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Understanding peripheral neuropathic pain in primary care: diagnosis and management

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Abstract. – OBJECTIVE: To describe an approach that allows for a dedicated clinical assessment and accurate recognition of peripheral neuropathic pain in primary care and to provide an update on the available pharmacologic therapies

MATERIALS AND METHODS: Medline was searched using the key word "neuropathic pain". Searches were refined for each pathophysiological mechanism, diagnosis and treatment by adding appropriate key words.

RESULTS: The distinction between neuropathic and nociceptive pain is essential for an adequate treatment because these forms of pain differ in their underlying mechanisms and therefore in their response to different drugs.

CONCLUSIONS: Chronic pain with neuropathic characteristics presents a significant challenge as it is often unresponsive to conventional analgesics. The correct diagnosis and early management of peripheral neuropathic pain not only improve health-related outcomes, but also yield significant cost benefit to society.

Key Words:
Neuropathic pain, Pathophysiological mechanisms, Bedside examination, Pharmacotherapy, Primary care.

Introduction

Neuropathic pain, which is widely recognised as one of the most difficult pain syndromes to manage, is a clinical challenge for primary care physicians (PCPs) and specialists as treatment outcomes are often unsatisfactory. Neuropathic pain is usually associated with impaired quality of life, causing suffering and disability and is an important public health concern. Psychological factors such as feelings of depression and anxiety, and difficulty in sleeping are frequently present in patients with neuropathic pain, and these comorbidities have an important impact on the overall pain experience[1,2]. PCPs play a key diagnostic role in the management of patients with chronic pain. In particular, the primary care physician must be able to diagnose the type of pain (neuropathic/nociceptive), using simple tools available in the clinic, to measure its intensity and impact on quality of life, and initiate an appropriate drug therapy while awaiting specialist assessment (if required). The purpose of this review is to provide guidance for the identification and pharmacological management of peripheral neuropathic pain in the primary care setting where it is underdiagnosed and undertreated.

Materials and Methods

A literature search was conducted using an electronic bibliographic database, Medline, from 1980 until 2019. There were 7462 articles published in the subject area. Searches were refined for each pathophysiological mechanism, diagnosis and treatment by adding appropriate key words. Meta-analyses, systematic reviews considered to have the highest evidential strength were assessed. Recent guidelines were consulted. Only articles written in English were included.

Results

The distinction of neuropathic from nociceptive pain is essential for an adequate treatment

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because these forms of pain differ in their underlying mechanisms and therefore in their response to different drugs. Pain usually results from activation of afferent nociceptive fibres by potentially harmful stimuli (high-threshold stimuli) and from processing of this nerve activity within the nociceptive system. This type of pain is defined as physiological[3]. Pain, however, can also originate from the activity of the nociceptive system without activation of the nociceptive terminations. This type of pain is called neuropathic pain. The Neuropathic Pain Special Interest Group (NeuPSIG) has recently redefined neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"[3]. Pain secondary to plastic changes in the nociceptive system, resulting from intense and persistent nociceptive stimulation, needs to be distinguished from neuropathic pain. It is important to note that neuropathic and nociceptive pain can coexist in the same patient. In particular, both nociceptive and neuropathic processes can contribute to pain, taking the form of mixed pain syndrome. One example is low back pain with a neuropathic component, which includes a nociceptive component arising from muscles, ligaments and the spine, and a neuropathic component arising from the spinal roots (radicular pain) or lesions of nociceptive sprouts within a degenerated vertebral disc (local neuropathic pain)[4]. In developed countries the most frequent causes of peripheral neuropathic pain are compressive radiculopathy and diabetic peripheral neuropathy (DPN). A prospective multi-centre study[5] carried out in Germany has demonstrated that patients with chronic lower back pain had a prevalence of 37% of the neuropathic component. Based on published studies[6], the European prevalence of painful DPN ranges from 6% to 34% in diabetes mellitus patients. Unsatisfactory diabetes control, diabetes duration, and nephropathy have been associated with increased risk of painful DPN. Post-surgical pain is an important and underestimated iatrogenic cause of neuropathic pain in the primary care[7]. Postherpetic neuralgia (PHN) is a common cause of peripheral neuropathic pain. Prodromal pain, severe acute pain, severe rash and ophthalmic involvement are risk factors for PHN[8]. Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. Neuropathic pain-generating mechanisms have been reviewed within recent years. As illustrated in the Figure 1, peripheral and central mechanisms of neuropathic pain are targets for drugs currently used in clinical practice. A mechanism-based treatment approach is suggested to improve therapeutic response. The following is a brief description of pathophysiological mechanisms observed to be important in neuropathic pain conditions.

Ectopic Impulse Generation

Ongoing burning pain (stimulus-independent pain) is caused by spontaneous abnormal activity in C fibres. In fact, intraneural microstimulation (INMS) of C fibres evokes burning pain in healthy subjects[9]. After peripheral nerve lesion, pathological spontaneous firing of C fibres occurs at the multiple sites, such as the neuroma, the dorsal root ganglia (DRG) of injured neurons, and in uninjured afferent fibres[10-12]. This hyperexcitability of injured small diameter DRG neurons is mainly due to changes in transcription of voltage-gated sodium channel genes. After peripheral nerve injury, the sodium channels begin to accumulate along the length of the axon resulting in ectopic spontaneous activity in both injured and neighbouring uninjured nociceptive afferents[10-12].

Central Sensitization

In the spinal cord dorsal horn, spontaneous activity in C fibres causes an increase in the excitability of wide-dynamic-range neurons (WDR), which manifests as hypersensitivity to pain. This phenomenon is called central sensitization[12,13]. If central sensitization is established, there is an exaggerated response of WDR neurons to innocuous stimuli that travel along Aβ fibres and consequently dynamic mechanical allodynia is observed. The spread of pain beyond the innervation territory of an injured nerve is the result of central sensitization[11].

Disinhibition of Nociception

Peripheral nerve injury may induce selective apoptosis of GABAergic inhibitory interneurons in the superficial laminae of the spinal cord dorsal horn, resulting in a reduced synthesis of gamma-amino-butyric acid (GABA)[12,14]. This reduced GABA production might result in a loss of the inhibitory tone on nociceptive transmission. It was hypothesized[12] that a reduced activity of descending inhibitor systems contributes to central sensitization and chronic pain.

Sympathetically Maintained Pain

The term sympathetically maintained pain (SMP) is used to indicate the component of pain

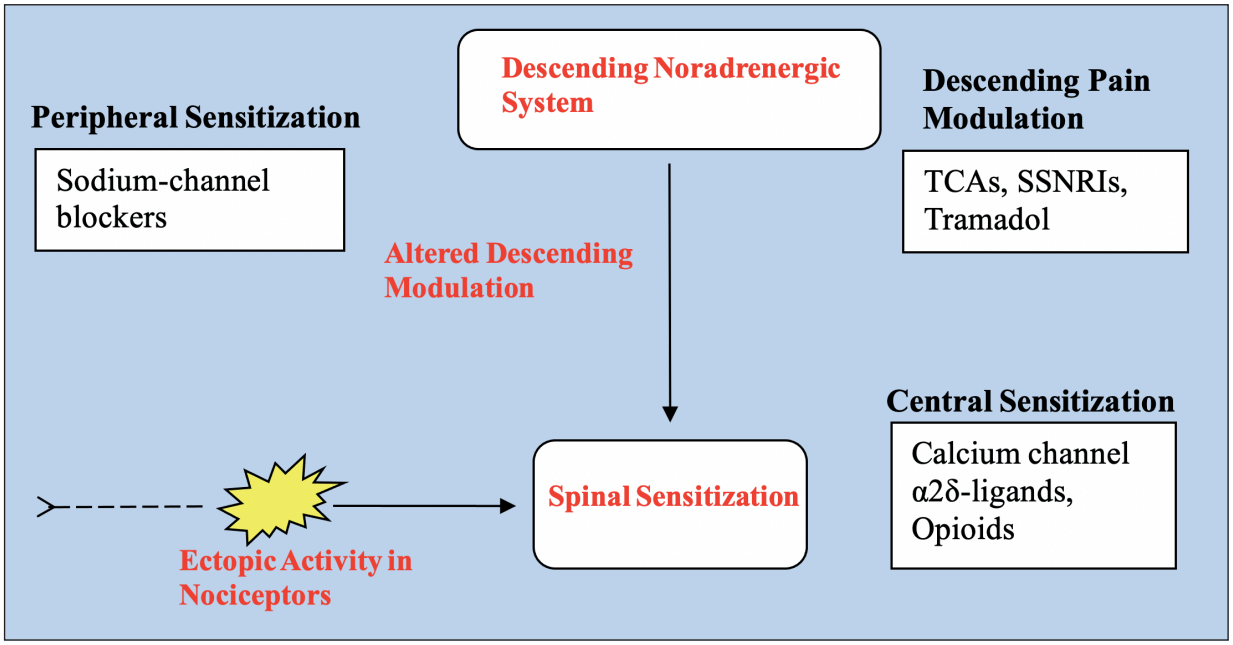

Figure 1. This simplified diagram is an attempt to link mechanisms of neuropathic pain and possible therapeutic targets. Topical lidocaine acts directly on damaged pain fibres under the patch reducing aberrant firing of voltage-gated sodium channels. Gabapentinoids inhibit calcium currents in the spinal cord, thus decreasing the release of excitatory transmitter and central sensitization. Also, opioids modulate central sensitization by activating post-synaptic opioids receptors, thereby controlling the hyperexcitability of spinal neurons. Nociceptive impulse transmission in the spinal cord is physiologically modulated by descending noradrenergic system. After nerve injury, an impairment of descending noradrenergic system contributes to central sensitization and pain chronicity. Therefore, antidepressants drugs also modulate central sensitization. Moreover, it has been shown that amitriptyline can also act as local anaesthetic by blocking voltage-gated sodium channels. Some antiepileptics as carbamazepine also act through the blockade of voltage-gated sodium channels.

relieved by the anaesthetic sympathetic blockade. SMP is pain maintained by sympathetic efferent innervation or by circulating catecholamines. Following a peripheral nerve injury and tissue inflammation, nociceptive afferent fibres develop a chemical sensitivity to catecholamines. This sympathetic-afferent coupling is mediated by α-adrenoceptors[15].

Deafferentation

Deafferentation pain is due to a nerve injury in the dorsal root ganglion or proximal to the ganglion. Denervated dorsal horn neurons begin to fire spontaneously at high frequency[12]. This mechanism, called "denervation supersensitivity", is associated with ongoing burning pain. Brachial plexus and root avulsion are examples of deafferentation pain.

Discussion

Peripheral neuropathic pain is typically characterized by positive and negative sensory symptoms and signs. Negative symptoms and signs are an expression of loss of function of the somatosensory system (i.e., hypoesthesia, hypoalgesia, hypopallesthesia) while positive symptoms and signs indicate a gain in function of the somatosensory system. Positive sensory phenomena are represented by paraesthesia (i.e., tingling, pricking), which are bothersome but not painful, by stimulus-independent pain that may be ongoing (often described as burning) or paroxysmal (electric shock-like sensations), and by stimulus-induced pain. Stimulus-evoked pain (i.e., allodynia, hyperalgesia) may be adjacent to or intermingled with skin areas of sensory deficit[12,16]. The verbal descriptors most frequently used by patients to describe neuropathic pain are the following: burning, electric shock, tingling, pricking, itching, cold. These verbal descriptors have represented for many years the fundamental elements for the diagnosis of neuropathic pain. However, the diagnostic role of the quality of pain perceived by the patient has been reduced since no symptoms or signs seem to be pathognomonic of neuropathic pain[17].

Peripheral neuropathic pain occurs in the innervation territory of a peripheral nerve, of a plexus, of a spinal root. The algological history begins with the identification of the body area in which the patient feels pain. It is possible to hypothesize peripheral neuropathic pain if this has a peripheral neuroanatomical distribution and the patient history is suggestive of a lesion or disease of the peripheral somatosensory system[3]. PCPs have to test the hypothesis of possible peripheral neuropathic pain based on patient history by looking at signs of possible nerve fibre damage in the area of pain through a careful clinical examination. Bedside examination of somatosensory functions is straightforward and includes the following qualities: touch, pinprick, cold and warmth, and vibration. It is possible to assess the integrity of the somatosensory system in a general practice clinic with simple and easily available utensils, such as a cotton wool, a metal paper clip or a wooden cocktail-stick, a thermoroller or a test tube filled with hot (40°C) and cold (20°C) water[7,16]. PCPs assess in sequence tactile sense using a piece of cotton wool, pinprick sense using a wooden cocktail-stick, thermal sense using a thermoroller and possibly also vibration sense using a 128-Hz tuning fork[18]. Sensory testing must always be started on the unaffected side and manoeuvres must be performed in a comparative and symmetrical manner. This facilitates the detection of the negative sensory abnormalities (tactile, pinprick, thermal). A negative result of sensory testing indicates the integrity of sensory nerve fibres (Aβ, Aδ, C), and it is therefore likely that the pain is nociceptive. On the contrary, a positive result to one or more sensory tests is indicative of probable neuropathic pain. Bedside examination ends with the detection of signs of mechanical hypersensitivity that often extend to the skin area adjacent to that of sensory deficits (outside the innervation territory). In the presence of positive or negative somatosensory signs, a diagnostic test (neurophysiological methods, diagnostic imaging methods, skin biopsy) may demonstrate a lesion or disease of the peripheral somatosensory system responsible for neuropathic pain[3,19]. Therefore, it is necessary to refer the patient to a specialist for a definitive diagnosis of peripheral neuropathic pain, also initiating an appropriate pharmacological therapy immediately.

Neuropathic pain does not respond to conventional analgesics[7], such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, therefore it is often under-treated in primary care[20]. Furthermore, complete relief from pain is often impossible and analgesic drugs can reduce neuropathic pain by 30-50%. Several evidence-based guidelines[21-24] have been published for the treatment of neuropathic pain. Below is a compendious description of the various drug classes recommended by the guidelines for the treatment of neuropathic pain (Table I).

First Line Treatments for Neuropathic Pain

Calcium Channel α2δ Ligands

Gabapentin and pregabalin bind to the $\alpha_2\delta$ subunit of the voltage-gated calcium channels that are expressed at presynaptic nerve terminals. Both drugs are recommended as first-line drugs based on clinical evidence[21,22]. These drugs have a similar mechanism of action, inhibiting the entry of calcium into the presynaptic termination, and therefore the release of neurotransmitters by exocytosis. However, these drugs have different pharmacokinetic characteristics. Gabapentin is absorbed slowly in the intestine via a saturable transport system, with an oral bioavailability that is reduced with increasing dosages. In contrast, pregabalin is rapidly absorbed with peak plasma concentration reached within one hour and oral bioavailability at ≥ 90% irrespective of the dosage. These drugs are not metabolized in the liver, they are excreted unchanged in the urine; therefore, dosage reduction is required in patients with reduced kidney function[11]. The efficacy and tolerability of these two drugs seem similar; however, pregabalin has a linear pharmacokinetic, a simpler titration, and the results are much more predictable[25]. The most common side effects are somnolence and dizziness. These side effects are dose-dependent and can be reduced with low initial dosages and careful dose titration. These drugs have a good safety profile without clinically significant drug interactions[26].

Antidepressant Drugs

Tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine are recommended as first-line drugs[21,22,24]. TCAs are more effective than SNRIs but often provoke anticholinergic effects, sedation and orthostatic hypotension[21,22,25,26]. An electrocardiogram (ECG) is recommended before beginning treatment[11]. SNRIs should be preferable in elderly patients[25].

Table I. Summary of recommendations for pharmacological management of neuropathic pain.

Guidelines	NeuPSIG[22]	EFNS[24]	NICE[23]
Tricyclic antidepressants (TCAs)	First line	First line for PPN, PHN	Amitriptyline first line
SNRIs Duloxetine, Venlafaxine	First line	First line for PPN	Duloxetine first line, Venlafaxine not recommended in non-specialist settings
Channel α2δ ligands Pregabalin, Gabapentin	First line	First line for PHN and PPN	First line
Lidocaine patches	Second line for localized neuropathic pain	First line for PHN in the elderly due to its excellent tolerability	Not indicated
Tramadol	Second line	Second line in the PPN; use with caution in the elderly because of risk of confusion; not recommended with SNRIs	Long-term use not recommended; use only as acute rescue therapy if needed
Strong opioids	Third line	Third line for PPN, second line for PHN	Not recommended in non-specialist settings
Carbamazepine	Inconclusive recommendation	First line for Trigeminal neuralgia	First line for Trigeminal neuralgia

Abbreviation: NeuPSIG, Neuropathic Pain Special Interest Group; EFNS, European Federation of Neurological Societies; NICE, National Institute for Health and Care Excellence; PHN, Post-herpetic Neuralgia; PPN, Painful Polyneuropathy.

Second-Line Treatments for Neuropathic Pain

Topical Analgesics

Lidocaine 5% and capsaicin 8% patches were approved by the FDA in the USA to treat PHN. The NeuPSIG guidelines recommend lidocaine and high-concentration capsaicin patches as a second-line treatment for localized peripheral neuropathic pain[22]. The efficacy of lidocaine 5% patch has been assessed mainly in PHN in randomized controlled trials (RCTs) of short duration (less than 3 weeks)[26]. The quality of evidence is low, the recommendation for use is weak[22]. However, given the excellent safety profile (limited systemic absorption, no systemic adverse effects), topical lidocaine (a patch once a day for up to 12h) might be considered in the treatment of localised peripheral neuropathic pain as first-line particularly in elderly patients[22]. Capsaicin 8% patch is effective in PHN and HIV-related painful polyneuropathy. Capsaicin is an agonist of the vanilloid receptor 1 (TRPV1) expressed on Aδ and C fibres[26]. High-concentration capsaicin causes activation and subsequent desensitization of the TRPV1 receptors, and substance P (SP) depletion in peripheral terminations[27]. The capsaicin patch should be left in place for 30 minutes in HIV-related polyneuropathy, for 60 minutes in PHN[26]. The quality of evidence is high, but the recommendation for use is weak[22].

Tramadol

Tramadol is a weak opioid μ-receptor agonist that also inhibits the reuptake of noradrenaline and serotonin[26]. It is recommended as a second-line treatment (moderate quality of evidence, weak recommendation for use)[22]. The 2013 NICE guidelines[23] recommend its use in primary care only as a rescue therapy. The drug should be used with caution in elderly patients (risk of cognitive impairment) and in combination with antidepressants (risk of serotonin syndrome)[26].

Third-Line Treatments for Neuropathic Pain

Strong Opioids

The efficacy of strong opioids (particularly oxycodone and morphine) in peripheral neuropathic pain has been reported in several RTCs[11,26]. In fact, they have been recommended as a second-line therapy for neuropathic pain[25]. However,

due to the prescription opioid abuse and opioid overdose deaths in USA they are now recommended as third-line[22,28]. Constipation, nausea, and somnolence are the most common adverse effects of opioids[26]. Strong opioids should not be given to opioid-naive patients as primary treatment.

Combination Therapy

In clinical practice, a combination of two or more drugs is often needed to achieve satisfactory relief from pain. The rationale of the association of different drugs consists in the possibility of obtaining the maximum therapeutic efficacy and minimum adverse effects by exploiting different and complementary mechanisms of action. However, the efficacy of combination therapy was not confirmed in a large multicentre RCT (COMBO-DN Study)[29].

Conclusions

Peripheral neuropathic pain is a common debilitating condition affecting patients in primary care often treated sub optimally. The PCP can play a pivotal role in improving the diagnosis and treatment of peripheral neuropathic pain. An accurate diagnosis of peripheral neuropathic pain is key to improving treatment results. Since analgesic drugs must be selected based on the type of pain (nociceptive, neuropathic, mixed), the PCP has to perform a careful bedside examination of somatosensory functions that is the basis of neuropathic pain diagnosis. However, the diagnosis of peripheral neuropathic pain may be difficult and the response to analgesics may be unsatisfactory. Hence, in these cases it is essential to refer the patient to a specialist as inadequate or delayed treatment is associated with a deterioration in the emotional state and quality of life of the patient.

Conflict of Interest

The authors declare that there were no external funding sources for this study and that there is no conflict of interest.

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