Pharmacologic Aspect of Neuropathic Pain

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Abstract
Neuropathic pain is pain arising from nerve damage to the conductive pathways of pain (ranging from nociceptors to post central gyrus). Neuropathic pain can be caused by 1) Carcinomas, 2) Trap/compressive, 3) Congenital, 4) Immunomediated, 5) Infection, 6) Metabolic disorders, 7) nutritional deficiency, 8) Toxin, 9) Lesion, 10) Vasculitis, 11). Connective tissue disorders. To date, the pathophysiology of neuropathic pain can not be explained thoroughly, this problem leads to the treatment which has not given satisfactory results as expected. There are many types of drugs has been used for the treatment of neuropathic pain, and they are generally aimed to stop the flow of impulses in the nervous system which was activated as a result of ectopic generators in areas experiencing nerve injury. These drugs work in several locations such as: drugs that works on 'sodium channel voltage gate' (i.e Carbamazepine group), drugs that works on 'calcium channel' (i.e Gabapentin and Pregabalin), and also drugs that works on 'the synapses gap' (i.e Tricyclic class). Besides drugs that inhibit pain impulses propagation, the treatment of neuropathic pain also include drugs that have the ability of nervous system regeneration such as methylcobalamin group. The rationale of the use of this kind of drugs is that this drug expected to regenerate the damage of the nervous system damage which is lead to decrease the ectopic generator activity, the end result is the reducement of neuropathic pain experienced by patients.
Key words: neuropathic pain, pharmacologic, regeneratif

Introduction

Neuropathic pain is common, greatly impairs quality of life and has a high economic impact on society: the Institute of Medicine reports that at least 116 million American adults suffer from chronic pain, and estimates for people suffering from neuropathic pain are as high as 17.9%. Co-morbidities such as poor sleep, depression and anxiety are common in neuropathic pain patients, leading to unresolved arguments about whether pain causes mood and sleep changes or whether individuals with mood and sleep disorders are at a higher risk of developing pain (Hehn *et al*., 2012). Neuropathic pain (NP) is estimated to afflict as high as 7–8% of the general population in Europe (Attal *et al*., 2010), an estimated prevalence of 5% to 7% in France, compared with 20% to 31% for chronic pain (Delorme *et al*., 2011) and It is a common condition with an overall prevalence between 0.9 and 8.0% (Athanasakis *et al*., 2013).

The International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as pain ''initiated or caused by a primary lesion or dysfunction in the nervous system''. It is estimated to afflict millions of people worldwide, although precise figures are not available. Neuropathic pain can be caused by a number of different diseases (e.g., diabetes mellitus, herpes zoster, human immunodeficiency virus [HIV] infection), medical interventions (e.g., chemotherapy, surgery), and injuries (e.g., brachial plexus avulsion) cause NP by producing lesions in somatosensory pathways in the peripheral or central nervous system (Dworkin *et al*., 2007; O'Connor & Dworkin, 2009). The management of patients with NP is complex and response to existing treatments is often inadequate. Even with well-established NP medications, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed, and side effects are Common (Dworkin *et al*., 2007; Attal *et al*., 2010).

Materials and Methods

This article review form articles related with the pharmacologic aspect of neuropathic pain. All data contained in this article is the result of a number of articles search.

Results and Discussion

In 2006, the European Federation of Neurological Societies (EFNS) produced the first guidelines on pharmacological treatment of NP. Since 2006, new randomized controlled trials (RCTs) have appeared in various NP conditions, justifying an update (Dworkin *et al*., 2007; Attal *et al*., 2010).

Pharmacological treatment is the mainstream in post-herpetic neuralgia (PHN), diabetic peripheral neuropathic pain (DPNP), central post-stroke pain (CPSP), trigeminal neuralgia (TN), complex regional pain syndrome (CRPS), cancer pain, failed back syndrome etc, while polypharmacy is still the major prescriptions facing such kind of miserable patients. The tricyclic antidepressants (TCA), gamma-aminobutyric acid (GABA), voltage-dependent calcium channel blockers, selective non-epinephrine reuptake inhibitor (SNRI), opioid or morphine etc, are still evidence-based medicines (EBM) but with different outcome for individuals (Yang *et al*., 2012). Use of antiepileptics with demonstrated efficacy as first-line therapy has increased in neuropathic pain (Hall *et al*., 2013).

Table 1. Stepwise Pharmacologic Management of Neuropathic Pain (O'Connor & Dworkin, 2009)

Step 1
- Assess pain and establish the diagnosis of NP, if uncertain about the diagnosis, refer to a pain specialist or neurologist
- Establish and treat the cause of NP; if uncertain about availability of treatment addressing NP etiology, refer to appropriate specialist
- Identify relevant comorbidities (e.g., cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy
- Explain the diagnosis and treatment plan to the patient, and establish realistic expectations

Step 2
- Initiate therapy of the disease causing NP, if applicable
- Initiate symptom treatment with one or more of the following:
  - ✓ Antideppresant medication: either secondary amine TCA (nortriptyline, desipramin) or SSNRI (duloxetine, venlafaxine)
  - ✓ Calsium channel α_2-δ ligand: either gabapentin or pregabalin
  - ✓ For patients with localized peripheral NP: topical lidocaine used alone or in combination with 1 of the other first-line therapies
  - ✓ For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with 1 of the first-line therapies.
- Evaluate patient for nonpharmacologic treatments, and initiate if appropriate

Step 3
- Reassess pain and health-related quality of life frequently
- If substantial pain relief (e.g., average pain reduced to NRS ≤3/10) and tolerable side effects, continue treatment.
- If partial pain relief (e.g., average pain remains ≥4/10) after an adequate trial, add 1 of the other first-line medications
- If no or inadequate pain relief (e.g., <30% reduction) at target dosage after an adequate trial, switch to an alternative first-line medication

Step 4
- If trials of first-line medications alone and in combination fail, consider second-line medications or referral to a pain specialist or multidisciplinary pain Center

NP-neuropathic pain; NRS-numeric rating scale; SSNRI-selective serotonin and norepinephrin reuptake inhibitor; TCA-tricyclic antidepressant. Reprinted with permission from Pain.

Three classes of medications were recommended as firstline treatments: antidepressants with both norepinephrine and serotonin reuptake inhibition (TCAs and selective serotonin and norepinephrine reuptake inhibitors [SSNRIs]), calcium channel 2- ligands (gabapentin and pregabalin), and topical lidocaine (lidocaine patch 5%). Opioids and tramadol were recommended as generally second-line treatments, except in certain specific clinical situations in which it was recommended that first-line use could be considered. A number of medications were considered third-line choices (O'Connor & Dworkin, 2009). Based on efficacy and safety, pregabalin is considered a first-line drug together with gabapentin in the treatment of central pain (Finnerup & Jensen, 2007).

The guidelines acknowledge that a combination of medications with efficacy for neuropathic pain may provide greater analgesia than use of individual medications as monotherapy, although such combination therapy will often be associated with increased side effects, inconvenience, risk of drug interactions, and cost. Nevertheless, because 50% of patients in Neuropathic Pain trials of efficacious medications typically achieve satisfactory pain relief, many patients in clinical practice will require treatment with a combination of medications. Such combination therapy was incorporated into a

stepwise management strategy for patients with partial responses to treatment with first-line medications (O'Connor & Dworkin, 2009).

Table 2. Summary of the results of Randomized Clinical Trials Involving First and Second-Line Medications for Patients With Neuropathic Pain (O'Connor & Dworkin, 2009)

	TCA	Duloxetine	Venlafaxine	Gabapentin	Pregabalin	Topical lidocaine 5% patch	Opioid analgesic	Tramadol
Peripheral NP								
- Painful DPN	(+)	(+)	(+)	Both	Both	-	(+)	(+)
- PHN	(+)	-	(-)	(+)	Both	(+)	(+)	(+)
- Painful polyneuropathy	(+)	-	(+)	(+)	-	(+)	(+)	(+)
- Phantom limb pain	(-)	-	-	Both	-	-	(+)	(+)
- Postmastectomy pain	(+)	-	(-)	-	-	-	-	-
- GBS	-	-	-	(+)	-	-	-	-
- Neuropathic cancer pain	(-)	-	-	(+)	-	-	-	-
- CPRS type I	-	-	-	(-)	-	-	-	-
- Chronic lumbal root pain	(-)	-	-	-	-	-	(-)	-
- Chemotherapy induced neuropathy	(-)	-	-	(-)	-	-	-	-
- HIV Neuropathy	(-)	-	-	(-)	-	-	-	-
Central NP								
- Central poststroke pain	(+)	-	-	-	(+)	-	-	-
- Spinal cord injury pain	(-)	-	-	(+)	(+)	-	-	-

The NeuPSIG guidelines note that few medications have been found to be efficacious in neuropathic pain originating from a lesion in the central nervous system. RCTs have demonstrated efficacy for TCAs in central poststroke pain, and for calcium channel _2-_ ligands in spinal cord injury and poststroke central neuropathic pain. The Canadian Pain Society created 4 levels of recommendation, with first- and second-line medications differentiated by "the quality of evidence and the evidence of efficacy" based on NNTs. Medications were classified as third-line treatments if they have good evidence of efficacy, but require specialized monitoring and follow-up not required of drugs at the other levels. Fourth-line medications were described as having "at least 1 positive RCT, but required further study" (O'Connor & Dworkin, 2009).

As with the NeuPSIG and Canadian Pain Society guidelines, the EFNS guidelines grade the level of evidence for different available treatments. However, unlike the other 2 sets of guidelines, separate recommendations were made for the treatment of patients with painful polyneuropathies (including painful diabetic peripheral neuropathy), postherpetic neuralgia, trigeminal neuralgia, and central neuropathic pain. Consistent with the NeuPSIG and Canadian Pain Society guidelines, the EFNS guidelines recommended gabapentin, pregabalin, and TCAs as first-line treatments for painful polyneuropathies, postherpetic neuralgia, and central neuropathic pain (Moulin *et al*., 2007; O'Connor & Dworkin, 2009; Rhodes, 2011).

Table 3. Comparison of Neuropathic Pain Treatment Guidelines, Excluding Trigeminal Neuralgia (O'Connor & Dworkin, 2009).

Medication Class	NeuPSIG Guidelines	CPS Guidelines	EFNS Guidelines
Tricyclic antidepressants	First line	First line	First line for PPN, PHN, and CP
Calcium channel α_2-δ ligands (gabapentin and pregabalin)	First line	First line	First line for PPN, PHN, and CP
SSNRIs (duloxetine and venlafaxine)	First line	Second line	Second line for PPN
Topical lidocaine	First line for localized peripheral NP	Second line for localized peripheral NP	First line for PHN if small area of pain/ allodynia
Opioid analgesics	Second line except in selected circumstances†	Third line	Second-third-line for PPN, PHN, and CP
Tramadol	Second line except in selected circumstances†	Third line	Second-third-line for PPN and PHN

CP = central pain; CPS = Canadian Pain Society; EFNS = European Federation of Neurological Societies; NeuPSIG = Neuropathic Pain Special Interest Group; NP = neuropathic pain; PHN = postherpetic neuralgia; PPN = painful polyneuropathy; SSNRIs = selective serotonin and norepinephrine reuptake inhibitors.
*Only medications considered first or second-line in 1 of the guidelines are presented.
†Opioid analgesics and tramadol were considered first-line options in the following circumstances: for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.

Other EFNS recommendations for painful polyneuropathies were duloxetine and venlafaxine as second-line treatment ("because of moderate efficacy"), and opioids, tramadol, and lamotrigine as "second-/thirdline therapy." Additional recommendations for postherpetic neuralgia were topical lidocaine as a first-line treatment for patients with localized pain and allodynia, and opioids, tramadol, capsaicin, and valproic acid as second-line treatment options. "Second-/third-line" treatment options for patients with central neuropathic pain were lamotrigine, opioids, and cannabinoids (Moulin *et al*., 2007; O'Connor & Dworkin, 2009; Rhodes, 2011).

Two drugs have been approved for neuropathic pain in the US – pregabalin and duloxetine – but neither of these afford complete relief, even when used in combination (Vinik & Cassellini, 2012). In addition, several novel drug treatments such as botulinum toxin, capsaicin patch and lacosamide have been also used for neuropathic pain therapy. Table 5 summarizes the major pharmacological treatments for neuropathic pain and their analgesia mechanisms (Xu *et al*., 2012).

Table 4. Major pharmacological treatment for neuropathic pain and their basic mechanisms (Xu *et al*., 2012)

Compound	Mode of action
Antidepressant	
- Nortriptiline	Inhibition of both serotonin and norepinephrine reuptake
- Desipramine	Inhibition of both serotonin and norepinephrine reuptake
- Duloxetine	Inhibition of both serotonin and norepinephrine reuptake Inhibition of both
- Venlafaxine	serotonin and norepinephrine reuptake
Anticonvulsants	
- Gabapentin	Decreases release of glutamate, norepinephrine and substance P, with ligands on α2-δ subunit of voltage
- Pregabalin	Decreases release of glutamate, norepinephrine and substance P, with ligands on α2-δ subunit of voltage
- Lacosamide	Decreases release of presynaptic transmitter inhibition of voltage-gated sodium channel
Opioid agonists	
- Morphine	μ-receptor agonism
- Oxycodon	μ-receptor agonism
- Methadone	μ-receptor agonism, κ-receptor antagonism
- Levorphanol	μ-receptor agonism
- Tramadol	μ-receptor agonism, inhibition of norepinephrine and serotonin reuptake
Topical therapy	
- 5% lidocaine patch	Block of sodium channel
- High dose capsaicin patch	Damage of nociceptive sensory axons, a highly selective activating ligand for TRPV1
- Botulinum toxin	Inhibition of both the exocytosis of acetylcholine and some other neurotransmitter

Pregabalin reduces the enhanced noxious stimulus-induced spinal release of glutamate seen in neuropathic rats (Kumar *et al*., 2010). Intranasal or intrathecal pregabalin relieves neuropathic pain behaviours, perhaps due to pregabalin's effect upon anterograde CaVa2δ-1 protein trafficking from the DRG to the dorsal horn. Intranasal delivery of agents such as pregabalin may be an attractive alternative to systemic therapy for management of neuropathic pain states (Martinez *et al*., 2012). The anti-allodynic effects of gabapentin may be caused by upregulation of IL-10 expression in the spinal cord, which leads to inhibition of the expression of pro-inflammatory cytokines in the spinal cords (Lee *et al*., 2013).

Capsaicin is a transient receptor potential vanilloid-1 agonist, which increases the intracellular calcium ion concentration. This triggers calcium-dependent protease enzymes causing cytoskeletal breakdown and leads to the loss of cellular integrity and 'defunctionalization' of nociceptor fibres. Efficacy and therapeutic effect has been shown in several clinical studies of PHN and HIV-DSP. The high-concentration capsaicin patch and its practical application are different from low-concentration creams; one application can help for up to 3 months (Irving *et al*., 2011; Webster *et al*., 2012; Baranidharan *et al*., 2013). A single 30-minute application of NGX-4010 (Capsaicin 8% patch) provides significant pain relief for at least 12 weeks in patients with HIV-DSP and is well tolerated (Simpson *et al*., 2008; Brown *et al*., 2013).

Activation of TRPV1 by capsaicin results in sensory neuronal depolarization, and can induce local sensitization to activation by heat, acidosis, and endogenous agonists. Topical exposure to capsaicin leads to the sensations of heat, burning, stinging, or itching. High concentrations of capsaicin or repeated applications can produce a persistent local effect on cutaneous nociceptors, which is best

described as defunctionalization and constituted by reduced spontaneous activity and a loss of responsiveness to a wide range of sensory stimuli (Anand & Bley, 2011; Bley, 2013).

Conclusions

All guidelines recommend TCAs, gabapentin, and pregabalin as first-line treatment options for patients with neuropathic pain (excluding trigeminal neuralgia). The NeuPSIG guidelines recommend duloxetine and venlafaxine as first-line treatment options, but the Canadian Pain Society and EFNS guidelines recommend these SSNRIs as second-line options for patients with painful polyneuropathies. Clinicians need to consider the advantage and disadvantage of these managements to avoid ineffective treatments, maximize curing proven beneficial in clinical trials, and minimize the side effect of therapies. To improve the current management of patients with neuropathic pain, evidence-based basic studies should be made for pharmacological approaches to guide the managements in the future.

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