Upcoming Issues

Chronic Pain after Injury
Neuropathic Cancer Pain
Dealing with Suffering

Vol. XVIII, Issue 9 — November 2010

Pharmacological Management of Neuropathic Pain

Background

Neuropathic pain may arise as a consequence of a lesion or disease affecting the somatosensory system.[1] Neuropathic pain is estimated to afflict as much as 7–8% of the general population in Europe.[2,3] Classical examples include diabetic polyneuropathies, postherpetic neuralgia, trigeminal neuralgia, central poststroke pain, and spinal cord injury pain, although traumatic/postsurgical neuropathies and painful radiculopathies represent common conditions in the general population.[2]

The management of patients with chronic neuropathic pain is challenging,[4–8] despite several attempts to develop a more rational therapeutic approach.[8,9] Most studies have been performed in postherpetic neuralgia (PHN) and painful diabetic neuropathy (PDN). These trials mainly studied the effects of monotherapy and were placebo controlled. Outcome measures were generally restricted to a global assessment of pain by

> *The management of patients with chronic neuropathic pain is challenging, despite several attempts to develop a more rational therapeutic approach*

the patient, and the quality of pain was seldom taken into account. However, newer studies have appeared that may allow us to revise this statement. Thus, studies have recently been performed in indications that were previously neglected, such as central pain and painful radiculopathies; combination studies and head-to-head comparative studies have appeared; and finally, a comprehensive assessment of patients, including the quality of their pain, is increasingly being performed in clinical trials. This issue of *Pain: Clinical Updates* will address new developments in the therapeutic management of neuropathic pain.

Evidence–Based Recommendations in Peripheral Neuropathic Pain (Diabetic Neuropathies and Postherpetic Neuralgia)

Tricyclic Antidepressants

The efficacy of tricyclic antidepressants (TCAs) has been established mainly in PDN and PHN.[5–8] The most common side effects are dry mouth, constipation, sweating, dizziness, blurred vision, drowsiness, palpitation, orthostatic hypotension, sedation, and urinary retention. TCAs can also cause cognitive disorders or confusion, gait disturbance, and falls, particularly in elderly patients.[5] Imipramine

and more selective TCAs (e.g., nortriptyline) cause fewer anticholinergic effects and less sedation.[5] TCAs should be initiated at low dosages (10–25 mg in a single dose at bedtime) and then slowly titrated as tolerated. Effective dosages vary from one subject to another (e.g., 25–150 mg amitriptyline or equivalent), the average dosage for amitriptyline being 75 mg/day. Due to substantial pharmacokinetic variability, monitoring of serum drug concentrations may be helpful in guiding treatment.

SNRI Antidepressants

The efficacy of the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine has been established mainly in PDN.[7,8] The most frequent adverse events with duloxetine are nausea, somnolence, dry mouth, constipation, reduced appetite, diarrhea, hyperhidrosis, and dizziness, with discontinuation rates of 15–20% across studies. Rare elevations of plasma glucose, hepatic enzymes, or blood pressure have been reported[10]; therefore, duloxetine is contraindicated in severe hepatic dysfunction and in unstable arterial hypertension. Venlafaxine extended-release is better tolerated than immediate-release, the main side effects being gastrointestinal disturbances. However, increased blood pressure and clinically significant ECG changes reported in 5% of patients with PDN[11] may be a concern at high dosages. Adequate dosages of duloxetine range between 60 and 120 mg/day, with no clear superiority of 120 mg. Treatment should be initiated at 30 mg/day to avoid nausea and titrated after 1 week to 60 mg/day.[7] Only high doses of venlafaxine (150–225 mg/day) are effective.

Pregabalin/Gabapentin

The efficacy of gabapentin and pregabalin has been established in PDN and PHN.[8,12–14] An extended-release formulation of gabapentin (1800 mg/day), administered twice a day, has also been found effective.[15] The most common side effects include dizziness and somnolence, peripheral edema, weight gain, asthenia, headache, and dry mouth. Effective dosages are 1800–3600 mg/day for gabapentin and 150–600 mg/day for pregabalin (with inconsistent effects at a dose of 150 mg/day). In clinical studies, pregabalin is initiated at 150 mg/day, but initial doses of 75 mg/day at bedtime are recommended to reduce side effects. Both drugs need individual titration, but the titration period is generally shorter for pregabalin (increase by 75 mg every 3 days). Gabapentin is generally administered three times a day (t.i.d.) except for the extended-release formulation, while pregabalin can be administered twice a day (b.i.d.).

Topical Lidocaine

The efficacy of topical lidocaine has been established mainly in PHN. However, based on a meta-analysis, the therapeutic gain is modest compared to placebo,[16] and one recent trial using an enriched-enrollment design failed to show a difference between lidocaine and placebo on the primary outcome measure.[17] Lidocaine patches are generally safe, with a low systemic absorption, and only local adverse effects (mild skin reactions) have been reported.[16] Up to four patches per day for a maximum of 12 hours within a 24-hour period may be used to cover the painful area. Titration is not necessary.

Tramadol

The efficacy of tramadol, including the combination with acetaminophen, has been established mainly in PDN.[7,8] Tramadol induces dizziness, dry mouth, nausea, constipation, and somnolence and can cause or aggravate cognitive impairment, particularly in the elderly.[24] There is an increased risk of seizures in patients with previous epilepsy or receiving drugs reducing the seizure threshold such as TCAs. Serotonergic syndrome may occur if tramadol is used in combination with serotonergic medications (particularly SSRIs). Tramadol should be initiated at low dosages, particularly in elderly patients (50 mg once daily), and then titrated as tolerated. The effective dosage range is 200–400 mg/day. Dose reduction is recommended in older patients and in those with renal impairment or cirrhosis.

Strong Opioids

The use of opioids for the treatment of chronic pain has increased dramatically over the past decade. There has been a longstanding debate about their efficacy in chronic neuropathic pain,[18] but it is now established that strong opioids (oxycodone, methadone, and morphine) have efficacy in peripheral neuropathic pain. The evidence is based on several positive randomized controlled trials (RCTs) in PDN and PHN using doses of oxycodone—the best-studied opioid drug in neuropathic pain—ranging from 10–120 mg.[7,8,18] However, the doses necessary to reach efficacy may be higher in neuropathic pain than in nociceptive pain, as indicated by a study comparing the effects

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of fentanyl in acute and chronic postoperative pain in the same patients.[19] Furthermore, the effects on neuropathic pain are not necessarily associated with a significant improvement in quality of life, psychological comorbidities, or sleep disorders.[7] The most common side effects are constipation, sedation, nausea, dizziness, and vomiting; these effects generally decrease after long-term treatment, with the exception of constipation.[5,20] Cognitive impairment has been reported to be negligible to significant, even at very high dosages.[7]

The problems associated with long-term opioid use are increasingly being assessed in chronic noncancer pain. Long-term morphine administration may be associated with immunological changes and hypogonadism (refs. in Dworkin et al.[5]). The risk of misuse or addiction in chronic pain, although low (2.6%) in recent systematic studies,[21] may represent a concern with regard to long-term use,[5] and it has been found recently that prescription opioid dependence is associated with structural and functional changes in brain regions implicated in the regulation of affect, reward, and motivational

Table 1

Classification of evidence for drug treatments in commonly studied neuropathic pain conditions and recommendations for their use. Treatments are presented in alphabetical order. Only drugs used in repeated dosages and available or soon to be available for use are shown here (with the exception of treatments with long-lasting effects such as capsaicin patches). Drugs marked with an asterisk were found effective in single class II or III studies and are generally not recommended.

Etiology	Level A Rating for Efficacy	Level B Rating for Efficacy	Level C Rating for Efficacy	Level A/B Rating for Inefficacy or Discrepant Results	Recommendations as First-Line Treatment	Recommendations as Second- or Third-Line Treatment
Diabetic neuropathy[1]	Duloxetine Gabapentin-morphine Gabapentin Oxycodone Pregabalin TCAs[2] Tramadol alone or with acetaminophen Venlafaxine ER	Botulinum toxin* Dextromethorphan Gabapentin-venlafaxine* Levodopa*	Carbamazepine Phenytoin	Capsaicin cream Lacosamide Lamotrigine Memantine Mexiletine Mianserin Oxcarbazepine SSRIs Topical clonidine Topiramate Valproate Zonisamide	Duloxetine Gabapentin Pregabalin TCAs Venlafaxine ER	Opioids Tramadol[3]
Postherpetic neuralgia	Capsaicin 8% patch Gabapentin Lidocaine plasters Opioids (morphine, oxycodone, methadone) Pregabalin TCAs[2]	Capsaicin cream Valproate*		Benzydamine (topical) Dextromethorphan Fluphenazine Memantine Lorazepam Mexiletine Tramadol	Gabapentin Pregabalin TCAs Lidocaine plasters[4]	Capsaicin Opioids
Central pain[5]	Cannabinoids (oromucosal, oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCAs (SCI, CPSP) Tramadol (SCI)* Opioids		Carbamazepine Gabapentin Duloxetine (found effective in allodynia in one study) Lamotrigine in SCI (except in patients with allodynia in one study) Levetiracetam Mexiletine S-ketamine iont. Valproate	Gabapentin Pregabalin TCAs	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI)

Source: Adapted from Attal et al. 2010.[7]
Abbreviations: iont.: iontophoresis; CPSP: central poststroke pain; ER: extended release; MS: multiple sclerosis; NK1: neurokinin 1; PHN: postherpetic neuralgia; SCI: spinal cord injury; TCAs: tricyclic antidepressants.
[1] Only TCAs, tramadol, and venlafaxine were studied in nondiabetic neuropathies.
[2] TCAs include amitriptyline, clomipramine, nortriptyline, desipramine, and imipramine.
[3] Tramadol is recommended first line in patients with acute exacerbations of pain, especially for the tramadol/acetaminophen combination.
[4] Lidocaine is recommended first line mainly in elderly patients.
[5] Cannabinoids and lamotrigine are proposed for refractory cases.

functions.[22] Opioid-induced hyperalgesia, which consists of an increase in pain sensitivity and can potentially aggravate pre-existing pain, may also be observed in patients receiving long-term opioids.[23] For these reasons, opioids are considered as second- or third-line treatments in noncancer neuropathic pain in all current recommendations.[5,7]

Other Drug Treatments

Other antiepileptics have been poorly studied in neuropathic pain, with the notable exception of carbamazepine for trigeminal neuralgia, or have shown generally mild or discrepant effects in large-scale RCTs (topiramate, oxcarbazepine, carbamazepine, and lacosamide). Initial data about valproate were

controversial,[5–7] but several recent RCTs, all from the same research group, were positive in diabetic neuropathic pain and PHN.[7] RCTs have reported greater pain relief from topical capsaicin 0.075% compared to an inactive vehicle, but due to the burning effect caused by capsaicin, blinding may have been compromised.[5–7]

Summary of Current Recommendations for First– and Second–Line Medications in Peripheral Neuropathic Pain

Tricyclic antidepressants, gabapentin, pregabalin, and SNRI antidepressants (duloxetine and venlafaxine) are recommended as first-line treatments for neuropathic pain by the Neuropathic Pain Special Interest Group of the IASP (NeuPSIG) and by the European Federation of the Neurological Society (EFNS),[5,7] although the EFNS guidelines limit the indication of SNRIs as a first-line treatment for painful polyneuropathies. Topical lidocaine, with its excellent tolerability, is recommended as a first-line treatment for PHN. EFNS guidelines suggest using topical lidocaine, particularly in the elderly, especially if there are concerns regarding the central side effects of oral medications. Second-line therapy includes strong opioids and tramadol, but these drug treatments are also recommended first-line in patients with episodic exacerbations of pain.[5]

Indications of Increasing Research Interest

Several trials have been recently performed in central neuropathic pain, particularly spinal cord injury (SCI) pain. These trials have confirmed the benefit of pregabalin in SCI pain,[25,26] and to a lesser extent in poststroke pain,[26] while lower-quality trials suggest a benefit of TCAs, gabapentin, and tramadol in SCI pain,[5] and one comparative trial also found greater efficacy of high doses

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of levorphanol compared with low dosages in central pain.[27] A recent high-quality trial showed no significant superiority of duloxetine over placebo on the primary outcome in central pain due to stroke or SCI, but several secondary outcomes—particularly allodynia to brush and cold—favored duloxetine.[28] Thus, central neuropathic pain seems to respond to the same drug treatments as peripheral neuropathic pain.

Recent large-scale trials have also appeared in post-traumatic neuropathy. One trial found that gabapentin (up to 2400 mg/day) had no effect on pain intensity but improved pain relief, sleep, and quality of life,[29] while pregabalin was moderately effective (a difference of 0.62 out of 10 from placebo on a numeric rating scale) on the primary outcome in another trial using a first placebo run-in phase.[30] Prior lower-class studies found moderate effects of amitriptyline and low-dose venlafaxine in postmastectomy pain and discrepant results with topical capsaicin (refs. in Attal et al.[6]).

HIV-related neuropathy and chronic radiculopathy are generally poorly responsive to drugs that are found useful in other neuropathic pain conditions. In lumbosacral radiculopathy, a recent

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large-scale study using an enrichment phase was totally negative with pregabalin.[31] Similarly, one crossover placebo-controlled study of the efficacy of nortriptyline, morphine, and their combination was negative on the primary outcome and found only slight effects of the combination on worst pain and pain relief, although the blinding was probably unmasked because of side effects.[32] In HIV neuropathy, results were negative with amitriptyline, topical lidocaine, gabapentin, and pregabalin,[7] while only lamotrigine, smoked cannabis, and more recently capsaicin patches were found to be moderately useful.[7] The reason for such disappointing results does not seem to be related to specific clinical phenotypes compared to other conditions.[33] However, given the lack of specific assessment of pain quality in most trials, one cannot exclude that these drugs might have been effective in a subset of patients exhibiting particular clinical phenotypes or might only improve specific dimensions of neuropathic pain. Very high responses in placebo-treated patients in HIV trials may also partly explain the negative results. In any case, new studies are warranted in these indications, particularly in failed back surgery syndrome, which probably represents the most common neuropathic pain condition in the general population.[3]

New Combination and Head–to–Head Studies

Several head-to-head comparative studies have been performed in neuropathic pain, but most studies were single-center, small-sample trials. Most initial studies aimed to compare drugs from the same class, particularly TCAs. These trials found similar efficacy of all TCAs.[5,8] In one study, venlafaxine 225 mg/day was equal to imipramine 150 mg/day in painful neuropathies with respect to overall pain intensity and tolerability, but it was less effective on the proportion of responders, pain relief, and quality of life.[34] In a trial comparing slow-release morphine and methadone with TCAs and placebo, pain relief was greater with morphine than with nortriptyline, whereas the analgesic efficacy of methadone was comparable with that of TCAs.[35] Other trials generally reported similar efficacy of gabapentin versus nortriptyline in diabetic neuropathic pain and PHN,[36,37] of pregabalin versus amitriptyline,[38] and of lamotrigine versus amitriptyline, in diabetic neuropathic pain.[39] Such lack of difference may be related to small sample sizes and does not exclude the possibility that these drugs may have distinct effects depending on the patients' clinical profiles, which were generally not described in detail at baseline.
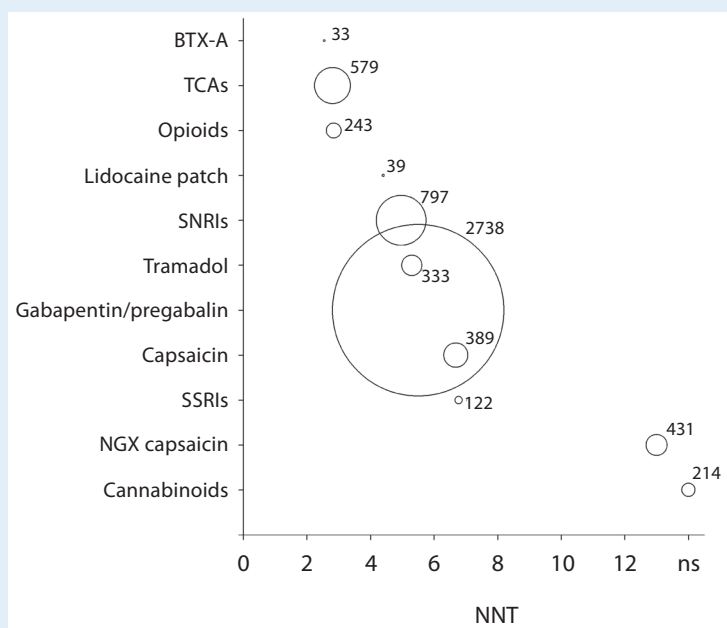
Fig. 1. Combined number-needed-to-treat (NNT) values for various drug classes in all central and peripheral neuropathic pain conditions (not including trigeminal neuralgia, cancer-related neuropathic pain, or radiculopathies).The circle sizes indicate the relative number (given in parentheses) of patients 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.[8] Abbreviations: BTX-A = botulinum toxin A; ns = absolute risk difference not significant; SNRIs = mixed serotonin-norepinephrine reuptake inhibitors.

Several placebo-controlled trials have confirmed the benefit of gabapentin combined with nortriptyline or morphine versus monotherapy in a mixed group of patients with PDN and PHN, with either combination providing better efficacy at lower dosages without any increase in side effects.[36,40] Similarly, in diabetic neuropathic pain, a combination of gabapentin and oxycodone was found superior to gabapentin alone,[41] and valproate combined with nitrate derivatives in painful neuropathy was superior to valproate.[42] These trials suggest the rationale of combination therapy with these agents, particularly when monotherapy is only partially effective.

Emerging Drug Treatments

Recently, three emerging drug classes have been studied in RCTs that may represent potential therapeutic options for the future.

Capsaicin Patches

Capsaicin is an agonist of the transient receptor potential vanilloid receptor (TRPV1) and activates TRPV1 ligand-gated channels on nociceptive fibers. This activation, in turn, causes depolarization, the initiation of an action potential, and the transmission of pain signals to the spinal cord.[43] After several days of capsaicin application, TRPV1-containing sensory axons are desensitized, which inhibits the transmission of pain. Standard capsaicin-containing creams have been found moderately effective in PHN, but they require many applications per day and cause a burning sensation for many days before the analgesic effects start. Recently, the efficacy of a one-time application of a highly concentrated (8%) capsaicin patch (for 30, 60, or 120 minutes) to the painful area compared to a patch with a low concentration (0.04%) has been demonstrated from weeks 2 to 12 in PHN or HIV neuropathy,[44–46] with safety confirmed in an open-label 48-week extension study.[46] However, the optimal duration of the patches to produce analgesic efficacy was distinct in PHN (60 minutes) and HIV neuropathy (30 minutes). The effects of this treatment on multiple symptoms, including mechanical allodynia or burning pain, which may be particularly sensitive to this drug, were not addressed. Adverse effects were primarily due to local capsaicin-related reactions at the application site (pain, erythema, and sometimes edema and itching),[44,45] but initial pain often necessitated opioids. Moreover, careful blood pressure monitoring is necessary because of a potential risk of high blood pressure during application

(probably due to severe pain in some patients). The drug did not impair sensory function, as tested with a standard sensory evaluation, in PHN and HIV neuropathy after repeated applications for up to 1 year,[47] but no in-depth assessment was performed. In human volunteers, only a transient impairment of density of epidermal fibers (lasting 1 week) has been evidenced on skin punch biopsies after a single application, but there was a 93% recovery rate after 6 months.[48] However, it is not clear whether these data are applicable to patients with peripheral nerve lesions after repeated applications. The capsaicin patch may be applied for 30 or 60 minutes to the painful area, limited to a maximum area of 1,000 cm^2.

Botulinum Toxin A

Several lines of investigation have suggested that botulinum toxin A (BTX-A), a potent neurotoxin commonly used for the treatment of focal muscle hyperactivity, may have analgesic effects independent of its action on muscle tone, possibly by acting on neurogenic inflammation.[49] Such mechanisms may be involved in some cases of peripheral neuropathic pain. Two recent monocentric RCTs reported long-term efficacy of a series of subcutaneous injections of BTX-A (from 100 to 200 units) injected into the painful area in patients with mononeuropathies (mainly of traumatic origin) associated with mechanical allodynia,[50] and more recently in patients with diabetic painful polyneuropathies.[51] Interestingly, in these two studies, the onset of efficacy (about 1 week) and the duration of effects (3 months) were remarkably similar. The drug had an excellent safety profile with no systemic side effects and pain only during injection. However, in sharp contrast, one unpublished large-scale RCT of subcutaneous BTX-A in painful neuropathies performed by the sponsor was negative (refs. in Dworkin et al.[5]). One reason may be that the injection was too limited in extent compared to the painful area. Another possibility is that the patients' phenotypes were distinct from those included in the two smaller trials. For example, one study found that one possible predictor for the response was the preservation of warmth thresholds.[5] These discrepant data indicate the need for further large-scale trials with this compound in peripheral neuropathic pain. New perspectives also include the use of peptide-mediated transdermal delivery[52] and engineering of recombinant chimera from two botulinum toxins.[53]

Cannabinoids

The therapeutic potential of cannabinoids has extensively investigated in chronic pain following the discovery of cannabinoid receptors and their endogenous ligands. Oromucosal cannabinoids (2.7 mg delta-9-tetrahydrocannabinol/2.5 mg cannabidiol) have been found effective in multiple sclerosis-associated pain and in refractory peripheral neuropathic pain associated with allodynia (refs. in Attal et al.[7]). Adverse events include dizziness, dry mouth, sedation, fatigue, gastrointestinal effects, and oral discomfort.[7] Although no impairment of cognition or psychoactive effects was found in neuropathic pain, it is well known that cannabis may exacerbate mental conditions.[54]

Therefore, cannabinoids are not recommended in patients with mental disorders. Controversy exists with regard to tolerance and dependence after long-term treatment.[54] Oromucosal cannabinoids are not currently available for the treatment of neuropathic pain, except in Canada.

Is It Possible to Improve Therapeutic Outcome?

Despite newer drugs and the rationale for combination therapy that may improve the therapeutic response, the response to most treatments of neuropathic pain is generally modest, with a number needed to treat for 50% pain relief (the number of patients

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who must be treated to obtain one responder to the active drug but not to placebo) ranging from 3 to 5 in recent meta-analyses[8] (Fig. 1). One reason for this outcome may be related to increasing placebo effects in recent trials.[55] Original enrichment designs have recently been proposed to overcome this problem in neuropathic pain trials.[56] Another reason may be related to the fact that psychological comorbid conditions are generally insufficiently taken into account in RCTs. Thus, it has been found that catastrophizing plays a role in the persistence of pain in PHN.[57] Maladaptive coping and catastrophizing tend to be associated with a poor response to drugs. However, perhaps the most important issue relates to the methodology of the trials. In particular, it may be argued that RCTs performed in neuropathic pain failed to identify responder profiles to therapy mostly because they did not take into account the heterogeneity of neuropathic pain syndromes, which include a variety of symptoms (i.e., burning pain, electric shocks, and brush-evoked pain) and symptom combinations that are presumably linked to distinct mechanisms.[58–60] The assessment of symptoms and signs in clinical trials is best performed with specific assessment questionnaires as regards symptoms, and an extension of the clinical examination such as quantitative sensory testing for clinical signs (refs. in Haanpää et al.[61]). Several studies have reported in post hoc analyses that patients with mechanical (static or dynamic) allodynia were better responders to systemic sodium channel blockers (refs. in Finnerup and Jensen[9]) or pregabalin.[62] These findings suggest that it may be useful to differentiate patients with from those without evoked pain in therapeutic studies. Preservation of thermal sensation has also been associated with a better outcome of focal therapy.[50] Classification according to sensory profiles based on specific neuropathic pain questionnaires and quantitative sensory testing rather than based merely on etiology could help minimize pathophysiological heterogeneity within study groups and increase positive treatment responses.[33,63,64]

Conclusion

All recommendations for the pharmacological treatment of neuropathic pain now propose antiepileptics (gabapentin or pregabalin), TCA or SNRI antidepressants, or topical lidocaine as the first line of treatment for neuropathic pain in general or for

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specific neuropathic pain conditions. Clinical advances in the management of neuropathic pain include the implementation of comparative trials and of combination therapy trials, the study of neglected neuropathic pain conditions, and the identification of responder profiles based on a detailed characterization of symptoms and signs using sensory examination and specific pain questionnaires. Emerging treatments should also help improve the management of neuropathic pain.

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