

Multimodal Analgesia for Neuropathic Pain

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1. Introduction

Neuropathic pain can be caused by a number of different diseases such as diabetes mellitus (DM), herpes zoster, Human Immunodeficiency virus (HIV), cancer or secondary to treatment i.e. radiotherapy, chemotherapy or surgery. Alterations in the nerve pathways such as trigeminal or nerve roots can lead to pain.

Another study from Mayo Clinic reported neuropathic pain in 66% of insulin-dependent diabetic patients and 59% in non-insulin dependent diabetic patients (Davies 2006). Epidemiological study in Minnesota reported an annual incidence of postherpetic neuralgia to be 11.6 per 100,000 people per year, similar to seen in UK with a lifetime incidence of 70/100,000. (Dyck 1993)

Traditionally, neuropathic pain has been classified into peripheral and central, taking into account the anatomical location of the lesion or anatomical dysfunction. The current definition of neuropathic pain indicates that it is "pain that arises as a direct result of an injury or illness affecting the somatosensory system" (Treede 2008). Several recent studies have shown that neuropathic pain may adversely affect the overall quality of life including physical and emotional health (Oster 2005), which are associated with significant social costs (O' Connor 2009).

Neuropathic pain is associated with suffering, disability, decreased quality of life and increased costs. The exact prevalence is unknown. German Studies state that 37% of patients with chronic low back pain have predominantly neuropathic pain, in terms of painful diabetic neuropathy occurs in 16% in patients with diabetes in the UK, one third of these patients had never received Treatment for this type of pain. In the United States two-thirds of patients with painful diabetic neuropathy workers reported absence from work or decreased productivity due to pain and only one fifth of these employees were satisfied with their treatment prescribed analgesic (Bouhassira 2008).

Of the various etiologies of neuropathic pain DM needs the most attention due to the increasing number of patients expected by 2025. It is estimated that the present number of 246 million people worldwide will increase to 380 million especially in developing countries. Though estimated 80% of these patients live in developing or under developed countries only 20% increased will be in the budget to treat this condition (Walters1992/Davies 2006).

These epidemiological data support that neuropathic pain has severe impact on the economic, social and emotional aspects of patient population.

Neuropathic pain is considered a diagnostic and therapeutic challenge because it can often be the result of a diverse group of diseases, which differ in etiology, and symptomatology. In some disorders the clinical picture may or may not be related to the anatomical distribution.

Although a primary goal of pain management is to relieve pain using a single agent, the reality is that monotherapy rarely provides adequate relief from chronic neuropathic pain. In these complex and refractory situations, combination therapy using two or more agents with synergistic mechanisms of action (eg, gabapentin + tramadol) is frequently necessary. In clinical practice, some patients begin to respond to a particular monotherapy, but often are restricted by dose-related side effects. In such cases, combination therapy with two or more agents with different modes of action at suboptimal doses may provide the additive effects or even synergistic effects necessary for optimal pain relief without compromising the side-effect profile of each agent. (NEJ 2005)

2. Clinical efficacy

Under the umbrella of the IASP (International Association for Study of Pain) a chapter or group with special interest in neuropathic pain (NeuPSIG) held a consensus to develop evidence-based guidelines for the pharmacological treatment of neuropathic pain that took into account the clinical efficacy, adverse effects, the impact on quality of life related to health, and costs. (Connor 2009)

Three classes of drugs were recommended as first line of treatment for neuropathic pain: antidepressants, which inhibit both norepinephrine and serotonin reuptake (tricyclic antidepressants and selective inhibitors and inhibitors of norepinephrine reuptake [SNRIs]), the ligand calcium channel blockers, gabapentin and pregabalin, and topical lidocaine (lidocaine patch 5%).

Opioids and tramadol are recommended as second-line treatment in general except in certain specific clinical situations in which they can be considered for first-line use.

Other medications are considered third-line therapy. The guidelines recognize that an effective drug combination for neuropathic pain may provide greater analgesia than the use of single drugs (monotherapy) (NEJ 2005), although this therapy can often be associated with more side effects or risk of drug interactions. However, the combination therapy was incorporated into a management strategy for patients with partial response to treatment with first-line drugs.

Four steps should be performed that may require treatment, dose adjustment or additional monitoring of therapy

Step 1.

- Establishing the diagnosis of neuropathic pain.
- Assess pain
- Establish and treat the cause of neuropathic pain.
- Identify relevant comorbidities (eg, heart, kidney or liver disease, depression) that may require treatment or dose adjustment or additional monitoring of therapy
- Explain the diagnosis and treatment plan for the patient and set realistic expectations

Step 2.

- Initiate therapy for the disease causing neuropathic pain.
- Start the treatment of symptoms with one or more of the following:

A ligand calcium channel alpha 2-delta (gabapentin)

- For patients with peripheral neuropathic pain localized topical lidocaine used alone or in combination with one of the other first-line therapies

- For patients with acute neuropathic pain, Neuropathic pain due to cancer, exacerbations or episodes of severe pain and / or when the system of pain relief during the assessment of a first-line drug to an effective dose is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies
- Assess the patient for non-pharmacological treatments and to initiate, if necessary

Step 3.

- Reassess the pain and often assess the quality of life related to health.
- If pain relief is adequate (for example, the average pain reduced to $\leq 3 / 10$) and tolerable side effects, continue the treatment.
- If there is partial relief of pain (for example, the average is still $\geq 4 / 10$) after appropriate treatment, add one of the other four first-line drugs.
- If no or inadequate pain relief (eg, reduction of $<30\%$) after appropriate treatment should be changed to an alternative first-line drug

Step 4.

- If the tests of first-line drugs alone and in combination fail, consider the second-and third-line and / or referral to a pain specialist (2009)

Importantly, the doses used (start, qualifications and maximum) and the duration of clinical trials are appended in the table below.

The duration of the trials with the use of gabapentin was 3-10 weeks with 4 weeks use of tramadol.

3. Treatment of neuropathic pain and pharmacological classes

3.1 Antidepressants

TCAs are often listed as first-line drugs for neuropathic pain. Typically, this class of agents is separated into two categories based on their chemical structure: tertiary and secondary amines. TCAs appear to affect pain transmission via multiple mechanisms including reuptake inhibition of both serotonin and norepinephrine at spinal cord receptor sites, including projections to the brain stem and dorsal horn nuclei. It has been postulated that the tertiary agents maintain a more balanced chemical profile, providing inhibition of both serotonin and norepinephrine. In contrast, the secondary amines appear to provide more reuptake inhibition of norepinephrine. The analgesic properties of TCAs appear to be independent of their antidepressant properties. Other possible mechanisms of action include: alpha-adrenergic blockade; anticholinergic effects; antihistaminic effects; reuptake inhibition of dopamine; effects on gamma-aminobutyric acid (GABA)-B and adenosine; potassium, calcium and, most importantly, sodium channel blockade; N-methyl-D-aspartic acid (NMDA)-receptor antagonism.

The secondary amines (eg, desipramine and nortriptyline) appear to be as effective as the tertiary agents (eg, imipramine and amitriptyline) as analgesics in neuropathic pain and produce markedly fewer side effects. This favorable side-effect profile makes secondary amine TCAs more clinically appropriate for many patients.

3.2 Anticonvulsants

As with epilepsy, the hallmark characteristic of neuropathic pain is thought to be neuronal hyperexcitability. Some of the known mechanisms of action of anticonvulsants include blockade of the membrane sodium currents, effects on calcium conductance, activation of the gamma-aminobutyric acid (GABA) inhibitory system by direct or indirect means, and reduction of the activity of the excitatory neurotransmitter glutamate. The net result is the

depression of synaptic transmission and the elevation of the threshold for repetitive firing of nociceptive neurons, as well as a reduction in discharges of the dorsal root ganglion cells.

To date, only five agents have been evaluated in randomized double-blind clinical trials. These are carbamazepine, gabapentin, lamotrigine, phenytoin, and pregabalin. Of these, carbamazepine and phenytoin require intensive monitoring of serum levels and maintain a fairly extensive adverse effect profile. Lamotrigine use is limited by a risk of Stevens–Johnson syndrome and other serious dermatological adverse events. Gabapentin produces markedly fewer adverse effects than many other anticonvulsants, and does not require blood tests.

Gabapentin has recently been shown to be an effective treatment option for both DPN and PHN in two large multicenter, randomized, double-blind, placebo-controlled, parallel group trials. Gabapentin was also compared to amitriptyline in a small-scale prospective, randomized, double-blind, double-dummy, crossover study in DPN. Although both drugs provided analgesia, no significant difference was shown between gabapentin and amitriptyline with respect to pain scores or global pain assessment. The authors concluded that gabapentin is an effective alternative to amitriptyline for treatment of DPN pain, but could not be recommended over amitriptyline due to cost.

The most common side effects of gabapentin are drowsiness, somnolence, and generalized fatigue. These side effects are usually transient, lasting an average of 2 to 3 weeks. Treatment should be initiated at 300 mg at bedtime, with a test dose of 100 mg at bedtime for elderly patients. The dose is then increased by 300 mg every 3 to 5 days, until the patient has adequate pain relief. The median effective daily dose ranges between 900 and 1800 mg, although some patients respond to daily doses as low as 100 mg and others require 3600 mg. Gorson and colleagues reported that doses less than 900 mg per day (300 mg TID) are either ineffective or only minimally effective for the treatment of painful diabetic neuropathy. The average age of the patients evaluated in this report was 62 years. Because of its short half-life, gabapentin should be administered on a TID schedule. The drug is excreted unchanged by the kidneys, with clearance directly proportional to creatinine clearance. Therefore, dosage reduction may be needed in patients with renal impairment. As a result of the lack of drug–drug interactions, gabapentin may be an attractive agent for patients receiving multiple medications.

Stacey (2005) identified several randomized, double-blind clinical trials (level 2 evidence) demonstrating that gabapentin had significantly greater efficacy than placebo in PHN (at 1800 to 3600 mg/day) and DPN (900 to 3600 mg). In DPN, gabapentin showed comparable efficacy to amitriptyline. Controlled clinical trials suggest that carbamazepine (100 to 4000 g/day) is effective in TGN and DPN, but not PHN or central pain (all level 2 evidence). Compared to the first-generation anticonvulsants, gabapentin has a more favorable safety and tolerability profile. Pregabalin (300 or 600 mg/day) also appears to be effective in some types of neuropathic pain, with level 2 evidence indicating that 50% of patients with PHN achieved a decrease in pain of 50% or more. Sodium valproate has demonstrated efficacy in painful DPN (level 2 evidence), but the evidence for other anticonvulsants (levetiracetam, oxcarbazepine, topiramate, zonisamide) in the treatment of neuropathic pain was not as good. These results were in accordance with those from earlier studies. Anticonvulsants are thought to hold significant promise in the treatment of CRPS. Carbamazepine has a traditional and perhaps clinically important place in this indication, and gabapentin holds significant promise (level 4 evidence).

3.3 Opioids and tramadol

Opioid agonists work by mimicking the activity of enkephalins and endorphins in the central descending pathways of the pain-processing loop. By binding to mu-opioid

receptors in the central nervous system, opioid agonists dampen neuronal excitability and elicit pain relief. Despite concerns regarding the efficacy of opioids in neuropathic pain, several double-blind RCTs (level 2 evidence) have demonstrated that oxycodone, morphine, and methadone can be modestly effective in PHN, DPN, phantom limb pain, and other types of neuropathic pain. A recent review demonstrated that opioids had significant efficacy over placebo for neuropathic pain in intermediate-term studies. Although reported adverse events with opioids were common, they were not life-threatening. When compared to treatment with TCAs, opioids were as effective but resulted in a greater number of dropouts. Nevertheless, patients who finished the study preferred treatment with opioids over TCA.

Tramadol is a centrally acting agent with a weak affinity for mu-opioid receptors and weak reuptake inhibition of the neurotransmitters norepinephrine and serotonin. It has shown utility in a variety of pain syndromes, most notably neuropathic pain. Treatment should generally be initiated at a dose of 50 mg daily and increased by 50 mg increments every 3 to 5 days. Adverse events increase with more rapid dose titration. Effective daily doses range between 100 and 400 mg, administered in divided doses four times daily. The most common adverse effects of tramadol are dizziness, vertigo, nausea, constipation, headache, and somnolence. In addition, patients with a history or potential for seizure activity should avoid use of this agent.

3.4 Topical agents

Topical agents work locally, directly at the site of application, with minimal systemic effects. Lidocaine, like other local anesthetics, seems to act through inhibition of voltage-gated sodium channels. Capsaicin is thought to elevate the pain threshold in which it is applied through depletion of the nociceptive neurotransmitter, substance P, from the terminals of unmyelinated C fibers. It also causes degeneration of substance P-positive epidermal nerve fibers. Ketamine works through antagonism of the NMDA receptors and clonidine is thought to act at the presynaptic alpha-2 adrenergic receptors, subsequently inhibiting release of norepinephrine.

The evidence supporting the 5% lidocaine patch for the treatment of neuropathic pain is strong. The lidocaine patch is effective in PHN (level 2 evidence), with minimal risk of drug interactions or systemic adverse effects. However, the current approved dose of 12-hour on/12-hour off was found to be insufficient for some patients. The lidocaine patch also has shown efficacy in DPN (level 2 evidence), with the number needed to treat in some studies comparing favorably to those of other treatments for neuropathic pain. Complete or some pain relief has been noted in patients with myofascial pain (two-thirds of whom had lower back pain) and in those with lower back pain. Both types of pain may result, in part, from neuropathic mechanisms. The lidocaine patch also may be useful in the treatment of CRPS. Capsaicin cream (0.075%) was evaluated in several clinical studies for DPN and PHN (both level 2 evidence). Although results were inconsistent, clinical experience suggests it may occasionally be effective in individual circumstances. Capsaicin also has partial efficacy in CRPS (level 3 evidence). Level 3 evidence was noted for the efficacy of ketamine gel in the treatment of neuropathic pain.

3.5 Anesthetics for systemic use

Abnormal electrical activity in injured nerves and neuromas is partly generated by abnormal accumulation of sodium channels. Therefore, a sodium channel-blocking agent may help to relieve neuropathic pain. Such medications include intravenous lidocaine

(which also depresses C-fiber polysynaptic evoked activity and thus suppresses dorsal horn neurons to the C-fiber input), oral mexilitene (which has a similar mode of action to lidocaine), and oral tocainamide. The GABAergic system in the spinal cord also plays a pivotal role in modulating pain control and as a result, baclofen (a GABA-B-receptor agonist) has been shown to be effective for neuropathic pain.

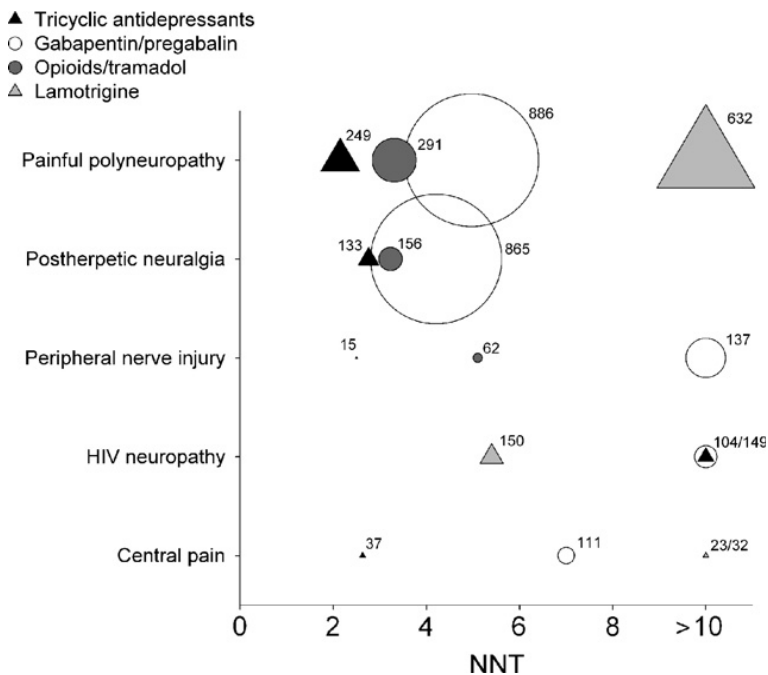


Fig. 1. Combined number-needed-to-treat (NNT) values for various drug classes in all central and peripheral neuropathic pain conditions (not including trigeminal neuralgia, cancer-related neuropathic pain, or radiculopathies). The circle sizes indicate the relative number (given in parentheses) of patients who received active treatment drugs in trials for which dichotomous data were available. It is important to note that because studies on tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and opioids are mainly crossover trials and studies on SNRIs and gabapentin or pregabalin are mainly parallel-group design studies, a direct comparison of NNT values across drug classes cannot be made. Adapted from Finnerup et al. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150:573–81.

Abbreviations: BTX-A = botulinum toxin A; ns = absolute risk difference not significant; SNRIs = mixed serotonin/norepinephrine reuptake inhibitors.

Mexilitene, an orally available lidocaine congener antiarrhythmic, has been evaluated in several double-blind clinical trials for treatment of painful diabetic neuropathy. Only one of these trials demonstrated significant pain relief with mexilitene, and even then only limited nighttime pain relief with high doses (675 mg per day). Mexilitene is not a benign drug, and as such has a less than favorable adverse effect profile. Common adverse effects include chest pain, dizziness, gastrointestinal disturbances, palpitations, and tremor. As with other antiarrhythmics, mexilitene may worsen existing arrhythmia. The daily effective dose

ranges between 450 and 675 mg, usually administered on a thrice daily schedule. As a function of its questionable efficacy and its toxicity, mexilitene should be considered an option only when other measures have failed.

In clinical practice, a combination of two or more drugs is often needed to achieve satisfactory pain relief, although there have been few trials done to support this clinical observation. However, combination therapy with gabapentin and extended-release morphine in patients with postherpetic neuralgia or painful diabetic neuropathy and extended-release morphine and pregabalin in different neuropathic pain syndromes (neuropathic back pain, postherpetic neuralgia, radiculopathy, painful diabetic neuropathy) had higher pain relief with lower doses compared with administration of one drug alone. These results have also been confirmed for the combination of nortriptyline and gabapentin, as well as for pregabalin and topical lidocaine, in patients with painful diabetic neuropathy and postherpetic neuralgia. Taken together, these results substantiate the usefulness of combination therapy in patients with neuropathic pain.

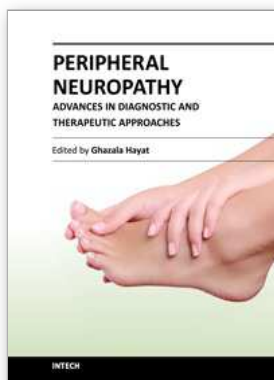
4. Conclusions

Although a primary goal of pain management is to relieve pain using a single agent, the reality is that monotherapy rarely provides adequate relief from chronic neuropathic pain. In these complex and refractory situations, combination therapy using two or more agents with synergistic mechanisms of action (eg, gabapentin + lamotrigine or tramadol + gabapentin) is frequently necessary. In clinical practice, some patients begin to respond to a particular monotherapy, but often are restricted by dose-related side effects. In such cases, combination therapy with two or more agents with different modes of action at suboptimal doses may provide the additive effects or even synergistic effects necessary for optimal pain relief without compromising the side-effect profile of each agent. However, it is essential that a careful patient history is taken before initiating a polypharmacy regimen.

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Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches

Edited by Dr. Ghazala Hayat

ISBN 978-953-51-0066-9

Hard cover, 206 pages

Publisher InTech

Published online 29, February, 2012

Published in print edition February, 2012

Over the last two decades we have seen extensive progress within the practice of neurology. We have refined our understanding of the etiology and pathogenesis for both peripheral and central nervous system diseases, and developed new therapeutic approaches towards these diseases. Peripheral neuropathy is a common disorder seen by many specialists and can pose a diagnostic dilemma. Many etiologies, including drugs that are used to treat other diseases, can cause peripheral neuropathy. However, the most common cause is Diabetes Mellitus, a disease all physicians encounter. Disability due to peripheral neuropathy can be severe, as the patients suffer from symptoms daily. This book addresses the advances in the diagnosis and therapies of peripheral neuropathy over the last decade. The basics of different peripheral neuropathies is briefly discussed, however, the book focuses on topics that address new approaches to peripheral neuropathies.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Jorge Guajardo Rosas, Faride Chejne Gomez and Ricardo Plancarte Sanchez (2012). Multimodal Analgesia for Neuropathic Pain, *Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches*, Dr. Ghazala Hayat (Ed.), ISBN: 978-953-51-0066-9, InTech, Available from:
<http://www.intechopen.com/books/peripheral-neuropathy-advances-in-diagnostic-and-therapeutic-approaches/multimodal-analgesia-for-neuropathic-pain>

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