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RECOMMENDATIONS FOR NEUROPATHIC PAIN TREATMENT

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SUMMARY – Damage to the somatosensory nervous system poses a risk for the development of neuropathic pain. Such an injury to the nervous system results in a series of neurobiological events resulting in sensitization of both the peripheral and central nervous system. The symptoms include continuous background pain (often burning or crushing in nature) and spasmodic pain (shooting, stabbing or "electrical"). The diagnosis of neuropathic pain is based primarily on the history and physical examination finding. Although monotherapy is the ideal approach, rational polypharmacy is often pragmatically used. Several classes of drugs are moderately effective, but complete or near-complete relief is unlikely. Antidepressants and anticonvulsants are most commonly used. Opioid analgesics can provide some relief but are less effective than for nociceptive pain; adverse effects may prevent adequate analgesia. Topical drugs and a lidocaine-containing patch may be effective for peripheral syndromes. Sympathetic blockade is usually ineffective except for some patients with complex regional pain syndrome.

Key words: *Neuralgia – etiology; Neuralgia – physiopathology; Neuralgia – therapy; Pain – therapy; Guideline ; Practice – guideline*

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction of the peripheral or central nervous system"[1]. Damage to the somatosensory nervous system represents a risk for the development of neuropathic pain. The consequences of such an injury to the nervous system include a series of neurobiological events resulting in sensitization of both the peripheral and central nervous system.

The symptoms include continuous background pain (often burning, tight or crushing in nature) and spasmodic pain (shooting, stabbing or sometimes "electrical"). Recently, therapeutic strategies aiming at selecting treatments by targeting the putative mechanisms of pain (mechanisms based strategies) have been proposed, yet this approach remains difficult to apply in clinical practice due to heterogeneity of the etiologies, symptoms and signs[1-3].

Table 1. The most common causes of neuropathic pain

1. *Metabolic:*	5. *Immune:*
Diabetes mellitus	Guillain-Barre syndrome
Uremia	Multiple sclerosis
Hypothyroidism	Monoclonal gammopathies
Porphyria	Eosinophilia-myalgia syndrome
Amyloidosis	
Vitamin B deficiency	6. *Genetic:*
2. *Toxic:*	Fabry disease
Alcohol	HMSN (hereditary motor and sensory neuropathy)
Chemotherapy agents, especially vincristine, cisplatin, taxanes	7. *Vascular:*
Glue sniffing	Cerebrovascular disease (ischemic and hemorrhagic stroke)
Gold	Vasculitis (cryoglobulinemia, lupus erythematosus, polyarteritis nodosa)
Lead	
Mercury	8. *Carcinomatous:*
Other drugs including hydralazine, isoniazid, nitrofurantoin, pheny toin, thalidomide	Paraneoplastic syndrome
	Compressive
	Infiltrative
3. *Traumatic:*	9. *Diverse:*
Carpal tunnel syndrome	Syrinx
Cervical or lumbar radiculopathy	Epilepsy
	ALS
Complex regional pain syndrome	10. *Head and face neuralgia*
Spinal cord injury	Trigeminal
Stump pain	Glossopharyngeal
Amputation (phantom limb pain)	Hypoglossal
4. *Infections*	
Herpes zoster	
HIV	
Borreliosis	
Epstein Barr virus	

Etiology of neuropathic pain

Any condition that damages neural tissue or impairs its function can be a source of neuropathic pain. Injury, inflammation, ischemia, metabolic derangement, toxins, tumor and primary neurological disease may lead to neuropathic pain[4-8]. Neuropathic pain that is associated with disorders such as diabetes mellitus and herpes zoster is most frequently described and studied. However, these disorders are certainly not the exclusive causes of neuropathic pain[8-15].

Radiculopathy, which may be an underlying cause in many cases involving lower back pain, is probably the most frequent peripheral nerve pain generator.

The pathophysiology of neuropathic pain is very complex and includes both peripheral and central mechanisms (Table 1). Usually, a combination of peripheral and central mechanisms accounts for the clinical presentation of neuropathic pain. The mechanisms involved in causing different clinical phenomena of neuropathic pain include: 1) pathological activity in sensitized or awakened silent nociceptors; 2) ectopic activity along damaged axons and in dorsal root ganglion cells; 3) facilitated transmitter release due to upregulation of calcium channels; 4) central sensitization of dorsal horn neurons from increased afferent input; and 5) central sensitization from the loss of central inhibition/increased central facilitation. The complexity of neuropathic pain is emphasized by the fact that there is no known direct relationship between the mechanisms and symptoms or signs caused by such a mechanism[8-12].

The generator of pain can be located in the peripheral or central nervous system, or both. One of the characteristics of neuropathic pain is that pain continues in the absence of ongoing non-neurological tissue damage. It may be the result of damage or pathological changes in the nervous system, which are responsible for the peripheral and central mechanism of neuropathic pain.

Clinical features

Neuropathic pain can be stimulus-independent and stimulus-dependent.

Stimulus-independent pain

Stimulus-independent pain is spontaneous pain. Spontaneous pain (continuous or intermittent) is commonly described as burning, shooting or shock-like. Paresthesias and dysesthesias can originate peripherally *via*

ectopic impulses along the Aβ, Aδ, and C fibers, arising as spontaneous activity due to the processes such as damaged sodium channels that accumulate along affected nerves, causing a drift towards threshold potential. Paroxysmal shooting or electrical pain as well as continuous burning pain most likely occur from ectopic or ephaptic discharges arising in any type of fiber. Stimulus-independent pain may also occur as the result of reduced inhibitory input from the brain or spinal cord[4-8].

Stimulus-evoked pain

Stimulus-evoked pain includes allodynia (pain evoked by a non-painful touch) and hyperalgesia (increased pain evoked by a painful stimulus). Allodynia can be caused by the lightest stimulation such as skin contact with clothing. Hyperalgesia is an exaggerated pain response produced by a normally painful stimulus, while allodynia is pain produced by a stimulus that is not usually painful.

An essential part of neuropathic pain is the loss (partial or complete) of afferent sensory function and the paradoxical presence of certain hyperphenomena in the painful area.

In peripheral neuropathic pain, the sensory loss involves either all or selected sensory modalities. In central neuropathic pain, there is a partial or complete loss of spino-thalamo-cortical functions[4-8].

The distribution of sensory loss represents an important step for pain assessment and identification of the nervous system damage, and can be transferred to a phantom map. Combined with pain location, the distribution of sensory loss can determine whether this loss is confined to one or several nerves, to a group of fascicles, to nerve roots, to dermatomes, to the somatosensory map of damaged brain structures, or whether the sensory loss is part of a somatization disorder[4].

In neuropathic pain, the sensory loss is confined to the innervation territory corresponding to the damaged part of the nervous system, be it peripheral or central.

Examples of neuropathic pain include diabetic neuropathy, trigeminal neuralgia, radiculopathies, phantom limb pain, and complex regional pain syndrome[4-7,11].

Neuropathic pain assessment

The diagnosis of neuropathic pain is based primarily on the history and physical examination finding. A detailed history, physical examination and diagnostic procedures are necessary to properly and fully define the putative mechanisms involved in a given neuropathic pain syndrome.

On physical examination, it is important to identify the location, quality, intensity and pattern of pain. Neurological examination uses simple bedside tests to assess the patient for the presence or absence of specific stimulus-evoked signs. Testing of reflexes, a comprehensive motor examination, and autonomic examination are all essential to the understanding of neuropathies. The motor, sensory and autonomic systems may be tested by electromyoneurography, microneurography, quantitative sensory testing, and quantitative sudomotor axon reflex test.

Treatment

Regardless of the cause, neuropathic pain affects multiple aspects of the patient's life. The management of neuropathic pain involves a multidisciplinary approach. Therapy for neuropathic pain includes the use of both non-interventional (pharmacological, psychological and physical therapy) and interventional therapies[15-30].

Without due consideration of the diagnosis, rehabilitation and psychosocial issues, treatment has a limited chance of success. For peripheral nerve lesions, mobilization is needed to prevent trophic changes, disuse atrophy, and joint ankylosis. Surgery may be needed to alleviate compression. Psychological factors must be constantly considered from the start of treatment. Anxiety and depression must be treated appropriately. When dysfunction is entrenched, patients may benefit from the comprehensive approach provided by a pain clinic[9-13].

Pharmacotherapy

The best clinical approach to applied pharmacology currently incorporates empiric observation and identification of the possible mechanisms of the neuropathic lesion[31-55]. Then the clinician should use the best pharmacological therapy available that matches the putative drug mechanisms. Although monotherapy is the ideal approach, rational polypharmacy is often pragmatically used. Several classes of drugs are moderately effective, but complete or near-complete relief is unlikely. Antidepressants and anticonvulsants are most commonly used. Evidence of efficacy is strong for several antidepressants and anticonvulsants[31-55].

Opioid analgesics can provide some relief but are less effective than for nociceptive pain; adverse effects may prevent adequate analgesia. Topical drugs and a lido-

caine containing patch may be effective for peripheral syndromes. Sympathetic blockade is usually ineffective except for some patients with complex regional pain syndrome[9,10,56-89].

ANTIDEPRESSANTS

Antidepressants have a well-established beneficial effect in various neuropathic pain states. Antidepressants used in neuropathic pain treatment include tricyclic antidepressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SSNRIs) (duloxetine and venlafaxine), while the effect of selective serotonin reuptake inhibitors (SSRIs) is lower[15,16].

TCAs have been widely used to treat various types of neuropathic pain including central post-stroke pain, post-herpetic neuralgia, painful diabetic and nondiabetic polyneuropathy, but not spinal cord injury pain, phantom limb pain, or pain in HIV-neuropathy[15,66].

Antihyperalgesic effects of tricyclic antidepressants may be related to enhancement of the noradrenergic descending inhibitory pathways and partial sodium channel blockade, the mechanisms that are independent of their antidepressant effects[16]. Starting doses of TCAs should be low and dosage should be titrated slowly until pain is adequately controlled or side effects limit continued titration.

Some of the third generation antidepressants, especially venlafaxine and duloxetine, have shown comparable efficacy to TCAs, but with a better side effect profile.

Duloxetine is an SSNRI that inhibits the reuptake of both serotonin and norepinephrine. It has demonstrated significantly greater pain relief compared with placebo in few trials in patients with diabetic polyneuropathy. The optimal dosage of duloxetine is 60 mg/day[33].

Venlafaxine is an SSNRI that inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages. The efficacy dosage of venlafaxine is 150-225 mg/day. Two-to-four weeks are often required to titrate to an effective dosage[31,32,51].

Side effects of TCAs

TCAs have many side effects which include dry mouth, constipation, sweating, dizziness, disturbed vision, drowsiness, palpitation, orthostatic hypotension, sedation and urinary hesitation[38,54,70,73,74]. An electrocardiogram is mandatory before the initiation of treatment. TCAs should be used with caution in patients at risk of suicide. They can cause cognitive impairment and gait disturbances in elderly patients. SSNRIs (duloxetine, venlafaxine) are safer to use than TCAs and are a better option in patients with cardiac disease[15,16,31-35].

ANTICONVULSANTS

The anticonvulsant compounds are some of the best-studied drugs for neuropathic pain, and there is substantial evidence for their efficacy based on meta-analyses and randomized clinical trials[17,19]. They have several pharmacological actions that can interfere with the processes involved in neuronal hyperexcitability, either by decreasing excitatory or increasing inhibitory transmission, thereby exerting a net neuronal depressant effect.

Perhaps the most extensively studied agent is ***pregabalin***, which has shown, in a large number of multicenter clinical studies, clear efficacy in reducing pain and improving sleep in patients with postherpetic neuralgia and diabetic polyneuropathy. The effective dosage is 300-600 mg/day, administered in two to three divided doses. Improvement can be seen within days[49,50,52,53,77,78].

Pregabalin is believed to exert its analgesic effect by binding to the $\alpha 2$ delta subunit of voltage-gated calcium channels on primary afferent nerves and reducing the release of neurotransmitters from their central terminals. Multicenter clinical trials have shown the efficacy of **gabapentin** at a dosage of 900-3600 mg/day in the treatment of postherpetic neuralgia and diabetic polyneuropathy. Gabapentin is a GABA receptor agonist. The ability of the drug to block L-type voltage-dependent Ca^{2+} channels is the probable reason for its antiepileptic and analgesic properties[17,46-48,71,75,76].

Gabapentin has also shown efficacy in other forms of neuropathic pain such as HIV-associated painful polyneuropathy, pain in Guillain-Barre syndrome, phantom limb pain, cancer-related neuropathic pain, but only on the basis of single or limited numbers of studies. The most common side effects of gabapentin and pregabalin include dizziness, somnolence, peripheral edema and dry mouth.

There is also evidence for the efficacy of topiramate, lamotrigine, carbamazepine and oxcarbamazepine in the treatment of different neuropathic pain conditions[41,42].

Carbamazepine and perhaps ***oxcarbamazepine*** are used as first-line therapy for trigeminal neuralgia. Both

drugs should be initiated at low dosages and slowly increased up to the efficacy or side effects. The effective dosages of carbamazepine are in the range of 200-1200 mg/day and of oxcarbamazepine 600-1800 mg/day[18].

Side effects of anticonvulsants

The most common side effects of anticonvulsants include sedation, dizziness and gait abnormalities. Liver enzymes, blood cells, platelets and sodium levels must be monitored for at least one year because of the possible risk of hepatitis-anaplastic effects or hyponatremia[39-51].

Lamotrigine is generally well tolerated. Side effects include dizziness, nausea, headache and fatigue[40,43-45,63].

OPIOIDS

Opioids may be useful, especially in acute stage, but their use for chronic pain management remains somewhat controversial[55-61,90-96]. Opioids inhibit pain transmission mainly *via* presynaptic and postsynaptic receptors in the dorsal horn. Although neuropathic pain does not respond reliably to opioids, randomized trials have shown an effect of opioids (oxycodone, morphine and methadone) in painful polyneuropathy, postherpetic neuralgia, phantom limb pain, and mixed neuropathic pain.

Opioid analgesics and tramadol have shown efficacy in many trials in patients with different kinds of neuropathic pains, and when patients do not have good response to first-line medications, opioid agonists can be used as a second-line treatment alone or in combination with the first-line medications. In some specific cases, opioid analgesics and tramadol can be used as first-line medications. Circumstances in which opioid analgesics and tramadol can be used as first-line medications are during titration of a first-line medication to an efficacious dosage, episodic exacerbation of severe pain, acute neuropathic pain, and neuropathic cancer pain.

Opioids exert their analgesic effect through at least four groups of receptors. The distribution of these receptors throughout the body, along with their tissue densities within numerous organ systems, accounts for the global and varied effects of these drugs[55-60]. Opioids are available in a variety of preparations. In addition to common ways of administration, they may be given transdermally (fentanyl or buprenorphin patch), transmucosally (fentanyl oral) and intraspinally[83,88-91].

Side effects

Opioids have many side effects including constipation, sedation, nausea, dizziness and vomiting. In elderly patients, opioids can cause cognitive impairment and gait disturbances. Physical dependence develops in all patients chronically treated with opioid analgesics, and patients must be advised that they should not discontinue these medications on their own.

Tramadol

Tramadol is a weak μ-opioid agonist and a mixed serotonin-norepinephrine reuptake inhibitor. Tramadol at an average dose of around 200 mg/day for 6 weeks was shown to produce a statistically significant reduction in the mean pain intensity in patients with painful diabetic neuropathy compared with those receiving placebo[87,88].

Topical treatments

Lidocaine patches are increasingly used in the treatment of postherpetic neuralgia and focal peripheral neuropathic pain. Side effects of lidocaine are mild skin reactions (erythema and localized rash). Lidocaine patch 5% should be avoided in patients receiving antiarrhythmic medications and in patients with severe hepatic dysfunction[80-85]. Topically applied capscain has shown significant effect in diabetic neuropathy and postherpetic neuralgia.

Non-pharmacological treatment for neuropathic pain

ACUPUNCTURE

Acupuncture is a complementary and alternative medical modality. Since 1998, a considerable number of acupuncture studies have been reported. It has been integrated into palliative care medicine. Most of controlled clinical trials (23/27) have shown results favoring acupuncture use for the conditions such as headache or pain. They also have shown that acupuncture is safe and clinically cost-effective for the management of common symptoms in palliative care and hospice patients. There is a risk of skin irritation or an allergic reaction from the application of needles to the skin, but these problems are relatively rare and easily managed by shifting the needle position. There are not yet enough evidence-based treatment recommendations[20-22,65].

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

TENS seems to be better than placebo in the treatment of painful diabetic neuropathy[23-26].

OTHER

Laser therapy, mechanotherapy (massage), electrotherapy (galvanization, iontophoresis), ultrasound therapy, thermotherapy (cold and warm), hydro/balneotherapy, and behavioral therapy (relaxation, biofeedback) have been reported. As yet, there are no evidence based treatment recommendations due to the lack of controlled studies in this field.

Painful Polyneuropathy

According to many guidelines, established efficacy in painful polyneuropathy (PPN) has been reported for tricyclic antidepressants (TCAs), duloxetine, venlafaxine, gabapentin (GBP), pregabalin, opioids and tramadol[9,12,15]. The best approach is to start therapy with TCA or GBP/pregabalin. The serotonin-noradrenaline reuptake inhibitors (SNRIs) duloxetine and venlafaxine are considered second choice because of moderate efficacy, but are safer and have less contraindications than TCAs and should be preferred to TCA, particularly in patients with cardiovascular risk factors[9,15]. Second/third-line therapy includes opioids and lamotrigine (LTG)[15]. Treatments with weaker/lack of efficacy include capsaicin, topical lidocaine, mexiletine, oxcarbazepine (OXC), selective serotonin reuptake inhibitors (SSRIs), and topiramate[35,62].

HIV-associated neuropathy and chemotherapy-induced neuropathy

HIV-associated polyneuropathy has been found refractory to most currently assessed drugs. This may be due to the particular mechanisms of pain in this often progressive condition and/or to a high placebo response, observed in many trials[62-69].

Postherpetic Neuralgia

In postherpetic neuralgia (PHN), drugs with established efficacy include TCAs, GBP, pregabalin, topical lidocaine and opioids. Less effective drugs are capsaicin, tramadol and valproate[79-82,84-87]. Many guidelines

*Table 2. Classification of evidence for the main categories of neuropathic pain drug treatment**

Pain condition	Recommendations for first line	Recommendations for second or third line
PPN	Gabapentin (1200-3600 mg/day) Pregabalin (150-600 mg/day) Opioids SNRI(venlafaxine:150-225 mg/day; duloxetine: 60-120mg/day) TCA (amitriptyline: 10-60 mg/day) Gabapentin	Lamotrigine Opioids SNRI Tramadol (275-400 mg/day)
PHN	(1200-3600 mg/day) Pregabalin (150-600 mg/day) 5% Lidocaine patches TCA	Capsaicin Opioids Tramadol Valproate
TN	CBZ (200-1200 mg/day) OXC (600-1800 mg/day)	Surgery
CP	TCA (amitriptyline: 10-60 mg/day) Gabapentin up to 3600 mg/day Pregabalin up to 460 mg/day	Cannabinoids Lamotrigine Opioids

*Modified according to EFNS Guidelines on Pharmacological Treatment of Neuropathic Pain 2006
PPN = painful polyneuropathies; PHN = postherpetic neuralgia; TN = trigeminal neuralgia; CP = central pain

recommend TCAs, GBP/pregabalin and lidocaine patches as first-line therapy. Opioids are second choice although they are very effective in treating PHN[92-94]. Topical capsaicin may also provide relief, although it is often poorly tolerated. Owing to excellent tolerability, topical lidocaine may be preferred in the elderly, particularly in patients with allodynia and small area of pain. Intrathecal corticosteroid injection can be considered for patients that continue to have intractable pain despite the above measures. These injections do not work for trigeminal nerve-related pain.

The effectiveness of therapies such as TENS and acupuncture has not been proven.

Trigeminal Neuralgia

The most widely used drug in idiopathic trigeminal neuralgia (TN) is CBZ (200 to 1200 mg/day). The drug is highly effective and side effects are generally manageable, particularly if low doses are prescribed initially with gradual titration. Patients with symptoms that are refractory to CBZ monotherapy may benefit from combination therapy with gabapentin, lamotrigine, topiramate, baclofen or tizanidine[95,96,102-111]. Patients with TN that are unresponsive or suffer intolerable adverse effects with medical therapy are candidates for surgery. The two major types of procedures are microvascular decompression and ablative procedures such as radiofrequency rhizotomy and gamma knife. Ablative procedures are less invasive and are generally associated with a high initial response rate, but recurrence is common and the incidence of facial numbness is higher than with microvascular decompression[109].

Central Pain

Considering the small number of randomized controlled trials in central pain and the generally small sample sizes, the treatment may be based on the general principles for peripheral neuropathic pain treatment and for side effect profile. There is level B evidence for the use of LTG, GBP, pregabalin or tricyclic antidepressants for post-stroke or spinal cord injury pain. In central pain associated with multiple sclerosis, cannabinoids have shown significant efficacy (level A), but may raise safety concerns[112-122].

References

1. MERSKEY H, BOGDUK N. Classification of chronic pain. Seattle: IASP Press, 1994.
2. FINNERUP NB, OTTO M, McQUAY HJ. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005;118:289-305.
3. BAŠIĆ-KES V, DEMARIN V. Recommendations for treatment of neuropathic pain. Acta Med Croat 2008;62:237-40.
4. WOOLF CJ, MAX MB. Mechanism-based pain diagnosis: issues for analgesic drug development. Anesthesiology 2001;95: 241-9.
5. ATTAL N. Chronic neuropathic pain: mechanisms and treatment. Clin J Pain 2000;16(Suppl 3):S118-S130.
6. HANSSON P. Difficulties in stratifying neuropathic pain by mechanisms. Eur J Pain 2003;7:353-7.
7. JENSEN TS, BARON R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1-8.
8. DUBINSKY RM, KABBANI H, El-CHAMI Z. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004;63:959-65.
9. ATTAL N, CRUCCU G, HAANPAA M, HANSSON P. EFNS guidelines on neuropathic pain assessment. Eur J Neurol 2006;13:1153-69.
10. BRAININ M, BARNES M, BARON JC. Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations. Eur J Neurol 2004;11:577-81.
11. RASMUSSEN PV, SINDRUP SH, JENSEN TS. Symptoms and signs in patients with suspected neuropathic pain. Pain 2004;110:461-9.
12. FINNERUP NB, OTTO M, JENSEN TS, SINDRUP SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005;118:289-305.
13. ADRIAENSEN H, PLAGHKI L, MATHIEU C. Critical review of oral drug treatments for diabetic neuropathic pain – clinical outcomes based on efficacy and safety data from placebo-controlled and direct comparative studies. Diabet Metab Res Rev 2005;21:231-40.
14. HEMPENSTALL K, NURMIKKO TJ, JOHNSON RW, *et al*. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Medicine 2005;2:628-44.
15. SAARTO T, WIFFEN P. Antidepressants for neuropathic pain. Cochrane Database of Systemic Reviews 2005; 20a: CD005454.
16. SINDRUP SH, OTTO M, FINNERUP NB. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Ther 2005;96:399-409.
17. WIFFEN P, McQUAY H, EDWARDS J. Gabapentin for acute and chronic pain. Cochrane Database Systematic Reviews 2005; 20: CD005452.

18. WIFFEN P, McQUAY H, MOORE R. Carbamazepine for acute and chronic pain. Cochrane Database Systematic Reviews 2005b; 20: CD005451.

19. WIFFEN P, COLLINS S, McQUAY H. Anticonvulsant drugs for acute and chronic pain. Cochrane Database Systematic Reviews 2005c; 20: CD001133.

20. STANDISH Lj, KOZAK L, CONGDON S. Acupuncture is underutilized in hospice and palliative medicine. Am J Hosp Palliat Care 2008 (Epub ahead of print).

21. LEWITH J, FIELD J. Acupuncture compared with placebo in postherpetic neuralgia. Pain 1983;17:361-8.

22. SPACEK A, KRESS HG. Acupuncture in symptomatic reflex dysthrophy? Pain 1997;11:20-3.

23. CAUTHEN JC, RENNER EJ. Transcutaneous and peripheral nerve stimulation for chronic pain states. Surg Neurol 1975;4:102-4.

24. MEYLER WJ, de JONGSTE MJL, ROLF CAM. Clinical evaluation of pain treatment with electrostimulation: a study of TENS in patients with different pain syndromes. Clin J Pain 1994;10:22-7.

25. SOMERS DL, CLEMENTE R. TENS for the management of neuropathic pain. Phys Ther 2006;86:698-706.

26. CHESTERTON LS, FOSTER NE, WRIGHT CC. Effects of TENS frequency, intensity and stimulation site parameter manipulation on pressure pain thresholds in healthy human subjects. Pain 2003;106:73-80.

27. OTTO M, BAK S, BACH FW. Pain phenomena and possible mechanisms in patients with painful polyneuropathy. Pain 2003;101:187-92.

28. SINDRUP SH, JENSEN TS. Pharmacologic treatment of pain in polyneuropathy. Neurology 2000;55:915-20.

29. VRETHEM M, BOIVIE J, ARNQVIST H. A comparison of amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and nondiabetics. Clin J Pain 1997;13:313-23.

30. SINDRUP SH, GRAM LF, SKJOLD T. Clomipramine *vs* desipramine *vs* placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. Br J Clin Pharmacol 1990;30:683-91.

31. ROWBOTHAM MC, GOLI V, KUNZ NR. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004;110:697-706.

32. SINDRUP SH, BACH FW, MADSEN C. Venlafaxine *versus* imipramine in painful polyneuropathy. A randomized, controlled trial. Neurology 2003;60:1284-9.

33. GOLDSTEIN DJ, LU Y, DETKE MJ. Duloxetine *versus* placebo in patients with painful diabetic neuropathy. Pain 2005;116:109-18.

34. RASKIN J, PRITCHETT YL, WANG F. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med 2005;6:346-56.

35. WERNICKE JF, PRITCHETT YL, D'SOUZA DN, WANINGER A, TRAN P. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67:1411-20.

36. RULL JA, QUIBRERA R, GONZALEZ-MILLAN H. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. Diabetologia 1969;5:215-8.

37. WILTON TD. Tegretol in the treatment of diabetic neuropathy. S Afr Med J 1974;48:869-72.

38. GOMEZ-PEREZ FJ, CHOZA R, RIOS JM. Nortriptyline-fluphenazine *vs*. carbamazepine in the symptomatic treatment of diabetic neuropathy. Arch Med Res 1996;27:525-9.

39. DOGRA S, BEYDOUN S, MAZZOLA J. Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo controlled study. Eur J Pain 2005;9:543-54.

40. EISENBERG E, LURIE Y, BRAKER C. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. Neurology 2001;57:505-9.

41. THIENEL U, NETO W, SCHWABE SK, *et al*. Topiramate Diabetic Neuropathic Pain Study Group. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol Scand 2004;110:221-31.

42. RASKIN P, DONOFRIO PD, ROSENTHAL NR. Topiramate *vs* placebo in painful diabetic polyneuropathy: analgesic and metabolic effects. Neurology 2004;63:865-73.

43. KOCHAR DK, JAIN N, AGARWAL RP. Sodium valproate in the management of painful polyneuropathy in type 2 diabetes – a randomized placebo controlled study. Acta Neurol Scand 2002;106:248-52.

44. KOCHAR DK, RAWAT N, AGRAWAL RP. Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. Q J Med 2004;97:33-8.

45. OTTO M, BACH FW, JENSEN TS. Valproic acid has no effect on pain in polyneuropathy: a randomized controlled trial. Neurology 2004;62:285-8.

46. BACKONJA M, BEYDOUN A, EDWARDS KR. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280:1831-6.

47. DOOLEY DJ, DONOVAN CM, MEDER WP. Preferential action of gabapentin and pregabalin at P/Q voltage-sensitive calcium channels: inhibition of K+ evoked /3H/-norepinephrine release from rat neocortical slices. Synapse 2002;45:171-90.

48. NICHOLSON B. Gabapentin use in neuropathic pain syndromes. Acta Neurol Scand 2000;101:359-71.

49. LESSER H, SHARMA U, LaMOREAUX L. Pregabalin relieves symptoms of painful diabetic neuropathy. Neurology 2004;63:2104-10.

50. ROSENSTOCK J, TUCHMANN M, LaMOREAUX L. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110:628-38.

51. SIMPSON DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. J Clin Neuromusc Dis 2001;3:53-62.
52. RICHTER RW, PORTENOY R, SHARMA U. Relief of diabetic peripheral neuropathy with pregabalin: a randomized placebo-controlled trial. J Pain 2005;6:253-60.
53. FREYNHAGEN R, STROJEK K, GRIESING T. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005;115:254-63.
54. MORELLO CM, LECKBAND SG, STONER CP. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931-7.
55. WATSON CP, MOULIN D, WATT-WATSON J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain 2003;105: 71-8.
56. GIMBEL JS, RICHRDS P, PORTENOY RK. Controlled-release oxycodone for pain in diabetic neuropathy. A randomized controlled trial. Neurology 2003;60:927-34.
57. DWORKIN RH, O'CONNOR AB, BACKONJA M, FARRAR JT, FINNERUP NB, JENSEN TS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237-51.
58. SINDRUP SH, ANDERSEN G, MADSEN C. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. Pain 1999;83:85-90.
59. SANG CN, BOOHER S, GILRON I. Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia. Efficacy and dose-response trials. Anesthesiology 2002;96:1053-61.
60. NELSON KA, PARK KM, ROBINOVITZ E. High-dose oral dextromethorphan *versus* placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurology 1997;48:1212-8.
61. ERTAS M, SAGDUYU A, ARAC N. Use of levodopa to relieve pain from painful symmetrical diabetic polyneuropathy. Pain 1998;75:257-9.
62. SIMPSON DM, OLNEY R, McARTHUR JC. A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. Neurology 2000;54:2115-9.
63. SIMPSON DM, McARTHUR JC, OLNEY R. Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. Neurology 2003;60:1508-14.
64. HAHN K, ARENDT G, BRAUN JS. German Neuro-AIDS Working Group. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. J Neurol 2004;251:1260-6.
65. SHLAY JC, CHALONER K, MAX MB. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. JAMA 1998;280:1590-5.
66. KIEBURTZ K, SIMPSON D, YIANNOUTSOS C. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. Protocol Team. Neurology 1998;242:1682-8.
67. ESTANISLAO L, CARTER K, McARTHUR J. The Lidoderm-HIV Neuropathy Group. EFNS Eur J Neurol 2006;13:1153-69.
68. KEMPER CA, KENT G, BURTON S, DERESINSKI SC. Mexiletine for HIV-infected patients with painful peripheral neuropathy: a double-blind, placebo-controlled, crossover treatment trial. J Acquir Immune Defic Syndr Hum Retrovirol 1998;19:367-72.
69. PAICE JA, FERRANS CE, LASHLEY FR. Topical capsaicin in the management of HIV-associated peripheral neuropathy. J Pain Symptom Manag 2000;19:45-52.
70. HAMMACK JE, MICHALAK JC, LOPRINZI CL. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. Pain 2002;98:195-203.
71. GILRON I, BAILEY JM, TU D, *et al*. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352:1324-34.
72. NURMIKKO T, BOWSHER D. Somatosensory findings in postherpetic neuralgia. J Neurol Neurosurg Psychiatry 1990;53:135-41.
73. WATSON CP, CHIPMAN M, REED K, *et al*. Amitriptyline *versus* maprotiline in postherpetic neuralgia: a randomized, double-blind, crossover trial. Pain 1992;48:29-36.
74. WATSON CP, VERNICH L, CHIPMAN M. Nortriptyline *versus* amitriptyline in postherpetic neuralgia: a randomized trial. Neurology 1998;51:1166-71.
75. ROWBOTHAM MC, HARDEN N, STACEY B. Gabapentin for treatment of postherpetic neuralgia. JAMA 1998;280:1837-43.
76. RICE ASC, MATON S, Post Herpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia; a randomised, double-blind, controlled study. Pain 2001;94:15-24.
77. DWORKIN RH, CORBIN AE, YOUNG JP Jr. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003b;60:1274-83.
78. SABATOWSKI R, GALVEZ R, CHERRY DA. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 2004;109:26-35.
79. KOCHAR DK, GARG P, BUMB RA. Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study. Q J Med 2005;98:29-34.
80. GALER BS, ROWBOTHAM MC, PERANDER J. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain 1999;80:533-8.
81. GALER BS, JENSEN MP, MA T. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Clin J Pain 2002;5:297-301.

82. WASNER G, KLEINERT A, BINDER A, *et al*. Postherpetic neuralgia: topical lidocaine is effective in nociceptor deprived skin. J Neurol 2005;252:677-86.

83. MEIER T, WASNER G, FAUST M. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo controlled study. Pain 2003;106:151-8.

84. BERNSTEIN JE, KORMAN NJ, BICKERS DR. Topical capsaicin treatment of chronic postherpetic neuralgia. J Am Acad Dermatol 1989;21:265-70.

85. WATSON CP, TYLER KL, BICKERS DR. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. Clin Ther 1993;15:510-26.

86. WATSON CP, BABUL N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 1998;50:1837-41.

87. CHONG MS, HESTER J. Diabetic painful neuropathy. Current and future treatment options. Drugs 2007;67:569-85.

88. HARATY Y, GOOCH C, SWENSON M. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998;50:1842-6.

89. FOLEY KM. Opioids and chronic neuropathic pain. N Engl J Med 2003;348:1279-82.

90. EISENBERG E, McNICOL ED, CARR DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pin of nonmalignant origin. JAMA 2005;293:3043-8.

91. ROWBOTHAM MC, TWILLING L, DAVIES PS. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med 2003;348:1223-32.

92. BOUREAU F, LEGALLICIER P, KABIR-AHMADI M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Pain 2003;104:323-31.

93. EISENBERG E, KLEISER A, DORTORT A. The NMDA (N-methyl-D-aspartate) receptor antagonist memantine in the treatment of postherpetic neuralgia: a double blind, placebo-controlled study. Eur J Pain 1998;2:321-7.

94. MAX MB, SCHAFER SC, CULNANE M. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology 1988;38:1427-32.

95. CRUCCU G, TRUINI A. Trigeminal neuralgia and orofacial pains. In: PAPPAGALLO M, ed. The neurological basis of pain. New York: McGraw-Hill, 2005:401-14.

96. SINDRUP SH, JENSEN TS. Pharmacotherapy of trigeminal neuralgia. Clin J Pain 2002;18:22-7.

97. CAMPBELL FG, GRAHAM JG, ZILKHA KJ. Clinical trial of carbamazepine (Tegretol) in trigeminal neuralgia. J Neurol Neurosurg Psychiatry 1966;29:265-7.

98. JENSEN TS. Anticonvulsants in neuropathic pain: rationale and clinical evidence. Eur J Pain 2002;6(Suppl A):61-8.

99. KUTLUAY E, McCAGUE K, D'SOUZA J. Safety and tolerability of oxcarbazepine in elderly patients with epilepsy. Epilepsy Behavior 2003;4:175-80.

100. LIEBEL JT, MENGER N, LANGOHR H. Oxcarbazepine in der Behandlung der Trigeminus Neuralgie. Nervenheilkunde 2001;20:461-5.

101. BEYDOUN A. Safety and efficacy of oxcarbazepine: results of randomized, double-blind trials. Pharmacotherapy 2000; 20:152S-158S.

102. ZAKRZEWSKA JM, CHAUDHRY Z, NURMIKKO TJ. Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. Pain 1997;73:223-30.

103. FROMM GH, TERRENCE CF, CHATTHA AS. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. Ann Neurol 1984;15:240-4.

104. FROMM GH, TERRENCE CF. Comparison of L-baclofen and racemic baclofen in trigeminal neuralgia. Neurology 1987;37:1725-8.

105. LINDSTROM P, LINDBLOM U. The analgesic effect of tocainide in trigeminal neuralgia. Pain 1987;28:45-50.

106. LECHIN F, van der DIJS B, LECHIN ME. Pimozide therapy for trigeminal neuralgia. Arch Neurol 1989;46:960-3.

107. KONDZIOLKA D, LEMLEY T, KESTLE JR. The effect of single-application topical ophthalmic anesthesia in patients with trigeminal neuralgia. A randomized double blind placebo-controlled trial. J Neurosurg 1994;80:993-7.

108. EPSTEIN JB, MARCOE JH. Topical application of capsaicin for treatment of oral neuropathic pain and trigeminal neuralgia. Oral Surg Oral Med Oral Pathol 1994;77:135-40.

109. BENNETTO L, PTEL NK, FULLER G. Trigeminal neuralgia and its management. BMJ 2007;334:201-8.

110. FROMM GH, AUMENTADO D, TERRENCE CF. A clinical and experimental investigation of the effects of tizanidine in trigeminal neuralgia. Pain 1993;53:265-71.

111. NURMIKKO TJ, ELDRIDGE PR. Trigeminal neuralgia – pathophysiology, diagnosis and current treatment. Br J Anaesth 2001;87:117-32.

112. BOIVIE J. Central pain. In: MacMAHON SB, KOLTZENBURG M, eds. Wall and Melzack's textbook of pain. Oxford: Churchill Livingstone – Elsevier, 2005:1057-75.

113. ATTAL N, BOUHASSIRA D. Central neuropathic pain. In: PAPPAGALLO M, ed. The neurological basis of pain. New York: McGraw-Hill, 2005:301-19.

114. LEIJON G, BOIVIE J. Central post-stroke pain – a controlled trial of amitriptyline and carbamazepine. Pain 1989;36:27–36.

115. CARDENAS DD, WARMS CA, TURNER JA. Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. Pain 2002;96:365-73.

116. VESTERGAARD K, ANDERSEN G, GOTTRUP H. Lamotrigine for central poststroke pain: a randomized controlled trial. Neurology 2001;56:184-90.

117. FINNERUP NB, SINDRUP SH, BACH FW. Lamotrigine in spinal cord injury pain: a randomized controlled trial. Pain 2002;96:375-83.

118. LEVENDOGLU F, OGUN CO, OZERBIL O. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. Spine 2004;29:743-51.

119. DREWES AM, ANDREASEN A, POULSEN LH. Valproate for treatment of chronic central pain after spinal cord injury.A double-blind cross-over study. Paraplegia 1994;32:565-9.

120. CHIOU-TAN FY, TUEL SM, JOHNSON JC. Effect of mexiletine on spinal cord injury dysesthetic pain. Am J Phys Med Rehabil 1996;75:84-7.

121. SVENDSEN KB, JENSEN TS, BACH FW. The cannabinoid dronabinol reduces central pain in multiple sclerosis. A randomised double-blind placebo controlled cross-over trial. BMJ 2004;329:253-61.

122. ROG DJ, NURMIKKO TJ, FRIEDE T. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812-9.

Sažetak

Oštećenje somatosenzornog sustava predstavlja rizik za nastanak neuropatske boli. Rezultat takvog oštećenja su promjene koje dovode do senzitizacije perifernog i središnjeg živčanog sustava. Simptomi uključuju kontinuiranu bol (koja se opisuje kao žareća, paleća) ili sporadičnu bol (najčešće se opisuje kao probadajuća, trgajuća, poput strujnog udara). Dijagnoza se temelji na anamnezi i nalazu fizikalnog pregleda. Prvu liniju u liječenju neuropatske boli predstavljaju antidepresivi i antiepileptici. Opioidi ponekad mogu dovesti do analgezije, iako puno slabije nego kod nociceptivne boli. Širu uporabu sprječavaju nuspojave. U perifernim bolnim sindromima učinkovitim su se pokazali flasteri lidokaina. Simpatički blokovi su uglavnom neučinkoviti osim u slučaju kompleksnog regionalnog bolnog sindroma.

Ključne riječi: *Neuralgija – etiologija; Neuralgija – fiziopatologija; Neuralgija – terapija; Bol – terapija; Smjernice; Praksa – smjernice*