Pharmacological treatment of neuropathic pain: review of oral and topical therapy recommendations

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Abstract

Background: Neuropathic pain is defined as pain initiated or caused by injury or disease of the somatosensory system. It is a chronic pain with an extremely high impact on patients quality of life, which is progressively incapacitating. This paper reviews the evidence-based guidelines on the management of neuropathic pain, aiming at establishing specific and targeted recommendations based on oral and topical drugs available in Portugal.

Methods: We reviewed the literature on the treatment of neuropathic pain from Medline and Cochrane databases. Guidelines proposed by several global organizations and implemented clinically in patients with different neuropathic pain conditions were analyzed and compared. The present recommendations focus on oral and topical drugs available in Portugal.

Recommendations: Recommendations for the treatment of neuropathic pain are based on three therapeutic lines. For best use of therapeutic resources, the evaluation of neuropathic condition is essential, allowing a detailed breakdown of drugs. In general, first-line therapy comprises tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, calcium channels α2-δ ligands and topical lidocaine. Second-line therapy includes strong opioids and tramadol. Third-line therapy includes other antidepressants and anticonvulsants, N-methyl-D-aspartate (NMDA) receptor antagonists, topical capsaicin and gamma-aminobutyric acid (GABA) B receptor agonists. Combination therapy is also recommended.

Conclusion: Confirmatory diagnosis of neurological injury is essential to proper orientation of therapeutic strategies. An assessment of comorbidities and complete characterization of the neuropathic condition is recommended to establish specific profiles and provide individualized treatment.

Keywords: Neuropathic pain, Pharmacological management, Neuropathic pain syndromes.
Pharmacological treatment of neuropathic pain

Introduction

Neuropathic pain is defined as pain initiated or caused by injury or disease of the somatosensory system, characterized by sensory and motor disorders [1-3]. It is a chronic pain with an extremely high impact on patients quality of life, which is progressively incapacitating [14,15]. It is estimated that 7% of the population in Portugal and 7-8% of the population in Europe is suffering from neuropathic pain [8,9,16,17,20]. Neuropathic pain results from several causes such as tumors, nerve compression, infection, surgery, degenerative diseases, drugs, among others predictive risk factors for pain such as diabetes mellitus [2,4,17]. The etiology of neuropathic pain is variable, presenting several symptoms that vary with the clinical condition manifested [2,6,7,11]. The therapeutic management of neuropathic pain is based on the clinical scenario and the diagnosis obtained after complementary exams, focusing on drugs such as antidepressants, anticonvulsants, opioids, tramadol, topical agents, gamma-aminobutyric acid (GABA) B receptor agonist and N-methyl-D-aspartate (NMDA) receptor antagonists [18-21,37,40,44]. Therapeutic lines for the treatment of neuropathic pain are recommended based on efficacy [35] and safety profiles observed in randomized controlled trials (RCTs), systematic reviews and guidelines that support the clinical superiority of these drugs.

The pharmacological treatment of neuropathic pain is essential but at the same time unpredictable. Treatment response is multifactorial. It becomes imperative to establish a treatment that promotes analgesia and effectively relieves pain with a plausible cost-effectiveness ratio. This paper reviews the evidence-based guidelines on the management of neuropathic pain, aiming at establishing specific and targeted recommendations based on oral and topical drugs available in Portugal.

Methods

The recommended therapeutic lines are based on a review of guidelines on the management of neuropathic pain. We collected and reviewed recently published or updated (2002-2011) international guidelines developed by specialized organizations such as the International Association for the Study of Pain (IASP), European Federation of Neurological Societies (EFNS) and Canadian Pain Society and National Institute for Health and Clinical Excellence (NICE). We searched both Medline and Cochrane databases, filtering for temporal limits (2002-2011), guideline publications, practice guidelines, randomized controlled trials (RCTs), and systematic reviews. We used as inclusion criteria updated publications, implemented clinically in patients with defined neuropathic pain, written in English, presenting oral and topical therapeutic options that were feasible and currently available. We excluded painful conditions noninflammatory absent of nervous system injury (for example, fibromyalgia, low back pain), articles based on the diagnosis and preventive treatment. This review strategy yield a total of 26 documents.

The therapeutic approaches considered in this review include drugs with proven levels of evidence. We present comparisons of efficacy, safety, doses and duration of treatment (which generally does not exceed three months in RCTs), based on available evidence.

General management considerations and recommendations

Neuropathic pain should not be considered a disease by itself, but considered as a clinical condition common to different pathologies [3,5]. The diffuse and complex etiology of the injury or damage in the nervous system, compromises the diagnosis and consequently the therapeutic decision [6,10,11,17].

Proper assessment and diagnosis of painful process can be key to treatment success. The subdivision of neuropathic pain according to clinical conditions ensures a therapeutic approach grounded and oriented. The assessment involves the identification of comorbidities that emerge from the painful process such as depression, anxiety, sleep disorders, among other changes in quality of life, which may affect the choice of the therapeutic plan [12,14,46]. A frequent reassessment of the clinical condition also preserves the patient’s state of health.

The choice of therapeutic lines is based on a correct diagnosis, but many other factors may influence the decision, including adverse effects, drug interactions, comorbidities and the cost of treatment (Figure 1)[11,13,19,20,37,40].

The economic analysis of the treatment is essential, because it also supports the decision [8,9,15]. A comparison by pharmaceutical group indicates little cost variation between the main therapeutic lines. Although the evidence-based recommendations encourage the use of specific drugs, the overall approach should be recognized as a phased process designed to identify the drug or combination of drugs that provide greater pain relief and less adverse effects for the patient [34].

First-line drugs

Tricyclic Antidepressants

This class of drugs presents results with extensive evidence in the treatment of neuropathic pain. The mechanism of action lies on blocking the reuptake of norepinephrine and serotonin to pre-synaptic level, limiting the hyperalgesia induced by N-methyl-D-aspartate agonists, blockade of sodium channels that allows the stabilization of neuronal peripheral level and modulation of neuronal hyperactivity at central level, anti-histamine action on the H1 and H2 receptors, blockade of alpha receptors that can eliminate pain maintained by noradrenergic stimulation and stimulation of µ-opioid receptors (despite the low affinity) [3,19-21]. The more relevant agents in this context are the tertiary amines such as amitriptyline and imipramine and the secondary
amines such as nortriptyline (better tolerated). The most common side effects are sedation, confusion, anxiety, anti-cholinergic effects such as dry mouth, increased intraocular pressure, constipation, urinary retention, and orthostatic hypotension [36,44]. Its use is limited in patients with conduction disturbances and patients who have suffered myocardial infarction. Treatment starts with low doses and should be titrated slowly until there is an adequate control of pain.

**Serotonin-norepinephrine reuptake inhibitors**
This agents are potent inhibitors of the reuptake serotonin and norepinephrine. Both venlafaxine and duloxetine also show weak inhibitory action on dopamine reuptake [21,44]. These drugs present favorable results in the treatment of neuropathic pain in multiple RCT’s especially in diabetic polyneuropathy, HIV neuropathy and oncologic neuropathic pain [20,37,40]. The adverse effects include asthenia, fatigue, nausea, vomiting, dry mouth, sedation, drowsiness, tremors, presenting particular caution in patients with renal and hepatic failure in the case of duloxetine and in patients with cardiovascular risk if the treatment focus on venlafaxine [3,20,21].

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**Figure 1.** Treatment of neuropathic pain.
*First-line in trigeminal neuralgia.
**Neurosurgery based in injury topography in special cases duly selected.
GABAB: Gamma-aminobutyric acid B; NMDA: N-methyl-D-aspartate; SNRI: Serotonin and norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitor.
Calcium channel α2-δ ligands

The union of the gabapentin and pregabalin to the subunit α2-δ of calcium channels voltage-dependent, decreases the release of glutamate, norepinephrine and substance P, decreasing the neuronal excitability [3,22,36]. Used of these drugs in various conditions of neuropathic pain is supported by evidence from several studies. The adverse reactions that may limit their use include drowsiness, dizziness and peripheral edema, which can be reduced with gradual dose titration [34,38-40]. Treatment starts with low doses and several weeks may be required to achieve the effective dose [39,40]. Special precautions are necessary in patients with renal insufficiency [3].

Carbamazepine

This drug is a classic antiepileptic, which blocks voltage-dependent sodium channels, inhibiting repetitive neuronal discharges and the propagation of synaptic excitation impulses in depolarized neurons [3,20,22,37]. Carbamazepine is the first-line to treat the trigeminal neuralgia [19,20,37,48]. Evidence on the use of carbamazepine in other conditions of neuropathic pain is scarce. Common side effects resulting from the administration of carbamazepine include drowsiness, ataxia, dizziness, nausea, fatigue and skin reactions [38,39]. Hematologic changes such as aplastic anemia, leukopenia and thrombocytopenia can also arise [3]. Caution in advised in patients with impaired hepatic function.

Lidocaine

Lidocaine is a local anesthetic that causes a blockade of the movement of sodium ions to the interior of the membranes, causing a reversible blockade in the propagation of the pulse along the nerve fibers [3,37]. Lidocaine 5% patches are the formulation most widely studied, constituting a therapeutic option with proven effectiveness in peripheral neuropathies and allodynia, even in combination with other first-line drugs [9,19,20,24]. The adverse effects include skin rash, erythema, burning sensation and itching [24]. Its use is restricted in patients with severe hepatic impairment, in which excessive blood concentrations are possible [3,24].

Second-line drugs

Opioids

The benefit of opioids is constantly justified in the literature, in a variety of central and peripheral conditions such as postherpetic neuralgia, diabetic neuropathy and phantom limb neuropathy [19,20,37,40]. In contrast to their clinical benefits, adverse reactions often result, however, in the discontinuation of therapy. The most common adverse reactions include constipation, nausea, vomiting, dizziness, drowsiness, headache and dry mouth [3,23]. Given the possibility of addiction and modification of the behavioral pattern, the prescription should be handled with caution [43,44]. However, the evidence demonstrates that, given proper use, these situations become unusual [23,24]. Opioids are regarded as second-line treatment due to their side effects, compared with tricyclic antidepressants or anticonvulsants. Furthermore, the safety of long-term treatment has not been systematically studied. Within this group, the drugs used are the fentanyl and morphine, whose treatment is reserved for patients who do not respond adequately to the drugs of first-line [20,37,40,43].

Tramadol

Tramadol has a dual mechanism of pharmacological action which consists of agonist activity on the μ-receptors, although this affinity is much lower than the effect exerted by morphine [3,18,41]. On the other hand, it blocks synaptic reuptake of the amines, which causes similar effects to those of monoaminoxidase inhibitors [41]. It inhibits the reuptake of norepinephrine and serotonin in central nervous system, preventing the transmission of the pain through the medulla [3]. Patients with different types of neuropathy, such as diabetic polyneuropathy and postherpetic neuralgia felt less pain and improvement in quality of life [19,20,37] following tramadol treatment. Such as with opioids, the risk of abuse of tramadol is also present. The adverse reactions arising from tramadol administration are common to opioids. The administration of tramadol may precipitate seizures in patients with history of seizures and their association with the serotonergic drugs such as duloxetine, venlafaxine, fluoxetine, paroxetine among others, may increase the risk of serotonin syndrome [37,43,44].

Third-line drugs

Antidepressants

The use of serotonin reuptake inhibitors in the treatment of neuropathic pain is supported by weak evidence, asreleaded by a Cochrane review [43,44]. Other antidepressants such as citalopram and paroxetine had positive effects in diabetic polyneuropathy, whereas fluoxetine did not put forward any benefit [19,37,44]. Bupropion inhibits the reuptake of dopamine and norepinephrine, with benefit in some neuropathic conditions [44]. The adverse effects of serotonin reuptake inhibitors include nausea, vomiting, drowsiness, dizziness, agitation and tremors, with special caution in patients with risk of seizures, suicide and glaucoma [3]. Bupropion presents adverse reactions such as insomnia, anorexia, agitation, headaches and tinnitus [3]. Clinical trials demonstrate that citalopram, paroxetine and bupropion may constitute a therapeutic line when the tricyclic antidepressants and inhibitors of reuptake of serotonin and norepinephrine are not effective.

Anticonvulsants

The action of antiepileptic drugs lies on stabilization of neuronal membrane to reduce the ectopic discharges in injured nerves, through various mechanisms depending on the type of drug [21,36]. In general, antiepileptic drugs facilitate inhibitory neurotransmission (GABA), reduce the excitatory neurotransmitter (glutamate) and modulate ionic channels existing in neuronal membrane (block
sodium and calcium channels and activation of potassium channels) [39,40]. Lamotrigine acts on the voltage-gated sodium channels, stabilizing the neuronal membrane [3]. Valproic acid obtained positive results for diabetic polyneuropathy and postherpetic neuralgia in three studies, however, other randomized clinical study yield negative results [37]. Three randomized controlled clinical trials of oxcarbazepine in patients with diabetic polyneuropathy were published, one of which was positive and the other two negative [37]. Carbamazepine is the first-line treatment of trigeminal neuralgia, but in other clinical conditions evidence is limited [20,37]. These drugs are therapeutic options when patients do not respond to first or second-line treatment.

**NMDA receptor antagonists**
The effectiveness of memantine is limited or non-existent [37]. According to the European Federation of Neurological Societies these drugs, as well as the benzodiazepine – lorazepam (non-NMDA receptor antagonist) are ineffective in neuropathic pain [43].

**Capsaicin**
Capsaicin is a topical drug potential transitional vanilóide type 1 (TRPV1) receptor agonist, present in C fibers and, to a lesser extent in Aδ fibers [3]. Capsaicin reduces and prevents the accumulation of substance P in peripheral sensory neurons, blocking the painful impulse [37]. Common adverse reactions include skin irritation and burning sensation [19,20]. The capsaicin to 0,075% (cream) have demonstrated benefit in some RCTs, however, the reactions of local burn generated due to the need for multiple applications, may compromise its effectiveness [20,45]. Recently, a single application of capsaicin to 8% through plasters for 30, 60 or 120 minutes, compared to applications of capsaicin at low concentrations (0.04%), showed benefit from 2 to 12 weeks in postherpetic neuralgia and HIV neuropathy, being an effective analgesic plaster for 60 minutes in postherpetic neuralgia and 30 minutes in HIV neuropathy [40].

**GABAB receptor agonists**
Baclofen is a muscle relaxant, specific agonist of the metabotropic GABAB receptor, used in clinical practice for the treatment of skeletal muscle spasticity [46]. Common side effects include drowsiness, ataxia, sedation and dizziness [3,46]. The mechanism by which provides analgesia is thought to be related to the inhibition of glutamate release in primary afferent terminals (Aδ and C) [3]. Clinical evidence from several studies indicates low levels of recommendation.

**Recommendations for specific conditions**
Recommendations for the treatment of neuropathic pain are based on three therapeutic lines. For best use of therapeutic resources, the evaluation of neuropathic condition is essential, allowing a detailed breakdown of drugs (Table 1).

**Diabetic polyneuropathy**
Diabetic polyneuropathy as defined by the IASP include patients with treatment of daily insulin or oral hypoglycemic agents who suffer from chronic pain for more than three months, located in the feet or hands and with evidence of a physical examination that determines a distal symmetrical polyneuropathy (loss or reduction of bilateral deep tendon reflexes, decreased sensitivity to the touch, paresthesias, cold or vibration in the feet or hands and feet) [3]. The first-line for the treatment of diabetic polyneuropathy is amitriptyline or nortriptyline, duloxetine, pregabalin or gabapentin [20-22,37,39,40]. In the presence of adverse reactions that prevent the continuation of treatment or patients who present special precautions, the second-line therapy is venlafaxine, tramadol or opioid drugs such as morphine or fentanyl. The third-line therapy includes carbamazepine, lamotrigine or plasters of lidocaine 5% (that can be used in association with first-line treatments). The combination of opioids with gabapentin or nortriptyline is plausible.

**Postherpetic neuralgia**
The postherpetic neuralgia is a common consequence of herpes zoster, whose factors that reactivate the latent virus are unknown. There is a common point to all manifestations of this condition—the immunosuppression [3,20]. The definition of postherpetic neuralgia determines the presence of pain more than three months after the eruption of vesicles and formation of crusts caused by viruses [17]. The treatment focuses on tricyclic antidepressants such as amitriptyline or nortriptyline, pregabalin, gabapentin and/or topical lidocaine (plaster to 5%) as first-line therapy. After the trial period and if the response to treatment is not satisfactory, opioids such as morphine or fentanyl or topical capsaicin 0,025% are suggested as second-line therapy. The third-line therapy is considered in the absence of positive results with previous lines, opting for baclofen or tramadol. Other therapeutic options such as memantine and lorazepam did not showed any pain relief efficacy [20].

**Trigeminal neuralgia**
Trigeminal neuralgia is characterized by intense and unilateral pain (such as electric shock), resulting from traumatic consequences, physiological degenerative processes associated with vascular compression [48] or viral infections, tumor lesions, multiple sclerosis, cerebral aneurysm and alveolar involvement after tooth extraction [3,47]. The first-line treatment is carbamazepine or oxcarbazepine. Oxcarbazepine may be the option of choice due to its lower potential for drug interactions. The presence of hematologic changes, cases of cardiac or liver failure, or adverse reactions should lead to the use of second-line therapy that includes lamotrigine or baclofen. Third-line therapy includes gabapentin, pregabalin, amitriptyline, duloxetine or venlafaxine. If there is no remission of pain with drugs, surgery may be considered [37,48].
Table 1. Considerations of drugs by therapeutic lines.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Therapeutic doses</th>
<th>Time</th>
<th>Common side effects</th>
<th>Special Precautions</th>
<th>Costs</th>
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<tr>
<td><strong>First-line drugs</strong></td>
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<tr>
<td>Tricyclic antidepressants</td>
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<td>Nortriptyline</td>
<td>25 – 150 mg/day</td>
<td>6 – 8 weeks</td>
<td>Sedation, anticholinergic effects (dry mouth, constipation and urinary retention), orthostatic hypotension</td>
<td>Cardiovascular diseases, glaucoma, convulsions, suicide risk. Association with tramadol not recommended</td>
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<tr>
<td>Amitriptyline</td>
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<td>Imipramine</td>
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<td>Serotonin and norepinephrine reuptake inhibitors</td>
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<td>Duloxetine</td>
<td>30 – 120 mg/day</td>
<td>4 weeks</td>
<td>Asthenia, fatigue, nausea, vomiting, dry mouth, sedation, drowsiness, tremors</td>
<td>Hepatic impairment, renal insufficiency. Association with tramadol not recommended</td>
<td>€€</td>
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<td>Venlafaxine</td>
<td>37.5 – 225 mg/day</td>
<td>4 – 6 weeks</td>
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<td>Anticonvulsants</td>
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<td>Gabapentin</td>
<td>100 – 3600 mg/day</td>
<td>3 – 8 weeks</td>
<td>Sedation, drowsiness, dizziness, peripheral edema</td>
<td>Renal insufficiency</td>
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<td>Pregabalin</td>
<td>150 – 600 mg/day</td>
<td>4 weeks</td>
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<td>Carbamazepine</td>
<td>100 – 1200 mg/day</td>
<td>4 weeks</td>
<td>Drowsiness, nausea, dizziness, ataxia</td>
<td>Hepatic insufficiency, hematologic changes as aplastic anemia, leukopenia and thrombocytopenia</td>
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<td>Topical agents</td>
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<td>Lidocaine</td>
<td>3 plasters/day</td>
<td>3 weeks</td>
<td>Skin rash, erythema, burning sensation, itching</td>
<td>Renal insufficiency, severe hepatic impairment</td>
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<td><strong>Second-line drugs</strong></td>
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<td>Opioids</td>
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<tr>
<td>Fentanyl</td>
<td>25 – 100 µg/h</td>
<td>4 weeks</td>
<td>Nausea, vomiting, constipation, drowsiness, dizziness</td>
<td>Abuse, addiction, respiratory depression.</td>
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<td>Morphine</td>
<td>15 – 200 mg/day</td>
<td>4 – 6 weeks</td>
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<td>Abuse, suicide risk, withdrawal syndrome</td>
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<td>Tramadol</td>
<td>50 – 400 mg/day</td>
<td>4 weeks</td>
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<td>Abuse, risk of seizures in epileptic patients. Association to antidepressants increase the risk of serotonin syndrome</td>
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<td><strong>Third-line drugs</strong></td>
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<td>Others anticonvulsants</td>
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<td>Lamotrigine</td>
<td>25 – 400 mg/day</td>
<td>4 – 6 weeks</td>
<td>Drowsiness, dizziness, skin rash</td>
<td>Hepatic and renal impairment</td>
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<td>Oxcarbazepine</td>
<td>300 – 1800 mg/day</td>
<td>4 weeks</td>
<td>Fatigue, drowsiness, dizziness, hyponatremia</td>
<td>Cardiac and renal insufficiency, hypersensibility</td>
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<td>Others antidepressants</td>
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<td>Citalopram</td>
<td>10 – 40 mg/day</td>
<td>4 weeks</td>
<td>Nausea, vomiting, drowsiness, dizziness, agitation, tremors</td>
<td>Combination with MAOI, convulsions, suicide, glaucoma.</td>
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<td>Paroxetine</td>
<td>100 – 400 mg/day</td>
<td>3 weeks</td>
<td>Insomnia, anorexia, agitation, tinnitus, headache</td>
<td>Convulsive disease, hepatic disease</td>
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<td>Memantine</td>
<td>10 – 20 mg/day</td>
<td>4 – 6 weeks</td>
<td>Dizziness, headache, constipation, drowsiness</td>
<td>Risk in epileptic patients</td>
<td>€€</td>
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<tr>
<td>Baclofen</td>
<td>40 – 80 mg/day</td>
<td>4 weeks</td>
<td>Drowsiness, dizziness, ataxia, sedation</td>
<td>Renal insufficiency, epilepsy, nerve diseases, peptic ulcer</td>
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<td>NMDA receptor antagonists</td>
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<td>Capsaicine</td>
<td>0.025%</td>
<td>4-6 weeks</td>
<td>Skin rash, erythema, burning sensation</td>
<td>Skin sensibility</td>
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<td>GABA, receptor agonists</td>
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<td>1 First-line in trigeminal neuralgia</td>
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Central pain
Central pain is produced at medullary and cerebral level by trauma, multiple sclerosis, vascular injury (stroke, hemorrhage or arteriovenous malformations), infection (HIV, spinal tuberculosis) and tumors [5,37,49]. Can be produced by degeneration of the spinal cord by deficit of vitamin B12, dysraphism and syringomyelia [3,49]. Amitriptyline or nortriptylne, pregabalin or gabapentin are recommended as first-line therapy. As the second and third-line therapy lamotrigine, tramadol or opioids such as morphine or fentanyl are recommended.

HIV neuropathy
Is associated with infection by the human immunodeficiency virus. Its origin can be directly correlated with the infected neurons of the dorsal root ganglion and/or local infiltration of macrophages assets that segregate neurotoxic cytokines and other metabolites [3,20,37]. Antiretroviral therapy can cause anti-retroviral toxic neuropathy [3]. The recommendations for the first-line treatment include amitriptyline or nortriptyline, pregabalin or gabapentin, duloxetine or venlafaxine. As a second-line therapy tramadol or tramadol in combination with paracetamol are recommended. Strong opioids such as morphine or fentanyl, lamotrigine or topical capsaicin are the third-line options. The association with topical agents such as capsaicin and lidocaine with first and second-line therapy may increase the treatment effectiveness.

Phantom limb pain
Phantom limb pain is a common condition after traumatic amputation. It is thought that the pain can be caused by peripheral mechanisms such as sensitization of dorsal horn by ectopic discharges and increased sensitivity of the neurona and by central mechanisms due to the reorganization of nerve fibers in the cerebral cortex, occurring a cortical remapping [50]. First-line therapy includes strong opioids such as morphine and fentanyl or tramadol. In patients with risk of seizures, abuse or suicide or intolerance of adverse reactions, it is suggested as a second-line amitriptyline or nortriptyline, pregabalin or gabapentin. Mantine or carbamazepine may be third-line options. For most patients this pain can be resolved gradually over time, however, in situations in which the pain remains, the opioids are the election as post-amputation treatment (control acute pain post-surgery), modifying later to another class of drugs.

Oncologic neuropathic pain
Oncologic neuropathic pain can be a direct consequence of the tumor (compression and/or infiltration) or iatrogenic (tumor treatment and diagnosis) [3]. First-line therapy includes amitriptyline or nortriptyline, pregabalin or gabapentin, duloxetine, venlafaxine or carbamazepine. As a second-line therapy tramadol, strong opioids and/or topical lidocaine are recommended. In the absence of remission of pain, the third-line of treatment consists of selective serotonin reuptake inhibitors such as paroxetine and citalopram, bupropiom, lamotrigine, topiramate, mantine and/or topical capsaicin.

Radiculopathy
Radiculopathy is produced as a result of compression of the nerve roots of the cervicobrachial, thoracic or lumbosacral plexus [3]. The associated causes are changes in the intervertebral discs and anatomical degenerations (discal, vertebral joints), which cause an inflammatory process in the nervous structures [3,11]. Tricyclic antidepressants such as amitriptyline or nortriptyline, pregabalin or gabapentin are recommended as first-line treatments. The titration should be done gradually and in absence of remission of pain, duloxetine, venlafaxine or opioids such as morphine or fentanyl are suggested. Other therapeutic options such as infiltration of epidural steroids may be beneficial for relief of acute pain. Consider surgery if pharmacological treatment is ineffective.

Conclusions
The suggested recommendations are based on efficacy/safety ratio of drugs, depending on the clinical condition, the comorbidities associated with the pathological process and costs. It is very important to establish a confirmatory diagnosis of nerve lesion [46] for tailoring pharmacological treatment [2-4, 6]. After treatment selection, continuous treatment assessment is essential, in order to carry out therapeutic interventions (adjustment of doses, drug association, suspension of treatment) and ultimately ensure treatment success.

The treatment of neuropathic pain is dependent on the clinical condition [7]. However, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, calcium channel a2-δ ligands and lidocaine showed demonstrated efficacy in practically all conditions of neuropathic pain, therefore they become recommendations of first-line [18-20,37,38,40]. The titration of these drugs should be made gradually, starting at low doses, reducing the likelihood of undesirable effects. When there is intolerance of adverse reactions or special precautions to prevent the use of this therapeutic line, the use of strong opioids (fentanyl or morphine) or tramadol is recommended [20,37,42,43]. The association of opioids with first-line drugs is a treatment option with proven efficacy, allowing better control of the pain, if it does not respond to the drugs administered in an isolated form [20,37,40-42]. The concomitant use of tricyclic antidepressants and gabapentin, shows consistent results [37]. The association of topical agents such as lidocaine also has an added value in control of peripheral neuropathic pain [19,20,24,37]. Carbamazepine and oxcarbazepine are unique first-line treatment of trigeminal neuralgia [20,37,40,42,43].

The various therapeutic alternatives recommended relieve pain, but this might be only a partial pain relief. The
implementation of non-pharmacological treatments (nerve block, radio frequency, electrical stimulation, physiotherapy, acupuncture) [25-31] associated to pharmacological therapy may benefit the patient, relieving pain more effectively [32]. When all treatment options fail, resort to neuromodulation is something plausible in particular cases [33].

Abreviations

EFNS: European Federation of Neurological Societies; GABA: Gamma-aminobutyric acid; IASP: International Association for the Study of Pain; NMDA: N-methyl-D-aspartate; NICE: National Institute for Health and Clinical Excellence; RCT: Randomized controlled trial.

Competing interests

The authors declare no conflict of interest.

References

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