

## Mechanisms and clinical management of pain\*

Patrick Raymond Nicolas Andre  
Ghislain Stump<sup>(a)</sup>  
Gisele da Silva Dalben<sup>(b)</sup>

<sup>(a)</sup>Pain Group of Hospital das Clínicas,  
Faculdade de Medicina, Univ de São Paulo  
- USP, São Paulo, SP, Brazil.

<sup>(b)</sup>Pediatric and Community Dentistry Sector,  
Hospital de Reabilitação de Anomalias  
Craniofaciais - HRAC, Univ de São Paulo -  
USP, Bauru, SP, Brazil.

**Abstract:** Pain is an unpleasant, sensitive and emotional experience associated with or described in terms of tissue lesion, and may be acute or chronic. It may also be classified as nociceptive, neuropathic or psychogenic. Nociceptive pain involves the transformation of environmental stimuli into action potentials carried to the central nervous system, where they are modulated and integrated up to final interpretation in the cerebral cortex. Neuropathic pain may arise as a consequence of the direct lesion of axons, or of an increase in the production of neurotrophic factors. Chronic pain is always associated with anxiety and some degree of depression. Drug therapy should be selected according to its efficacy; nonetheless, the professional should also consider the tolerability and adverse effects that may occur, for example, in elderly individuals. It is necessary to emphasize the safety—considering the possibility of drug interactions—and define the posology to promote better adherence. However, the treatment of neuropathic pain should not be limited to the use of analgesic drugs, which are just one among several options enabling patients to participate in bio-psycho-social rehabilitation programs.

**Descriptors:** Pain; Myofascial Pain Syndromes; Drug Therapy; Therapeutics.

\*Paper presented at the “Oral Health Under an Integrality Perspective” International Symposium, held at the 17<sup>th</sup> Congress of the Brazilian Association for Oral Health Promotion (ABOPREV), May 31 to June 2, 2012, Salvador, BA, Brazil.

**Declaration of Interests:** The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

**Corresponding Author:**  
Gisele da Silva Dalben  
E-mail: [gsdalben@usp.br](mailto:gsdalben@usp.br)

### Introduction

Sensation is the “mental process (such as seeing, hearing, or smelling) resulting from the immediate external stimulation of a sense organ often as distinguished from a conscious awareness of the sensory process.” Perception, in turn, is the “awareness of the elements of environment through physical sensation [alone], or a physical sensation interpreted in the light of experience.” It is currently known that pain is not a sensation, except when it acts as an alert; rather, pain is a perception.

Pain is defined by the International Association for the Study of Pain (IASP) as an “unpleasant sensitive and emotional experience, associated with or described in terms of tissue lesion.”<sup>1</sup> It may be classified as acute, when it plays an alerting role, or chronic, when it becomes a symptom that worsens the quality of life, and thus loses its protective function. Pain may also be considered as chronic when it lasts over three to six months.

Pain may be classified according to its physiopathological mechanism, as nociceptive, neuropathic or psychogenic. Nociceptive pain is triggered by algogenic substances released at the site of the inflammation. These

Submitted: Sep 03, 2012  
Accepted for publication: Oct 02, 2012  
Last revision: Oct 23, 2012

substances reduce the excitation threshold and give rise to nerve impulses in nerve endings.<sup>2</sup> Neuropathic pain is defined as a chronic pain triggered or caused by a lesion that affects both the central and the peripheral somatosensory nervous system.<sup>2</sup> Psychogenic pain is rare and should be diagnosed according to positive psychopathogenic bases, such as hysteria and depression, and is not to be confused with the humor disorders caused by the pain status.<sup>1</sup>

## Discussion

### Mechanism causing nociceptive pain

First, intensive physical or chemical environmental stimuli are transformed into action potentials that are carried by thin A $\delta$  and unmyelinated C fibers from the free nerve endings to the central nervous system, where they are modulated and integrated in different levels of the neural axis (medulla, mesencephalon and thalamus) up to final interpretation in the cerebral cortex. In the case of tissue lesion, there is a release of several substances, such as bradykinin, acetylcholine, glutamate, adenosine, ATP, serotonin, histamine, H<sup>+</sup>, K<sup>+</sup> and prostaglandins. Inflammation-causing prostaglandins are produced from arachidonic acid by enzymatic reactions. The isoform of cyclooxygenase 2 (COX2) is responsible for the release of prostaglandins Pge2 and Pgh, which sensitize the free nerve endings in both the periphery and the central nervous system via interleukin. When the inflammatory process persists, there are changes in the plasticity of the peripheral and central nervous system. These changes facilitate the perpetuation of pain regardless of the intensity of the stimuli. This process is called central sensitization.<sup>3</sup>

In dentistry, nociceptive pain may occur in the presence of gingivitis, and infectious or inflammatory disorders.

### Mechanisms generating neuropathic pain

In the peripheral nervous system, neuropathic pain may arise as a consequence of the direct lesion of axons. This lesion may trigger ectopic discharges, which reach the central nervous system and are interpreted as pain coming from the region of corresponding innervation. Neuropathic pain may also

be caused by a greater production of neurotrophic factors. This increase may lead to hyperexcitability of the partially damaged axon, as well as of intact adjacent axons.<sup>4</sup>

The central mechanisms involved in the genesis of neuropathic pain are related to an imbalance between mechanisms of inhibitory control and facilitators of pain impulse transmission. The reorganization of synaptic connections may occur from the lesion of thin C and A $\delta$  fibers (nociceptive), leading to the atrophy of nerve endings in the dorsal root. Consequently, A $\beta$  fibers (tactile) may appear toward the free synapses, widening the receptive field of the pain stimulus.<sup>4</sup> Trigeminal and glossopharyngeal neuralgias are some examples of neuropathic pain in the orofacial region. Other neuropathic disorders include iatrogenic accidents related to dental anesthesia and burning mouth syndrome.

### Models for management of chronic pain

Two models are available for the management of chronic pain:

- the End-Organ Dysfunction Model, based on tissue lesion and respective functional alteration, in which the symptoms reflect the structural anomaly; and
- the Altered Nervous System Processing Model, based on central sensitization, nociceptive stimuli from other structures, hypersensitivity, and genetic and psychological factors, with emphasis on a higher susceptibility to pain. This model considers that pain-activated areas are different for each patient, and that different pathologies cause changes in certain areas of the brain.

### Clinical status

Nociceptive pain may present a “mechanical” rhythm as the pain worsens through the course of the day and as the structure is loaded, and may exacerbate with rest, especially low back pain and arthritis. There may also be an “inflammatory” rhythm when the pain worsens with rest; this frequently occurs during the night, especially in spine metastasis.

Neuropathic pain may appear spontaneously and continuously, usually described as “burning, pungent or badly defined,” or else paroxysmally,

described as “in shock, stinging, piercing or acute,” and both forms may occur concomitantly. The pain may also be caused and be referred to as intense, or even unbearable when something that should not cause pain gently touches the skin (for example, when a shirt touches someone on his trunk in individuals with postherpetic intercostal neuralgia).

There are direct measures to characterize the nature of pain in regard to sensitive, affective, cognitive and behavioral impact. Several scales may be used:

- the visual analogue scales (VAS), used to analyze the intensity of pain;
- the McGill pain questionnaire, used to analyze the properties of pain;
- the neuropathic pain scale, applied to determine the different qualities of pain associated to neuropathic pain syndromes.

Indirect measures may also be used to estimate the impact of pain on the quality of life. These measures are used in questionnaires to assess functional deficiencies, social losses, behavior disturbances, as well as sleep disorders.

Reevaluations at regular intervals are highly valid for monitoring and recording treatment effects.

### Physical examination

Physical examination allows determining the presence of a nerve lesion and differentiating it from other mechanisms of chronic pain, such as skeletal muscle, inflammatory, myofascial or psychogenic triggers.<sup>5</sup>

Neurological examination is fundamental and may determine the topography of the lesion through positive and negative signs (central: encephalic or medullary; peripheral: radicular, plexular, trunk, mono or polyneuropathic), degree of involvement (total or partial), and types of affected nerve fibers (sensitive: myelinated or unmyelinated, motor and neurovegetative).

Sensory testing may reveal:

- Hyperalgesia: exacerbated and disproportional reaction to usually painful stimuli (investigated with a needle).
- Allodynia: painful or unpleasant sensation

caused by usually non-painful thermal or mechanical stimuli (investigated with cotton and test tubes containing cold or hot water).

- Hyperpathia: exacerbated reaction to intense or repeated painful stimuli applied in hypoesthetic regions.<sup>4</sup>

There are several tools currently available to aid in diagnosing neuropathic pain, such as the DN4 questionnaire (neuropathic pain 4) designed by Bouhassira *et al.* in 2004<sup>6</sup> and validated to Brazilian Portuguese in 2008.<sup>7</sup> This questionnaire is composed of two sections. The first is an interview composed of seven aspects, in which the first three of these refer to the characteristics of pain, and the next four aspects are related to symptoms felt in the painful area. The second section is related to the physical examination, which assesses the tactile sensitivity to pain in the area of pain, as well as the presence of allodynia. The examiner assigns one point to each item analyzed if the response is yes, and zero if the response is no. When the sum of partial results is equal to or higher than four, the patient is considered as having neuropathic pain. DN4 sensitivity is 82.9% and specificity is 89.9%<sup>6</sup> (Figure 1).

A detailed muscular and skeletal examination is fundamental to evaluate the joint status, edema, flo-gistic signs, limitation of movement angles, antalgic posture, etc. The trigger points should also be evaluated routinely, due to the high prevalence of myofascial pain syndrome in chronic pain of any etiology.

### Auxiliary examinations

There are no specific auxiliary examinations for pain in general or for neuropathic pain specifically. Examinations are important to aid in diagnosing the base pathology causing the neural lesion, such as glycemia in diabetic polyneuropathy, or else imaging examinations in cervical or lumbar compressive radiculopathies.

The functional evaluation of the peripheral nervous system is performed by electromyography and analysis of the conduction rate. This technique provides information on the functional status of thick myelinated nerve fibers, but does not allow assessment of thin myelinated and unmyelinated fibers.

**Figure 1** - DN4 questionnaire (neuropathic pain 4).

<p><b>PATIENT INTERVIEW</b></p> <p>Question 1: Does your pain have one or more of the following characteristics?</p> <ol style="list-style-type: none"><li>1. Burning</li><li>2. Painful cold</li><li>3. Electric shock</li></ol> <p>Question 2: Is the pain associated with one or more of the following symptoms in the same area?</p> <ol style="list-style-type: none"><li>4. Tingling</li><li>5. Pins and needles</li><li>6. Numbness</li><li>7. Itching</li></ol> <p><b>PATIENT EXAMINATION</b></p> <p>Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?</p> <ol style="list-style-type: none"><li>8. Touch hypoesthesia</li><li>9. Pricking hypoesthesia</li></ol> <p>Question 4: In the painful area, can the pain be caused or increased by:</p> <ol style="list-style-type: none"><li>10. Brushing</li></ol>
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These may be visualized in biopsies of peripheral nerves.

Quantitative tests of thermal sensitivity are used to differentiate minimal variations of thermal stimuli (evaluation of thin fibers). These require patient compliance and the use of sophisticated techniques and machines, and are restricted to applications in research.

Functional magnetic resonance allows observation of alterations in the brainstem, thalamus, sensorial cortex, cingulate gyrus and insula, and aids in diagnosing pain of central origin. This method may be available in the near future for daily clinical practice.

The cornerstone of treatment is diagnosis, which frequently requires evaluation by several specialists owing to the complexity involved.

## Treatment

Pharmacological therapy is the first line of pain treatment, yet it is not the only available option. Evidence suggests that early and aggressive treatment

of acute pain may prevent progression to a chronic pain status. The treatment of patients experiencing pain initially entails treating the base pathology and removing the causal factor, should it still persist or should this be possible.

Selection of the most appropriate drug therapy depends on the efficacy demonstrated in clinical studies, tolerability, patient profile and potential adverse effects in specific populations (e.g. elderly individuals), as well as possible drug interactions, when addressing underlying diseases in the case of patients under polytherapy. It is important to adopt a simple posology scheme to allow better adherence.<sup>8</sup>

## Drug therapy for pain

Drugs for nociceptive and neuropathic pain with efficacy demonstrated by randomized and controlled studies have different mechanisms of action, which allow associations when necessary. Anti-inflammatories and analgesic drugs are the most widely used for nociceptive pain, and anticonvulsants and tricyclic antidepressants for neuropathic pain.

### Drug therapy for nociceptive pain

#### Non-steroidal anti-inflammatory drugs (NSAIDs)

The mechanism of action of these drugs is the inhibition of cyclooxygenase (COX, both COX-1 and COX-2), an enzyme that catalyzes the conversion of arachidonic acid in intermediate unstable cyclic endoperoxides (prostaglandins, prostacyclins) involved in the inflammatory process and the sensitization of central and peripheral pain units.

#### Drug therapy for neuropathic pain

The guidelines suggested by both the European Federation of Neurological Societies and the American Pain Society suggest the treatment of neuropathic pain in a hierarchic manner. Medications qualify as first-line if their efficacy was demonstrated in blind, randomized and multicenter studies. Second-line drugs present similar efficacy, yet involve a risk of addiction. The efficacy of third-line medications is based on current clinical practice<sup>9,10</sup> (Table 1).

## Conclusion

The treatment of neuropathic pain should not be limited to analgesic drugs, which are just one among several alternatives enabling patients to participate in bio-psycho-social rehabilitation programs.

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**Table 1** - Drugs indicated for the treatment of pain in the United States (US) and Europe.

Therapy	US	Europe
First-line medications	<ul style="list-style-type: none"> <li>• Antidepressants (tricyclic and dual inhibitors)</li> <li>• Calcium channel ligands (gabapentin)</li> <li>• Topical lidocaine (for example, for post-herpetic neuralgia)</li> </ul>	<ul style="list-style-type: none"> <li>• Tricyclic and dual antidepressants</li> <li>• Gabapentin</li> <li>• Pregabalin</li> </ul>
Second-line medications	<ul style="list-style-type: none"> <li>• Tramadol (adrenalin and noradrenalin reuptake)</li> <li>• Opioids</li> </ul>	<ul style="list-style-type: none"> <li>• Opioids</li> <li>• Lamotrigine</li> </ul>
Poor efficacy		<ul style="list-style-type: none"> <li>• SSRI (selective serotonin reuptake inhibitors)</li> <li>• Capsaicin</li> <li>• Mexiletine</li> <li>• Oxcarbazepine</li> <li>• Topiramate</li> </ul>
Weak evidence of efficacy and concern over safety	<ul style="list-style-type: none"> <li>• Antiepileptics</li> <li>• Antidepressants</li> <li>• NMDA receptor antagonists</li> <li>• Mexiletine</li> <li>• Capsaicin</li> <li>• Cannabinoids</li> </ul>	<ul style="list-style-type: none"> <li>• Carbamazepine</li> <li>• Valproate</li> </ul>