therefore repeated treatments may be important to maintain the analgesic effect.[35, 39]

stronger in the first weeks after treatment and therefore repeated treatments may be important to maintain the analgesic effect.[35, 39]

The published bibliography states that high doses of capsaicin, like the 8% patch, induce analgesia thru the defunctionalization of nociceptive nerve fibers due to a localized structural ablation of TRPV1-expressing afferent terminals.[18, 22-24, 26, 29] However, this defunctionalization is reversible. The affected nerve fibers may regenerate, usually from 12[26] to 24[22, 25, 31] weeks after the treatment. This knowledge supports the hypothesis that repeated treatment over time is necessary for a long-term analgesic effect.[35, 36]

Other than long-term effects, repeated applications may be necessary for better response. Multiple studies concluded that repeated applications led to higher response rates.[11, 36, 38, 39, 41] Our results fall in line with this data given that no patient reported great improvement with only one application, but in the 49 patients that received 2 to 6 treatments, only 10 reported no changes in pain. Furthermore, repeated treatments can be essential to a specific group of patients denominated slower responders. In these patients, two or three treatments more than 8 weeks apart may be needed to induce the analgesic effect.[40] Therefore, the absence of an initial response, as was the case with twelve of our patients, should not be a motive to not proceed with the treatment.[38, 40]

When discussing repeated applications, it is important to consider tolerability. Although it was not evaluated in this study, during the telephonic survey a few patients referred to local reactions like burning pain in the first hours to days after treatment. Among this set of patients, only one patient affirmed that would not want to repeat treatment due to intense burning pain.

Literature defends that capsaicin 8% patch treatment is overall well tolerated given the fact that is absorbed in the skin with minimal systemic concentration minimizing systemic adverse effects.[11, 28, 36-39] The most common side effects involve small transient elevation of blood pressure and local reactions like burning pain, pruritus, and erythema at the application site.[18, 22, 23, 51] These reactions, especially the intense burning pain, are one of the barriers to the wider use of capsaicin treatment. There is no effective method to eliminate these side effects, but attenuation of pain is recommended.[18, 22] In most cases are used topical agents, paracetamol, or nonsteroidal anti-inflammatory drugs to manage the pain.[12, 22, 28, 37, 51] Another possibility is skin cooling. Placing ice pads on the area of the patch during treatment does not affect the capsaicin effect[18] and has been found to attenuate burning pain, improve tolerance, and diminish the need for rescue analgesia.[12, 18, 37, 51]

Nevertheless, the low dose and transient side effects allow for treatment with capsaicin 8% patch to be well tolerated in repeated applications. Repeated treatment with capsaicin 8%

patch for over 48[51] and 52[11, 36] weeks was well tolerated without increasing the frequency of adverse reactions and minimal risk of adverse effects on neurological function.[11, 36, 51, 52]

Another crucial factor to consider besides tolerability is drug interactions. Our set of patients has an average age of 61.46 years old, meaning that the possibility of being poli-medicated or having liver or renal impairment should be taken into account. Moreover, chronic pain patients are frequently poli-medicated, no matter their age. As previously stated, topical capsaicin treatment has a low total systemic dose and it does not inhibit or induce cytochrome P450 enzymes, meaning it will not interfere with the metabolism of other drugs.[11, 18, 22, 26, 28, 36, 37, 39]

Regarding HRQoL, ten patients report no pain interference in quality of life. However, 50% of patients claim an interference between 3 and 8 on a scale from 1 to 10. The median in this variable was 7. It is important to note that the median value in BPI for interference is higher than the intensity. This shows that patients value the interference of pain in their quality of life over pain severity, proving that interference is an equally important variable as pain reduction when evaluating pain treatments.

The results in EQ-5D-3L show that the majority of patients have mobility limitations, problems in performing their daily activities and moderate pain or discomfort. Only in personal care do the majority of patients claim to not have limitations. 41.2% of patients report extreme anxiety or depression. Nevertheless, 30.9% report not having anxiety or depression associated with the pain. Studies using the EQ-5D-3L questionnaire affirm a meaningful improvement in quality of life when compared to pre-treatment values.[11, 36, 38, 41, 42]

The main limitation of this study is the fact that there were no baseline values of the applied questionnaires to establish a comparison. These values would be particularly relevant in the discussion of BPI and EQ-5D-3L results in order to evaluate the effect of capsaicin 8% patch treatment on pain intensity and quality of life. Another variable that could be taken into account is side effects prevalence to establish tolerability and patient willingness to repeat treatment. It would also be relevant to define the time between the last treatment and the telephonic survey, as several patients referred to improvement right after treatment but currently feel no effect at all of the analgesia provided by capsaicin. The study of this correlation would allow us to establish the period in which the treatments should be repeated to maintain the analgesic effect. In accordance with the available literature, repeated applications may be considered over 10-12 weeks.[35] Lastly, the small number of patients included in this study can limit the application of these results to the general population.

Conclusion

PNP is one of the most challenging diseases to treat. Several barriers arise in its therapeutic approach, from the poor effectiveness of drugs to their adverse effects that condition adherence to therapy. Furthermore, PNP has a significant negative impact on the patients' quality of life, affecting their daily activities, relationships with others, sleep and mental health.

Capsaicin, in low doses, has been on the market for several decades as a compound in topical application analgesics. Recently, in the last 2 decades, the benefit of applying high doses of capsaicin in localized PNP has been explored.

Although this study has some limitations, it demonstrates that a significant percentage of patients show at least a small notion of improvement with the application of the capsaicin 8% patch, proving that the 8% capsaicin patch is effective in PNP treatment. However, the analgesic effect seems to decrease with time and increase with the number of applications, establishing the need for repeated applications. The low systemic dose and few side effects mean that the treatment is generally well tolerated by patients. Due to the analgesic effect, capsaicin can provide an improvement in the quality of life of patients with PNP.

Postface

The article "Topical Capsaicin in Peripheral Neuropathic Pain: Efficacy and Quality of Life", elaborated by Márcia Pitrez Santos, Francisco Lemos, Joana Gomes, José Romão and Dalila Veiga, was submitted on the 15th of May 2023 for publishing in the British Journal of Pain.

Topical Capsaicin in Peripheral Neuropathic Pain: Efficacy and Quality of Life

Journal:	*British Journal of Pain*
Manuscript ID	BJP-23-0065
Manuscript Type:	Original Manuscript
Keywords:	Capsaicin, Neuropathic Pain, Quality of life, Effectiveness, Safety
Abstract:	Introduction: Peripheral neuropathic pain (PNP) is one of the most challenging diseases to treat with a significant negative impact on the patients' health-related quality of life (HRQoL). Capsaicin 8% patch has arisen in the last decades as an alternative to oral drugs in the treatment of PNP with fewer side effects and promising results in efficacy. Objectives: This work aims to evaluate the effectiveness of the topical application of capsaicin in PNP and its impact on patients' HRQoL based on the use of capsaicin in Centro Hospitalar Universitário de Santo António (CHUdSA). Methods: This study included 100 patients with localized PNP with poor pain control and without improvement with previous treatments that were treated at least once with an 8% capsaicin patch to access its effectiveness on pain relief, number of treatments needed, safety and their impact on HRQoL through a set of questionnaires. Results: Regarding the aetiology of PNP, 67.6% (N=46) have post-surgery or trauma induced PNP with 64.7% (N=44) of patients reporting pain in the lower limb. After the treatment, 30.9% (N=21) felt minimally improved, 22.1 (N=15) felt much improved and 13.2 (N=9) felt very much improved. On a scale from 1 to 10, in the week prior to the survey, the median intensity of pain was 6 and the median interference in quality of life was 7. The majority of patients still report limitations in mobility and daily activities and moderate pain. Conclusion: Capsaicin 8% patch is effective in PNP treatment at least in the short term. Repeated applications may be important for long-term analgesia. The low systemic dose and few side effects mean that the treatment is generally well tolerated by patients. Due to the analgesic effect, capsaicin can improve the HRQoL of patients with PNP. Keywords: Capsaicin, neuropathic pain, effectiveness, safety, quality of life

Attachments

Tables

Table I. Characterization of Variables

Variable	Codification
Pain Aetiology	Amputation pain Diabetic polyneuropathy Post-surgical or trauma pain HIV-neuropathy Chemotherapy neuropathy Trigeminal neuralgia Post-herpetic neuralgia Other
Pain Location	Face Cranium Cervical region Superior limb Dorsal region Thoracic region Abdominal region Lumbar region Pelvic region Inferior limb
BPI – In the last week, how effective were the medications you used to relieve your pain?	Nothing A little More or less Much Completely
BPI – In the last week, how frequently do you felt pain after taking medication?	Always Frequently Sometimes Rarely Never

HIV – Human Immunodeficiency Vírus

Table II. Gender Characterization

Gender	Frequency
Female	53 (77.9%)
Male	15 (22.1%)

Table III. Age Characterization

Mean	61,46
Median	64,00
Standard-deviation	12,068
Interval	49
Minimum	30
Maximum	79

Table IV. Aetiology Characterization

Aetiology	**N (%)**
Amputation pain	1 (1.5)
DNP	1 (1.5)
Post-surgical or trauma pain	46 (67,6)
HIV-neuropathy	0 (0)
CINP	4 (5.9)
Trigeminal neuralgia	0 (0)
Post-herpetic neuralgia	3 (4.4)
Other	13 (19.1)
Total	68 (100)

Table V. Relation between Number of Treatments and Global Perception of Change

PGIC		***Number of treatments***							***Total***
		1	2	3	4	5	6	7	
No change	N (%)	12 (70.6)	6 (27.3)	4 (30.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	23 (33.8)
Minimally improved	N (%)	3 (17.6)	6 (27.3)	5 (38.5)	1 (25.0)	4 (66.7)	2 (50.0)	0 (0.0)	21 (30.9)
Much improved	N (%)	2 (11.8)	7 (31.8)	1 (7.7)	2 (50.0)	1 (16.1)	1 (25.0)	1 (50.0)	15 (22.1)
Very much improved	N (%)	0 (0.0)	3 (13.6)	3 (23.1)	1 (25.0)	1 (16.1)	1 (25.0)	0 (0.0)	9 (13.2)
Total		17	22	13	4	6	4	2	68

Table VI. Relation between Aetiology and Global Perception of Change

PGIC		***Aetiology***						***Total***
		Amputation	DNP	Post-surgical or trauma	CINP	Post-herpetic	Other	
No change	N (%)	1 (100.0)	0 (0.0)	15 (32.6)	3 (75.0)	1 (33.3)	0 (0.0)	23 (33.8)
Minimally Improved	N (%)	0 (0.0)	1 (100.0)	14 (30.4)	0 (0.0)	0 (0.0)	6 (46.2)	21 (30.9)
Much improved	N (%)	0 (0.0)	0 (0.0)	10 (21.7)	1 (25.0)	1 (33.3)	3 (23.1)	15 (22.1)
Very much improved	N (%)	0 (0.0)	0 (0.0)	7 (15.2)	0 (0.0)	1 (33.3)	1 (7.7)	9 (13.2)
Total		1	1	46	4	3	13	68

DNP - Diabetic Polyneuropathy, CINP – Chemotherapy-Induced Peripheral Neuropathy

Figures

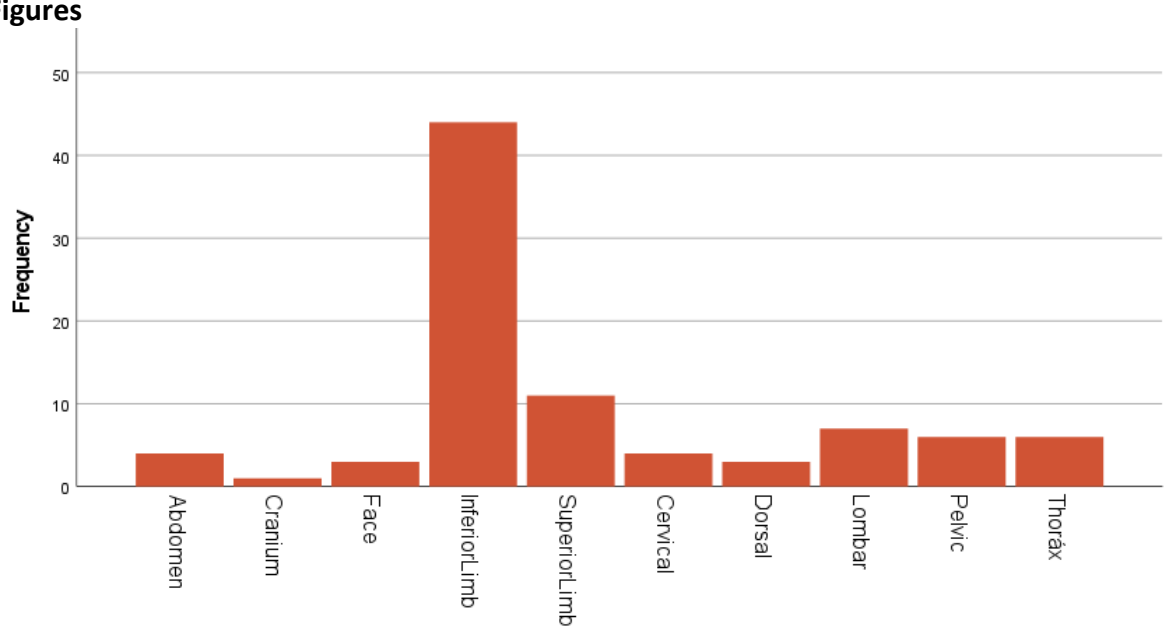

Figure 1. Pain Location

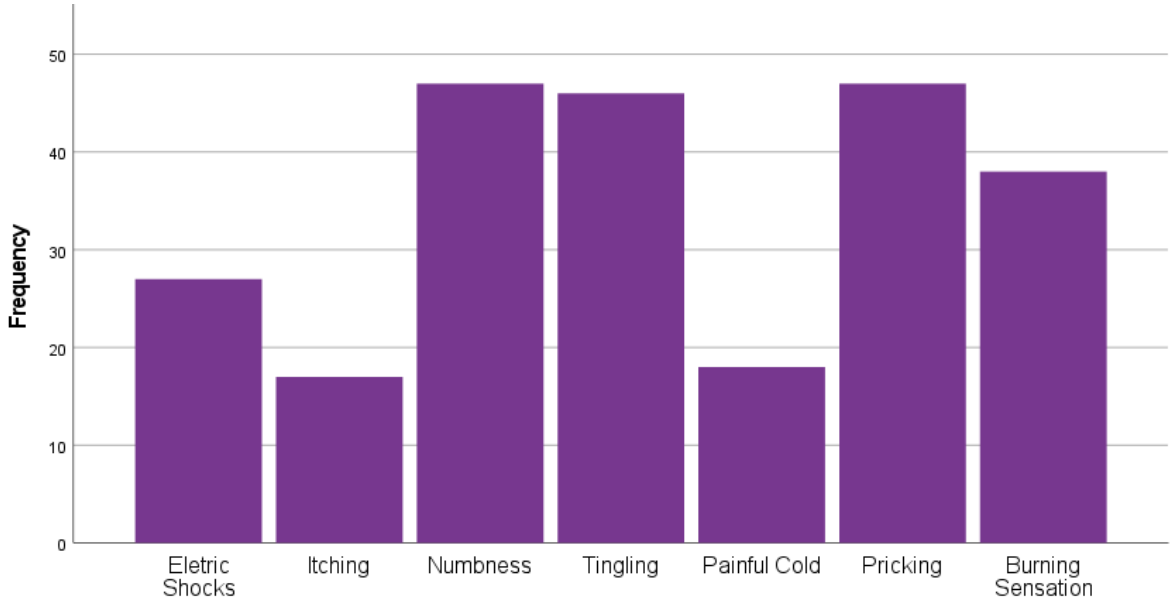

Figure 2. Pain Characteristics (DN4 questionnaire)

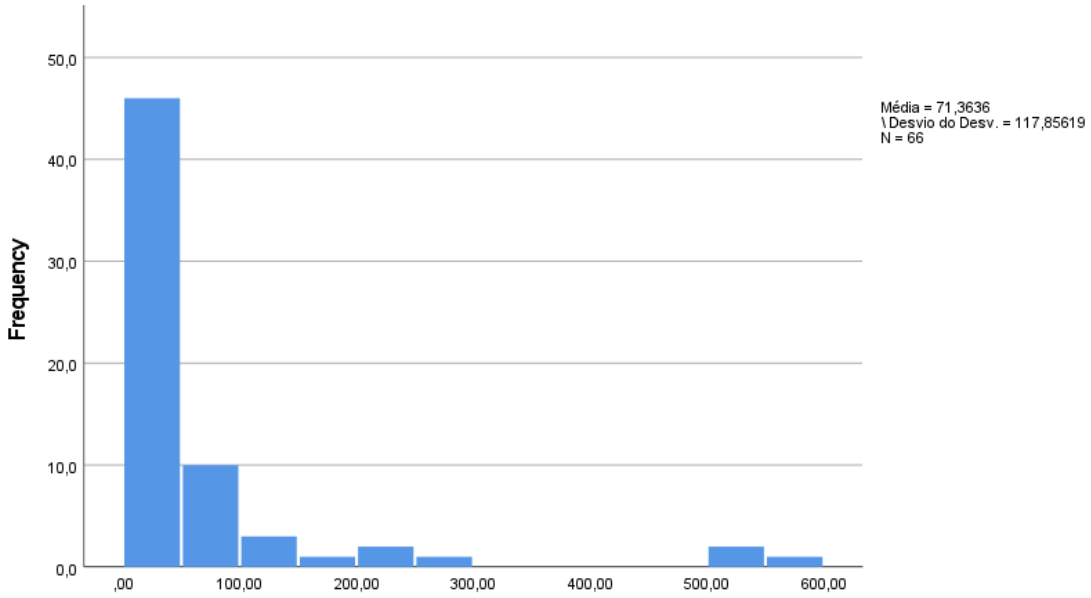

Figure 3. Pain Duration

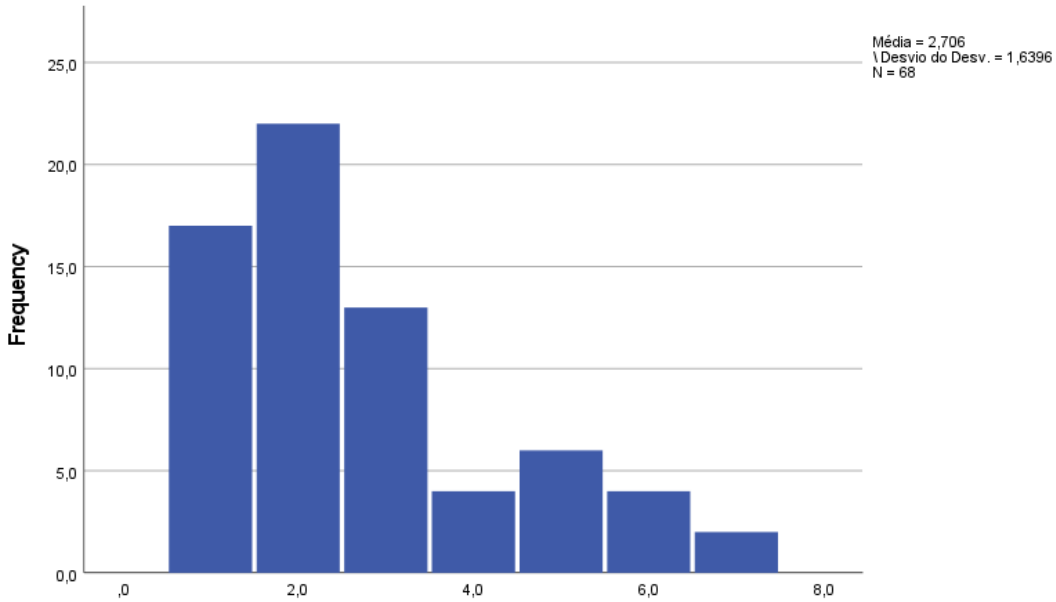

Figure 4. Number of Treatments

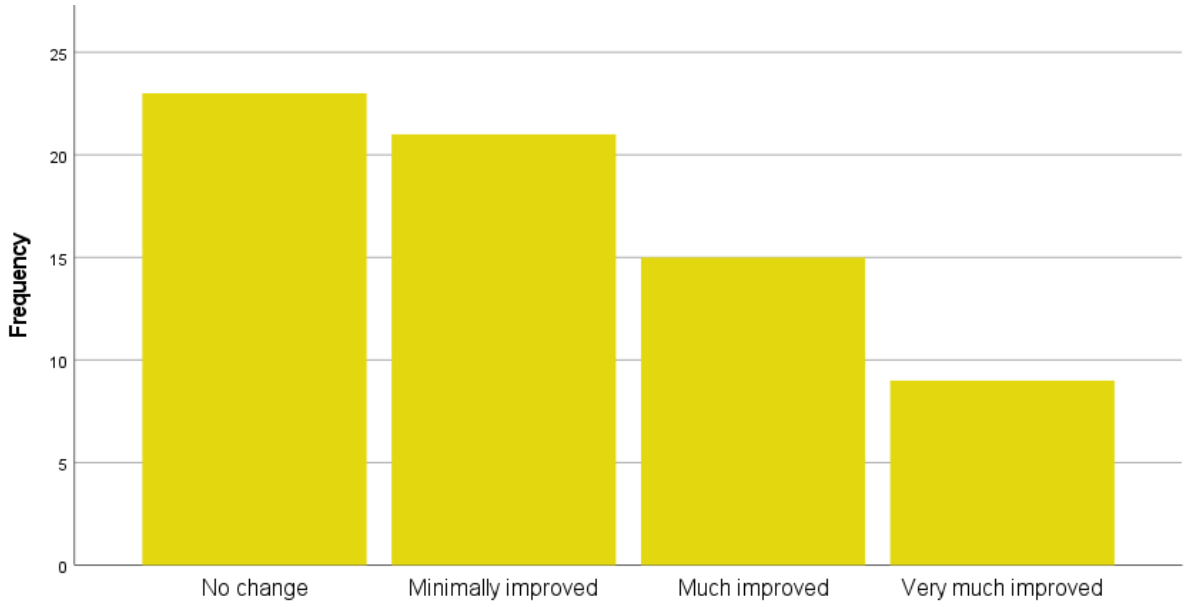

Figure 5. PGIC

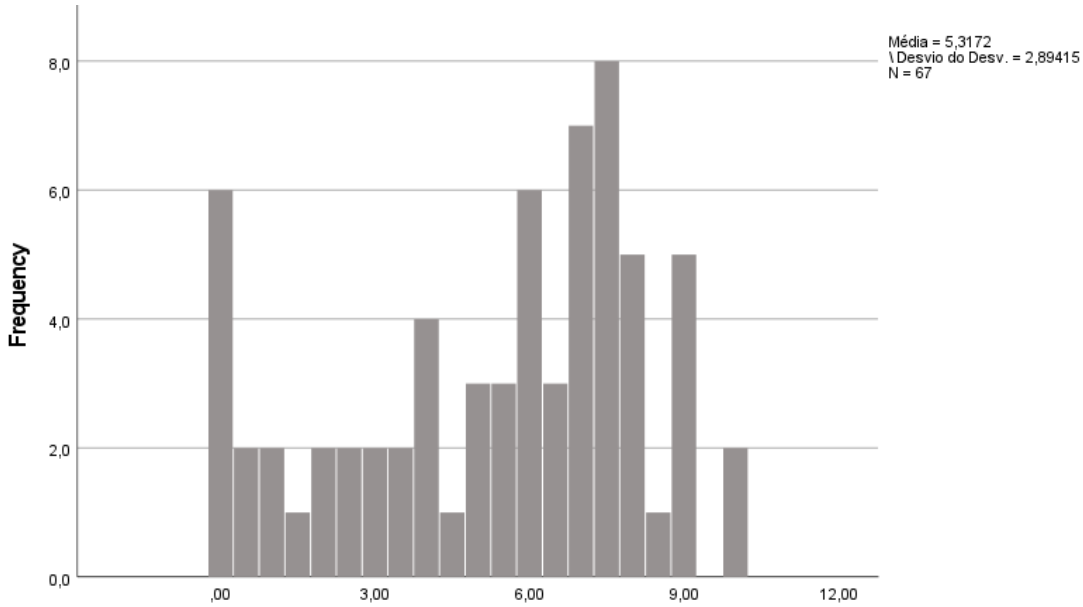

Figure 6. BPI Severity

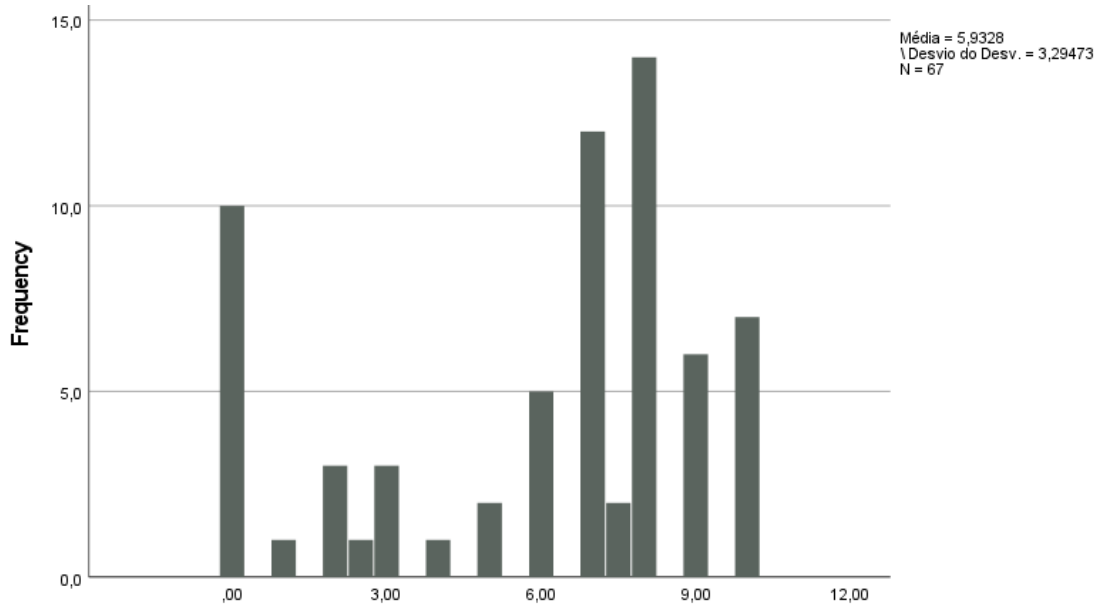

Figure 7. BPI Interference

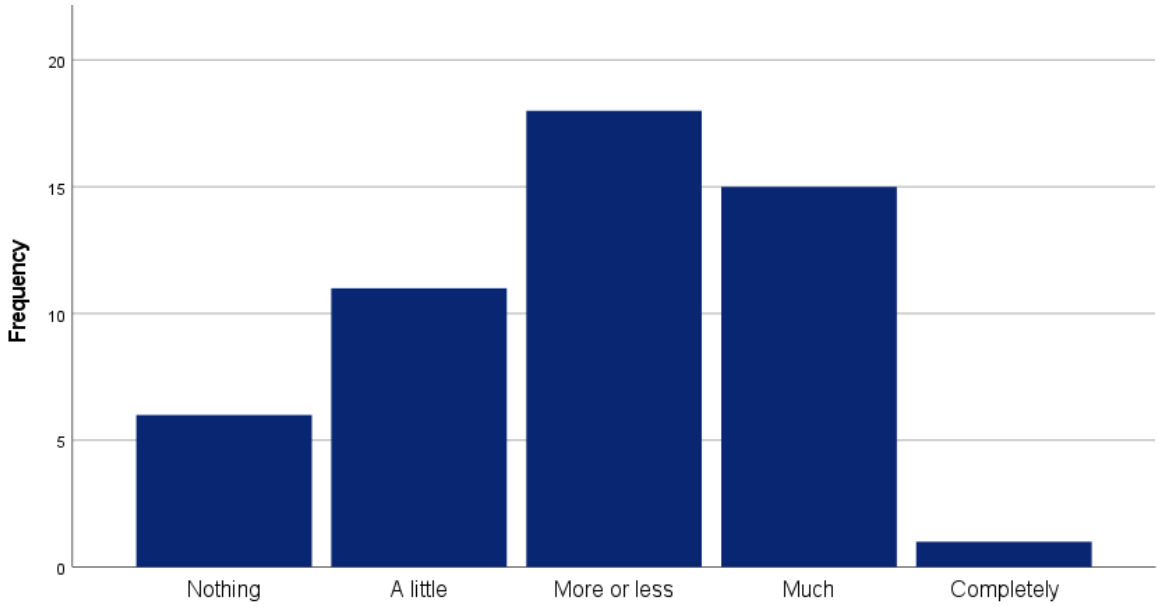

Figure 8. BPI "In the last week, how effective were the medications you used to relieve your pain?"

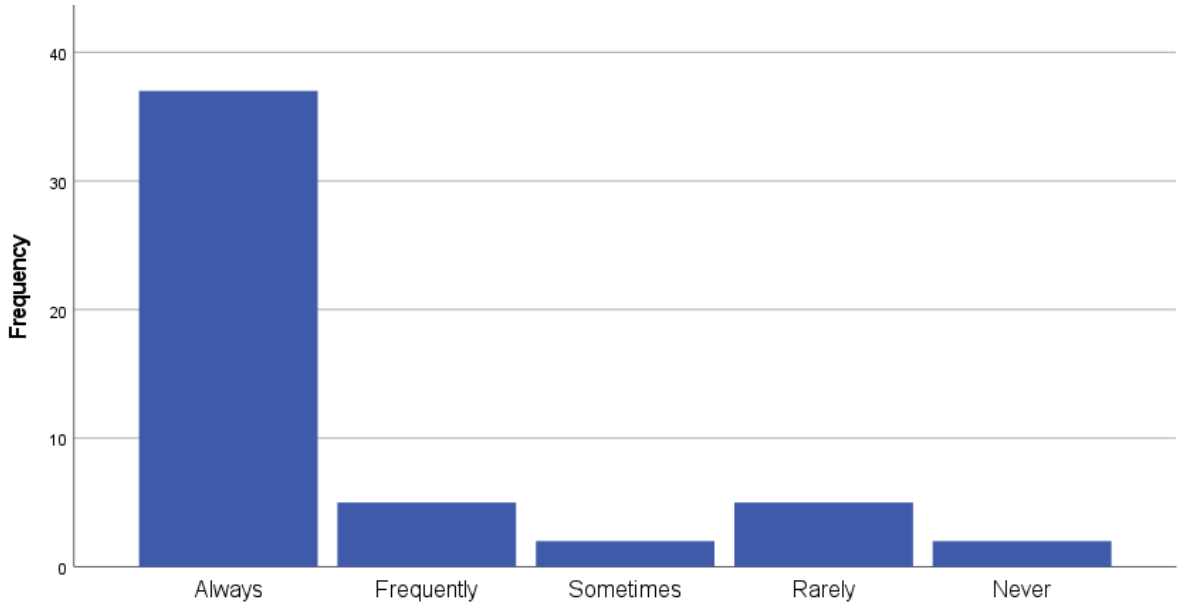

Figure 9. BPI “In the last week, how frequently do you felt pain after taking medication?"

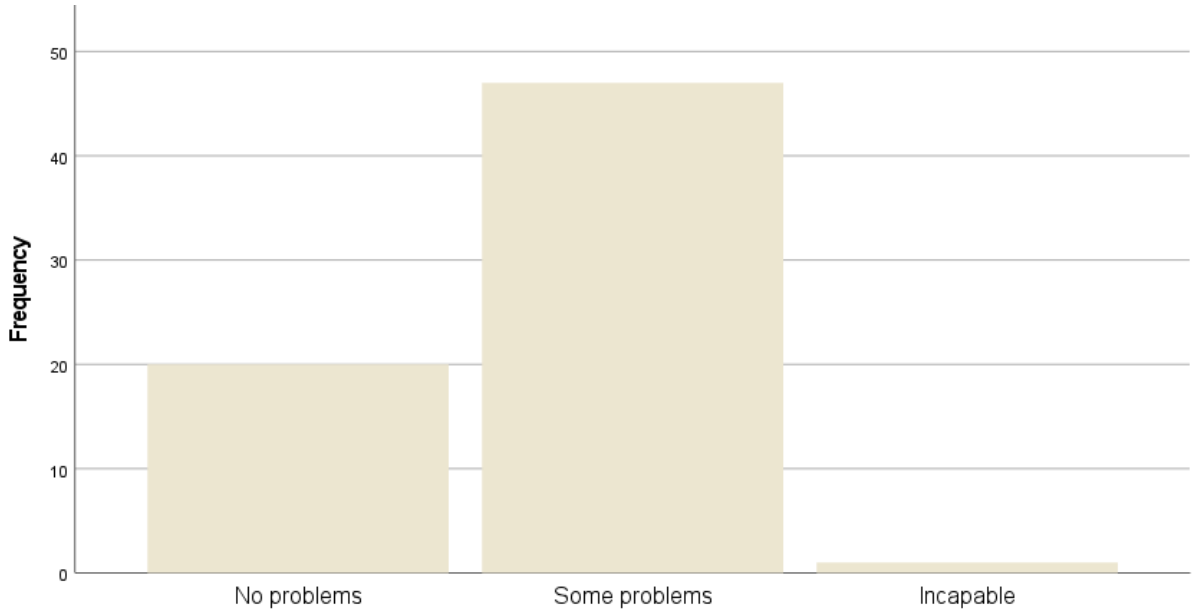

Figure 10. EQ-5D-3L Mobility

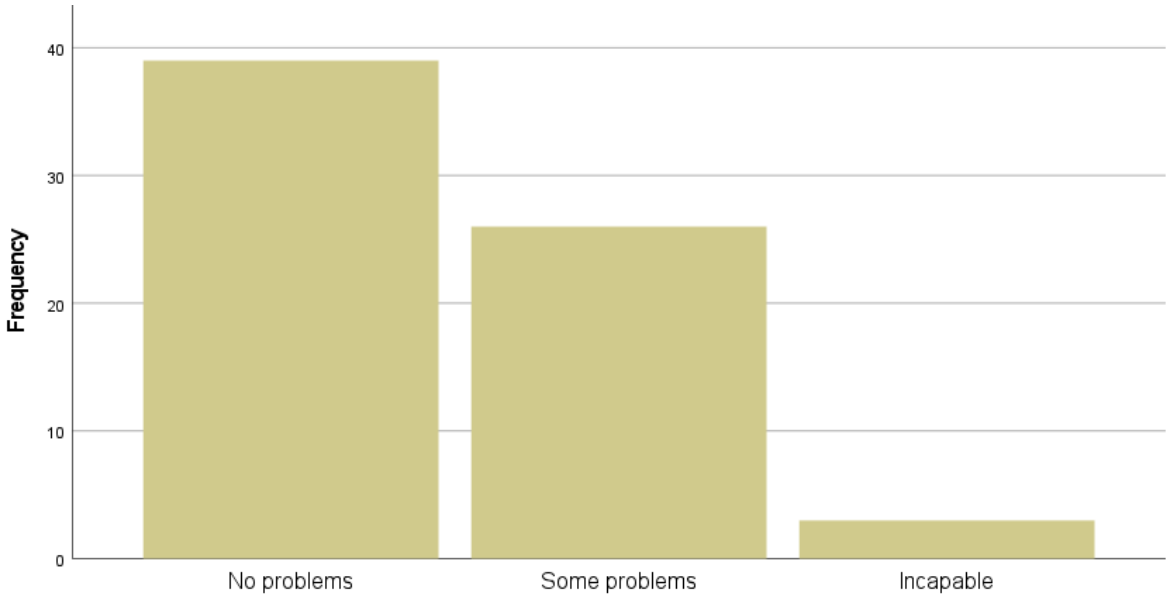

Figure 11. EQ-5D-3L Personal Care

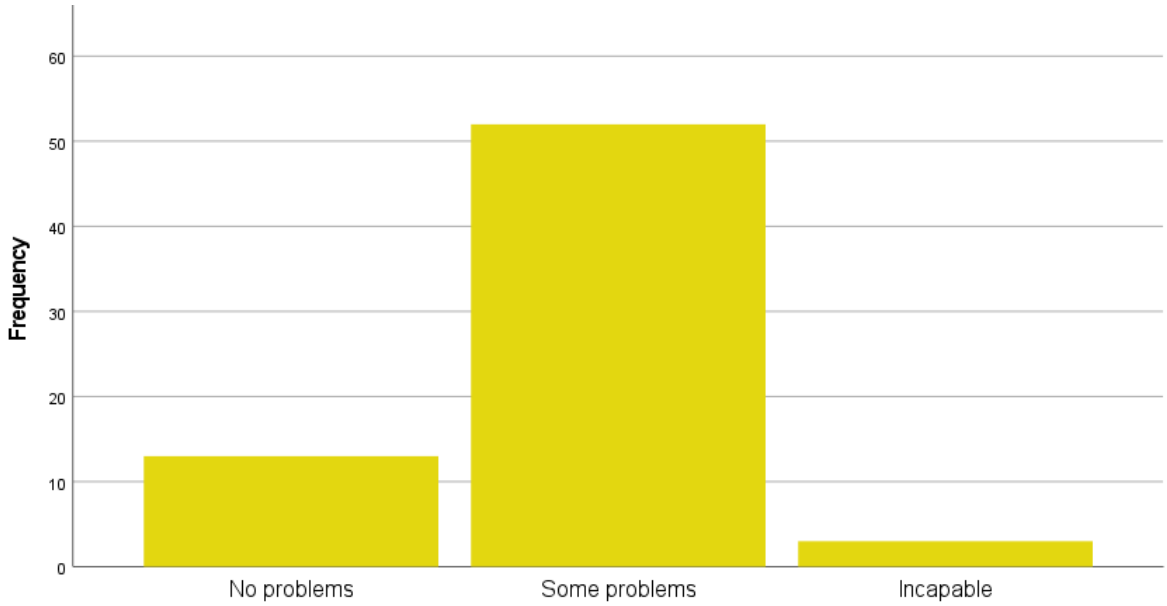

Figure 12. EQ-5D-3L Daily Activities

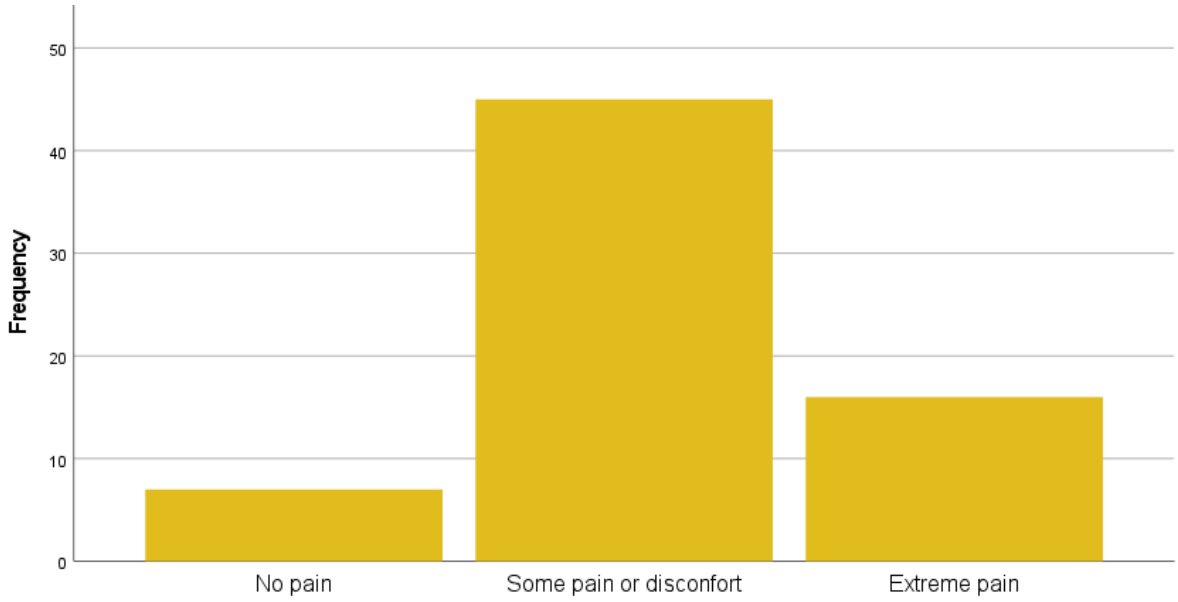

Figure 13. EQ-5D-3L Pain/Disconfort

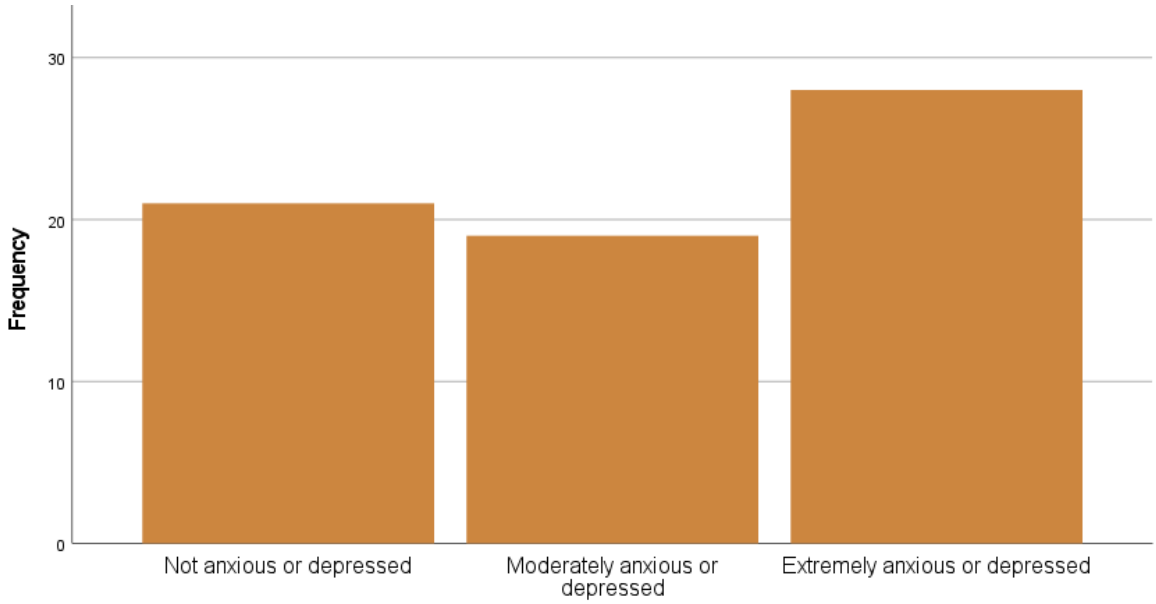

Figure 14. EQ-5D-3L Anxiety/Depression

Questionnaires

Neuropathic Pain Questionnaire (DN4) (adapted)

Por favor, responda às seguintes questões, assinalando uma única resposta para cada alínea:

1. A dor apresenta uma, ou mais, das características seguintes?

	Sim	Não
1 - Queimadura		
2 - Sensação de frio doloroso		
3 - Choques elétricos		

2. Na mesma região da dor, sente também um ou mais dos seguintes sintomas?

	Sim	Não
4 - Formigueiro		
5 - Picadas		
6 - Dormência		
7 - Comichão		

Patient Global Impression of Change (PGIC)

Assinalando apenas um quadrado, após o tratamento, a sua dor:

- ☐ Melhorou imenso
- ☐ Melhorou muito
- ☐ Melhorou um pouco
- ☐ Não se alterou
- ☐ Piorou um pouco
- ☐ Piorou muito
- ☐ Piorou imenso

Brief Pain Inventory (BPI) (adapted)

Por favor, classifique a sua dor indicando o número que melhor descreve a sua dor no seu máximo durante a última semana:

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Por favor, classifique a sua dor indicando o número que melhor descreve a sua dor no seu mínimo durante a última semana:

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Por favor, classifique a sua dor indicando o número que melhor descreve a sua dor em média durante a última semana:

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Por favor, classifique a sua dor indicando o número que melhor descreve a sua dor neste preciso momento:

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Por favor, indique o número que descreve em que medida é que, durante a última semana, a sua dor interferiu com:

A. Atividade geral

   0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

B. Disposição

   0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

C. Capacidade para andar a pé

   0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

D. Trabalho (tanto doméstico como fora de casa)

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

E. Relações com outras pessoas

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

F. Sono

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

G. Prazer de viver

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Por favor, indique qual o grau de eficácia dos medicamentos que usa par aliviar as suas dores:

Nada ☐ Pouco ☐ Mais ou menos ☐ Muito ☐ Completamente ☐

Por favor, indique com que frequência, na última semana, sentiu dores mesmo sob o efeito dos medicamentos:

Nunca ☐ Raramente ☐ Por vezes ☐ Frequentemente ☐ Sempre ☐

<u>EuroQol-5D-3L (EQ-5D-3L)</u>

Assinale um quadrado de cada um dos seguintes grupos, indicando qual das afirmações melhor descreve o seu estado de saúde hoje.

1. Mobilidade:
   - ☐ Não tenho problemas em andar
   - ☐ Tenho alguns problemas em andar
   - ☐ Tenho de estar na cama
2. Cuidados Pessoais:
   - ☐ Não tenho problemas com os meus cuidados pessoais
   - ☐ Tenho alguns problemas com os meus cuidados pessoais
   - ☐ Sou incapaz de me lavar ou vestir sozinho(a)
3. Atividades Habituais (trabalho, estudos, atividades domésticas, atividades em família ou de lazer):
   - ☐ Não tenho problemas em desempenhar as minhas atividades habituais
   - ☐ Tenho alguns problemas em desempenhar as minhas atividades habituais
   - ☐ Sou incapaz de desempenhar as minhas atividades habituais
4. Dor/Mal-Estar:
   - ☐ Não tenho dores ou mal-estar
   - ☐ Tenho dores ou mal-estar moderados
   - ☐ Tenho dores ou mal-estar extremos
5. Ansiedade/Depressão:
   - ☐ Não estou ansioso(a) ou deprimido(a)
   - ☐ Estou moderadamente ansioso(a) ou deprimido(a)
   - ☐ Estou extremamente ansioso(a) ou deprimido(a)

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