

Systemic drug therapy for neuropathic pain

Farmacoterapia sistêmica da dor neuropática

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ABSTRACT

BACKGROUND AND OBJECTIVES: Neuropathic pain involves different etiologies, syndromes, pathophysiologic mechanisms and clinical symptoms, in addition to different treatment modalities. Most commonly used drugs to control neuropathic pain are antidepressants, anticonvulsants and opioids, and even so, they have moderate efficacy, with 50% pain relief in less than one third of patients. This study aimed at developing a guiding protocol for pharmacologic neuropathic pain management and also at introducing other drugs which may also relieve neuropathic pain.

CONTENTS: This study has evaluated updated protocols of the Canadian Pain Society, the International Association for the Study of Pain, the European Federation of Neurological Societies and relevant references, being developed an algorithm for systemic drug therapy for neuropathic pain, made up of first line medications (tricyclic antidepressants, gabapentinoids and serotonin and norepinephrine reuptake inhibitors), second line medications (weak and strong opioids) and third line medications (selective serotonin reuptake inhibitors, dopamine and norepinephrine reuptake inhibitors and other anticonvulsants). Other drugs (anti-inflammatory, steroids and baclofen) and venous drug therapy (lidocaine and ketamine) used to control pain were also addressed. Major pharmacological actions, titration, interactions and relevant adverse effects of drugs indicated in the study were highlighted.

CONCLUSION: Ideally, initial screening for pain control should be done with single therapy. If needed, other drugs may be combined to reach different pathophysiologic mechanisms and better neuropathic pain control. The algorithm should be a guide for analgesia, treatment should be tailored and, when indicated, combined with topical therapy and other non-pharmacological approaches.

Keywords: Anticonvulsants, Antidepressants, Chronic pain, Neuralgia, Opioids, Pain management.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor neuropática envolve etiologias, síndromes, mecanismos fisiopatológicos e sintomas clínicos diversos, assim como seu tratamento. No controle da dor neuropática os fármacos mais utilizados são os antidepressivos, anticonvulsivantes e opioides, e mesmo assim, apresentam eficácia moderada, com 50% do alívio da dor em menos de um terço dos pacientes. O objetivo deste estudo foi elaborar um protocolo orientador do tratamento farmacológico da dor neuropática e apresentar outros fármacos que também podem aliviar a dor neuropática.

CONTEÚDO: Este trabalho avaliou os protocolos atualizados da *Canadian Pain Society*, da *International Association for the Study of Pain*, da *European Federation of Neurological Societies* e referências relevantes sendo desenvolvido um algoritmo para a farmacoterapia sistêmica da dor neuropática composto por fármacos de primeira linha (antidepressivos tricíclicos, gabapentinoides e inibidores da recombinação da serotonina e noradrenalina), fármacos de segunda linha (opioides fracos e fortes) e fármacos de terceira linha (inibidores seletivos da recombinação da serotonina, inibidores da recombinação da dopamina e nor-

adrenalina e outros anticonvulsivantes). Outros fármacos (anti-inflamatórios, corticosteróides e baclofeno) e farmacoterapia venosa (lidocaína e cetamina) utilizadas no controle da dor também foram abordados. As principais ações farmacológicas, titulação, interações e efeitos adversos relevantes dos fármacos indicados no estudo foram destacados.

CONCLUSÃO: Idealmente, a triagem inicial do controle da dor deve ser com monoterapia. Se necessário, outros fármacos podem ser combinados a fim de atingir diferentes mecanismos fisiopatológicos e melhor controle da dor neuropática. O algoritmo deve ser orientador na condução da analgesia, o tratamento deve ser individualizado e, quando indicado, combinado com terapia tópica e outras abordagens não farmacológicas.

Descritores: Anticonvulsivantes, Antidepressivos, Dor crônica, Manuseio da dor, Neuralgia, Opioides.

INTRODUCTION

Neuropathic pain (NP) is induced by central or peripheral somatosensory nervous system¹, making up a heterogeneous group of etiologies, pathophysiological mechanisms and clinical symptoms. NP severity and its impact on daily life activities are variable, as well as response to treatment. Specific diagnosis and treatment of the baseline disease (e.g., diabetes), evaluation of clinical and emotional comorbidities, especially anxiety and depression, are critical. Often, primary treatment objective is to make pain “bearable”, because total relief is a difficult target. So, improved sleep, functionality and quality of life are relevant secondary objectives. Treatment objectives should be shared with patients. Multidisciplinary approach, topical and non-pharmacological treatment, such as physiotherapy and psychotherapy, should be jointly applied with systemic drug therapy. Commonly prescribed drugs for NP relief (antidepressants, anticonvulsants, opioids) have moderate efficacy – 50% pain relief in less than one third of patients². Some treatments have better evidences than others; others provide relief in a minority of patients, however significant. Without adequate therapeutic screening there is no way to determine the most effective drug³.

This study is based on consensus and reviewed recommendations of the Canadian Pain Society⁴, of NeuPSIG IASP (Group of Special Interest in Neuropathic Pain of the International Association for the Study of Pain)⁵ and its updated reviews^{6,7}, of the European Federation of Neurological Societies Task Force⁸ and on relevant references. Cannabinoids are not approved for analgesic use in Brazil and were not included in this study. Figure 1 shows NP systemic drug therapy algorithm which may be associated to topical treatment when indicated.

<p>First line drugs: Gabapentinoids ↔ TAD ↔ SNRI</p> <p>Second line drugs: Weak opioids ↔ strong opioids</p> <p>Third line drugs: SSRI ↔ DNRI ↔ Other anticonvulsants</p>
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Figure 1. Neuropathic pain systemic drug therapy algorithm

TAD = tricyclic antidepressants; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; DNRI – dopamine and norepinephrine reuptake inhibitors.

Ideally, initial treatment screening is with single therapy. Many drugs in indicated doses induce adverse effects which often prevent necessary doses for adequate analgesia to be reached. The combination of two or more drugs is an attractive and common therapeutic strategy in the clinical prac-

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tice. Recent advances in the understanding of NP pathophysiology suggest that there are different mechanisms, both peripheral and central, indicating that combined or multimodal drug therapy, simultaneously directed to multiple mechanisms, may provide better analgesic efficacy. Synergistic effects among drugs may decrease adverse effects by decreasing combined doses^{2-4,9}.

ANTICONVULSANTS

Anticonvulsants have been used as analgesics since 1942 when Bergouignan¹⁰ published his first article on the use of phenytoin to treat trigeminal neuralgia. Later, carbamazepine and hydantoin were used for this purpose. As from the 1960s, studies were intensified about clinical characteristics of neuropathic pain (excruciating and in shock) of different etiologies. New scenario appears with alpha-2-delta subunit ligands of pre-synaptic voltage-gated calcium channels which have shown positive results for postherpetic, diabetic and other neuropathic pains¹¹.

GABAPENTINOIDS

Gabapentinoids, pregabalin and gabapentin act as ligands to alpha-2-beta subunits of pre-synaptic voltage-gated calcium channels. These drugs regulate calcium entry in pre-synaptic neuron decreasing excitatory neurotransmitters release in the synaptic cleft. Both are well tolerated and have few pharmacological interactions, because they are not metabolized by the liver and are excreted by kidneys needing dose adjustment in patients with kidney disease. Gabapentinoids have been successfully used in NP of different diseases, in chronic pain prevention after acute events, and they also decrease intraoperative opioids consumption. These are first line drugs for NP.

Gabapentin

Gabapentin has no linear pharmacokinetics due to absorption saturation, which requires careful titration.

Titration: start with low doses and gradually increase, according to pain control, until 3600mg/day divided in three daily doses.

Pregabalin

Pregabalin has linear pharmacokinetics, with easier and faster titration. Most patients are able to start treatment with already effective doses.

Titration: 75mg 2 to 3 times a day. Maximum dose of 600mg/day.

Major gabapentinoids adverse effects: sleepiness, dizziness, weight gain, vertigo, dry mouth and lower limbs edema.

Phenytoin

Phenytoin has historical value for having been the first drug used to treat NP. The development of more effective drugs, with simpler pharmacokinetics and lower pharmacological interactions, has made phenytoin a less attractive option. It is still an option for trigeminal neuralgia when carbamazepine fails.

Major adverse effects: gingival hyperplasia, hirsutism, polyneuropathy and liver toxicity.

Carbamazepine

Carbamazepine blocks voltage-gated sodium channels, delays ionic recovery after activation and suppresses spontaneous activity without blocking normal conduction. It also inhibits norepinephrine uptake. Its major indication is for trigeminal neuralgia, being considered the gold standard and, in this case, first line drug. Several studies have shown less expressive results in the treatment of painful diabetic neuropathy, postherpetic neuropathy, Guillain-Barre syndrome and other neuropathic pains.

Titration: should be slow and may reach 1200mg/day.

Major adverse effects: sleepiness, nausea, vomiting, ataxia, diplopia and vertigo are common. Liver disorders, leucopenia and skin rash are less frequent.

Oxcarbazepine

Oxcarbazepine, developed as from carbamazepine, is a pro-drug rapidly metabolized in 10-mono-hydroxide which has pharmacological function. For being safer and more effective than carbamazepine, it is first line drug in many countries, especially for trigeminal and glossopharyngeal neuralgia.

Lamotrigine

Lamotrigine blocks voltage-gated sodium channels and inhibits glutamate and aspartate release. It has been used for refractory trigeminal neuralgia, being considered a third line drug.

Titration: should be slow. Start with 25mg/day and increase the dose every two weeks in one or two daily doses. Analgesic effect is in general reached with up to 400mg/day¹².

Major adverse effects: skin erythema which may evolve to Stevens-Johnson syndrome in 10% of patients.

Topiramate and valproic acid

Good results for migraine but to date with conflicting results.

ANTIDEPRESSANTS

The history of antidepressants for pain is similar to that of anticonvulsants. As from 1960, it was observed that imipramine, tricyclic antidepressant, had analgesic efficacy for NP and rheumatic pain and that its analgesic action was independent of the antidepressant action. Analgesic dose was lower than that for mood disorders. Since then, it has been widely used for postherpetic neuralgia and diabetic polyneuropathy. Their action on mood and sleep disorders has made tricyclic antidepressants the most commonly prescribed drugs second only to anti-inflammatory and opioids.

Tricyclic antidepressants (TADT)

Amitriptyline and nortriptyline are the most popular drugs of this group. They block serotonin and norepinephrine reuptake, NMDA agonist-induced hyperalgesia and block sodium channels.

Titration: initial dose of 10mg, with gradual increase every 3-7 days until maximum dose of 150mg in a single dose, preferably at night.

Major adverse effects: sleepiness, dizziness, postural hypotension, cardiac conduction block, urinary retention, constipation, dry mouth, blurred vision, weight gain and decreased convulsive threshold. Slow titration with low doses minimizes such effects.

Contraindications: ventricular conduction abnormalities, urinary retention, closed angle glaucoma and uncontrolled epilepsy.

Observation: risk of serotonergic crisis with other antidepressants or tramadol.

Serotonin and norepinephrine reuptake inhibitors (SNRI)

SNRI or dual antidepressants, duloxetine and venlafaxine, in lower doses predominantly act as selective serotonin reuptake inhibitors (SSRI) and in higher doses also inhibit norepinephrine reuptake. These are first line drugs for NP.

Duloxetine

Has good evidence for diabetic neuropathy pain, postherpetic neuralgia and also musculoskeletal pain and fibromyalgia.

Titration: initial dose of 30mg, with weekly increase up to 120mg/day. There are few evidences that doses above 60mg are more effective.

Major adverse effects: nausea, sedation, constipation, dry mouth, decreased appetite, anxiety, dizziness, fatigue, insomnia, sexual dysfunction, hyperhidrosis, hypertension and ataxia.

Contraindication: glaucoma.

Observation: careful use in patients with history of seizures, urinary retention, under anticoagulants, antidepressants and tramadol.

Venlafaxine

Venlafaxine inhibits serotonin and norepinephrine reuptake in different percentages – 70 and 30%. Effective for polyneuropathies of different origins, especially diabetic.

Titration: initial dose of 37.5mg, with gradual weekly increase up to 375mg/day, in one or two doses.

Observation: adverse effects and risks similar to duloxetine. With high doses, sudden interruption may induce withdrawal syndrome.

Selective serotonin reuptake inhibitors (SSRI)

In this group, paroxetine and citalopram have shown some efficacy to handle NP, being third line of treatment.

Bupropion

Bupropion is specific norepinephrine reuptake inhibitor, weak dopamine reuptake inhibitor and without significant affinity for muscarinic, histaminergic and alpha-adrenergic receptors. Its adverse effects are better tolerated by patients with difficulties to use tricyclic antidepressants or SSRI.

Titration: start with 150mg once a day. Seven days later, if necessary, increase to two doses per day.

Major adverse effects: dry mouth, insomnia, headache, shivering, constipation and dizziness.

OPIOIDS

Opioids may be an option for patients with no or partial NP relief with first line drugs (gabapentinoid/ TAD/ SNRI) in adequate doses. Before prescription it is important to evaluate differential diagnoses, comorbidities, history of using alcohol and other drugs, and risk-benefit analysis, because opioids might not be adequate for all patients.

Opioids have common adverse effects: nausea, vomiting and sedation which develop tolerance, but for constipation there is no tolerance, being prudent the association of laxatives. Adequate control of adverse effects is critical for treatment adherence. Long acting opioids in fixed schedule cause less psychic sensations (sedation, euphoria or intoxication), provide more stable analgesia, better adhesion to treatment and lower risk of addiction or abuse¹³.

Morphine is a prototype drug and standard of comparison for other opioids. Opioids share similar pharmacological profile, but are different in dose (relative analgesic potency), pharmacokinetics (half elimination life), biotransformation (pharmacologically active metabolite) and action mechanism (opioid receptors, NMDA receptors, serotonergic and dopaminergic pathways)¹⁴. All opioids may be effective for NP, but some, due to action mechanism, induce better analgesia, such as tramadol, methadone, oxycodone and buprenorphine¹⁵.

In some clinical situations, opioids are considered first line drugs for NP: for immediate relief of moderate to severe pain during titration of other drugs, in episodic severe pain exacerbations, in acute or cancer-related NP.

Tramadol

Tramadol is a synthetic weak opioid, indicated for moderate to severe pain (second step of the World Health Organization Analgesic Ladder)¹⁶. It has double action mechanism: selective action on *mu* opioid receptor and inhibition of norepinephrine and serotonin reuptake, modulating descending monoaminergic inhibitory pathways.

Titration: start with 50mg twice a day and, if necessary, gradually increase 50 to 100mg every 3 to 7 days up to 400mg/day. There are commercial presentations of immediate or prolonged release. Doses above 400mg/day increase the risk of seizures. Elderly patients or with kidney or liver failure are at increased risk of drug buildup. Synergistic action of tramadol with other anti-inflammatory analgesics, paracetamol and dipirone, favors its total dose decrease.

Major adverse reactions: nausea, vomiting, constipation, dizziness and sleepiness.

Important pharmacological reactions: monoaminoxidase inhibitors (MAOI) and serotonin modulator drugs due to risk of serotonergic crisis and drugs which decrease convulsive threshold.

Methadone

Methadone is a synthetic strong opioid, *mu* and delta receptors agonist, NMDA receptors antagonist and serotonin and norepinephrine reuptake inhibitor¹⁵. This justifies its higher efficacy for NP relief and less development of tolerance as compared to morphine. Methadone is metabolized by the liver and inactive metabolites are excreted by the kidney, making this drug indicated in renal failure and patients under dialysis. Methadone is lipophilic, with long elimination half-life and takes 5 to 7 days to reach plasma-tissue balance. Methadone is less sedative as compared to morphine in doses adequate to pain intensity.

Titration: start with 2.5mg every 12 hours. Adjust dose and/or interval (8 to 12 hours) every 5-7 days.

Major adverse reactions: similar to other opioids, but before inducing sedation and respiratory depression methadone causes more nausea, vomit-

ing and sleepiness, which may be seen as a good warning¹⁶. There is risk of prolonging QT wave and causing arrhythmias in doses above 200mg/day.

Important pharmacological interactions: in combined use, drugs should have their doses readjusted: fluoxetine, serotonergic, cimetidine increase methadone effects; carbamazepine, phenytoin, rifampicin, ketoconazole and protease inhibitors ritonavir, indinavir and nevirapine decrease the efficacy of methadone; warfarin increases anticoagulant effect; tricyclic antidepressants have increased anticholinergic effects.

Oxycodone

Oxycodone is a semi-synthetic opioid with action on *mu*, *delta* and *kappa* receptors. It is metabolized by the liver and excreted by kidneys, which may lead to drug and its metabolites buildup in case of failure. Commercial presentations in Brazil are controlled-release pills which cannot be divided.

Titration: start with 10mg every 12 hours. If indicated, weekly increase 10mg/dose up to 20 to 60mg/dose.

Major adverse reactions: euphoria, nausea, vomiting, sedation and constipation.

Observation: as other opioids there might be risk of addiction and tolerance.

Buprenorphine

It is a partial *mu* agonist. Administered by sublingual (SL) or transdermal route, it exceeds the hepatic first-pass. Buprenorphine is highly lipophilic with major affinity to and slow dissociation of *mu* opioid receptor, leading to long-lasting analgesia.

Titration: SL pills of 0.2mg every 8 hours. After dose stabilization, maintenance is done with transdermal adhesives changed every seven days. In other opioids rotation, transdermal presentation may be used in equipotent dose.

OTHER DRUGS

Common analgesics and non-steroid anti-inflammatory drugs (NSAIDs)

These drugs are not part of NP treatment algorithm, however studies on diabetic neuropathy and postherpetic pain among others, have shown that many patients with mild NP use NSAIDs, dipirone and paracetamol, with good response. Pain and fever respond with lower doses as compared to inflammation.

Titration: dose varies individually.

Major adverse effects: kidney disease, heart failure, gastric disease or bleeding and hypertension.

Relevant pharmacological interactions: anticoagulants, antiplatelet, steroids, cyclosporin and methotrexate.

Steroids

Systemic steroids are indicated for acute neuropathic pain, especially mechanical compression by edema, such as in surgical procedures or tumor growth. Epidural long-acting steroids for radicular pain are very common.

Baclofen

Baclofen is a synthetic derivative of the gamma-amino butyric acid (GABA) inhibitory neurotransmitter, and is commonly used to treat spasticity.

Titration: start with 5mg 2 to 3 times a day, increasing every 3 days up to 90mg/day.

INTRAVENOUS DRUG THERAPY¹⁷

Intravenous lidocaine

Lidocaine is a class 1B antiarrhythmic inhibiting sodium and potassium channels, NMDA receptor and glycine transportation¹⁸. Its effect on granulocytic migration and on pro-inflammatory cytokines results in anti-inflammatory action. Its intravenous (IV) administration has been effective for chronic pain, including painful neuropathic syndromes.

Titration: initial load of IV 1 to 2mg/kg in 15 to 20 min. if pain improves, consider continuous infusion of 1 to 3 mg/kg/h. Therapeutic plasma level is 2 to 6µg/mL, which should be analyzed after 8-10 hours of infusion. Careful administration in patients with renal dysfunction on long-lasting infusions (more than 24 hours) and in patients with liver or heart failure.

Contraindications: hypersensitivity to any amine-type local anesthetic,

in Adams-Stroke, Wolff-Parkinson-White syndromes and severe sinoatrial, atrioventricular or intraventricular cardiac blocks.

Relevant pharmacological interactions: CYP3A4 and CYP1A2 inhibitors, betablockers and amiodarone increase serum lidocaine concentration. **Major adverse effects:** related to lidocaine plasma level and may be cardiac or neurologic. They vary from perioral and tongue numbness to muscle contractions and seizure¹⁹.

Observation: lidocaine has been used in NP of different etiologies, and in nociceptive or neuropathic pain refractory to opioids. There are evidences of efficacy in peripheral nerve injury pain, diabetic and postherpetic neuropathy, spinal cord injury, CRPS, phantom pain and fibromyalgia. The strategy of using IV lidocaine for chronic pain is to rapidly decrease pain intensity, while oral drug dose is being adjusted, and this might be done for weeks to months.

Ketamine

Ketamine is a dissociative non-barbiturate anesthetic agent. It acts as NMDA receptor antagonist, has activity on opioid receptors and inhibits dopamine and serotonin reuptake. In sub-anesthetic doses, it has analgesic and anti-hyperalgesic effects.

Titration: initial dose of 0.1 to 0.5mg/kg/h until maximum dose of 600-700mg in 24 hours. When intravenous formulation is orally administered, dose is 10-25mg 3 to 4 times a day. The conversion of IV to VO dose is 1:1. Due to its enteral metabolism, the active metabolite norketamine increases analgesic potency.

Relative contraindications: pregnancy and breastfeeding, history of psychiatric disease (bipolar disorder, schizophrenia and psychoses), severe hypertension, bradycardia, tachycardia, coronary disease, glaucoma, intracranial hypertension and brain trauma.

Observations: documented efficacy on CRPS. New studies are being carried out with different diseases. Analgesia with single IV ketamine dose lasts approximately 60 minutes and is dose-relative. When orally administered it may last up to 6 hours. Patients under opioids should have their dose decreased in 25 to 50% due to possible decrease in opioid tolerance and consequent overdose.

CONCLUSION

Systemic drug therapy is the most common approach for neuropathic pain treatment. Antidepressants, anticonvulsants, opioids and other drugs have

moderate efficacy and often doses escalation is limited by adverse effects. Therapeutic screening, single or combined therapy, should look for the most adequate treatment for each case. Continuous re-evaluation should focus both on pain control and improved quality of life of patients.

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