

Treatment of painful neuropathy

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Purpose of review

With the aging of the population, treatment of painful neuropathies is becoming more and more important for neurological practice. This short review highlights recent findings and current problems.

Recent findings

In addition to tricyclic antidepressants and gabapentin, the reliability of which is established, some drugs have more recently been demonstrated to be efficacious: major and minor opioids, pregabalin, and serotonin–noradrenaline-reuptake inhibitors. In contrast, some other drugs have yielded disappointing results: memantine, mexiletine, topiramate, and – very recently – lamotrigine. Three main questions are currently being debated. Notwithstanding their proven efficacy, should opioids be used in chronic noncancer pain? In which patients should serotonin–noradrenaline-reuptake inhibitors be preferred to tricyclic antidepressants? What is the difference between pregabalin and gabapentin? The whole field suffers from important limitations that make evidence-based medical data hard to translate in clinical practice: most clinical trials were and still are focused on two conditions only (diabetic neuropathy and postherpetic neuralgia) and studies on polytherapy are insufficient.

Summary

A large variety of drugs are being tried in the treatment of painful neuropathy. Neurologists now have a wide choice. Recent publications can help in choosing the best treatment course.

Keywords

neuropathic pain, painful neuropathy, pain relief, pharmacological treatment

Introduction

Painful neuropathy is used here to mean the neuropathic pain conditions associated with any peripheral neuropathy, with the exception of trigeminal neuralgia, which – although arising from damage to the primary sensory neuron – is unique in terms of its pain characteristics and treatment.

This review draws from previous studies addressing the problem of pathophysiology of pain in peripheral neuropathy and its treatment [1–3]. Confirming an old trend, from January 2006 to date diabetic polyneuropathy and postherpetic neuralgia have been the target of most treatment trials [4[•]–6[•]], with alcoholic polyneuropathy, carpal-tunnel syndrome, and HIV sensory neuropathy each having one randomized controlled trial (RCT) alone. Luckily the first comprehensive guidelines on pharmacological treatment of neuropathic pain [7^{••}] provide useful indications on how to manage painful neuropathy in general and constitute the basis of this review. In agreement with these guidelines, we believe that pathophysiological mechanisms are more important than etiology and thus, when the available data in a specific condition are few or weak, it is advisable to rely first on those drugs for which sound evidence was obtained in other conditions with similar pathophysiological mechanisms of pain.

This review only deals with pharmacological treatment because surgical interventions have established efficacy only in entrapment neuropathies and trigeminal neuralgia and because the complex field of neurostimulation procedures for neuropathic pain will soon be covered by dedicated guidelines.

First I report and comment on the most recently published trials, then I try to address issues that are being most debated, namely the role of opioids, the choice between tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitors (SNRIs), the difference between gabapentin and pregabalin, and, finally, the problem of combination therapy.

New findings

In painful neuropathies, the recent guidelines of the European Federation of Neurological Societies (EFNS) [7^{••}], which assessed publications up to 2005, found high-level evidence for four groups of drugs: opioids, tricyclic antidepressants, SNRI antidepressants, and pregabalin/gabapentin. In contrast, the antiarrhythmic mexiletine,

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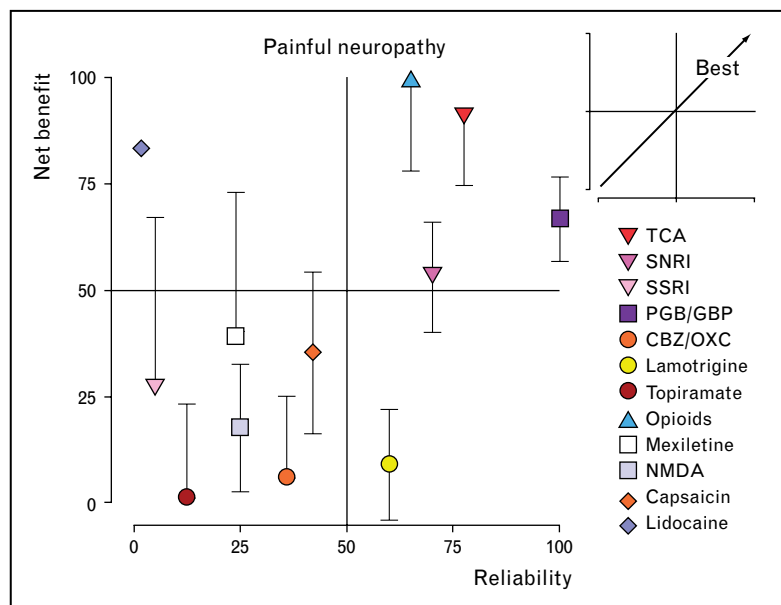
Abbreviations

EBM	evidence-based medicine
EFNS	European Federation of Neurological Societies
NMDA	<i>N</i> -methyl- <i>D</i> -aspartate
NNT	number-needed-to-treat
RCT	randomized controlled trial
SNRI	serotonin–noradrenaline-reuptake inhibitor

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Figure 1 The reliability and net benefit of treatments for painful neuropathies

On the *x* axis reliability provides a quantitative measure of the evidence, assessing both quality of the trials and their sample size; on the *y* axis net benefit calculates in one metric the advantage over placebo both as efficacy (proportion of patients with pain relief >50%) and tolerability (proportion of drop-outs due to adverse events). Methods are detailed in [8,9]. Drugs in the top right-hand quadrant provide the highest benefit and are supported by sound evidence. The diagram shows (normalized) results from 77 randomized controlled trials in 7716 patients with all kind of painful neuropathies with the exclusion of trigeminal neuralgia. Symbols indicate mean values \pm 95% confidence interval. TCA, tricyclic antidepressants; SNRI, serotonin–noradrenaline-reuptake inhibitors; SSRI, selective serotonin-reuptake inhibitors; PGB/GBP, pregabalin/gabapentin; CBZ/OXC, carbamazepine/oxcarbazepine; Opioids, strong and weak, including tramadol; NMDA, antagonists of the glutamate *N*-methyl-D-aspartate (NMDA) receptor; Capsaicin, cream; Lidocaine, patch.



antagonists of the *N*-methyl-D-aspartate (NMDA) receptor dextromethorphan and memantine, and the antiepileptic drugs topiramate and oxcarbazepine were either considered ineffective or insufficient evidence was provided. Lidocaine patches were indicated for the treatment of allodynia in postherpetic neuralgia [7^{••}]. Studies published afterwards confirm most of the above conclusions. Figure 1 [8,9] provides an up-to-date view of the comparative efficacy and reliability of the various drugs in painful neuropathy.

Four recent meta-analyses confirm the efficacy of strong (morphine, methadone, oxycodone) and weak (tramadol, codeine) opioids in painful neuropathy. Medium-term studies (1 month) demonstrated significant efficacy of opioids over placebo, which is likely to be clinically important; adverse events of opioids were common (11–33% drop-out rate) but not life-threatening [10^{••},11]. Tramadol was also effective, with a combined number-needed-to-treat (NNT) value (calculated as the reciprocal of the absolute risk reduction; the term indicates how many patients should be treated to obtain one responder improving >50%) of 3.8 [12[•]]. Besides opioid efficacy on spontaneous pain, oxycodone was also found to be effective in reducing allodynia in painful neuropathy [13[•]].

Regarding antidepressants, recent studies in painful neuropathy have concentrated on the action of the SNRI duloxetine. One new RCT, one meta-analysis, and three open-label, long-term studies [14[•],15[•],16,17] confirmed its efficacy, safety, and limitations. The efficacy was

moderately good (with NNT values of 3.9–6.5 in the new RCT) and the tolerability very good, but all previous and newer trials were on diabetic neuropathy only.

Among the antiepileptic drugs, while gabapentin and pregabalin continue to receive positive reports [18[•],19[•],20], the most important information regards lamotrigine. As with topiramate, which was eventually proved to be ineffective by high-quality studies in over 1200 patients with painful neuropathy [7^{••},8,21], now lamotrigine also appears to have failed to live up to its initial promise. Both recent RCTs in patients with diabetic neuropathy [22[•]] and a Cochrane systematic review on all kinds of neuropathic pain [23^{••}] concluded that lamotrigine, even at 300–400 mg/day, is no better than placebo in relieving pain and entails a significant risk of skin rash (about 7%).

Oxcarbazepine, a sodium-channel blocker which is as efficacious as carbamazepine in trigeminal neuralgia, keeps on scoring equivocal results in diabetic neuropathy: in a previous RCT it was only moderately effective [24], and in two recent RCTs it was effective only on some pain measures [25] or no better than placebo [26[•]].

There have been several other new studies regarding other drugs. It is worth mentioning those studies dealing with new drugs or with painful neuropathies other than diabetic or postherpetic neuropathies because in the last year there have been so few reports. Unfortunately there is no good news from new drugs. A new antagonist of the NK1 receptor for substance P was found to be no better

than placebo in diabetic neuropathy [27]. A chemical modification of the opioid peptide dynorphin A, which should prolong dynorphin's duration of action, did better than placebo in patients with postherpetic neuralgia, but only for the first 8 h [28].

The NMDA-receptor antagonist memantine was no better than placebo in HIV-associated neuropathy [29[•]]. Lidocaine 5% patches were significantly effective and slightly better than naproxen 500 mg twice daily in relieving pain in carpal-tunnel syndrome [30[•]]. In an RCT in over 300 patients with alcoholic polyneuropathy, treatment with B₁, B₂, B₆, B₉ and B₁₂ vitamins did better than placebo in several measures, including pain [31[•]]. Naturally vitamin B complex yields an analgesic effect only indirectly; thus the results from alcoholic neuropathy cannot be transferred to other neuropathies, as for α -lipoic acid in diabetic neuropathy [3,5[•]].

The problem with opioids

In contrast with the established notion that drugs acting on the opioid μ receptor are poorly effective in neuropathic pain, the amount of evidence nowadays available demonstrates that strong and weak opioids are indeed very effective in relieving neuropathic pain. Still, the EFNS guidelines [7^{••}] recommended them only as second-line therapy, because of two problems. One is quality of life: in the same trials that did so well on pain and which surprisingly produced so few side effects, the results on comorbidities and the overall quality of life were weak or not significant. The other problem with regard to risk – until we are provided with very long-term studies – is that in the long run tolerability decreases and tolerance/addiction develop. Further controlled trials are needed to establish long-term effects on quality of life and safety (including addiction potential) [10^{••}]. Methadone, for instance, has been increasingly used to manage neuropathic pain, but its use is causing an alarming number of deaths in the USA. According to the US National Center for Health Statistics, methadone was involved in more overdose deaths than any other prescription drug [32[•]]. Although methadone has several unique properties that can be beneficial in the treatment of neuropathic pain, some of these properties make it dangerous. As a result of these factors, methadone should not be the first-choice drug for pain [32[•]]. Although remembering the statement from the European recommendations that opioids should be considered for chronic noncancer pain as second-line therapy after other reasonable therapies fail [7^{••},33], in my opinion oxycodone and tramadol probably represent a fair compromise between power and safety.

Serotonin–noradrenaline-reuptake inhibitors compared with tricyclic antidepressants

The SNRI antidepressants duloxetine and venlafaxine are thought to be efficacious in neuropathic pain

because their action on serotonin and noradrenaline is balanced. This balance is optimal with daily doses of venlafaxine 225 mg and duloxetine 60 mg. Indeed the best results on pain are achieved with these doses (duloxetine 60 mg/day has similar efficacy to duloxetine 120 mg/day but is far more tolerable). The strength of the pain-relieving action is lower than that of tricyclic antidepressants, with a combined NNT value in painful neuropathies of about 5 for the two SNRIs and 2.3 for tricyclic antidepressants. Indeed, for this very reason, the EFNS guidelines recommended SNRIs as second-line treatment [7^{••}]. Hence, why or when should we prefer SNRIs? The whole question concerns tolerability and safety [15[•]]. Unfortunately, tricyclic antidepressants in elderly patients often provoke dizziness, sedation, orthostatic hypotension, dry mouth, and, most of all, constipation, to a level that may cause withdrawal (nortriptyline, with less-anticholinergic effects and sedation, is better tolerated than nonselective tricyclic antidepressants) [34]. Furthermore, tricyclic antidepressants are contraindicated in patients with glaucoma, prostate hypertrophy, or some cardiac conduction disturbances. Finally, a 2004 epidemiological study has raised concern about the association between tricyclic antidepressant treatment and sudden cardiac death, suggesting caution for older patients [35]. As a result, demonstrated by a survey in 1700 patients with painful neuropathy, older patients are currently being prescribed tricyclic antidepressants at daily doses that are far too low: on average 25 mg [36[•]].

Pregabalin compared with gabapentin

The specific mechanism of action of pregabalin on the α -2- δ subunit of the presynaptic Ca²⁺ channels has also been confirmed for gabapentin [37[•]]. On the basis of controlled studies of evidence-based medicine (EBM), pregabalin is indeed similar to gabapentin. It does not bring higher efficacy or tolerability. Hence, why should we prefer pregabalin? In this case the answer lies with the bad pharmacokinetic profile of gabapentin. Gabapentin was very popular among doctors who did not specialize in pain because of its excellent tolerability and lack of interactions with any other drug, which made its prescription safe. But gabapentin, with a pharmacokinetic profile which is nonlinear and very variable between subjects, is very unpredictable: it needs slow individual titration with initial doses of 300 mg/day (or less in elderly patients); some patients may have effects with 900 mg/day, whereas some need 3600 mg/day, which entails lengthy periods to establish whether a patient is a responder or not. Pregabalin has a linear pharmacokinetic profile, which makes the suggested dose (300 mg/day) and the dose increments meaningful and the results far more predictable. Furthermore, the onset of the pain-relieving action of

pregabalin is quicker, significant differences compared with placebo taking less than 1 week [7^{**},19^{*},20].

Combination therapy

Despite advances in the area, with new drugs and trials constantly being added to the list, still there is a gap in our ability to treat neuropathic pain. With respect to old drugs such as carbamazepine and amitriptyline, the new drugs seem to be designed for greater tolerability than for greater efficacy. A considerable number of patients do not get sufficient pain relief. In real life sufficient pain relief should probably be that which allows the patient to have a decent quality of life. In evidence-based studies on pain it is customary to consider responders to treatment as those patients who report a pain relief greater than 50%. On that basis, the evidence tells us that in painful neuropathies, regardless of type of pharmacological treatment, we are only able to succeed in 30–40% of patients [7^{**},38]. Hence it is natural to try combination therapy and we all do it in clinical practice.

Unfortunately there are too few controlled studies (complying with modern requirements for EBM) on combination therapy for neuropathic pain. We are aware of three studies only, all regarding the association of gabapentin, with venlafaxine, morphine, and oxycodone: all reported positive synergistic effects [39–41]. This is too little from which to draw any conclusions. For instance, a recent preclinical study demonstrated that venlafaxine, rather than adding to the effect of gabapentin, compromises its antiallostatic action [42^{*}].

Hence we must rely on good sense. Combination therapy should preferably use drugs with complementary mechanisms [43^{*}]. The synergistic interactions between opioids, antidepressants, and gabapentin/pregabalin are not only logical but also encouraged by results from preclinical studies [44–47]. Still, because many use combinations without direct evidence, controlled studies in patients are badly needed [7^{**}].

Conclusion

Four drug classes have shown strong evidence of being effective in painful neuropathy: opioids, tricyclic antidepressants, gabapentin/pregabalin, and SNRIs (listed in order of efficacy on pain). In choosing the individual treatment, however, many other considerations should be taken into account, including the cardiac risk with tricyclic antidepressants in older patients and the risk of tolerance/addiction in the long-term treatment with strong opioids.

Only 30–40% of patients are satisfactorily treated with monotherapy, but we lack controlled trials with polytherapy. The great majority of the available literature is

dedicated to diabetic neuropathy and postherpetic neuralgia. Because treatment choice depends more on pain pathophysiology than etiology, it is probably better to rely on well established compounds rather than on sparse reports in specific neuropathies.

Clearly we need more controlled studies on combination therapy and on painful neuropathies other than diabetic neuropathy and postherpetic neuralgia. The current feeling, however, is that these problems are going to be taken into account by both producers and investigators and we are moving towards a remarkable change of direction.

Meanwhile, because this review mostly adhered to EBM rules, leaving the readers with results for classes of drugs, and few practical indications, I would like to express my personal opinion on which drug and daily dose to prefer for each of the four classes that scored best: oxycodone 40 mg, nortriptyline 75 mg, pregabalin 300 mg, and duloxetine 60 mg.

References and recommended reading

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 602–604).

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