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(CASE REPORT)

# Treatment of universal hyperpathy and pain threshold control

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## Abstract

This article presents a disease fundamentally characterized by an alteration of the pain threshold. In this disease, the pain threshold can change and, in general, is lower, so pain is perceived before. The cause of the decrease is a continuous pressure stimulus of intensity above or close to the threshold that persists over time. The duration to reduce the threshold will depend on the degree of intensity: It will be longer if it is of lower intensity. In the absence of medication, the decrease in threshold is characterized by a sensation of electrical pain followed by allodynia, hyperalgesia, and dysesthesia in the affected area. The level of pain tolerance in that area drops, so the patient cannot support that area. The disease becomes completely disabling. The patient was diagnosed with universal hyperpathy; in fact, the decrease in the threshold can affect both somatic and visceral pain. Although the disease itself would have a minimum level of incidence worldwide, since the probability of survival of individuals is small, the content presented here is useful for the treatment of hyperpathy and the control of the pain threshold. Carbamazepine and topiramate turn out to be two medications that allow modulation of the threshold. Performing aerobic exercise is also essential. Furthermore, it is necessary to control the stimuli of the afferent pathways at all times, both in duration and intensity.

**Keywords:** Threshold Pain; Hyperpathy; Carbamazepine; Topiramate

## 1. Introduction

Chronic pain is pain that persists after a cured disease or that arises as an alteration of the nervous system itself. Therefore, neuropathic pain involves changes or damage to the somatosensory system. Several options are accepted for the treatment of this condition: anticonvulsants, norepinephrine-serotonin reuptake inhibitors, and tricyclic antidepressants [1]. The first line of treatment for chronic pain includes the use of the first type of drugs. However, in most cases, treatments with antiepileptic drugs are not very effective and are accompanied by side effects that limit their use, especially when they must be carried out in the very long term, as in the case at hand. In general, the prescription of one drug or another corresponds to a trial-and-error strategy.

Pain becomes centralized if the central nervous system becomes sensitized to pain, that is, if the pain threshold becomes lower. There are different mechanisms that can produce central sensitization [2]. Among them, the most interesting related to this article is the change in the genetic expression of $Na^+$ channels both in the nociceptive terminals and in the dorsal root ganglia. It is also interesting to highlight the role of N-type $Ca^{2+}$ channel blockers such as ziconotide. These channels are located in the terminal part of the primary afferent neurons. They reduce synaptic transmission and have powerful antinociceptive effects [3].

Digging deeper into the topic, loss-of-function mutations in the gene that encodes $Na_v1.7$ in humans lead to the inability to feel pain. On the contrary, gain-of-function mutations cause opposite conditions characterized by episodic pain, such as primary erythromelalgia or extreme paroxysmal pain disorder [4]. $Na_v1.7$ is a threshold channel that sets the gain of

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the nociceptors. In fact, blocking this channel in animal models increases the pain threshold [5]. Carbamazepine (CBZ) treatment for painful peripheral neuropathy responded successfully by reinforcing channel inhibition [**Error! Bookmark not defined.**]. Mutations in the $Na_v1.8$ channel also cause neuropathic pain and are treated with CBZ [6].

## 2. Clinical case

This article is based on the case of a 56-year-old man. At 16 years old, due to injury, he spent a long period of time without practicing any type of aerobic exercise. Then he began to experience, first, electrical pain and then, continuously, burning pain in the area of the perineum. The patient suffered allodynia, hyperpathy, hyperalgesia, and dysesthesia in that area that he could not support. Treatment with the most common analgesics: non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids failed. The inability to sit forced the patient to walk and stand for long periods of time, so he began to report the same symptoms on his heels. Intense physical exercise and the use of antishock foams in the supports managed to minimally recover the affected areas [7]. According to the literature, in the case of musculoskeletal pain, aerobic exercise activates descending pain-inhibiting mechanisms and/or endogenous opioid and cannabinoid systems [8]. At age 24, the patient's symptoms reappeared in both areas, he was diagnosed with universal hyperpathy, and was prescribed CBZ (50 mg daily). With this medication, the recovery of the pain threshold was faster (a few months, compared to the previous recovery that lasted several years). However, the patient always had to support the sensitive areas against foams, avoiding stimuli that exceed a certain level. CBZ and aerobic physical activity prevented sudden alterations in the pain threshold. The threshold was always gradually recovered, although it could no longer be returned to its original state.

Threshold variations could also affect visceral pain. Thus, prolonged intravenous infusion of lidocaine (LDC) together with an NSAID caused chronic bladder pain in the patient. Currently, this pain makes it impossible for him to take practically any medication. The only medical test that reflects any significant finding is heel telethermography. Thermograms of both heels show a notable hypoemission pattern. Hyperpathy would deactivate local sympathetic function and pain could be maintained sympathetically [9]. At 55 years of age, the patient had acquired considerable tolerance to CBZ (1200 mg daily) and was prescribed topiramate (TPM, 150 mg daily) with the same success as CBZ. Finally, in this article we wanted to reflect on all the mechanisms of action of the drugs that can have an effect on the management of pain threshold control and, therefore, on the treatment of hyperpathy.

## 3. Treatments and mechanisms of action

Behind chronic pain lies a functional alteration that is generally unknown, to which is added the difficulty of finding an effective treatment. The problem is even greater when this treatment must be maintained throughout the life of the individual, as in the case at hand. 25 years of daily intake of CBZ caused liver damage in the patient that forced him to look for other therapeutic alternatives. The use of CBZ is associated with a high level of serum gamma-glutamyltransferase (GGT) activity. In this sense, TPM allowed these levels to return to normal values, resulting in normalization of the activity of the hepatic CYP450 enzyme system [10].

The key to controlling the pain threshold for both drugs is based on their mechanisms of action. In Table 1 we have collected both. There are several common features in the mechanisms of CBZ and TPM. CBZ and TPM reduce the frequency of sustained repetitive firing of action potentials in central neurons. Specifically, they inhibit high frequency, not low frequency. This effect is exerted on voltage-gated $Na^+$ channels [11,12]. Both drugs also block persistent $Na^+$ currents, transported mainly by the $Na_v1.6$ channel subtype, significantly influencing neuronal excitability [13]. Another essential common characteristic of both drugs is that they modulate voltage-gated $Ca^{2+}$ ion channels [**Error! Bookmark not defined.**,**Error! Bookmark not defined.**]. Specifically, both drugs block the L-type channel [14]. This channel is involved in the processing of synaptic inputs at the somatodendritic neuronal level. TPM also blocks R- and N-type $Ca^{2+}$ currents [**Error! Bookmark not defined.**,**Error! Bookmark not defined.**] and CBZ also has an effect on T-type currents [15]. Both medications affect different receptors [**Error! Bookmark not defined.**,**Error! Bookmark not defined.**,16,17], they also do not coincide in the modulation effect they exert on other systems that could affect pain transmission [**Error! Bookmark not defined.**,**Error! Bookmark not defined.**].

In view of the set of mechanisms, it is clear that two are common to both medications: the inhibition of $Na^+$ and L-type $Ca^{2+}$ channels. These two mechanisms may be responsible for the control of the pain threshold. In fact, the latter channel has a close relationship with migraine control [18]. To reinforce the previous hypothesis, we will discuss the mechanisms of action of other medications that have been used in the treatment of this condition with no success. In Table 1 we also include the mechanisms of action of oxcarbazepine (OXC), a derivative of CBZ with fewer side effects. However, the patient had to stop treatment with this drug due to a constant headache. In principle, OXC is also a blocker

of $Na^+$ and $Ca^{2+}$ channels [**Error! Bookmark not defined.**]. Therefore, it shares the main mechanisms of action of CBZ and TPM. However, the most significant difference is that CBZ interacts with $Ca^{2+}$ channels mediated by L-type $Ca^{2+}$ currents, while OXC exerts its effect through N-, P- and/or R-type currents [**Error! Bookmark not defined.**]. OXC shares another series of common mechanisms with CBZ, as reflected in Table 1, although we do not believe that they are significant for the case at hand [**Error! Bookmark not defined.**,**Error! Bookmark not defined.**].

**Table 1** Mechanisms of action of CBZ, TPM and OXC

| **CBZ** | **TPM** | **OXC** |
|---|---|---|
| -Inhibits neuronal $Na^+$ channels (high freq.) | -Inhibits neuronal $Na^+$ channels (high freq.) | -Inhibits neuronal $Na^+$ channels (high freq.) |
| -Blocks the persistent $Na^+$ current | -Blocks the persistent $Na^+$ current | -Blocks the persistent $Na^+$ current |
| -Inhibits T- and L-type $Ca^{2+}$ channels | -Inhibits R-, N- and L-type $Ca^{2+}$ channels | -Inhibits N-, P- and R-type $Ca^{2+}$ channels |
| -Modulates glutamate (NMDA) receptors | -Modulates glutamate (AMPA/kainate) receptors | |
| -Inhibits NMDA-induced responses | -Inhibits kainate-induced responses | |
| -Modulates adenosine receptors | | -Modulates adenosine receptors |
| -Decreases the release of glutamate | | -Decreases the release of glutamate |
| -Increases the dopaminergic transmission | | -Increases the dopaminergic transmission |
| -Modulates peripheral benzodiazepine receptors | -Modulates $GABA_A$ receptors | -Modulates acetylcholine receptors |
| -Modulates acetylcholine receptors | -Enhances GABA-induced responses | |
| -Decreases the release of cAMP | -Inhibits the production of carbonic anhydrase isoenzymes | |
| -Induces the release of serotonin | | |

**Table 2** Mechanisms of action of GBP, PGB and LDC

| **GBP** | **PGB** | **LDC** |
|---|---|---|
| -Inhibits $Ca^{2+}$ channels (α2δ subunits) | -Inhibits $Ca^{2+}$ channels (α2δ subunits) | -Inhibits neuronal $Na^+$ channels (high, low) |
| -Affects $K^+$ channels | -Affects $K^+$ channels | -Blocks the persistent $Na^+$ current |
| -Decreases the release of glutamate | -Decreases the release of glutamate | -Inhibits neuronal $K^+$ channels |
| -Moderately inhibits HCN channels | | -Modulates glutamate (NMDA) receptors |
| | | -Modulates G-protein coupled (adenosine, $GABA_B$,…) receptors |
| | | -Inhibits HCN channels |
| | | -Inhibits transient receptor potential (TRP) ion channels |
| | | -Inhibits acid-sensing ion channels (ASICs) |
| | | -Modulates acetylcholine receptors |
| | | -Induces the release of serotonin |
| | | -Decreases the release of pro-inflammatory mediators |

The importance of blocking $Na^+$ channels is evident in the failure of other medications such as gabapentin (GBP) or pregabalin (PGB), the latter being considered the successor of the former in terms of its chemical structure. Both are $Ca^{2+}$ channel blockers and have some effect on glutamate release [19] (Table 2). As $Ca^{2+}$ current blockers, they differ from the previous ones in that they have a specific binding site known as α2δ subunit. In the case of PGB, the patient

had to suspend the medication due to the appearance of muscle weakness and contractures as a result of practicing aerobic sports activity.

Hyperpathy at the visceral level, specifically pain in the bladder, appeared after the systematic application of intravenous LDC infusions together with an NSAID, specifically ketorolac. The main cause of pain undoubtedly points to this second drug. LDC is a local anesthetic that shares, with CBZ and TPM, its ability to block $Na^+$ channels [20-22] . In fact, $Na_v1.8$ is five times more sensitive to LDC than $Na_v1.7$ or the rest of the channels [**Error! Bookmark not defined.**]. Hyperpathy did not respond to treatment with this drug, implying that there are supraspinal mechanisms different from inhibition of $Na^+$ channels. By comparing the mechanisms of CBZ and LDC, we can also rule out the possibility that NMDA or adenosine receptors, or even serotonin release, have effects in this disease.

The patient also received several intrathecal injections of a potent local anesthetic, bupivacaine [23, 24] (BPV), as treatment, also without success. BPV has a prominent blocking effect on voltage-gated $Na^+$ and $K^+$ channels [**Error! Bookmark not defined.**,25] (Table 3). It coincides with CBZ and TPM in blocking the former type of channels. However, BPV also inhibits NMDA receptors and NMDA-evoked currents. NMDA receptors play a key role in dorsal horn plastic events responsible for central sensitization. CBZ also shares this characteristic, which suggests, as we had said before, that its influence is minor in this condition. BPV can also inhibit L-type $Ca^{2+}$ channels if injected into the blood circulation; however, it is cardiotoxic, which excludes its therapeutic use through that route in that case [26].

**Table 3** Mechanisms of action of BPV, LCS and LTG

| **BPV** | **LCS** | **LTG** |
|---|---|---|
| -Inhibits neuronal $Na^+$ channels (high, low)<br>-Blocks the persistent $Na^+$ current<br>-Inhibits neuronal $K^+$ channels<br>-Modulates glutamate (NMDA) receptors<br>-Inhibits NMDA-induced responses | -Inhibits neuronal $Na^+$ channels (low)<br>-Inhibits neuronal $Na^+$ currents<br>-Inhibits the production of carbonic anhydrase isoenzymes | -Inhibits neuronal $Na^+$ channels (high, low)<br>-Inhibits neuronal $Na^+$ currents<br>-Inhibits N-, P- and Q-type $Ca^{2+}$ channels<br>-Decreases the release of glutamate and aspartate<br>-Enhances GABA-induced responses<br>-Activates HCN channels<br>-Reduces neuroinflammation<br>-Has neuroprotective effects |

Two other antiepileptic drugs, lacosamide (LCS) and lamotrigine (LTG), used to treat neuropathic pain, also failed to control the pain threshold. These medications once again produced chronic pain in the patient at the visceral level (bladder pain), so the patient's intolerance was immediate. LCS, unlike CBZ and TPM, enhances the slow inactivation of $Na^+$ channels [27]and does not block $Ca^{2+}$ channels. It has the same effect as TPM on carbonic anhydrases, which could rule out the influence of this factor on hyperpathy. For its part, LTG inhibits slow and fast activating $Na^+$ channels in addition to permanent currents [**Error! Bookmark not defined.**,28]. In this sense, its characteristics are similar to those of the CBZ and the TPM. However, LTG inhibits R-, N- and P-type $Ca^{2+}$ channels [29, 30], but not L-type channels. This fact would rule out its effectiveness in the treatment of hyperpathy.

**Table 4** Mechanisms of action of DLX, AMT and PRX

| **DLX** | **AMT** | **PRX** |
|---|---|---|
| -Inhibits the reuptake of serotonin and noradrenaline<br>-Induces the release of dopamine | -Transports the reuptake of serotonin and noradrenaline<br>-Induces the release of serotonin and noradrenaline | -Selectively inhibits the reuptake of serotonin |

During some episodes of prevalence of the disease (low threshold), the patient has suffered depressive episodes. Table 4 shows the mechanisms of action of some treatments that the patient has received. Duloxetine (DLX) and amitriptyline (AMT) caused intolerance in the patient, while paroxetine (PRX) was the only well tolerated drug. DLX is a serotonin

and noradrenaline reuptake inhibitor [31] while AMT, a tricyclic antidepressant, is a serotonin and noradrenaline reuptake transporter [32]. Even the last drug is used in the treatment of chronic pain. However, both medications lack direct use in controlling the threshold, since they cause chronic pain. In fact, everything points to the use of selective inhibitors for the treatment of depression in these patients.

The use of a centrally acting analgesic with a morphine-related mechanism of action also had no significant effect on the patient. Specifically, we would be referring to tramadol (TMD) [33]. This fact would indicate that opioid agonists (Table 5) are not effective drugs in this condition. We cannot assess whether it causes intolerance because the patient took it before LDC infusions.

**Table 5** Mechanisms of action of TMD, ZNS and FLN

| TMD | ZNS | FLN |
|---|---|---|
| -Weakly modulates the μ opioid receptors<br>-Inhibits the reuptake of serotonin and noradrenaline | -Inhibits neuronal $Na^+$ channels (high)<br>-Inhibits neuronal T-type $Ca^{2+}$ channels<br>-Increases the dopaminergic transmission<br>-Increases the serotonergic transmission<br>-Induces the release of GABA<br>-Has neuroprotective effects | -Inhibits neuronal $Na^+$ channels (high)<br>-Inhibits neuronal $Na^+$ currents<br>-Inhibits T- and L-type $Ca^{2+}$ channels<br>-Induces the release of serotonin<br>-Reduces neuroinflammation |

Finally, we discuss two other drugs prescribed to the patient that allow us to draw some final conclusions. One of them is an anticonvulsant, zonisamide (ZNS). The effect of ZNS is based on the blockage of repetitive firing of voltage-gated $Na^+$ channels [***Error! Bookmark not defined.***] and the reduction of voltage-sensitive $Ca^{2+}$ currents (Table 5) [34]. This drug did not produce any results in the treatment of this condition, probably because it blocks T-type currents. In fact, it also caused him intolerance. The rest of the properties do not seem to be decisive [35]. There are several drugs with a very similar profile to ZNS. Among them, we can mention eslicarbazepine acetate [36], which is a derivative of carbamazepine that shares its basic chemical structure, phenytoin [37] or valproic acid [38], these last two with quite a few side effects.

The last drug prescribed is flunarizine (FLN). This medication also shares the same mechanism of action as CBZ and TPM [***Error! Bookmark not defined.***,39,40] (Table 5), although it is primarily a $Ca^{2+}$ channel blocker. It also has few side effects. This medication is prescribed for migraine, a disease that involves ion channels and many neurotransmitter systems. Its use made it possible to successfully replace part of the TPM dose. This fact confirms the initial hypothesis that hyperpathy is controlled by inhibiting $Na^+$ and L-type $Ca^{2+}$ channels.

## 4. Conclusions

Universal hyperpathy is a rare disease characterized by alterations in the pain threshold. If painless stimuli are perceived as painful by the individual, this patient sees their daily life completely altered. Pain manifests itself especially in the musculoskeletal system in the support areas, mainly the heels and perineal area, which for some reason have suffered sensitization above the threshold. However, it can also appear as visceral pain.

The physiological mechanism responsible for controlling the threshold, as concluded in this article, is the blockade of voltage-dependent $Na^+$ channels and L-type $Ca^{2+}$ currents. Therefore, the most effective drugs for the treatment of this disease or, if preferred, for controlling the threshold are carbamazepine and topiramate. However, we should not forget that the descending inhibitory mechanisms induced by physical activity also intervene in the control of the threshold, as well as the absence of afferent (sensitive) activity of the peripheral nervous system during this activity.

## Compliance with ethical standards

*Statement of Ethical Approval*

The authors consider that the study carried out complies with all applicable ethical requirements.

*Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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