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Fisiopatologia da Dor Crónica

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Resumo

A dor crónica é considerada uma experiência desagradável, pessoal, com carácter multidimensional, associada a um alto impacto socioeconómico, na medida em que é uma das principais causas de sofrimento, bem como de baixa produtividade e de incapacidade laboral. Devido à sua alta prevalência e impacto, constitui um dos principais motivos para a procura de cuidados de saúde por parte da população em geral. É considerada um problema de saúde pública cada vez mais frequente, afetando cerca de 40 % da população portuguesa. Pode ser definida como uma dor persistente ou recorrente, com uma duração superior a 3-6 meses, cuja função protetora deixa de existir, passando a ter um papel prejudicial para o organismo.

Muito embora os processos fisiopatológicos estejam identificados e bem compreendidos nos casos da dor crónica de etiologia nociceptiva ou neuropática, há ainda dificuldade em compreender claramente os mecanismos que estão na origem de doenças como a fibromialgia, em que fenómenos de sensibilização central estão presentes, na ausência de lesão tecidular ou de compromisso nervoso. Sabe-se, porém, que a cronicidade da dor está intimamente relacionada com os fenómenos de sensibilização periférica e central que sinergicamente causam um aumento do estímulo álgico perpetuado no tempo.

A presente revisão foca-se nos mecanismos fisiopatológicos que estão na base das diversas etiologias de dor crónica, explorando os fenómenos que vão desde a receção do estímulo pelos nociceptores à perceção e integração do estímulo álgico a nível cerebral.

Por fim, um papel de destaque é dado à terapia farmacológica e não farmacológica da dor crónica, bem como às últimas inovações neste campo, que permitirão, a longo prazo, uma abordagem mais racional e individualizada da terapia, diminuindo a incidência de efeitos secundários desnecessários e aumentando significativamente a qualidade de vida dos doentes.

Palavras Chave: Fisiopatologia, Nociceptividade, Sensibilização do Sistema Nervoso Central, Neuralgia, Dor Crónica, Tratamento Farmacológico

Abstract

Chronic pain is considered an unpleasant, personal experience, with a multidimensional character, associated with a high socioeconomic impact, as it is one of the main causes of suffering, as well as low productivity and incapacity for work. Due to its high prevalence and impact, it is one of the main reasons for the demand for health care by the general population. It is considered a public health problem more and more frequent nowadays, affecting about 40% of the portuguese population. It can be defined as a persistent or recurrent pain, lasting more than 3-6 months, whose protective function ceases to exist, having a harmful role for the body.

Although pathophysiological processes are identified and well understood in cases of chronic pain of nociceptive or neuropathic etiology, there is still difficulty in clearly understanding the mechanisms that cause diseases such as fibromyalgia in which central sensitization phenomena are present, in the absence of tissue damage or nervous compromise. However, it is known that the chronicity of pain is closely related to the phenomena of peripheral and central sensitization that synergistically cause an increase in the pain stimulus perpetuated over time.

This review focuses on the pathophysiological mechanisms that underlie the various etiologies of chronic pain, exploring the phenomena that range from nociception to the perception and integration of pain stimulus at the brain level.

Finally, a prominent role is given to pharmacological and non-pharmacological therapy for chronic pain, as well as the latest innovations in this field, which will allow, in the long term, a more rational and individualized approach to therapy, reducing the incidence of unnecessary side effects and significantly increasing patient's quality of life.

Keywords: Physiopathology; Nociception; Central Nervous System Sensitization; Neuralgia; Chronic Pain; Drug Therapy

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Introduction

Pain is a complex and subjective experience that can be understood based on our personal, social and cultural motivations, therefore, conditioning the way we accept and communicate it. It can be defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensorial and emotional experience associated with actual or potential tissue damage or described in terms of such damage”.(1)

While acute pain is critical for survival, mandatory for the removal of the harmful factor, chronic pain has been recognized as pain that persists over normal healing time, hence lacking the acute warning function of physiological nociception, lasting or recurring for more than three to six months.(2,3) The transition from acute to chronic pain states has, in most of the cases, a direct relation to a well-known process called sensitization; the overall processes are not fully understood, although it is known that the chronicity of pain is under the control of spinal cord and brain at different levels.

In Portugal, chronic pain has a prevalence of 37 % in the general adult population.(3) The symptoms of chronic pain may manifest as spontaneous pain or in a form of abnormal response to a painful stimuli (hyperalgesia) and exaggerated response to non-painful stimuli (allodynia) states associated with negative affective and cognitive conditions and a persistent desire to eliminate pain by pharmacological or behavioural interventions.(4) In chronic pain, the efficacy of the nervous system to generate pain is increased due to altered sensitivity within cortical and spinal nociceptive networks. This complex phenomenon, which will be discussed later in this review, is called sensitization and creates a nonlinear relationship between nociceptive input, tissue damage and pain**.**(5) There are now enough studies showing that patients with chronic pain have alterations in brain regions involved in cognitive and emotional modulation of pain. This might explain the relation between anxiety and depression with long-term pain: patients are more prone to have psychological disorders when suffering chronic pain conditions and vice versa**.**(6)

Besides the temporal aspect, pain can be classified based on its pathophysiology, with specific mechanisms identified, as happens in nociceptive and neuropathic types, or having an unknown etiology, as in central hypersensitivity pain states like fibromyalgia or irritable bowel syndrome.(7) Pain can also have central or peripheral origin, a localized, generalized or referred distribution, low, medium or high intensity and also be caused by diverse type of injury: thermal, chemical, mechanical, ischemic, etc.).(1)

Based on the different etiologies, there are different pharmacological and non-pharmacological options to treat pain conditions and, by knowing its pathophysiology mechanisms, it is possible to develop more rational and individualized treatment approaches.(8)

The goal of the present review is to understand the pathophysiology mechanisms involved in all types of chronic pain, and to illustrate the most relevant clinical disorders in which chronic pain is present, as a symptom or as a disease. The ultimate goal is to develop a more specific and optimized therapy with the latest pharmaceutical innovations and reduce the overconsumption of opioid drugs, which have severe comorbidities associated. This is a highly important subject, considering the impact of chronic pain in our population, being one of the major causes of incapacity, low productivity of our workers and high health coast, but also in a social and economic scale.

Methods

For the elaboration of this review it was performed a bibliographic research of scientific articles and publications based on the theme of “Pathophysiology of Chronic Pain”. The resource source was mainly PUBMED using the combinations “chronic pain mechanisms” and “chronic pain management”. As inclusion and exclusion criteria was defined: online articles and publications between January of 2009 and December of 2019, regarding human species, and articles obtained for free, written in Portuguese or English. That way, after identification of 1327 articles, 105 were chosen by original title. After reading the abstracts 50 articles were chosen and those were the basis of the realization of this article. Additionally, the scientific magazine National Geographic was consulted for further examining specific themes.

Basic Pain Mechanisms

- **Pain transmission**

In order for pain to be experienced, four basic mechanisms must occur in the process of nociception: transduction, transmission, modulation and perception.

The first represents the physiological conversion of an intense (noxious) thermal, mechanical or chemical stimulus into activity in a non-sensitized nociceptor; transmission occurs in the neuronal pathways with the transmission of electrical events, while neurotransmitters in the synaptic cleft transmit information from a pre-synaptic terminal of one cell to a post-synaptic terminal of another. Modulation occurs in the dorsal horn; there are interactions between afferent neurons, interneurons and descending modulatory pathways and the balance between excitatory transmission and inhibitory signalling from descending pathways and interneurons determines whether or not pain signalling to higher brain centers occurs. Finally, perception occurs with integration of the neuronal information on the somatosensory cortex.(9,10,11)

The basic pain mechanisms can be better understood based on Figure 1.

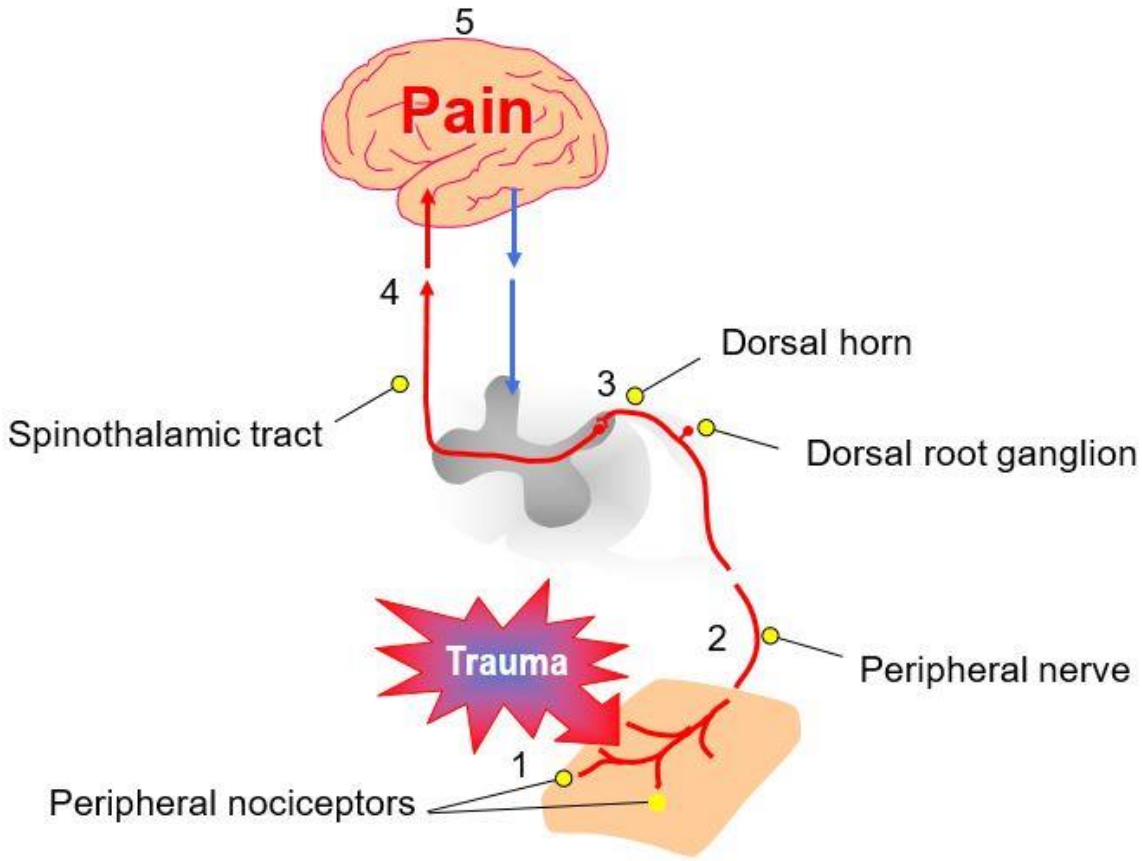

Figure 1- Basic route pain transmission*. In the somatosensory system, the transduction of painful stimulus perceived in the skin (**1**) by the nerve endings can generate an action potential on the nociceptors leading to depolarization through changes in the ion influxes. After depolarization, the information is transmitted via the afferent fibers, either A δ or C fiber **(2**) into the dorsal horn of the medulla **(3**), where modulation occurs through an interneuron, which can cause a normal reflexive acute painful stimulus or a pathophysiology chronic pain stimulus, according to the neurotransmitters present. At this point, a second order neuron will ascend through either a spinothalamic (**4**), spinoreticular or spinomesencephalic tract and then it will reach the thalamus, which at this point will synapse with a 3rd order neuron and project to a somatosensory cortex **(5)**. Image courtesy from lectures of Prof. Dra[a] Anabela Mota Pinto.*

- **Pain receptors and primary afferents**

Nociceptors are sensory end organs present in many body tissues like skin, muscle, joints, viscera, etc. When activated, they selectively respond to noxious or potentially tissue-damaging stimuli. Nociceptors excitability can be increased; therefore, a process called sensitization can happen as a consequence of tissue insult and/or inflammation. Sensitization is defined as a reduction in the threshold and an increase in the magnitude of a response to noxious stimulation.(11)

Structurally, nociceptors include the axon, cell body and central terminals associated with that end organ and their endings are uncapsulated, thus, they are called “free”.

Afferent nerve fibers, referred in the Peripheral Nervous System (PNS) as sensory fibers can be divided in three different types (A, B and C) based on myelination and speed conduction.(1) Sensory fibers terminate in the posterior grey columns of spinal cord, a place organized in Rexed laminae (I-VI), as evidenced in Figure 2.

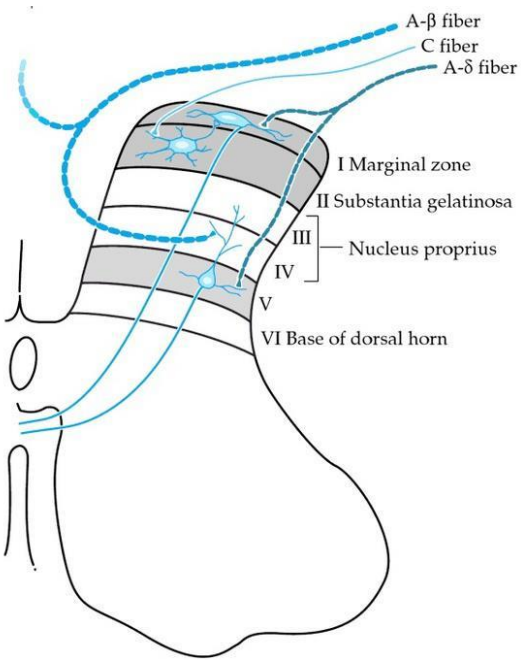

Figure 2 - Posterior grey column Rexed laminae*. The Rexed laminae represent an architectural classification of the structure of the spinal cord, based on the cytological features of the neurons in different regions of the grey substance. It consists of ten laminae (I–X), divided in the posterior(I-VI),*

lateral (VII and X) and anterior (VIII-IX) grey columns. In this image, the posterior grey column is evidenced. The subdivision in six areas illustrates the specific place where the different afferent nerve fibres (Aβ, Aδ and C) end. Adapted from Laminas de Rexed [Internet]. 2013. Available from: http://neurophilum.blogspot.com/2013/01/laminas-de-rexed.html.(12)

Globally, the Rexed laminae comprise a system of ten layers of grey matter (posterior, anterior and lateral grey columns). Group A fibers are myelinated and generally terminate in laminae I, III, IV and V of the dorsal horn (DH) of the spinal cord, with some lamina II inner projection.(10) Aβ fibers have some projections in Rexed lamina IV and V, being thick and highly myelinated, with a high speed conduction of impulses. In physiologic conditions they do not contribute for pain perception; on the other hand, their stimulation can reduce pain perception. Aδ are other type of myelinated fibers ending in Rexed lamina I and V, responsible for the sharp well localized pain, suddenly after the stimulus. Finally, C fibers project in lamina I and II, in a zone called central gelatinous substance, where there are also some Aβ projections. (13)They have an inferior diameter and are slowly, non-myelinated fibers. Their role is on the transmission of the diffuse, unspecific pain (like burning, for instance).(1) The basic characteristics of sensory afferent fibers are illustrated on Table 1.

Table 1 - Main characteristics of primary afferent fibers – *Adapted from Das V. An introduction to pain pathways and pain "targets." Prog Mol Biol Transl Sci. 2013;74(12):1–30.* (14)

	Aδ fibers	**Aβ fibers**	**C fibers**
Diameter	1-5 µm	6-12 µm	0.2-1.5 µm
Myelination	Thin	Highly	No
Conduction velocity	3- 30 m/s	33- 75 m/s	0.5 – 2.0 m/s
Receptor activation thresholds	High and low	Low	High
Sensation on stimulation	Sharp, immediate and rapid pain	Light touch, non-noxious	Slow, diffuse, dull pain

There are different subpopulations of C nociceptors: C "peptidergic" nociceptor subpopulation is defined by the presence of one or both neuropeptides - substance P (SP) and calcitonin gene–related peptide (CGRP). This subpopulation expresses the nerve growth factor (NGF)

receptor Tropomyosin receptor kinase A (TrkA). On the other hand, the C “non peptidergic” nociceptors are defined by the expression of a receptor for the glial cell line-derived family of neurotrophic factors (RET) and most of them also bind isolectin B4 and express the purinergic P2X3 receptor.(11)

There is an enormous heterogeneity in nociceptors. One common criterion is the response profile of the afferent: afferents that respond to mechanical, thermal and chemical stimuli are referred to as polymodal nociceptors. On the other hand, those that respond to mechanical and cold stimuli are referred to as mechano-cold (C-MC) fibers, and those that do not respond to mechanical stimuli are referred to as silent C nociceptors (MIAs).(11)

Another classification is based on the expression of certain receptors, associated with ion channels like transient receptor potential cation channel V1 (TRPV1) , melastatin-like transient receptor potential 8(TRPM8) , acid sensing ion channel (ASIC) and transient receptor potential ankyrin (TRPA1).(15)

- **Ascendant pain pathways**

After the convergence of primary afferent neurons in the dorsal horn of spinal cord, the somatosensory information must reach higher brain centers, including the thalamus, the brainstem and the amygdala. In order to do so, there are two different sensory pathways: lemniscal and extralemniscal pathways. The dorsal column medial lemniscal system (mechanosensory pathway) is related to the transmission of sensorial discriminative tactile (epicritic) information in a fast and very precise way (temporal and spatial). It concerns both sense of positioning (conscious proprioception) and light pressure variations**.**(1)

The extralemniscal tract is located in the anterolateral (also called ventrolateral) quadrant of the contralateral half of the spinal cord and consists of two parts: the lateral spinothalamic and anterior spinothalamic tracts (Figure 3). The first one carries information about temperature and pain (protopathic sensation); the second one is related to crude touch and firm pressure sensation.(10)

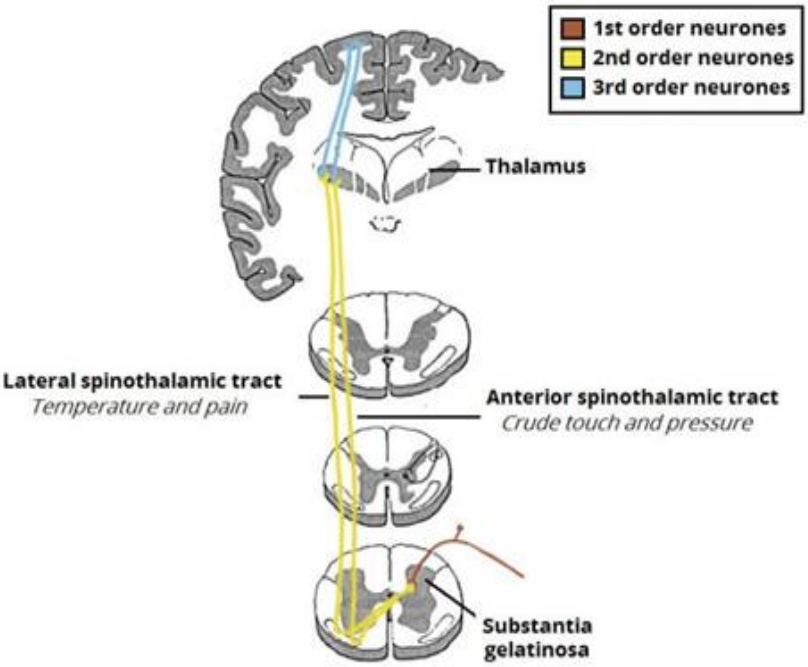

Figure 3 -*The spinothalamic tracts*. *On its ascending way, after decussate into the other side of the spinal cord ,via the anterior white commissure, the second order neurons will arise in the lateral and anterior spinothalamic tracts, transmitting pain, temperature , pressure and crude touch information respectively. The neurons ultimately synapse with third-order neurons in ventroposteriorlateral (VPL) nucleus of the thalamus, and from there project in the primary somatosensory cortex establishing pain perception. Adapted from Oliver Jones. The Ascending Tracts [Internet]. 2018. Available from: https://teachmeanatomy.info/neuroanatomy/pathways/ascending-tracts-sensory/.*(16)

The location of the spinothalamic tract is clinically important, because there is a phenomenon called dissociative sensory loss, that can happen, resulting from a unilateral spinal lesion. (Figure 4).

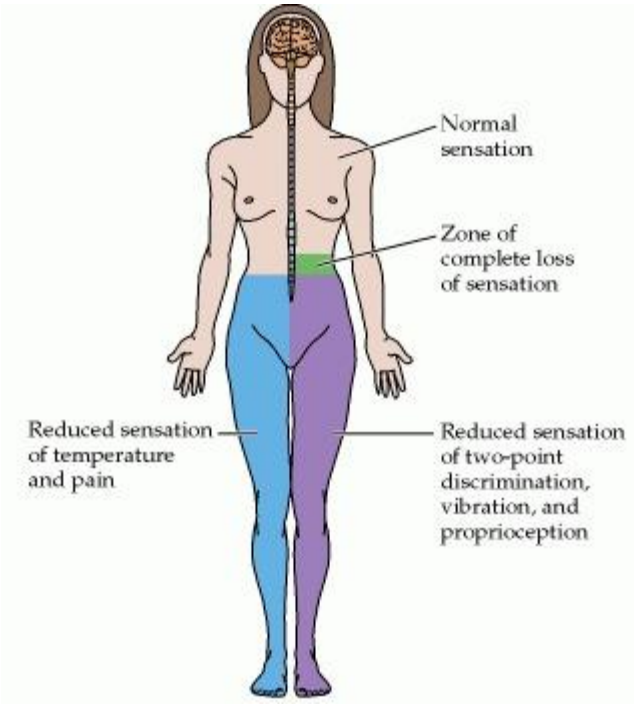

Figure 4 - Dissociative sensory loss. *If the woman has a unilateral left thoracic spinal lesion, sensations like pain and temperature will be diminished below the lesion on the opposite side because the spinothalamic tract runs up the opposite (contralateral) side. On the other hand, she will experience a reduced sense of touch on the left side of her body below the level of the injury, because the lemniscal pathway runs up the same (ipsilateral) side. As a result of this sensory dissociation, she will be able to feel a cup of coffee touching her right leg, but not the burning sensation of the hot coffee, when in contact with the skin. Adapted from Purves D, Augustine GJ, Fitzpatrick D et al. Central Pain Pathways: The Spinothalamic Tract. In: Associates S (MA): S, editor. Neuroscience 2nd edition [Internet]. 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10967/* .(17)

The spinothalamic tract is comprised of two distinct identities, based on synaptic differences in the CNS structures: the paleospinothalamic and the neospinothalamic tracts. The first one is the fastest and reaches the ventral posterior lateral nucleus of the thalamus, then projecting neurons into specific cortical and subcortical areas, like the hypothalamus, the amygdala, basal ganglia, grey periaqueductal matter, and also in the insula and anterior cingulate cortex, contributing to the subjective and emotional component of pain.(18) More recently, imaging studies demonstrate activation of prefrontal cortical areas, as well as regions commonly associated with pain processing, such as the basal ganglia and cerebellum.(13,19) On the

other hand, the neospinothalamic has a slower conduction velocity and helps with the discriminative pain, as it has a primary and secondary somatosensory cortical projection.

Sensitization Mechanisms

Sensitization mechanisms are responsible for chronic pain states where neuroplastic changes occur in the central nervous system resulting in the perpetuation of the painful stimulus.

- **Peripheral sensitization**

Peripheral sensitization is a process where a decreased threshold and increased responsiveness of nociceptors are present, as a result of posttranslational changes and altered trafficking of transducer receptors (e.g. TRPV1) and ion channels (e.g. Nav channels).(6,16)This occurs in response to chemical mediators released by nociceptors and non-neuronal cells (e.g. mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes and fibroblasts) at the site of tissue injury, as it is demonstrated in Figure 5. This will result in pain hypersensitivity symptoms restricted to the site of the inflamed tissue (zone of primary hyperalgesia).(21). The summation of the released intracellular contents includes: neurogenic factors, like SP and CGRP, tissue factors like prostaglandins (PgE2 and PgI2), blood factors (serotonin - 5-HT and norepinephrine - NE,) and neurotrophic factors (NGF). These substances are released at the site of the inflammatory process, contributing to the formation of the so-called “inflammatory soup”.(10) Besides these factors, a wide range of other chemical substances can actively contribute to this inflammatory local environment. These can be protons (causing acidity), adenosine triphosphate (ATP), Glutamate, Bradykinin, thromboxanes, leukotrienes, endocannabinoids, granulocyte- or granulocyte-macrophage colony stimulating factors (G-CSF, GM-CSF), cytokines, such as interleukin 6 and 1β (IL6 and IL1β), tumor necrosis factor alpha (TNFα), chemokines, lipids, and diverse proteases.(11)(22). These components act directly on nociceptors, connecting to one or several receptors on the cell surface, namely CGRP, TRP, ASIC, two pore potassium channels (K2P) and receptor tyrosine kinases (RTP)(15), creating an inflammatory microenvironment that continuously stimulates the nociceptors, which decreases the threshold and increases firing up at the peripheral ends of sensory nerve fibers.

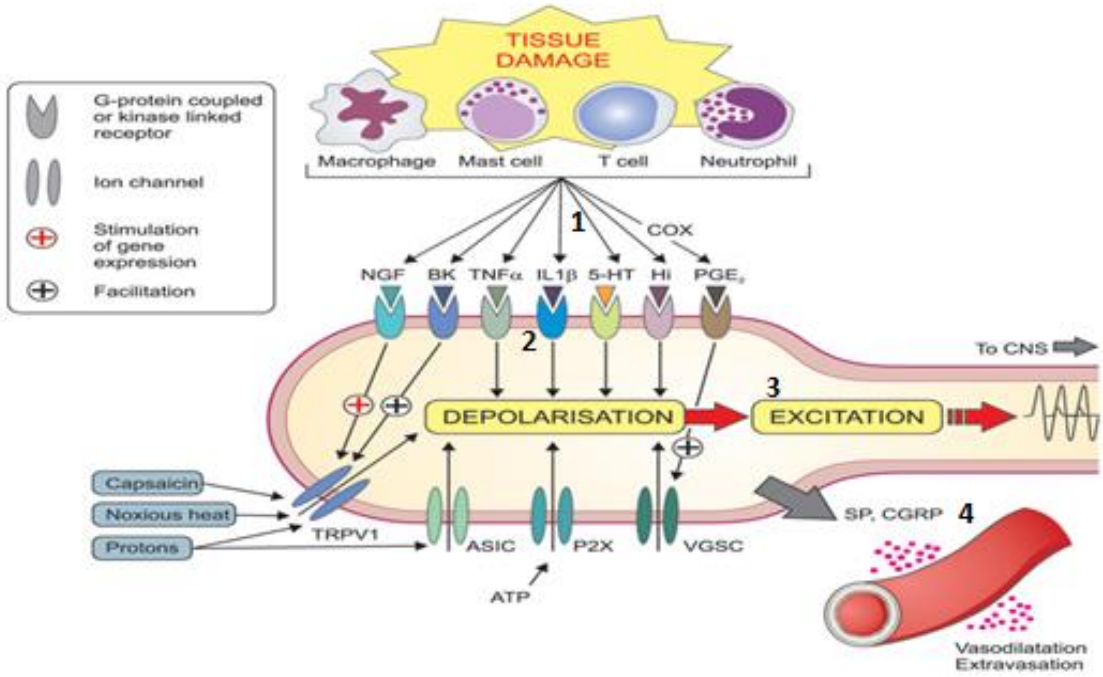

Figure 5 - Peripheral sensitization*. The release of proinflammatory factors* ***(1)*** *from the tissue inflammatory cells will activate different receptors* ***(2)*** *leading to a decreased threshold in activation of the peripheral nervous fibers, causing excitatory signals* ***(3)*** *that enhance the painful stimulus. In addition, peripheral nociceptor terminals can release SP and CGRP* ***(4)****, which cause vasodilatation and plasma extravasation (neurogenic inflammation*). *Adapted from Ernst Brodin ME and LO. Neurobiology: General considerations - from acute to chronic pain [Internet]. 2016. Available from: https://www.tannlegetidende.no/i/2016/1/d2e1410.*(23)

- **Central sensitization**

As previously explained, peripheral sensitization is responsible for an exaggerated response to a painful stimulus that occurs at the place of tissue damage (primary hyperalgesia). This is related to the activation of silent nociceptors by the inflammatory mediators locally released. However, pain is not confined to the place of the inflamed tissue. It can also be extended to other non-inflamed regions as a secondary hyperalgesia state, intimately related to a process known by central sensitization.

Central sensitization is described by the IASP as the “increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input”. (24). This way, normal inputs will start to cause abnormal responses. It is caused by an increase in membrane excitability (glutamatergic neurotransmission alterations), synaptic efficacy, as well as reduced inhibition and therefore, it is considered a manifestation of the extraordinary plasticity of the somatosensory nervous system in response to activity, inflammation, and neural injury.(25)

In this case, some changes occur in the properties of neurons in the CNS and pain is no longer associated to the presence, intensity or duration of peripheral stimuli, as occurs with acute nociceptive pain.(25) There are some spinal and supraspinal networks that contribute to the shifting of the sensory system from a physiological, high-threshold nociception to pathological low-threshold pain hypersensitivity. These alterations correspond to: homosynaptic and heterosynaptic long-term potentiation, central neuroinflammation changes (alterations in microglia, astrocytes and T lymphocytes), neuronal phenotypic changes (as a consequence of altered gene transcription), posttranslational modification of membrane proteins, and lastly, degeneration of inhibitory neurons.(26) Homosynaptic long-term potentiation is clinically demonstrated with temporal summation, an increased pain intensity with the repetition of identical noxious stimuli. Identical C-fiber strength stimuli get larger on each successive stimulus. An example is the “Windup phenomenon”, which results from the activation of neurokinin 1(NK1) and CGRP1 receptors after release of substance P and CGRP from peptidergic nociceptors, to produce a cumulative membrane depolarization from the temporal summation of slow synaptic potentials.(26) This is a progressive phenomenon that, on a long term basis, causes plasticity alterations in the nervous system, responsible for chronic pain.

On the other hand, the heterosynaptic potentiation is clinically present as a secondary hyperalgesia phenomenon, as happens in synapses not restricted to the initiating nociceptor input, resulting in tactile allodynia around the region of the tissue damage and hyperalgesia in a larger area. The recruitment of Aβ fibers (non-painful fibers) from lamina III and IV into more superficial areas of the dorsal horn like lamina I and II (sprouting phenomenon) to make contact with nociceptive-specific neurons is a structural change that contributes to allodynia.(25)

Central sensitization is composed by two temporal phases, each with specific mechanisms. The early phosphorylation-dependent phase and the later transcription-dependent phase.

The first one is explained by a fast augmentation of excitatory glutamatergic synapses in the superficial dorsal horn, as a result of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and *N*-Methyl-D-aspartate receptor (NMDAR) phosphorylation, which strengthens nociceptive transmission and recruits non-nociceptive input pathway; the second

one is related to the synthesis of the new proteins responsible for the longer-lasting form of central sensitization.(25)

Glutamate itself binds to several receptors on postsynaptic neurons in the dorsal horn of spinal cord, like AMPAR, NMDAR, Kainate (KA) receptors and several metabotropic (G-protein coupled) glutamate receptor subtypes (mGluRs). Under normal conditions, the NMDAR channel is blocked by one magnesium (Mg^{2+}) ion sitting in the receptor pore. Sustained release by nociceptors of glutamate and neuropeptides substance P and CGRP leads to membrane depolarization and forces Mg^{2+} to leave the NMDAR pore; this way, glutamate will cause an inward current, leading to hyperexcitabilty. The resulting augmented calcium influx ,which is a primer trigger for hyperexcitabilty, will activate multiple protein kinases: mitogen-activated protein kinase (MAPK), which seems to increase the phosphorylation of AMPA and NMDA receptors; protein Kinase C (PKC), which is responsible for decreasing inhibitory transmission at the segmental level by reducing gamma-aminobutyric acid (GABA) and glycine actions non-receptor protein-tyrosine kinase(SRC), as many other that are able to modulate ionotropic receptors contributing to long-lasting neuroplastic changes in the spinal cord that enhance synaptic efficacy. The increase in intracellular Ca^{2+} appears to be the key trigger for initiating activity-dependent central sensitization. Calcium influx through NMDAR appears to be particularly prominent in the induction phase, but can also occur through calcium permeable AMPARs.(25)

The late phase of central sensitization happens with the back diffusion of nitric oxide (NO) and prostaglandins into the pre-synaptic terminal, upregulating the synapse, leading to a greater release of glutamate, which causes an amplification of AMPARs expression in the post-synaptic neuron. This process ultimately affects the inhibiting interneuron, causing disinhibition.

The role of prostaglandins is very important, as it has been shown that prostaglandin E2 (PGE2 potentiates AMPAR and NMDAR currents.(21,23) A previous study identified that the B2 receptor, for which bradykinin is the natural ligand, is expressed by dorsal root ganglion and dorsal horn neurons and that B2-selective agonists facilitate glutamatergic synaptic transmission by increasing glutamate release and postsynaptic actions; however, kinin appears to require the coactivation of protein kinase A (PKA) and PKC followed by extracellular receptor kinase (ERK) activation to augment glutamate responsiveness.(27)

The multiple processes of central sensitization are illustrated in Figure 6.

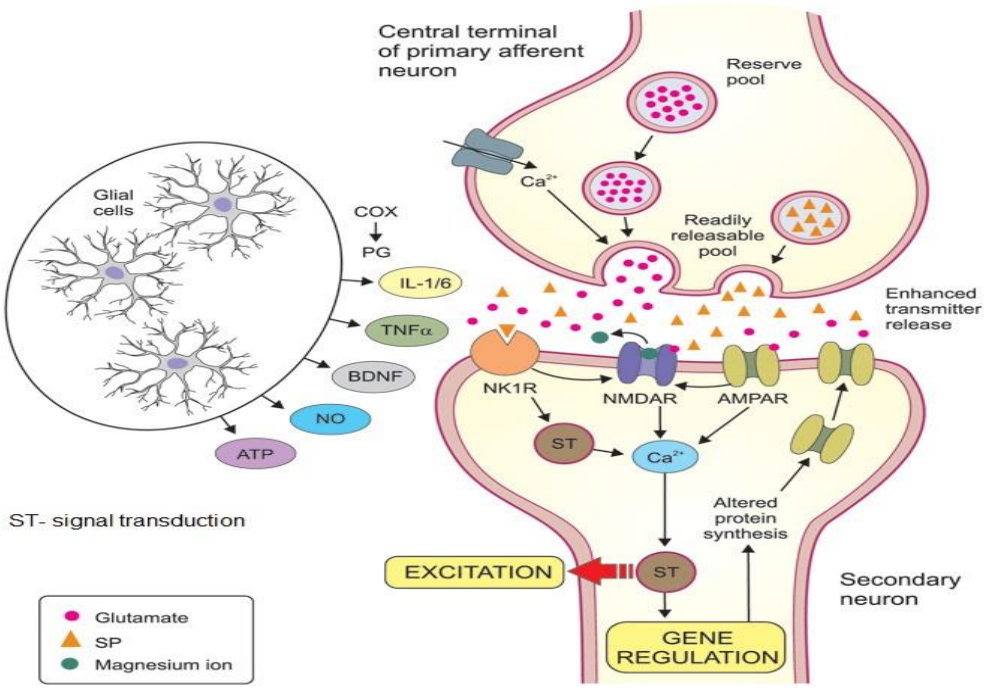

Figure 6 - Central sensitization mechanisms. *Glutamate and substance P are released by the primary afferents. Glutamate acts on AMPA and NMDA receptors, which are both ion channels that directly increase the inflow of calcium into the secondary neurons, while SP acts on neurokinin-1 receptors (NK1R) and increase intracellular calcium via transductional mechanisms. A massive release of glutamate and substance P and subsequent strong stimulation of AMPA and NK1R, causes a removal of the magnesium-ion-block, allowing increased amounts of calcium ions to flow into the postsynaptic cell. This causes an enhanced action potential in the postsynaptic neuron and long-term alterations of gene regulation, with AMPA receptor being upregulated and multiple kinases being formed in the postsynaptic membrane enhancing transmission. These mechanisms are triggered and/or facilitated by a large number of extracellular mediator molecules like cytokines, prostaglandins, nitric oxide, and other extracellular factors. Adapted from Ernst Brodin ME and LO. Neurobiology: General considerations - from acute to chronic pain [Internet]. 2016. Available from: https://www.tannlegetidende.no/i/2016/1/d2e1410***.***(23)

Another cause of hyperexcitabilty is the disinhibition caused by the decreased GABAergic and glycinergic tone, resulting in allodynia and hypersensitivity. In physiological states, these substances are released in order to activate the inhibitory interneurons, which results in an antinociceptive effect and inhibition of the pain. However, in a chronic pain pathological state,

the benefits of the GABA and glycine (Gly) molecules do not exist due to a loss of inhibition. This disinhibition can be caused by the loss of GABAergic or glycinergic interneurons after cell death, reduced GABA or GABA synthesizing enzyme (e.g. glutamate decarboxylase) or alterations on $GABA_A$ receptors, glycinergic receptors and cation-chloride cotransporters. In line with this concept, facilitation of GABAergic inhibition in the spinal dorsal horn should be a rational approach to compensate the inefficacy of inhibitory pain control. In fact, antihyperalgesic effects of several $GABA_A$ receptor agonists, such as muscimol, or of positive allosteric modulators of $GABA_A$ receptors, such as benzodiazepine site agonist (BDZs), have been repeatedly demonstrated in rodents. The use of pharmacological agents acting on specific $GABA_A$ receptor subtypes has an important clinical value, considering the reduction/avoidance of unwanted effects.(24,25)

Besides disinhibition, neuroinflammation is also responsible for the central sensitization state in the form of microglia cell interactions and cytokines production.

Astrocytes, other neuroglia cells, produce chemokines, such as C-C motif chemokine ligand 2 (CCL2) and C-X-C motif chemokine ligand 1(CXCL1). C-C motif chemokine receptor 2 (CCR2) is the major receptor for CCL2 and it is present in neurons of the dorsal root ganglion (DRG), as well in the spinal cord dorsal horn (SCDH), causing ERK activation and ERK-dependent potentiation of NMDA receptor, via the activation of CCR2 receptor. In the same time, CXCL1, which binds to C-X-C motif chemokine receptor 2 (CXCR2), can also induce ERK (which positively modulates the NMDA receptor) and activate cAMP response element-binding protein (CREB) in spinal neurons, enhancing the excitatory state of central sensitization**.**(29)

Glial cells also produce growth factors, such as brain-derived growth factor (BDNF) and basic fibroblast growth factor (BFGF), that enhance central sensitization and chronic pain by activation of ERK, which results in NMDA receptor potentiation**.**(29)

Proinflammatory cytokines, like TNF, IL-1β, IL-6, have been shown to rapidly modulate the function of neurotransmitter receptors, such as AMPA, NMDA, Gly and GABA receptors, which leads to enhanced excitatory and suppressed inhibitory synaptic transmission in the spinal cord pain circuit. TNF has been related, in electrophysiological analysis, to an increase in glutamate release in $TRPV1^+$ C-fiber terminals, leading to enhanced excitatory synaptic transmission in lamina II excitatory SCDH interneurons. On the other hand, IL-1β seems to contribute to the central sensitization and inflammatory pain hypersensitivity via transcriptional regulation that causes up-regulation of cyclooxygenase-2 (COX-2) and PGE_2.(29)

Endogenous Pain Modulation

Endogenous pain modulation results from a set of actions in the CNS with the predominant role of the brainstem pain control centers. These centers through descending messages to the spinal cord, can inhibit or facilitate the incoming nociceptive messages from the periphery. In fact, analgesia results in part from the activation of endogenous structures, such as the prefrontal cortex, periaqueductal gray (PAG), rostral ventral medulla (RVM), dorsolateral pontomesencephalic tegmentum and many others. However, pain modulation is not synonym of analgesia, as it can also sometimes lead to hyperalgesia. A deregulation of the endogenous analgesic system and a facilitation in the synaptic transmission are responsible for multiple chronic pain syndromes. To test the function of the endogenous pain modulation, quantitative sensory tests can be used to study pain facilitation or pain inhibition. Some of the most frequently used psychophysical tests of endogenous pain inhibition include: conditioned pain modulation; offset analgesia and habituation. On the other hand, pain facilitation can be assessed by testing temporal summation of second pain**.**(30) Endogenous pain modulation occurs at spinal and supraspinal levels respectively.

- **Spinal modulation**

Spinal or segmental control was first introduced with “gate control theory” (GCT) proposed by Melzack and Wall in 1965. It basically suggests that the substantia gelatinosa of the dorsal horn functions as a gate control system that modulates the afferent patterns. The gating component is composed by interneurons of the substantia gelatinosa (SG) that regulate input to the spinal transmission neurons through either presynaptic inhibition or facilitation of afferent fibers. When the neurons in the SG are excited by the large diameter A fibers, the gate is closed, thus inhibiting synaptic transmission and leading to hypoalgesia. Contrarily, the activity of small C fibres opens the gate and causes inhibition of SG neurons which will stimulate synaptic transmission, leading to hyperexcitabilty. Vibration can cause pain relief in the affected area via Aβ fibers activation, diminishing synaptic transmission of painful stimulus. Some authors propose the use of whole body vibration as a potential therapy in diabetic neuropathy.(31,32)

- **Supraspinal modulation**

Other mechanism by which our body can modulate pain is through the supraspinal modulation, a more complex phenomenon in which multiple areas of the CNS, including the hypothalamus, the amygdala, the rostral anterior cingulate cortex (rACC), the midbrain periaqueductal gray region (PAG) and the rostral ventromedial medulla (RVM) contribute to the descending pain modulatory system.

Early on scientists observed that when rabbit's brains were injected with morphine, a profound antinociceptive effect occurred when the PAG was the injection area. This area had such importance in pain control that Reynolds, in his cardinal study in 1969, found that electrical stimulation of the ventrolateral PAG of the rat produced such a powerful anti-nociception effect, that conscious rats could went into a laparotomy procedure without suffering.(33)

PAG is deeply interconnected with the hypothalamus and limbic forebrain structures, including the amygdala, and also receives direct spinomesencephalic input. The noradrenergic locus coeruleus **(**LC) receives inputs from the PAG, communicates with the RVM and sends descending noradrenergic inhibitory projections to dorsal horn laminae in the spinal cord. This fact supports the therapeutic use of NA reuptake inhibitors as an option in chronic pain treatment. Studies performed with electrical stimulation or microinjection of glutamate into the RVM revealed a biphasic function of the RVM via activation of two cell types: OFF (antinociceptive) and ON (pronociceptive). Prolonged delivery of a noxious thermal stimulus increased the firing rate of RVM on-cells as well as enhanced the intensity of the nociceptive response in rats, however, with the lidocaine microinjection in the RVM those phenomena were abolished. On the same studies it was also shown an increased on- cell activity with hyperalgesia due to naloxone precipitated withdrawal.(33)

Research in rats with induced allodynia showed that lidocaine injection into the RVM reversed the allodynia. However, when normal rats received the same injections, the lidocaine caused allodynia. This concludes that development of neuropathy might depend on RVM modulation. Thus, descending modulation from the RVM is unquestionably an important factor in determining whether or not chronic pain syndrome will manifest after acute injury or not.(33)

Opioids administered systemically or into the PAG directly have been shown to increase activity of off- cells through disinhibition. Oppositely, the on- cells are the only population of cells in the RVM directly inhibited by opioids, suggesting that these cells most likely express the μ-opioid receptors. These cells are also activated by cholecystokinin (CCK) via a CCK2 receptor contributing to hyperalgesia.(33)

- **Descending serotonergic pathways**

Serotonin has a role in the descending inhibition of pain through serotonergic neurons projecting from the RVM through the DLF (dorsolateral funiculus). It has a synergistic activity together with norepinephrine and opioids in the endogenous descendent modulatory pain control, as it is evidenced in Figure 7. Stimulation of the PAG or RVM was found to cause the release of serotonin in the spinal cord and intrathecal administration of 5-HT agonists elicited an antinociception effect**.** In some studies, it was demonstrated the presence of serotonergic projections to the spinal dorsal horn arising from the nucleus raphe magnus, a midline structure within the RVM as well as the nucleus paragigantocellularis and the ventral portion of the nucleus gigantocellularis.(33) Effective synaptic concentrations of 5-HT are strongly dependent on the activity of the serotonin transporter (5-HTT) whose gene (*SLC6A4*) is located on the long arm of chromosome 17. Fibromyalgia, migraine and depression have been associated with a polymorphism of this gene.(30).Recent evidence suggests that only 20% of RVM neurons are serotonergic, and most of the spinal projections from the RVM are either glycinergic or GABAergic. It has been proposed that serotonergic RVM neurons are neither on-cells nor off-cells but that they can modulate the activities of these neurons.(33)

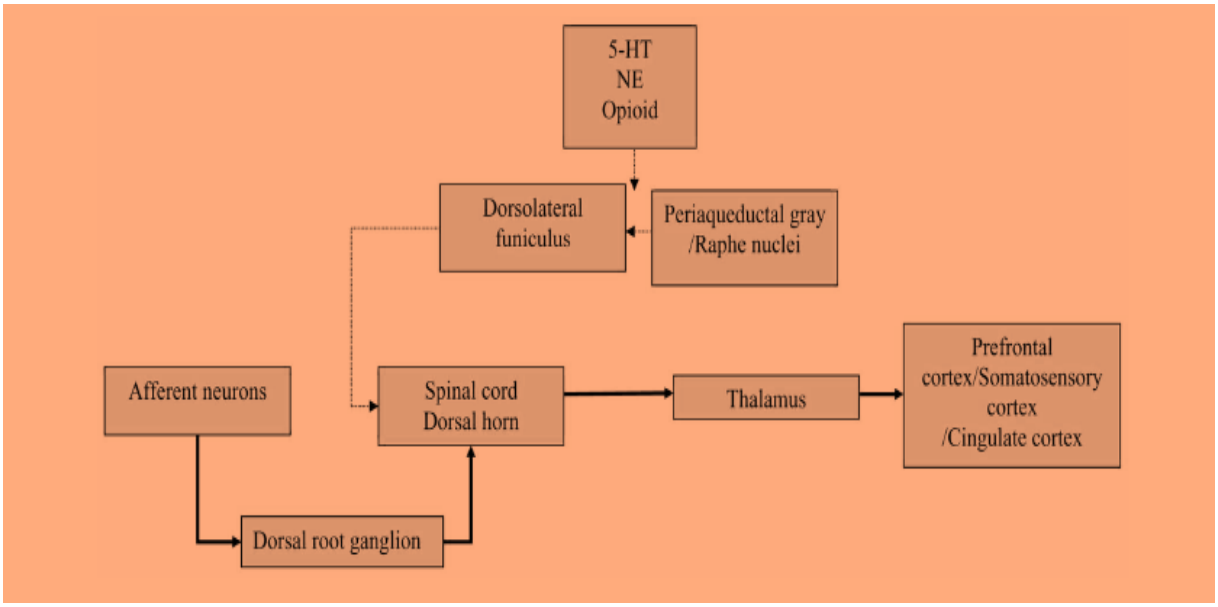

Figure 7 - Pain modulatory pathway*. Specific neurotransmitters (serotonin and norepinephrine) and endogenous opioids act in CNS structures which through descendent projections will produce an analgesic and inhibitory response in the dorsal horn of the spinal cord, modulating pain perception in the ascendant spinothalamic tract. Adapted from Marks D, Shah M, Patkar A, Masand P, Park G-Y, Pae*

C-U. Serotonin-Norepinephrine Reuptake Inhibitors for Pain Control: Premise and Promise. Curr Neuropharmacol. 2009;7(4):331–6.(34)

- **Noradrenergic pain modulation system**

While neither the PAG nor the RVM contain noradrenergic neurons, both regions have connections with noradrenergic sites important to pain modulation, including the locus coeruleus (LC). Originating here, there are numerous direct noradrenergic projections to the spinal cord, with the goal of inhibiting the response of presynaptic and postsynaptic spinal pain transmission neurons. It was demonstrated a spinal activation of α2-adrenergic receptors by a PAG activation which causes a strong antinociceptive effect, basically by two mechanisms: diminished release of excitatory neurotransmitters from primary afferent terminals and post synaptic sites and a hyperpolarization state of neurons. Additionally, it was also found that activation of α1-adrenergic receptors caused depolarization of GABA interneurons, leading to Clonidine, an α2 agonist, was found to block thermal and capsaicin-induced pain in healthy human volunteers.(33) Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) initially used as antidepressive or anxiolytic medications have now clinical efficacy in reducing pain. Duloxetine, and SNRI that was studied in a rat model by Chu, was found to decrease the firing of pain responsive neurons. It was later evaluated by Yarnitsky as a useful treatment in neuropathic pain in patients with diabetic peripheral neuropathy, being successfully approved for it.(31)

- **Stress-induced analgesia**

It is known that a stressful event activates mechanisms responsible for analgesia. This was first studied in rats with application of brief foot shock of the forepaws of rats. In this study, it was seen a reduction in the firing of RVM on-cells and an increase in the off-cells, consistent with opioidergic endogenous pain modulatory system. Stress induced analgesia (SIA) is associated with elevated PAG levels of β-endorphin, and microinjection of naloxone (μ-opioid receptor antagonist) into the PAG or RVM abolished SIA. More recently, it was demonstrated in preclinical studies the importance of endogenous cannabinoids in this regulatory system. There are two main receptors in the endocannabinoid system: CB1 and CB2. CB1 receptor is present in diverse areas, such as dorsal root ganglion (DRG), spinal cord, thalamus, PAG, amygdala and RVM. CB2 receptors exist in the immune system cells, microglia cells and

keratinocytes. It was shown that systemic injection of cannabinoid agonists increased RVM off-cell activity and reduced firing of the RVM on-cells, a similar effect of morphine, but without the blockage by naloxone. Furthermore, a microinjection of the CB1 antagonist rimonabant into the dorsolateral PAG abolished such antinociception state, suggesting the important role in opioid insensitive SIA of the endogenous cannabinoids acting on CB1 receptor.(33)

Types of Chronic Pain

- **Chronic primary pain**

In the new revision of the International Classification of Diseases 11 (ICD-11) a new definition of chronic primary pain is proposed due to some limitations in the previous ICD-10, which only considered the diagnosis if a biological or a psychological factor would have been identified. In fact, the new ICD-11 considers ambiguous the use of general terms like “nonspecific “, “somatoform” and “functional”. It also aims avoiding the use of the obsolete dichotomy between “physical” and “psychological”. (35) Therefore, the new ICD-11, has chosen the new term “chronic primary pain”, which can be defined by a “pain in one or more anatomical regions that persists or recurs for longer than three months, which is associated with significant emotional distress (eg., anxiety, anger, frustration or depressed mood) and/or significant functional disability (interference in activities of daily life and participation in social roles), and the symptoms are not better accounted for by another diagnosis.”(35) If a specific condition like cancer or arthrosis is present, pain is considered as a symptom and not a primary disease, establishing a chronic secondary pain diagnosis if it passes the three months period. Figure 8 clarifies the different primary and secondary chronic pain types considered in ICD-11.

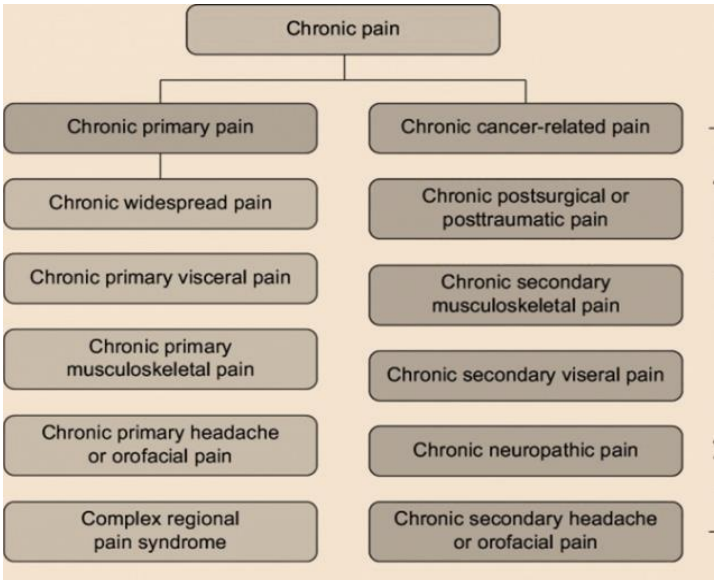

Figure 8 - Different chronic pain types based on the present diagnostic criteria of ICD-11. *Adapted from Barke A, Schiller J, Rief W, Treede R-D, Falter S, Schäfer P, et al. The IASP classification of chronic pain for ICD-11. Pain [Internet]. 2018;160(1):88–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30586076.*(35)

- **Nociceptive pain**

Nociceptive pain is usually acute and it develops when the nociceptive nerve fibers are triggered by inflammation, chemicals, or physical events. The pain transmission mechanisms are preserved and there is no neuronal lesion, as it is seen in neuropathic pain. It can be acute or chronic; in this paper it will be discussed the chronic nociceptive pain syndromes. Nociceptive pain can be divided in two types: somatic and visceral pain. The underlying mechanism of nociceptive pain is tissue damage, with the generation of an inflammatory environment, which is responsible for the painful sensation.(1) Rheumatology syndromes like rheumatoid arthritis or osteoarthritis and the post-surgical pain syndromes are the most frequent clinical findings of nociceptive pain.(15) With the ongoing inflammation, there is an increased sensitivity within the inflamed area and in contiguous non-inflamed areas, as a result of plasticity in peripheral nociceptors and central nociceptive pathways which leads to a detection of noxious stimuli and to an activation of low-threshold innocuous inputs. One factor that confirms the different pathophysiology mechanisms of neuropathic and inflammatory pain is the sensitivity to tetrodotoxin (TTX). Seven out of nine subtypes of sodium voltage-gated channels (Na_v) $Na_v1.1$ - $Na_v1.7$ are also called TTX-sensitive (TTX-S) sodium channels. $Na_v1.8$ and $Na_v1.9$ on the other hand are TTX-resistant (TTX-R) and it has been shown that

modulation of these TTX-resistant channels by proinflammatory mediators are likely responsible for inflammation-dependent neuronal hyperexcitabilty and therefore inflammatory-pain hypersensitivity.(9) Ablation of TTX-resistant sodium channel Na_v 1.8, eliminates inflammatory pain, but leaves neuropathic pain intact, indicating a fundamental difference in the neuronal pathways responsible for these pain states.(20). Several studies indicate that proinflammatory mediators like TNF-α and IL-1b increase TTX-R sodium current and that substance P, via neurokinin-1 receptor, produces sensitization of P2X3 receptors which contributes to inflammatory pain hypersensitivity.(9)

- **Neuropathic pain**

Neuropathic pain is defined as a lesion in the somatosensory system, including peripheral fibres and central neurons. It is a condition that affects around 7-10% of the general population.(36) Patients usually feel different sensations, like burning, numbness, electrical-like perceptions and pain from non-painful stimulus, like light touch, a condition described as mechanical allodynia; these symptoms persist and have tendency for chronicity. Neuropathic pain can have a central cause when the origin is in the Central Nervous System as it happens in neurodegenerative diseases like Parkinson disease, or cerebrovascular diseases like “post stroke pain”. On the other hand, peripheral conditions are more frequent due to the increased prevalence of diabetes mellitus, which normally originates peripheral neuropathy. In the same way, in cancer patients who submit to chemotherapy there is a higher prevalence of peripheral neuropathy as a consequence of the treatment, which compromises sensitivity by affecting all sensory fibres (Aβ, Aδ, and C fibres). Clinically, post-herpetic (or post-shingles) neuralgia, reflex sympathetic dystrophy / causalgia (nerve trauma), phantom limb pain, entrapment neuropathy (e.g., carpal tunnel syndrome), and peripheral neuropathy (widespread nerve damage) are the most frequent examples of neuropathic pain. Exposure to toxics (for instance chemotherapies) vitamin deficiencies (B12deficiency) and chronic alcohol abuse can also predispose to neuropathic pain.(36)

A rare inherited condition that causes neuropathic pain is erythromelalgia, a channelopathy associated with mutations in the sodium voltage-gated channel alpha subunit 9 *(SCN9A*), responsible for encoding the voltage-gated sodium channel $Na_v1.7$ (involved in the generation and conduction of action potentials), and is characterized by pain and erythema (reddening) in the extremities, which is exacerbated by heat.(36,37)

There are essentially three mechanisms implicated in the genesis of hyperexcitabilty in neuropathic pain: changes in the ion (sodium, potassium and calcium) channel function and

expression, changes in the second order nociceptive neuronal function and, lastly, a deregulation of the function of an inhibitory interneuron.(36)

The increased expression of sodium channels in dorsal root ganglia and around the terminal injury site (neuroma) of injured axons causes hyperexcitabilty. Sodium channels, such as $Na_v1.3$, $Na_v1.7$, and $Na_v1.8$, may lower the stimulation threshold and provoke ectopic discharges, resulting in spontaneous pain. Besides that, the overexpression on sodium channels can lead to central sensitization and allodynia phenomenon. Carbamazepine is an anti-epileptic drug whose mechanism is blocking the Na^+ channels; however, as it is not specific for these receptors, it has low therapeutic indices and many side effects. After nerve injury, the expression of α2δ calcium channels increases in and around the dorsal root ganglia, leading also to an hyperexcitabilty state. Gabapentinoids, drugs that block these channels, are a first-line treatment for neuropathic pain and have been shown to be a good therapeutic measure for reducing hyperexcitabilty and spontaneous pain.(38)

The enhanced excitability permits low-threshold fibres (the Aβ and Aδ fibres) to activate second order nociceptive neurons and expand their receptive fields (a given stimulus excites more second order neuron) contributing for central sensitization. The ongoing discharge of excitatory amino acids and neuropeptides causes changes in the post-synaptic second order nociceptive neurons due to the increase of NMDA and AMPA receptors. Physical allodynia can be explained by these changes.(36)

Lastly, the dysfunction on the inhibitory interneuron and descending modulatory system enhances even more the imbalance between excitatory and inhibitory states. Projections from the amygdala and cingulate cortex modulate descending controls from the periaqueductal grey area (an area involved in analgesia) to the brainstem causing an excitatory pathway that then acts on spinal signalling. Altered projections to the thalamus and cortex and parallel pathways to the limbic regions are related to high pain ratings, mood disorders like anxiety and depression as well as sleep problems. There is also an attenuation in the noradrenergic inhibitions, mediated through α_2-adrenergic receptors in the spinal cord, and enhanced serotonin signalling through the 5-HT_2 and 5-HT_3 serotonin receptors.(36)

- **Fibromyalgia**

Fibromyalgia (FM) is a common chronic widespread pain disorder that affects mainly young adult women and adolescents. Depending on the diagnostic criteria used, the prevalence is from 2 to 8% of the population. With the new diagnostic criteria, the disease has a female:

male ratio of 2:1. The prevalence is similar in different countries, cultures, and ethnic groups; there is no evidence that fibromyalgia has a higher prevalence in industrialized countries and cultures. Usually patients with fibromyalgia are likely to have a history of headaches, dysmenorrhea, temporomandibular joint disorder, chronic fatigue, irritable bowel syndrome and other functional gastrointestinal disorders, endometriosis and other regional pain syndromes (especially back and neck pain).(39)

It is considered one prototype of central chronic pain syndrome as it is not evidenced nerve or tissue damage, as occurs in neuropathic and inflammatory pain respectively, but instead a lack in identifying the trigger factor that leads to pain perception. Besides that, nowadays there is still a limited awareness and understanding of the physiopathology of FM, but it is known that allodynia and hyperalgesia are present as a form of central sensitization, causing an enhanced pain perception, as well as a decrease in the descendent pain control modulation system. Nevertheless, the diagnosis of FM is symptom-based and includes the presence of widespread pain and high levels of somatic symptoms such as fatigue, unrefreshed sleep and cognitive disturbances.(40)

Recently there has been an augmented interest in using brain neuroimaging to study pain in a more quantitative, objective manner and to better understand fibromyalgia. Central sensitization is assumed to have an important role in the disorder; however, it is not known if CNS changes are a cause or a consequence of centralized pain. Neuroimaging shows greater connectivity between pain-promoting regions, such as the insula and the default mode network, a network that is activated when an individual is not engaged with the external environment, leading to greater spontaneous clinical pain.(34,35)

Recent neuroimaging studies suggest that CNS changes in patients with FM can be altered with pharmacologic and non-pharmacologic treatment. Reinforcing this concept is the finding of an anti-epileptic drug approved by the Food and Drug Administration (FDA) that lowers glutamate levels in the posterior insula and diminishes the connectivity between the posterior insula and the default mode network.(40)

Genetic predisposition exerts a critical role in fibromyalgia. It is evidenced that the risk of developing this disorder is eightfold higher for first-degree relatives of patients with fibromyalgia than for an unrelated individual. Some specific genetic polymorphisms have been identified with increased risk of developing fibromyalgia, namely the short allele polymorphism in the regulatory region of solute carrier family 6 member 4 (*SLC6A4)*, the serotonin transporter gene. This polymorphism can also be found in patients with depressive disorders, further reinforcing the connection between mood disorders and chronic pain syndromes. Another polymorphism with particular interest is the catechol-O-methyltransferase (COMT), resulting in

a Val158Met polymorphism or a high pain sensitivity haplotype; however, the evidence is not clear for its role in FM. Nevertheless, studies are associating the study of the maladaptive coping mechanisms with chronic pain due to dopamine imbalances as a result of this polymorphism, suggesting that genetic variation affects pain in fibromyalgia through pathways of pain-related cognition.(42)

In the CNS, there is an imbalance of neurotransmitters and substances usually implicated in pain regulation. In fibromyalgia patients, it has been found an increase in substance P, glutamate and nerve growth factor (pain facilitating chemicals) and contrarily diminished levels of metabolites of neurotransmitters that typically inhibit pain transmission, such as serotonin, norepinephrine and dopamine. Paradoxically, encephalin levels are increased in fibromyalgia patients.(42)

Pharmacotherapy is essential, along with non-pharmacological approaches, to treat fibromyalgia. Several drugs have been studied and some were left behind, due to a lack of efficacy (like dopamine agonists) or to possible life-threatening side effects (such as serotonin syndrome and hypertensive crisis observed with the monoamine oxidase inhibitors). To date, three drugs have been approved by the FDA for the treatment of pain in fibromyalgia: pregabalin, which binds to the α2δ subunit of a voltage-dependent, presynaptic calcium channel, duloxetine and milnacipran, which selectively inhibit the reuptake of serotonin and norepinephrine. Amitriptyline and cyclobenzaprine have been found to have efficacy in treating not only pain, but also fatigue and poor sleep, due to their strong selective reuptake inhibitor effect on noradrenaline and moderate effects on 5-HT transporter. The selective serotonin reuptake inhibitors were found to be less efficacious than the tricyclic compounds or serotonin–norepinephrine compounds. Duloxetine and milnacipran have shown to be effective in reducing self-reported pain, stiffness, number of tender points, level of fatigue and improve physical functioning. On the other hand, calcium-channel blockers like gabapentin and pregabalin have both been shown to reduce pain and sleep disturbances in patients with fibromyalgia in response to a decrease in the release of excitatory neurotransmitters, such as glutamate and substance P; however, gabapentinoids have no effect on depressed mood, a frequent comorbidity in fibromyalgia. For future treatments, besides monoamine modulators and calcium channel modulators, GABA receptor modulators are also a good promise for treatment and are being studied.(42)

Non pharmacological treatments shall be considered as an essential component of therapy, including education, exercise and cognitive behavioural therapy. Unlike drugs, that predominantly act on the symptomatic improvement, these measures target different aspects

of fibromyalgia, including dysfunctional aspects, for instance: poor sleep, distress, maladaptive illness behaviours, isolation and decreased activity.(42)

For a better result, both type of therapies should be used simultaneously when a diagnostic of fibromyalgia is settled. Besides some lack of scientific evidence some alternative therapies like trigger-point injections, chiropractic manipulation, acupuncture and myofascial release therapy have been applied by patients who decide to manage their own illness. Tai chi, yoga and a number of other therapies might also be good therapeutic approaches, but these strategies need to be evaluated in larger studies.(42,43)

- **Chronic low back pain**

Low back pain (LBP) is the most common musculoskeletal condition affecting the adult population, with a prevalence of up to 84%.(38,39) Chronic low back pain (CLBP**)** is a chronic pain syndrome in the lower back region, lasting for at least three months(44). In about 10–15% of patients acute low back pain develops into chronic low back pain which is a greater challenge because it tends not to improve with time and consumes most resources(45). CLBP has multiple pathological origins, as so, it needs to be considered as a disease and not a symptom. Its prevalence has been increasing in the last decades and it is by now considered as worldwide disease and a major welfare and economic problem. Regarding its causes, they can vary from muscle tension or spasm (amongst the most common reasons in FM patients) but also from other pain generators with specific characteristics, such as radicular, facet joint, sacro-iliac, and discogenic pain, as well as spinal stenosis (Figure 9).

Radicular pain is an irradiated pain along the nerve rout without neurological impairment. The most common cause is disc herniation and the most frequent pathophysiology mechanism of pain is the inflammation of the nerve rout rather than its compression. Lumbar disc herniation with radiculopathy can be diagnosed during physical examination of the patient using manual muscle testing, supine straight leg raise, Lasègue sign, and crossed Lasègue sign. An MRI can be important to confirm the diagnostic and better assess the neurological impairment when symptoms of disc herniation with radiculopathy are present in physical examination, however the recommendation of the American College of Radiology is not to do imaging for LBP within the first 6 weeks unless *red flags* are present.(44) In the presence of these, a worst prognostic is expectable and the imaging exam are absolutely necessary. These include 23 different clinical parameters that screen for possible malignancy, fractures, infections and cauda equine syndrome. Amongst them we have: a constant progressive non mechanical pain with onset age less than 20 or higher than 50 years, pain associated with fever, pain during sleep that

does not ease with prone position; history of malignancy; unexpected weight loss, intravenous drug abuse, corticosteroid excessive use, osteoporosis, immunodeficiency, recent or active urinary or skin bacterial infection and many other.(46)

Lumbar zygapophyseal or “facet” joint pain on the other hand has been estimated to account for up to 30% of CLBP cases. Its inflammatory nature has origin in the nociception present in the synovial membrane, hyaline cartilage, bone, or fibrous capsule of the facet joint.

The management of CLBP pain ranges from education to the problem, staying active, non-steroidal anti-inflammatory drugs, weak opioids (short-term use), exercise therapy (of any kind), and spinal manipulation. Secondarily, multidisciplinary rehabilitation, adjunctive analgesics, cognitive behavioural therapy, and strong opioids can also be used. The use of antidepressive drugs is considered in some second line guidelines, but has low to moderate effect. The contraindications for therapy are intradiscal electrothermal therapy, percutaneous intradiscal radiofrequency thermocoagulation and radiofrequency facet joint denervation.(45)

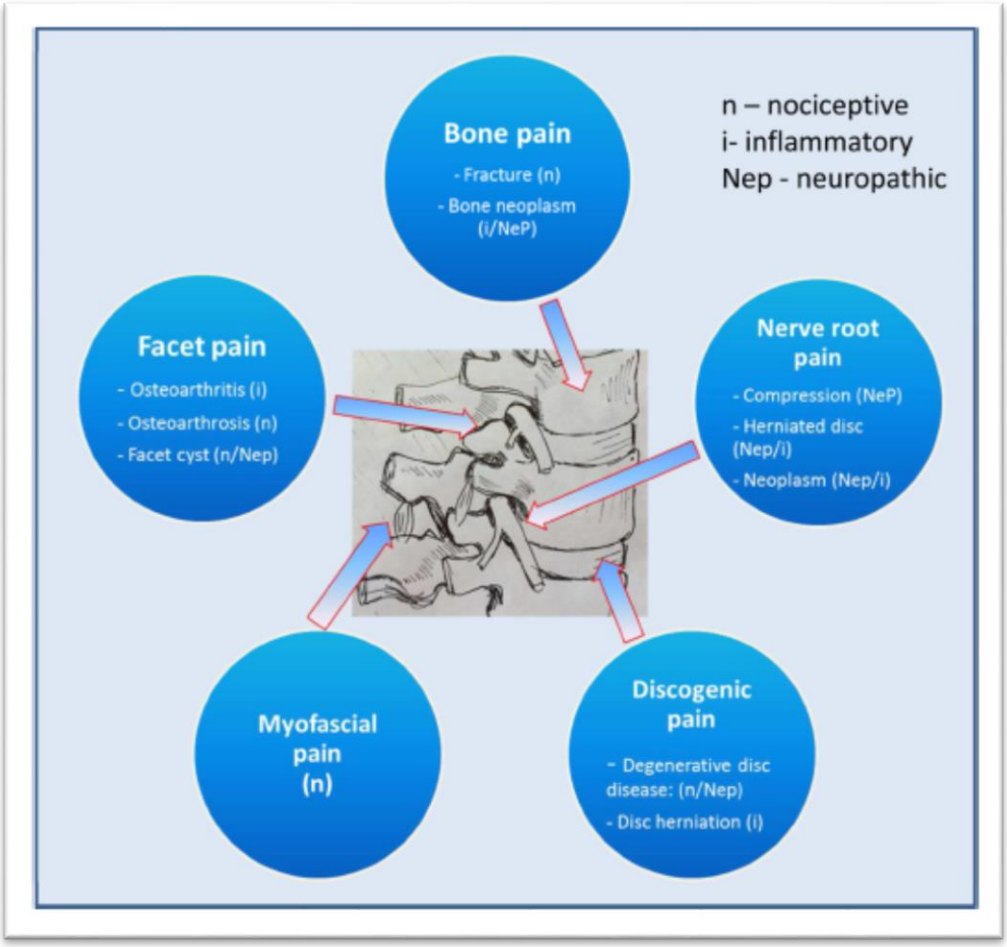

Figure 9 - Pain drivers in chronic low back pain. *Multiple different pathophysiology processes are in*

the origin of the clinical presentation of chronic low back pain syndrome. Adapted from Vardeh D, Mannion RJ, Woolf CJ.Toward a Mechanism-Based Approach to Pain Diagnosis. J Pain. 2016;17(9):T50–69. (26)

Chronic Pain Management

- **Pharmacological chronic pain management**

Chronic pain syndromes have multiple pathophysiologic mechanisms, therefore, therapy needs to be adapted to each kind of chronic pain manifestation. Central sensitization is the predominant aspect behind these syndromes, making it mandatory to intervene pharmacologically at a central level. Anti-inflammatory drugs are effective in reducing mild trauma or inflammation; however, specific central action drugs are required to deal with chronic pain. Even though, it is being proposed that some non-steroidal anti-inflammatory drugs (NSAIDs**)** also block pain through central mechanisms, besides their peripheral anti-inflammatory role. Peripherally, there is inhibition of inflammation, which origins a decreased nociceptor sensitization, ultimately attenuating C fibre-mediated central sensitization. Hence, peripherally acting anti-inflammatory drugs may be useful in shutting down peripheral sources of nociceptive input towards the CNS. However, they are unable to act directly on the mechanisms behind central sensitization.(47)

Several drugs, however, have centrally-mediated action mechanisms and can be used successfully in chronic pain**.** Acetaminophen, for instance, has both peripheral and central actions. Peripherally, just like some NSAIDs, it blocks the enzyme cyclooxygenase 2. This will cause a decrease in prostaglandins in CNS, contributing to decrease pain perception and inflammation. Centrally, it acts on the serotoninergic descendent pain pathway causing a inhibitory action on nociceptive input at the spinal segmental level.(47)

Another class of drugs acting on the descendent modulatory pain system are serotonin and norepinephrine-reuptake inhibitors (SNRIs). Stress induced hyperalgesia was demonstrated in animals with SNRIs. Agents that block the reuptake of either or both of these neurotransmitters, such as SSRIs, and SNRIs and tricyclic antidepressants (TCAs) provide benefit in the treatment of chronic pain. Serotonin seems to both enhance and depress pain transmission through different physiological mechanisms, on the other hand norepinephrine has one an inhibitory action through an alpha-2-adrenoceptor activation. Duloxetine, an SNRI, has proven efficacy in human studies in reducing chronic pain associated to central

sensitization syndromes like fibromyalgia and osteoarthritis. Studies strongly suggest that pain-inhibiting effects of tricyclic antidepressants like desipramine and amitriptyline and newer agents enhancing norepinephrine and serotonin neurotransmission like venlafaxine, milnacipran and duloxetine have more efficacy than SSRIs alone. In fact, studies revealed inconsistent evidence of efficacy for migraine or tension headaches, diabetic neuropathy, and fibromyalgia with SSRIs.(34,47)

Opioids are potent analgesics. Enkephalins, dynorphins, and β-endorphins are the main groups of endogenous opioid peptides derived from precursor proteins like proopiomelanocortin, prodynorphin, and proenkephalin. Opioids target opioid receptors (μ1, μ2, δ1, δ2, k1, k2, and k3-opioid receptors). Endogenous opioid peptide containing neurons are located in the Rexed laminae II, III, VIII and IX of the dorsal horn as well as in the thalamus, periaqueductal gray, limbic system and several regions of the cortex. When these receptors become activated, inhibitory actions take part: presynaptic inhibition of primary nociceptive afferents and postsynaptic inhibition of projecting neurons. Various opioids are available for clinical use: codeine, dextropropoxyphene, tramadol (causing a reuptake inhibition of serotonin and norepinephrine in addition to its opioid effects), buprenorphine, morphine, methadone, fentanyl and hydromorphone, among others. Morphine is a strong opioid whose main action is activation of μ-opioid receptor in CNS which will cause excitation of off-cells in RVM. Besides that, through δ -opioid agonism it also suppresses on –cells. It causes neuronal inhibition either by blocking the release of neurotransmitters or by hyperpolarization of the cell via alterations in potassium and calcium channels.(47)

NMDA-receptor antagonists are another class of drugs being studied clinically, and there is already evidence of its efficacy, however they have a narrow therapeutic window. In chronic pain states NMDARs at dorsal horn synapses are responsible for enhancing and amplifying pain signals to higher brain centers and this continued and prolonged nociceptive stimulation is responsible for central sensitization. NMDAR antagonists, such as ketamine, block the NMDA excitatory currents causing and antihyperalgesic and anti-allodynic state. Additional to its effect at the NMDAR, ketamine interacts with other receptor systems as well, including opioidergic, muscarinic and monoaminergic receptors, however these phenomenoms are not quite well understood and studied. Ketamine however has several risks and usually some unavoidable side effects. An emerging strategy in therapy is to associate opioid analgesics with NMDAR antagonists. This will potentiate the analgesic effects, and prevent tolerance and dependence of narcotics. Curiously, recent studies suggest that in the CNS ketamine binds with higher affinity to dopamine D2 receptors than to NMDA-receptors.(47,48)

Calcium channel alpha 2 delta ligands (α2δ) are therapeutic options in some chronic pain disorders, particularly in peripheral neuropathies and post-herpetic neuralgias. Gabapentin and pregabalin both bind to the a2δ subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine and substance P. There is also evidence in in vitro studies that gabapentin alters activity of glutamic acid decarboxylase. This potentially increases synthesis of GABA glutamate in neurological tissue which will modulate postsynaptic inhibition causing in inhibitory action in the CNS.

Another useful drug with a dual mechanism of action for the treatment of moderate to moderately severe pain in adults is tramadol. It is both considered a weak opioid with non-selective μ-receptor agonist action and also an inhibitor of reuptake of both serotonin and norepinephrine. A recent addition to the market is tramadol ER, a long-acting analgesic that provides a 24-h dosing interval for the management of moderate to moderately severe pain in patients that need analgesic treatment for an extended period of time. It is well tolerated and has an acceptable safety profile. In placebo-controlled clinical trials it was demonstrated to have efficacy in causing analgesia in chronic pain conditions. Common side effects include nausea, constipation, somnolence and pruritus.(49)

Tapentadol is a centrally acting analgesic drug, considered the first representative of the MOR-NRI class of drugs. It acts as μ-opioid receptor (MOR) agonism and inhibits noradrenaline reuptake (NRI). This synergism of action allows it to act both on ascending and descendent pathways. Tapentadol can be associated with other analgesics. A recent study made in CLBP patients suggests that the combination therapy (tapentadol PR + pregabalin) exerts its best clinical efficacy in subjects characterized by severe sleep disturbances and little anxiety. The reduced μ-load of Tapentadol allows it to have less risk of dependence than strong opioids such morphine and it also lessens the risk of secondary effects of opioids like nausea, vomiting and respiratory depression. This dual mechanism of action of Tapentadol have led some authors to name it “atypical opioid” and makes it very useful in chronic pain condition that have both nociceptive and neuropathic components like osteoarthritis and chronic low back pain. The common use of tapentadol is 100–250 mg twice daily, depending of pain intensity.(50,51) A summary of the main non-opioid drugs for chronic pain management is presented on Table 2.

Table 2 - Non-opioid analgesics for chronic pain

Drug	Dose	Indications
Acetaminophen	500 mg, per os, every 4/6hr (max 4000mg day)	Mild to moderate pain
NSAIDs	Dose depends on the specific drug	Mild to moderate pain- pain associated with inflammation
Amitriptyline (TCA)	25-150mg , per os, 1di, or 2di (max single dose 75 mg)	Neuropathic pain (first line therapy); fibromyalgia
Duloxetine (SNRI)	60-120mg, per os,1di or 2di	Neuropathic pain, chronic musculo-skeletal pain;
Gabapentin (gabapentinoid)	900/3600 mg, per os, 3 di	Neuropathic pain (first line treatment)
Pregabalin (gabapentinoid)	300-600 mg, per os, 2di	Neuropathic pain (first line treatment); fibromyalgia
Ketamine (NMDAR antagonist)	100 mg/mL IM or IV	Neuropathic pain, fibromyalgia, post herpetic neuralgia, phantom pain
Tapentadol ER (weak opioid and SNRI)	100-250 mg, twice daily	Moderate to severe chronic pain(osteoarthritis and CLPB)

- **Non-pharmacologic management of chronic pain**

In order to better treat chronic pain conditions, a multidisciplinary approach that conciliates both pharmacological and non-pharmacological pain management strategies must be applied.

Transcranial magnetic stimulation is a safe, non-invasive technique for stimulating the cerebral cortex that is being studied in chronic pain conditions in which central sensitization plays an important role like fibromyalgia. It stimulates both motor cortex and the dorsolateral prefrontal cortex areas. It is known that the efficacy in suppressing centrally pain states is higher with this technique comparing to peripheral pain states. Its mechanism of action is not yet totally understood and there are some practical obstacles ahead of its use, however the effects in CNS consist in addressing the sensory-discriminatory aspects of pain (with focal somatotopical frontal cortex stimulation) and reversing the inhibited intracortical motor cortex circuit which

might restore the descendent pain modulatory control. It also might restore normal blood flow in cerebral structures responsible for the descendent nociceptive inhibition and alter the emotional cognitive component of pain. However, this method is not used on a large scale due to some practical obstacles: its use is limited to some specialized centers and its effects on reducing centralized pain are to short lived during up to 1-3 weeks only.(47)

Manual therapy as a form of rehabilitation was found to be helpful in providing widespread analgesia in patients with fibromyalgia who performed manual joint mobilization. It was shown in animal studies that joint mobilization provided a short term (30-45 minutes) period of descendent nociceptive inhibition. This technique was also efficacious in reducing sensory hyperexcitabilty in patients with chronic whiplash evidenced by improvements in the nociceptive flexion reflex. However, it is speculated if this therapy as the capacity of long- term stimulation of the descendent anti- nociceptive pathway.(47)

Stress tolerance and neuronal feedback training are of enormous importance in the control of chronic pain. A stressful event and response can impair our capacity of pain processing. Stress causes a switch in primary afferent second messenger signalling for pronociceptive immune mediators and centrally it activates on-cells and supresses off-cells leading to stress induced hyperalgesia. Additionally, chronic stress has detrimental effects on GABA neurotransmission both at spinal and supraspinal levels. It is then obvious that stress-management programs target our cognitive and emotional components of central sensitization. The capacity of our descendent modulatory pain system can be influenced by our levels of attention, stress, depression, catastrophizing, vigilance and motivation. The improvement in perpetuating cognitive and emotional factors in patients with chronic pain associated with central sensitization might lead to desensitization as it was evidenced in patients with fibromyalgia.(47)

Transcutaneous electric nerve stimulation (TENS) is frequently used in patients with chronic pain, especially those with fibromyalgia. TENS activates large diameter afferent fibers, which in turn activate descending nociceptive inhibitory mechanisms by an activation of the ventrolateral periaqueductal gray and the rostral ventromedial medulla areas. TENS primarily activates poly segmental inhibitory circuits by activating spinal μ- and δ-opioid receptors and spinal GABA(A) receptors. Modest treatment responses have been reported in patients with fibromyalgia, however in those poorly widespread chronic pain syndromes TENS does not seem to be suitable for its treatment.(47)

Lastly cranial electrotherapy stimulation with transcutaneous microelectrodes applied in the head of the patients is a potential strategy for chronic pain treatment as it aims to activate the descending inhibitory pathways from the medial brainstem to the dorsal horn of spinal cord

through a direct action on the brain at the level of the limbic system, hypothalamus and the periaqueductal gray matter.(47)

Conclusion

In the last decade, chronic pain has become a critical and a very prevalent disorder in our society. Due to its high comorbidities and impact in our daily life, physicians and other health professionals have tried to reconceptualise the way pain is seen and approached. Ranging from the institution of pain as the fifth vital sign to the establishment of pain as a very complex disorder and not only a symptom, it is now recognized and accepted the holistic dimension of pain. Currently it is understood that pain manifestations vary widely according not only to its different pathophysiology mechanisms but also with our cognitive and emotional states that condition an individual and unique pain perception experience. In the latest years, diverse studies have suggested the complexity of the cellular and molecular mechanisms behind chronicity of pain, pointing to a new and more specific pharmacological and non-pharmacological pain management approach with higher efficacy and safety. It is also mandatory to continue research on the etiopathogenesis of syndromes like fibromyalgia, where central sensitization has a predominant role, and not all mechanisms of deregulation as well as therapeutic targets are identified and completely understood. Although, progress has been made regarding the investigation of new therapies in chronic pain management, an absence of knowledge and clinical integration of these latest developments is still noticed, especially in the primary health care. Therefore, divulgation of the latest discoveries, regarding chronic pain management would be of an enormous value inside our medical community. Lastly, it is obvious that a holistic approach must be covered between patients, health care professionals, social and health care facilities as well as governments, in order to recognize the necessary importance of chronic pain in our community. Specific measures must be prioritized in order to not only reduce the social and economic impact of chronic pain in our society but also to improve the quality of life of affected people.

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