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Algorithm for neuropathic pain treatment: An evidence based proposal

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Abstract

New studies of the treatment of neuropathic pain have increased the need for an updated review of randomized, double-blind, placebo-controlled trials to support an evidence based algorithm to treat neuropathic pain conditions. Available studies were identified using a MEDLINE and EMBASE search. One hundred and five studies were included. Numbers needed to treat (NNT) and numbers needed to harm (NNH) were used to compare efficacy and safety of the treatments in different neuropathic pain syndromes. The quality of each trial was assessed. Tricyclic antidepressants and the anticonvulsants gabapentin and pregabalin were the most frequently studied drug classes. In peripheral neuropathic pain, the lowest NNT was for tricyclic antidepressants, followed by opioids and the anticonvulsants gabapentin and pregabalin. For central neuropathic pain there is limited data. NNT and NNH are currently the best way to assess relative efficacy and safety, but the need for dichotomous data, which may have to be estimated retrospectively for old trials, and the methodological complexity of pooling data from small cross-over and large parallel group trials, remain as limitations.

Keywords: Neuropathic pain; Pharmacological treatment; Algorithm; Number needed to treat

1. Introduction

Neuropathic pains are characterized by partial or complete somatosensory change in the innervation territory corresponding to peripheral or central nervous system pathology, and the paradoxical occurrence of pain and hypersensitivity phenomena within the denervated zone and its surroundings (Jensen et al., 2001). These sensory phenomena are seen across aetiologically different conditions and across different locations of the nerve lesion. Rarely, if ever, can one single mechanism be claimed responsible for generating and maintaining the symptoms and signs seen in neuropathic pain (Jensen and Baron, 2003; Woolf, 2004). Treatment of neuropathic pain is still difficult despite new treatments, and there is no single treatment that works for all conditions and their underlying mechanisms. Given the increasing evidence for effective treatments of neuropathic pain, it is important for the clinician to know which drugs are most effective in relieving pain and associated with the fewest adverse effects, and there is a need for an evidence-based algorithm to treat neuropathic pain conditions.

Ideally, the evidence for the drug choices in such an algorithm would be based on direct comparisons of one drug with another, for both efficacy and side effects. There are very few such direct comparisons available. An alternative approach is to estimate relative efficacy and safety using number needed to treat (NNT) and number needed to harm (NNH). Recent systematic reviews have summarized the available treatments for neuropathic pain using NNT values (McQuay et al., 1995; Sindrup and Jensen, 1999, 2000).

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However, these reviews need to be updated because of the publication of new trials, and the limitations of the NNT and NNH approach need to be discussed. This paper provides up-to-date calculations of NNT and NNH in neuropathic pain as the basis of a proposal for an evidence-based treatment algorithm.

2. Methods

2.1. Search strategy

Full reports of randomized placebo-controlled double-blind studies published in peer-reviewed journals were identified using free-text searches of MEDLINE (1966–April 2005), EMBASE (1974–April 2005), Cochrane Review, and Cochrane CENTRAL. Each drug was only searched by one author. Additional papers were identified from previous published reviews and reference lists of retrieved papers. Letters were sent to corresponding authors of papers that did not provide dichotomous data to ask if they could provide us with such data.

2.2. Selection criteria

Randomized double-blind studies in neuropathic pain conditions using chronic dosing and placebo studying at least 10 patients were included. Studies not written in English were excluded. Studies on cancer neuropathic pain were also excluded except for well-defined post-mastectomy pain syndromes and post-surgical pain with post-operative pain compatible with a nerve section.

2.3. Data abstraction, quality assessment, and quantitative data synthesis

From each study we extracted information on study design, inclusion and exclusion criteria, number of participants, drug dose, randomization and blinding procedure, description of dropouts, change in primary outcome measure, and pain relief during active and placebo treatment.

Number needed to treat was the principal effect measure. NNT is defined as the number of patients needed to treat with a certain drug to obtain one patient with a defined degree of pain relief, in the present context 50% pain relief, and is calculated as the reciprocal of the absolute risk difference (Cook and Sackett, 1995; McQuay et al., 1996). If 50% pain relief could not be obtained directly from the publication, then the number of patients reporting at least good pain relief or reporting improvement was used to calculate NNT. NNT was only calculated when the relative risk was statistically significant. NNH in this review indicates the number of patients that need to be treated for one patient to drop out due to adverse effects. The 95% confidence interval (CI) of NNT and NNH was calculated as the reciprocal value of the 95% CI for the absolute risk difference using the normal approximation. NNTs are expressed in the text as NNT (95% CI). Pooled raw data was used to obtain combined measures of NNTs assuming clinically homogeneous trials (Moore et al., 2002).

The outcome of a trial (positive or negative) was judged by the reviewers in those cases where authors' conclusions were at odds with the change in the primary outcome measure.

Heterogeneity was examined visually using L'Abbé plots (L'Abbé et al., 1987). An instrument suggested by Jadad et al. (1996) was used as a measure of quality. Validity tests (e.g. Smith et al., 2000) were not used.

3. Results

3.1. Study and patients characteristics of included trials

Eligible randomized placebo-controlled trials with references, study characteristics, and quality score are provided in Table 2. One hundred and five randomized, double-blind, placebo-controlled studies that met the inclusion and exclusion criteria were included. Fifty-nine used a cross-over and 46 a parallel design. Five studies used an active placebo. Twenty-six trials examined antidepressants (21 cross-over and five parallel design), 39 anticonvulsants (18 cross-over and 21 parallel design), 11 examined opioids, seven NMDA antagonists, nine mexiletine, four topical lidocaine, three cannabinoids, 11 capsaicin, and one a glycine antagonist. The trials included patients with central post-stroke pain, spinal cord injury pain, multiple sclerosis, painful polyneuropathy, post-herpetic neuralgia, phantom limb pain, post-mastectomy and post-surgical pain, brachial plexus avulsion, trigeminal neuralgia, HIV-neuropathy, and mixed neuropathic pain conditions. The trials are discussed below by drug class.

3.2. Antidepressants

Tricyclic antidepressants (TCAs) in controlled trials (Table 2) relieve central post-stroke pain, post-herpetic neuralgia, painful diabetic and non-diabetic polyneuropathy and post-mastectomy pain syndrome, but not spinal cord injury pain, phantom limb pain, or pain in HIV-neuropathy. The doses used in these negative trials may make these conclusions less compelling. Negative results in spinal cord injury pain could be related to low dosing (amitriptyline average 55 mg/day) (Cardenas et al., 2002), and those in phantom limb pain by a very low inclusion pain score criteria (2) which gives little room for pain reduction (Robinson et al., 2004). Across the different conditions which are relieved by TCAs the NNT ranges from 2 to 3.

In painful polyneuropathy, there is a trend towards better effect of balanced serotonin and noradrenaline reuptake inhibitors (NNT: 2.1 (1.8–2.6)) than of the mainly noradrenergic drugs (NNT: 2.5 (1.9–3.6)) (Sindrup et al., 2005). In post-herpetic neuralgia there is the same trend

(balanced TCA NNT: 2.5 (1.8–3.9) vs noradrenergic TCA NNT: 3.1 (2.2–5.5)).

The selective serotonin reuptake inhibitors (SSRIs) and the mixed serotonin noradrenaline reuptake inhibitors (SNRIs) have been adequately tested in painful polyneuropathy. For SSRIs, the overall NNT is nearly 7 and one of the three trials did not find better effect with active than placebo. The SNRI venlafaxine has an NNT in painful polyneuropathies of around 4. Bupropion, a noradrenaline and dopamine reuptake inhibitor, was reported-in a small trial of 41 patients—to relieve pain in a group of patients with neuropathic pain of different etiologies.

The NNH is 14.7 (10.2–25.2) for TCA, and for SNRI and SSRI the relative risk for trial withdrawal is not significant.

3.3. Anticonvulsants

The early trials on carbamazepine do not meet current methodological standards (e.g. use of validated outcome measures, sample size calculation, and adequate description of randomization procedure, statistical methods, and patient flow), but an attempt to calculate NNT gives a combined NNT in trigeminal neuralgia of 1.7 (1.3–2.2). In painful diabetic neuropathy, the NNT from one trial with 30 patients on 200–600 mg daily was 2.3 (1.6–3.9) and in post-stroke pain there was a small but not statistically significant effect of 800 mg daily with a NNT of 3.4 (1.7–105). The combined NNH for carbamazepine in neuropathic pain is 21.7 (12.6–78.5), based on a total of 152 patients. Randomized controlled trials comparing oxcarbazepine to carbamazepine have reported comparable analgesic effect between the two treatments with fewer side effects during oxcarbazepine (for review, see Beydoun and Kutluay (2002), Carrazana and Mikoshiba (2003)), but these trials have not yet been published fully.

Phenytoin had a positive effect on painful diabetic neuropathy in one trial (NNT: 2.1 (1.5–3.6)), while another showed no analgesic effect. In patients with acute flare-ups of various neuropathic pain conditions intravenous phenytoin 15 mg/kg over 2 h had a significant pain-relieving effect (McCleane, 1999a).

Valproate in three parallel group trials from the same centre with 43–57 patients had high efficacy in relieving pain in painful diabetic neuropathy and post-herpetic neuralgia in doses up to 1200 mg with very low NNTs, while a crossover trial of 31 patients from another centre found no difference between valproate 1500 mg and placebo in treating painful polyneuropathy and also showed no effect in the subgroup of patients with diabetic neuropathy. Valproate in doses up to 2400 mg/day was not significantly better than placebo in relieving pain in patients with spinal cord injuries.

Gabapentin has been studied in several large trials and has a documented moderate effect on pain and quality of life measures including mood and sleep disturbance in mixed neuropathic pain states, post-herpetic neuralgia, painful diabetic neuropathy, and spinal cord injury. The overall NNT for gabapentin in neuropathic pain, including all conditions, high as well as low doses, is 5.1 (4.1–6.8), but by excluding the study using only 900 mg/day, the study on mixed neuropathic pain, and including only the high dose of 2400 mg in Rice and Maton (2001), the combined NNT is 3.8 (3.1–5.1). The NNH for withdrawal for gabapentin is 26.1 (14.1–170). One small crossover study (19 completed patients) compared gabapentin (up to 1800 mg) with amitriptyline (up to 75 mg) in painful diabetic neuropathy (Morello et al., 1999). There was no significant difference in pain scores during gabapentin and amitriptyline treatment, pain intensity score change from baseline, and global ratings of pain relief (52% with at least moderate pain relief during gabapentin and 67% during amitriptyline) ($P > 0.1$). Both treatments caused similar rates of adverse events. Post hoc analysis revealed that a sample size of approximately 260 patients is necessary to provide 80% power to detect a mean difference of one third of the difference between mild and moderate pain at a 0.05 significance level.

The efficacy of gabapentin in combination with venlafaxine was studied in painful diabetic neuropathy (Simpson, 2001). In the second part of the study including 12 patients who did not respond to gabapentin, gabapentin plus venlafaxine improved pain and quality of life compared with gabapentin plus placebo. In another study, the combination of gabapentin and morphine was superior to gabapentin alone, morphine alone and the active placebo lorazepam in patients with post-herpetic neuralgia or painful diabetic neuropathy (Gilron et al., 2005).

Pregabalin in post-herpetic neuralgia and painful diabetic neuropathy has a combined NNT for doses ranging from 150 to 600 mg of 4.2 (3.4–5.4), comparable to the effect of gabapentin. The NNH for withdrawal was 11.7 (8.3–19.9) indicating a relatively high withdrawal rate (see Section 4).

Lamotrigine up to 400 mg daily has a pain relieving effect in trigeminal neuralgia as an add-on treatment (NNT: 2.1 (1.3–6.1)), in painful diabetic neuropathy (NNT: 4.0 (2.1–42)), and in central post-stroke pain. In HIV-associated painful sensory neuropathy, a small study showed a significant effect of lamotrigine 300 mg daily, but an extended larger study using 600 mg daily only demonstrated an effect on some secondary parameters in those patients receiving neurotoxic antiretroviral therapy. In spinal cord injury pain lamotrigine had no effect, although it had an effect on spontaneous pain in a subgroup of patients with incomplete injury and evoked pain.

Topiramate in doses up to 400 mg failed to relieve pain in three large trials including in total 1259 patients with painful diabetic neuropathy, while another trial found a significant effect (NNT: 7.4 (4.3–28.5)). The four topiramate studies had a high withdrawal rate due to side effects (NNH: 6.3 (5.1–8.1)).

3.4. Opioids

Intravenous opioid administration has been shown to have an effect on peripheral neuropathic pain (Rowbotham et al., 1991), on mixed neuropathic pain conditions (Dellemijn and Vanneste, 1997), and on some components of central pain (Attal et al., 2002). Oral long-term treatment with opioids, more relevant in chronic pain than intravenous administration, has only been tested using placebo-controlled designs in peripheral neuropathic pain conditions (Table 2).

Morphine was superior to placebo in patients with post-herpetic neuralgia, phantom limb pain, and painful diabetic neuropathy with an NNT of 2.5 (CI 1.9–3.4).

Oxycodone has been tested in post-herpetic neuralgia and painful diabetic neuropathy, with a NNT of 2.6 (CI 1.9–4.1), comparable to the effect of morphine.

Tramadol studied in two trials in painful polyneuropathy and in one trial in post-herpetic neuralgia had an overall NNT of 3.9 (CI 2.7–6.7). The study in post-herpetic neuralgia (Boureau et al., 2003) had a very high placebo responder rate.

The combined NNH was 9.0 (6.0–17.5) for tramadol, whereas the relative risk was non-significant for oxycodone and morphine.

3.5. NMDA antagonists

NMDA antagonists given as intravenous infusions may relieve neuropathic pains of different origin (Sang et al., 2000). Oral NMDA antagonists, dextromethorphan, riluzole and memantine have been studied mainly in small trials in neuropathic pain, with either no or minor pain relieving effect (Table 2). High dose dextromethorphan apparently has a clinically relevant effect in painful diabetic polyneuropathy (NNT: 2.5 (1.6–5.4)), but seems to lack efficacy in post-herpetic neuralgia. Memantine in doses 20–30 mg/day had no effect in post-herpetic neuralgia, painful diabetic neuropathy or phantom limb pain. Patients with different types of neuropathic pain achieved no pain relieving effect using riluzole 100 or 200 mg/day.

The NNH for dextromethorphan is 8.8 (5.6–21.1) and non-significant for memantine.

3.6. Miscellaneous

Mexiletine studies have inconsistent results. The overall relative risk in two studies in painful diabetic neuropathy is non-significant and in peripheral nerve injury the NNT is 2.2 (1.3–8.7)). Mexiletine seems to lack a pain relieving effect in HIV neuropathy, spinal cord injury, and neuropathic pain with prominent allodynia. Mexiletine has proarrhythmic properties and side effects may limit dose escalation, but it was generally well tolerated in these studies with only mild side effects (gastrointestinal and neurological complaints) and surprisingly high NNHs for withdrawal. A new sodium channel antagonist 4030W92 had no significant effect on neuropathic pain at 25 mg/day, but higher doses may be tolerable (Wallace et al., 2002a).

Topical lidocaine has been shown to reduce pain in patients with post-herpetic neuralgia and allodynia. Severity of allodynia seems not to be correlated with response to lidocaine patch. The patch has been shown to alleviate several pain qualities including non-allodynic pain components (Galer et al., 2002). An enriched enrolment study confirmed the pain relieving effect (Galer et al., 1999). The use of lidocaine patches was safe with no systemic adverse effects and high NNHs. In patients with various localized peripheral neuropathic pain syndromes including the presence of mechanical allodynia, lidocaine patch 5% as add-on therapy reduced ongoing pain and allodynia with a NNT of 4.4 (2.5–17.5). Ophthalmic anaesthesia with topical application of proparacaine, however, failed to relieve pain in trigeminal neuralgia (Kondziolka et al., 1994).

Cannabinoids have recently been studied in a few randomized trials. The tetrahydrocannabinol dronabinol 5–10 mg daily relieved pain in multiple sclerosis with a NNT of 3.4 (1.8–23.4) compared with placebo, and cannabinoids also relieved pain after brachial plexus avulsion and mixed neuropathic pain. Cannabinoids were generally well tolerated with gradually increasing doses.

Capsaicin applied topically relieved pain in post-herpetic neuralgia, nerve injury pain, and mixed neuropathic pain conditions and in diabetic neuropathy capsaicin relieved pain in three out of five studies, with a combined NNT of 6.7 (4.6–12) and NNH of 11.5 (8.1–19.8).

3.7. Quantitative data synthesis and homogeneity/heterogeneity

Combined NNTs and NNHs for different drug classes and neuropathic pain conditions are shown in Table 1 and Fig. 1. Heterogeneity was examined visually using L'Abbé plots (supplementary material). From dose response studies (Lesser et al., 2004; Oskarsson et al., 1997; Rice and Maton, 2001; Richter et al., 2005; Rowbotham et al., 2004; Sabatowski et al., 2004), it is evident that dose optimization and lack of such is a major cause of heterogeneity. In addition, L'Abbé plots suggest that both the drug classes used and the neuropathic pain diagnoses were other major reasons for heterogeneity, with studies in HIV neuropathy, central and mixed neuropathic pain conditions showing the lowest effect. The greatest variation was in NNT values within TCAs. Again differences in neuropathic pain diagnoses seemed to be responsible for part of this variability and optimal dosing by drug level measurements may be responsible for one outlier with a high percentage of responders. Excluding gabapentin non-responders in gabapentin/pregabalin studies and variability in quality score (Jadad et al., 1996) seemed not to be responsible for outliers. The placebo response varied greatly among trials (figure in supplementary material). Smaller cross-over trials tended to have lower NNT values (thus greater treatment effect) than

Table 1
Combined numbers needed to treat (with 95% confidence interval) to obtain one patient with more than 50% pain relief

	Neuropathic pain[a]	Central pain	Peripheral pain	Painful polyneuropathy	Post-herpetic neuralgia	Peripheral nerve injury	Trigeminal neuralgia	HIV neuropathy	Mixed neuropathic pain	NNH in neuropathic pain
Antidepressants										
TCA	3.1 (2.7–3.7)	4.0 (2.6–8.5)	2.3 (2.1–2.7)	2.1 (1.9–2.6)	2.8 (2.2–3.8)	2.5 (1.4–11)	ND	ns	NA	14.7 (10–25)
SSRI	6.8 (3.4–441)	ND	6.8 (3.4–441)	6.8 (3.4–441)	ND	ND	ND	ND	ND	ns
SNRI	5.5 (3.4–14)	ND	5.5 (3.4–14)	5.5 (3.4–14)	ND	NA	ND	ND	ND	ns
DNRI	1.6 (1.3–2.1)	ND	ND	ND	ND	ND	ND	ND	1.6 (1.3-2.1)	ns
Antidepressants	3.3 (2.9–3.8)	4.0 (2.6–8.5)	3.1 (2.7–3.7)	3.3 (2.7–4.1)	2.8 (2.2–3.8)	2.5 (1.4–11)	ND	ns	1.6 (1.3–2.1)	16.0 (12–25)
Anticonvulsants										
Carbamazepine	2.0 (1.6–2.5)	3.4 (1.7–105)	2.3 (1.6–3.9)	2.3 (1.6–3.9)	ND	ND	1.7 (1.3–2.2)	ND	NA	21.7 (13–79)
Phenytoin	2.1 (1.5–3.6)	ND	2.1 (1.5–3.6)	2.1 (1.5–3.6)	ND	ND	ND	ND	ND	ns
Lamotrigine	4.9 (3.5–8.1)	ns	4.0 (2.1–42)	4.0 (2.1–42)	ND	ND	2.1 (1.3–6.1)	5.4 (3.1–20)	ns	ns
Valproate	2.8 (2.1–4.2)	ns	2.4 (1.8–3.4)	2.5 (1.8–4.1)	2.1 (1.4–4.2)	ND	ND	ND	ND	ns
Gabapentin, pregabalin	4.7 (4.0–5.6)	NA	4.3 (3.7–5.2)	3.9 (3.2–5.1)	4.6 (3.7–6.0)	NA	ND	ND	8.0 (4.8–24)	17.8 (12–30)
Topiramate	7.4 (4.3–28)	ND	7.4 (4.3–28)	7.4 (4.3–28)	ND	ND	NA	ND	ND	6.3 (5–8)
Anticonvulsants	4.2 (3.8–4.8)	ns	4.1 (3.6–4.8)	3.9 (3.3–4.7)	4.4 (3.6–5.6)	NA	1.7 (1.4–2.2)	5.4 (3.1–20)	10.0 (5.9–32)	10.6 (9–13)
Opioids										
Opioids	2.5 (2.0–3.2)	ND	2.7 (2.1–3.6)	2.6 (1.7–6.0)	2.6 (2.0–3.8)	3.0 (1.5–74)	ND	ND	2.1 (1.5–3.3)	17.1 (10–66)
Tramadol	3.9 (2.7–6.7)	ND	3.9 (2.7–6.7)	3.5 (2.4–6.4)	4.8 (2.6–27)	ND	ND	ND	ND	9.0 (6–18)
NMDA antagonists										
Dextromethorphan	4.4 (2.7–12)	ND	3.4 (2.2–7.6)	2.5 (1.6–5.4)	ns	ND	ND	ND	ns	8.8 (6–21)
Memantine	ns	ND	ns	ns	ns	ns	ND	ND	ND	ns
NMDA antagonists	7.6 (4.4–27)	ND	5.5 (3.4–14)	2.9 (1.8–6.6)	ns	ns	ND	ND	ns	12.5 (8–36)
Various										
Mexiletine	7.8 (4.0–129)	NA	5.2 (2.9–26)	ns	ND	2.2 (1.3–8.7)	ND	ns	NA	ns
Topical lidocaine	4.4 (2.5–17)	ND	NA	ND	NA	ND	ND	NA	4.4 (2.5–17)	ns
Cannabinoids	ns	3.4 (1.8–23)	ND	ND	ND	ND	ND	ND	9.5 (4.1–∞)	ns
Topical capsaicin	6.7 (4.6–12)	ND	6.7 (4.6–12)	11 (5.5–317)	3.2 (2.2–5.9)	6.5 (3.4–69)	ND	NA	NA	11.5 (8–20)

NNH, combined numbers needed to harm (95% confidence interval) to obtain one patients to withdraw because of side effects. TCA, tricyclic antidepressants; SNRI, serotonin noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; DNRI, dopamine noradrenaline reuptake inhibitors; ND, no studies done; NA, dichotomized data are not available; ns, relative risk not significant.

[a] Heterogeneity across different pain conditions.

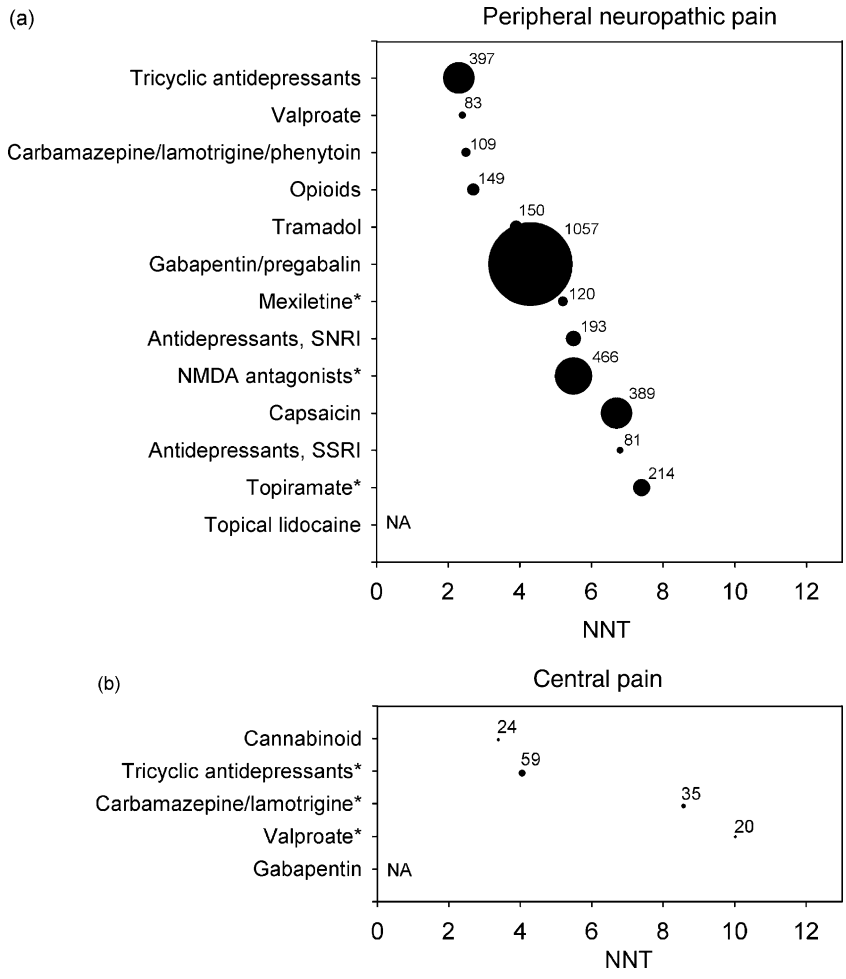

Fig. 1. Numbers needed to treat in peripheral and central neuropathic pain. Combined numbers needed to treat (NNT) to obtain one patient with more than 50% pain in (a) peripheral neuropathic pain (painful polyneuropathy, postherpetic neuralgia, and peripheral nerve injury pain) and (b) central pain (central post-stroke pain, pain following spinal cord injury and multiple sclerosis). SNRI, serotonin noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor. Circle size and related numbers indicate number of patients who have received active treatment. *At least half of conducted trials showed no significant effect.

larger parallel group trials. The differences in NNT values based on the intention-to-treat population as opposed to the completed population can be estimated by calculating NNTs in studies with a parallel group design and comparing it with the NNT using the completed population. This is, however, not possible based on the reports, as most studies carry forward the pain ratings for patients who do not complete the study, and use these data in the analysis. But based on the 'worst case', i.e. assuming that all patients withdrawn are non-responders, the NNT for pregabalin based on the completed population is 3.4 (2.7–4.3) compared with 4.2 (3.4–5.4) based on the intention-to-treat population.

4. Discussion

4.1. Numbers needed to treat and harm

This meta-analysis using numbers needed to treat (NNT) shows that it is possible to distinguish pharmacological treatment efficacy for different drugs as evidenced by NNT values which varied from 1.2 to non-significant relative risks. The question is whether the NNT method permits generation of a treatment algorithm for neuropathic pain.

The NNT method for comparing drugs can be criticized for various reasons:

1. The relative efficacy and safety is derived from placebo comparisons of each active drug. Trials which do not compare with placebo are therefore excluded.
2. Calculation of NNT is done retrospectively from studies with different cut-off points for defining pain relief.
3. Pain relief per se may be a crude measure, which does not take other specific measures into account like impact on daily living and quality of life.
4. Use of different inclusion and exclusion criteria makes it difficult to compare and to combine studies.
5. NNT values cannot be calculated when conversion to dichotomous data is not possible.

6. As for all meta-analyses there is a risk that NNT values will overestimate the efficacy if negative trials are not published.

The advantage of using NNTs is that they provide a clinically meaningful measure of effect and risk of each drug, and data from different trials, even with different outcome measures, can be pooled. The legitimacy of the pooling depends on similar therapeutic context, patients, duration of study, and clinical homogeneity.

It is important to bear in mind that some of these NNT values in neuropathic pain are obtained from studies of variable quality and most available studies are short-term studies with no information on long-term effect.

The choice of a 33 or 50% cutoff when calculating NNTs has little impact on NNT values because efficacy of both active and placebo treatments changes (McQuay and Moore, 1998).

In the present analysis, calculation of NNH was based on patients that withdrew from the study because of adverse effects, and we have not included other side-effects that may be bothersome for long-term treatment, e.g. constipation and dizziness. The design itself may influence the NNH value. A compound with a high NNH value from a short lasting trial may still be unsuitable for long-term use. An example is chronic phenytoin treatment causing gingival hyperplasia, hirsutism, polyneuropathy and hepatotoxicity (Rogvi-Hansen and Gram, 1995). Compounds may also cause serious side effects not reflected in the NNH value, e.g. sudden death associated with TCA (Ray et al., 2004) or Stevens-Johnson syndrome after treatment with lamotrigine (Mackay et al., 1997).

4.2. Quality of randomized controlled trials

Quality of trials varies for obvious reasons and the variation in quality may lead to bias in meta-analyses (Alderson et al., 2003; Detsky et al., 1992; Moher et al., 1999) and existing criteria have their limitations. It is possible that we had obtained other results if more stringent quality and validity criteria were used (Detsky et al., 1992; Smith et al., 2000).

4.3. Heterogeneity and selection bias

The major cause of heterogeneity was dose, pain diagnosis, and study design, with small, cross-over trials having the lowest NNT values. There was also a large variation in placebo response among studies.

Some of the studies on gabapentin and pregabalin excluded patients who failed to respond to previous treatment with gabapentin, which may bias efficacy comparisons with other drugs using NNT values. Calculating the impact of this enriched enrolment on the overall NNT, taking the worst case scenarios, the NNT for pregabalin is 5.4 (4.3–7.1) compared to 4.2 (3.4–5.4). However, a recent trial showed an NNT of 4.2 (2.7–9.4) without excluding gabapentin non-responders (Richter et al., 2005).

Combining cross-over and parallel designed studies in meta-analyses is another concern (Elbourne et al., 2002), and the generally lower NNT value with the tricyclic antidepressants may in part be due to the fact that 19/23 trials were cross-over trials compared to 2/12 of the gabapentin/pregabalin trials.

Selection bias may be present and includes publication bias, which arises from higher tendency for studies with a statistically significant effect of treatment to be published thereby introducing bias in meta-analyses (Moher et al., 1999). We have no direct evidence that this problem applies to this data set, and indeed there are a number of negative studies included in the analysis.

4.4. Treatment algorithm

Based on the available randomized clinical trials, it is of interest to see if an evidence-based approach for managing neuropathic pain is possible. In choice of treatment for neuropathic pain a set of different criteria are relevant including:

1. Consistent outcome in high-quality randomized controlled trials.
2. High degree of pain relief and superiority to existing treatments.
3. Persistent pain relieving effect.
4. Few and only mild side effects.
5. Effect on quality of life.
6. Low cost.

Because of heterogeneity across treatment of different pain conditions, algorithms need to be tailored to specific diseases or disease categories.

There are no existing data which permit generation of an algorithm based on a combination of all the above criteria mainly because of a lack of comparative studies between existing and new compounds using the same set of primary and secondary endpoints.

A treatment algorithm for peripheral neuropathic pain (painful neuropathy, painful diabetic neuropathy, postherpetic neuralgia and peripheral nerve injury pain) is described below. The algorithm deals only with pharmacological considerations. Needless to say for all pain conditions, non-pharmacological treatments should be considered. The algorithm can be described in a hierarchical fashion in which increasing numbers of criteria are taking into account:

If only one set of criteria: pain relief is used then the list of drugs for neuropathic pain look like this: TCA > opioids ≥ tramadol ≥ gabapentin/pregabalin.

If the criteria for efficacy are based on both pain relief and quality of life measures then such data are not existent

for several of the old compounds such as TCA, carbamazepine, and phenytoin and the list is likely to look as follows: gabapentin/pregabalin > tramadol > opioids > TCA.

If additional requirements such as side effects and study design are taken into account then important and occasionally dangerous side effects of TCA and strong opioids need to be considered. Under these conditions the algorithm for peripheral neuropathic pain may be as shown in Fig. 2. The effect of gabapentin and TCAs are documented in large and numerous trials with good quality and with consistent outcomes. One small trial compared gabapentin and amitriptyline and found no difference in pain scores (Morello et al., 1999). TCAs have lower NNT values than gabapentin/pregabalin but as discussed above part of this difference may be due to differences in study design. Furthermore, as gabapentin/pregabalin have higher NNH values and lack serious adverse effects it thus seems reasonable to have these two drug classes as first line treatment of peripheral neuropathic pain. As new studies on SNRIs (with fewer side effects than TCAs) are emerging, these drugs may replace TCAs. Tramadol and oxycodone may be considered second or third line drugs. The NNT values are for these and other opioids low, and a direct comparison study show equal or slightly better effect of morphine compared to gabapentin (Gilron et al., 2005). Anxieties about dependence, cognitive impairment, and tolerance issues, although there is no hard evidence for such problems, may make opioids a less attractive choice. Combination of drugs targeting separate mechanisms theoretically may improve treatment, but, except for the combination of gabapentin with venlafaxine or morphine, evidence for this is still lacking.

In trigeminal neuralgia, carbamazepine is suggested as first choice because of consistent outcome with a low NNT, although in studies of varying quality. Oxcarbazepine (as yet no published trials) may be an alternative.

In central pain few studies exist and it is unknown whether an effective treatment in one central pain condition can be expected to be effective in other central pain conditions. Therefore, a treatment algorithm in these pain conditions needs to be based partly on the experience in peripheral neuropathic pain conditions, until further studies arise. TCAs are often not tolerated in the elderly patients with stroke, so, in these cases, gabapentin/pregabalin seems to be first choice. TCAs, lamotrigine, cannabinoids, tramadol, and opioids may be second choice.

For future trials, we encourage authors to:

(1) report the trial to a central database (DeAngelis et al., 2004);
(2) to follow Good Clinical Practice (GCP) requirements (ICH, 1997; Jorgensen et al., 2004);
(3) to follow the guidelines in the consort statement (Moher et al., 2001);
(4) to do more head-to head comparisons.

The relative efficacy rank order obtained by the NNT method agree to some extent with the few head-to-head comparisons performed in neuropathic pain (Gilron et al., 2005; Morello et al., 1999; Raja et al., 2002; Sindrup et al., 2003), but to look for subtle differences head-to-head comparisons are needed. Furthermore, it may be inappropriate to use of placebo in severe pain, for instance in trigeminal neuralgia, making it difficult to obtain relative efficacy estimates based on placebo comparisons. This

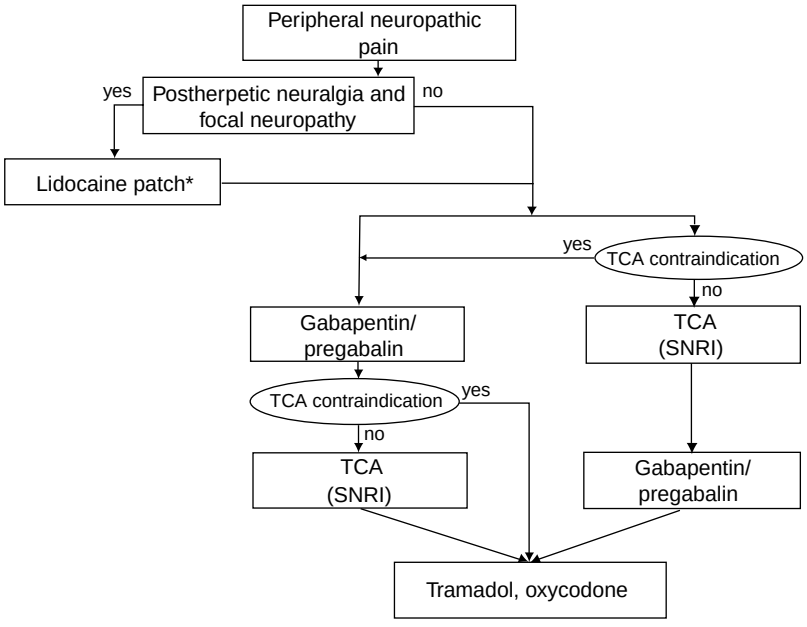

Fig. 2. Treatment algorithm. Proposed algorithm for the treatment of peripheral neuropathic pain. TCA, tricyclic antidepressants; SNRI, serotonin noradrenaline reuptake inhibitors. *Pain relieving effect of topical lidocaine has been shown in patients with allodynia.

Table 2
Randomized, double-blind, placebo-controlled trials of different drugs in various neuropathic pain conditions

Active drug daily drug dose	Study quality rating	Design patient nos	Outcome	Pain relief		NNT (95% CI)	Drop outs side effects		NNH (95% CI)
				Active	Placebo		Active	Placebo	
Antidepressants									
Central post-stroke pain									
Amitriptyline, 75 mg	Leijon and Boivie, 1989, 4	Cross-over, 15	Ami > pla	10/15	1/14	1.7 (1.2–3.1)	0/15	0/15	ns
Spinal cord injury pain									
Amitriptyline, average 50 mg	Cardenas et al., 2002, 4	Parallel, 84	Ami = pla	8/44	2/40	ns	7/44	2/40	ns
Painful polyneuropathy									
Imipramine, 100 mg	Kvinesdal et al., 1984, 4	Cross-over, 12	Imi > pla	7/12	0/12	1.7 (1.2–3.3)	1/13	0/13	ns
Nortriptyline, 30 mg	Gomez-Perez et al., 1985, 4	Cross-over, 18	Nor > pla	16/18	1/18	1.2 (1.0–1.5)	0/18	0/18	ns
Amitriptyline, average 90 mg	Max et al., 1987, 4	Cross-over, 29	Ami > pla	15/29	1/29	2.1 (1.5–3.5)	3/32	2/31	ns
Imipramine, average 200 mg	[a]Sindrup et al., 1990a, 4	Cross-over, 20	Imi > pla	17/19	3/20	1.3 (1.0–1.9)	7/29	0/20	4.1 (2.5–11.7)
Clomipramine, 75 mg	[a]Sindrup et al., 1990b, 4	Cross-over, 19	Clo > pla	10/19	1/19	2.1 (1.4–4.4)	3/24	0/20	ns
Desipramine, 200 mg	[a]Sindrup et al., 1990b, 4	Cross-over, 19	Des > pla	7/19	1/19	3.2 (1.8–13.0)	3/23	0/20	ns
Desipramine, average 201 mg	Max et al., 1991, 3	Cross-over, 20	Des > pla	11/20	2/20	2.2 (1.4–5.1)	2/24	1/24	ns
Imipramine, 150 mg	[a]Sindrup et al., 1992a, 4	Cross-over, 18	Imi > pla	8/18	2/18	3.0 (1.7–16.2)	1/22	0/20	ns
Amitriptyline, 75 mg	Vrethem et al., 1997, 4	Cross-over, 33	Ami > pla	22/33	8/33	2.4 (1.6–4.8)	3/36	0/33	ns
Maprotiline, 75 mg	Vrethem et al., 1997, 4	Cross-over, 33	Map > pla	14/33	8/33	ns	1/34	0/33	ns
Imipramine, 150 mg	Sindrup et al., 2003, 5	Cross-over, 29	Imi > pla	14/29	2/29	2.4 (1.6–4.8)	0/37	2/40	ns
Paroxetine, 40 mg	[a]Sindrup et al., 1990a, 4	Cross-over, 20	Par > pla	10/20	3/20	2.9 (1.6–12.4)	0/20	0/20	ns
Fluoxetine, 40 mg	Max et al., 1992, 3	Cross-over, 46	Flu = pla	22/46	19/46	ns	3/54	2/54	ns
Citalopram, 40 mg	Sindrup et al., 1992b, 4	Cross-over, 15	Cit > pla	3/15	1/15	ns	2/18	0/18	ns
Venlafaxine, 225 mg	Sindrup et al., 2003, 5	Cross-over, 30	Ven > pla	8/30	2/29	5.1 (2.6–68.8)	4/40	2/40	ns
Venlafaxine, 75–225 mg	Rowbotham et al., 2004, 4	Parallel, 244	Ven > pla	78/163	27/81	6.9 (3.7–58.6)	14/163	3/81	ns
St. John's Wort	Sindrup et al., 2000, 5	Cross-over, 47	SJW = pla	9/47	2/47	6.7 (3.6–44.4)	1/50	1/52	ns
Postherpetic neuralgia									
Amitriptyline, average 73 mg	Watson et al., 1982, 4	Cross-over, 24	Ami > pla	16/24	1/24	1.6 (1.2–2.4)	1/24	0/24	ns
Amitriptyline, average 65 mg	Max et al., 1988, 3	Cross-over, 34	Ami > pla	15/34	5/25	4.1 (2.1–82.1)	5/35	3/30	ns
Desipramine, average 167 mg	Kishore-Kumar et al., 1990, 3	Cross-over, 19	Desi > pla	12/19	2/19	1.9 (1.3–3.7)	5/23	3/21	ns
Nortriptyline, average 89 mg	[a]Raja et al., 2002, 5	Cross-over, 56	TCA > Pla	18/56	4/57	4.0 (2.6–8.9)	7/59	1/57	9.9 (5.3–84.6)
Desipramine, average 63 mg									
Phantom limb pain									
Amitriptyline, 10–125 mg	Robinson et al., 2004, 4	Parallel, 39	Ami = pla	NA	NA	NA	2/20	0/19	ns
Postmastectomy pain									
Amitriptyline, 100 mg	[a]Kalso et al., 1995, 3	Cross-over, 15	Ami > pla	8/15	2/15	2.5 (1.4–10.6)	4/20	0/20	5 (2.7–40.5)
Venlafaxine, 37.5–75 mg	Tasmuth et al., 2002, 4	Cross-over, 13	Ven = pla	11/13	NA	NA	1/15	0/13	ns
HIV-neuropathy									
Amitriptyline, 25–100 mg	Kieburtz et al., 1998, 5	Parallel, 98	Ami = pla	23/46	24/50	ns	3/46	1/50	ns
Amitriptyline, 25–75 mg *Mixed patients*	Shlay et al., 1998, 4	Parallel, 110	Ami = pla	27/58	24/50	ns	NA	NA	NA
Clomipramine, 25–100 mg	Panerai et al., 1990, 3	Cross-over, 24	Clo > pla	NA	NA	NA	0/27	1/27	ns
Nortriptyline, 25–100 mg	Panerai et al., 1990, 3	Cross-over, 24	Nor > Pla	NA	NA	NA	2/27	1/27	ns
Bupropion, 300 mg	[b]Semenchuk et al., 2001, 3	Cross-over, 41	Bup > pla	30/41	4/41	1.6 (1.3–2.1)	2/41	1/40	ns

(*continued on next page*)

Table 2 (*continued*)

Active drug daily drug dose	Study quality rating	Design patient nos	Outcome	Pain relief		NNT (95% CI)	Drop outs side effects		NNH (95% CI)
				Active	Placebo		Active	Placebo	
Anticonvulsants									
Central post-stroke pain									
Carbamazepine, 800 mg	Leijon and Boivie, 1989, 4	Cross-over, 15	Carb = pla	5/14	1/15	3.4 (1.7–105)	1/15	0/15	ns
Lamotrigine, 200 mg	Vestergaard et al., 2001, 5	Crossover, 30	Ltg > pla	NA	NA	NA	3/30	0/27	ns
Spinal cord injury pain									
Lamotrigine, 200–400 mg	Finnerup et al., 2002, 5	Crossover, 22	Ltg = pla	4/21	4/21	ns	1/27	2/28	ns
Valproate, 600–2400 mg	Drewes et al., 1994, 3	Crossover, 20	Val = pla	6/20	4/20	ns	0/20	0/20	ns
Gabapentin, up to 3600 mg	Levendoglu et al., 2004, 4	Crossover, 20	Gab > pla	NA	NA	NA	0/20	0/20	ns
Painful polyneuropathy									
Carbamazepine, 200–600 mg	[cd]Rull et al., 1969, 2	Crossover, 30	Carb > pla	26/42	8/45	2.3 (1.6–3.9)	2/30	0/30	ns
Carbamazepine, 600 mg	[c]Wilton, 1974, 3	Crossover, 40	Carb > pla	NA	NA	NA	NA	NA	NA
Phenytoin, 300 mg	[c]Saudek et al.1977, 2	Crossover, 12	Phe = pla	NA	NA	NA	2/12	0/12	ns
Phenytoin, 300 mg	[c]Chadda and Mathur, 1978, 2	Crossover, 38	Phe > pla	28/38	10/38	2.1 (1.5–3.6)	0/38	0/38	ns
Lamotrigine, 50–400 mg	Eisenberg et al., 2001, 5	Parallel, 59	Lam > pla	12/29	5/30	4.0 (2.1–42)	2/29	2/30	ns
Valproate, 1200 mg	Kochar et al., 2002, 4	Parallel, 57	Val > pla	24/29	5/28	1.5 (1.2–2–2)	1/29	0/28	ns
Valproate, 1500 mg	Otto et al., 2004, 5	Crossover, 31	Val = pla	8/31	3/31	ns	2/36	1/37	ns
Valproate, 500–1000 mg	[a]Kochar et al., 2004, 4	Parallel, 43	Val > pla	NA/22	NA/21	2 (1–3)	1/22	0/21	ns
Gabapentin, up to 3600 mg	Backonja et al., 1998, 5	Parallel, 165	Gab > pla	47/84	25/81	4.0 (2.5–9.6)	7/84	5/81	ns
Gabapentin, 900 mg	[e]Gorson et al., 1999, 2	Crossover, 40	Gab = pla	17/40	9/40	ns	0/40	0/40	ns
Gabapentin, 3600 mg	Simpson, 2001, 2	Parallel, 60	Gab > pla	15/30	7/30	3.8 (2.0–30.9)	2/30	2/30	ns
Pregabalin, 300 mg	[f]Rosenstock et al., 2004, 4	Parallel, 146	Pre > pla	30/76	10/70	4.0 (2.6–8.7)	8/76	2/70	ns
Pregabalin, (150) 300, 600 mg	[f]Lesser et al., 2004, 5	Parallel, 337	Pre > pla	76/163	17/97	3.4 (2.5–5.5)	13/163	3/97	ns
Pregabalin, (150) 600 mg	Richter et al., 2005, 5	Parallel, 246	Pre > pla	32/82	13/85	4.2 (2.7–9.4)	7/82	4/84	ns
Topiramate 400 mg	Raskin et al., 2004	Parallel, 323	Top > pla	74/214	23/109	7.4 (4.3–28.5)	52/214	9/109	6.2 (4.2–12.0)
Topiramate 100, 200, 400 mg	Thienel et al., 2004	Parallel, 1259	Top = pla	NA	NA	NA	213/878	32/381	6.3 (5.0–8.4)
Postherpetic neuralgia									
Gabapentin, 1200–3600 mg	Rowbotham et al., 1998, 5	Parallel, 229	Gab > pla	47/113	14/116	3.4 (2.5–5.4)	21/113	14/116	ns
Gabapentin, 1800–2400 mg	[f]Rice and Maton, 2001, 5	Parallel, 334	Gab > pla	74/223	15/111	5.1 (3.5–9.3)	34/223	7/111	11.2 (6.5–41.6)
Pregabalin, 300–600 mg	[f]Dworkin et al., 2003, 4	Parallel, 173	Preg > pla	44/89	17/84	3.4 (2.3–6.4)	28/89	4/84	3.7 (2.7–6.2)
Pregabalin, 150, 300 mg	[f]Sabatowski et al., 2004, 5	Parallel, 238	Preg > Pla	42/157	8/81	5.9 (3.8–13.6)	21/157	8/81	ns
Valproate, 1000 mg	Kochar et al., 2005, 3	Parallel, 45	Val > pla	13/23	2/22	2.1 (1.4–4.2)	1/22	0/22	ns
Phantom limb pain									
Gabapentin, 1800 – 2400 mg	Bone et al., 2002, 5	Crossover, 19	Gab > pla	NA	NA	NA	0/19	0/19	ns
Trigeminal neuralgia									
Carbamazepine, up to 800 mg	[c]Campbell et al., 1966, 4	Crossover, 70	Carb > pla	NA	NA	NA	1/77	0/77	ns
Carbamazepine, 600 mg	[c]Rockliff and Davis, 1966, 3	Crossover, 9	Carb > pla	NA	NA	NA	NA	NA	NA
Carbamazepine, 400–1000 mg	[cg]Killian and From, 1968, 4	Crossover, 27	Carb > pla	19/27	0/27	1.4 (1.1–1.9)	3/30	0/30	ns
Carbamazepine, 100–2400 mg	[ch]Nicol, 1969, 2	Crossover, 44	Carb > pla	27/37	6/24	2.1 (1.4–3.9)	NA	NA	NA
Lamotrigine, up to 400 mg	[i]Zakrzewska et al., 1997, 4	Crossover, 14	Lam > pla	7/13	1/14	2.1 (1.3–6.1)	0/14	0/14	ns
HIV-neuropathy									
Lamotrigine, 300 mg	Simpson et al., 2000, 5	Parallel, 42	Lam > pla	NA	NA	NA	6/20	0/22	3.3 (2.0–10.1)
Lamotrigine, up to 600 mg	Simpson et al., 2003, 3	Parallel, 227	Lam = pla	86/150	30/77	5.4 (3.1–20.4)	10/150	7/77	ns
Gabapentin, 1200–2400 mg	Hahn et al., 2004, 5	Parallel, 26	Gab = pla	NA	NA	NA	1/15	0/11	ns
Mixed patients									
Carbamazepine, 400–600 mg	[bj]Harke et al., 2001, 2	Parallel, 43	Carb > pla	NA	NA	NA	NA	NA	NA

Lamotrigine, 200 mg	[kl]McCleane, 1999b, 5	Parallel, 100	Lam = pla	0/50	0/50	ns	5/50	5/50	ns
Gabapentin, 900–2400 mg	[bf]Serpell, 2002, 5	Parallel, 307	Gab > pla	32/153	21/152	ns	24/153	25/152	ns
Gabapentin, 3200 mg	Gilron et al., 2005, 5	Cross-over, 41	Gab = pla	27/44	13/42	3.3 (2.0–9.7)	4/48	1/44	ns
Opioids									
Painful polyneuropathy									
Tramadol, 200–400 mg	[a]Harati et al., 1998, 5	Parallel, 127	Tra > pla	43/63	23/64	3.1 (2.1–6.3)	9/63	1/64	7.9 (4.6–28.1)
Tramadol, 200–400 mg	Sindrup et al., 1999, 5	Cross-over, 34	Tra > pla	11/34	3/33	4.3 (2.4–21.1)	7/43	2/40	ns
CR Oxycodone, 20–80 mg	[a]Watson et al., 2003, 5	Cross-over, 36	Oxy > pla	21/34	8/34	2.6 (1.7–6.0)	7/45	4/45	ns
CR Oxycodone, average 37 mg	Gimbel et al., 2003, 5	Parallel, 159	Oxy > pla	NA	NA	NA	7/82	4/77	ns
Postherpetic neuralgia									
Oxycodone, 20–60 mg	Watson and Babul, 1998, 4	Cross-over, 38	Oxy > pla	22/38	7/38	2.5 (1.7–5.1)	5/50	3/50	ns
Morphine, average 91 mg	[a]Raja et al., 2002, 5	Cross-over, 65	Opio > pla	29/65	4/57	2.7 (1.9–4.2)	7/66	1/57	11.3 (5.9–147)
Methadone, average 15 mg									
Tramadol 300–400 mg	Boureau et al., 2003, 5	Parallel, 127	Tra > pla	41/53	31/55	4.8 (2.6–26.9)	6/64	0/63	10.7 (6.1–44.8)
Phantom limb pain									
Retarded morphine, 70–300 mg	Huse et al., 2001, 4	Cross-over, 12	Mor > pla	5/12	1/12	3.0 (1.5–73.8)	NA	NA	NA
Mixed patients									
Sust. Release morphine 60–90 mg	[bj]Harke et al., 2001, 2	Parallel, 38	Mor = pla	NA	NA	NA	NA	NA	NA
Methadone 10/20 mg	[bm]Morley et al., 2003, 5	Cross-over, 18	Met > pla	NA	NA	NA	NA	NA	NA
Morphine, 120 mg	Gilron et al., 2005, 5	Cross-over, 41	Mor > pla	35/44	13/42	2.1 (1.5–3.3)	5/49	1/44	ns
NMDA antagonists									
Painful polyneuropathy									
Dextromethorphan, average 381 mg	Nelson et al., 1997, 5	Cross-over, 13	Dex > pla	7/13	0/13	1.9 (1.2–3.7)	0/13	0/13	ns
Dextromethorphan, 400 mg	Sang et al., 2002, 4	Cross-over, 19	Dex > pla	13/19	7/19	3.2 (1.6–68.6)	0/19	0/19	ns
Memantine, 55 mg	Sang et al., 2002, 4	Cross-over, 19	Mem = pla	9/19	7/19	ns	1/23	0/19	ns
Postherpetic neuralgia									
Dextromethorphan, average 439 mg	Nelson et al., 1997, 5	Cross-over, 13	Dex = pla	5/13	3/13	ns	4/18	0/15	4.5 (2.4–33.2)
Dextromethorphan, 400 mg	Sang et al., 2002, 4	Cross-over, 17	Dex = pla	5/17	2/17	ns	1/21	0/17	ns
Memantine, 20 mg	Eisenberg et al., 1998, 4	Parallel, 24	Mem = pla	2/12	2/12	ns	3/12	1/12	ns
Memantine, 35 mg	Sang et al., 2002, 4	Cross-over, 17	Mem = pla	2/17	2/17	ns	0/17	0/17	ns
Phantom limb pain									
Memantine, 20 mg	Nikolajsen et al., 2000, 4	Cross-over, 15	Mem = pla	1/15	1/15	ns	2/15	2/15	ns
Memantine, 30 mg	Maier et al., 2003, 5	Parallel, 18	Mem = pla	10/18	6/18	ns	2/18	0/18	ns
Mixed patients									
Riluzole, 100 mg	Galer et al., 2000, 3	Cross-over, 22	Ril = pla	0/22	2/22	ns	NA	NA	NA
Riluzole, 200 mg	Galer et al., 2000, 3	Cross-over, 21	Ril = pla	NA	NA	NA	NA	NA	NA
Dextromethorphan, 81 mg	McQuay et al., 1994, 4	Cross-over, 17	Dex = pla	6/17	6/17	ns	5/17	0/17	3.4 (2–12.9)
Mexiletine									
Spinal cord injury pain									
Mexiletine, 450 mg	Chiou-Tan et al., 1996, 3	Cross-over, 11	Mex = pla	NA	NA	NA	0/14	0/14	ns
Painful polyneuropathy									
Mexiletine, 10 mg/kg	Dejgard et al., 1988. 3	Cross-over, 16	Mex > pla	NA	NA	NA	0/19	0/19	ns
Mexiletine, 225,450,675 mg	Stracke et al., 1992, 3	Parallel, 95	Mex = pla	NA	NA	NA	NA	NA	NA
Mexiletine, 225,450,675 mg	[n]Oskarsson et al., 1997, 4	Parallel, 126	Mex = pla	65/95	21/31	ns	8/95	1/31	ns
Mexiletine, 600 mg	Wright et al., 1997, 5	Parallel, 31	Mex = pla	7/14	4/15	ns	2/15	3/16	ns

(*continued on next page*)

Table 2 (*continued*)

Active drug daily drug dose	Study quality rating	Design patient nos	Outcome	Pain relief		NNT (95% CI)	Drop outs side effects		NNH (95% CI)
				Active	Placebo		Active	Placebo	
Peripheral nerve injury									
Mexiletine, 750 mg	Chabal et al., 1992, 3	Cross-over, 11	Mex > pla	6/11	1/11	2.2 (1.3–8.7)	0/11	0/11	ns
HIV-neuropathy									
Mexiletine, up to 600mg	Kieburtz et al., 1998, 5	Parallel, 98	Mex = pla	22/48	24/50	ns	4/48	1/50	ns
Mexiletine, up to 600 mg	Kemper et al., 1998, 3	Cross-over, 16	Mex = pla	NA	NA	NA	2/22	9/22	ns
Mixed patients									
Mexiletine, 900 mg	[bo]Wallace et al., 2000, 3	Cross-over, 20	Mex = pla	NA	NA	NA	0/20	0/20	ns
Topical lidocaine									
Postherpetic neuralgia									
Lidocaine gel, 5%	[o]Rowbotham et al., 1995, 4	Cross-over, 39	Lid > pla	NA	NA	NA	1/46	2/46	ns
Lidocaine patch, 5%	[o]Rowbotham et al., 1996, 4	Cross-over, 35	Lid > pla	NA	NA	NA	0/35	0/35	ns
HIV-neuropathy									
Lidocaine gel, 5%	Estanislao et al., 2004, 3	Cross-over, 56	Lid = pla	NA	NA	NA	2/61	0/59	ns
Mixed patients									
Lidocaine patch, 5%	[aop]Meier et al., 2003, 5	Cross-over, 40	Lid > pla	12/39	3/37	4.4 (2.5–17.5)	0/51	1/58	ns
Cannabinoids									
Multiple sclerosis									
Dronabinol 5–10 mg	Svendsen et al., 2004, 5	Cross-over, 24	Can > pla	11/24	4/24	3.4 (1.8–23.4)	0/24	0/24	ns
Brachial plexus avulsion									
THC 129,6 mg +/-CBD 120 mg	Berman et al., 2004, 4	Parallel, 141	Can > pla	1/93	0/48	ns	1/93	1/48	ns
Mixed patients									
CT3 80 mg	[aq]Karst et al., 2003, 5	Cross-over, 21	Can > pla	2/19	0/19	ns	1/20	2/20	ns
Capsaicin									
Painful polyneuropathy									
Capsaicin, 0.075% qid	Chad et al., 1990, 2	Parallel, 46	Caps = pla	17/28	11/26	ns	NA	NA	NA
Capsaicin, 0.075% qid	Scheffler et al., 1991, 3	Parallel, 54	Caps > pla	17/19	11/22	2.5 (1.6–6.9)	2/28	0/26	ns
Capsaicin, 0.075% qid	Capsaicin Study Group, 1991, 4	Parallel, 277	Caps > pla	65/138	57/139	ns	18/138	5/139	10.6 (6.3–33.0)
Capsaicin, 0.075% qid	Tandan et al., 1992, 3	Parallel, 22	Caps > pla	6/11	2/11	ns	1/11	0/11	ns
Capsaicin, 0.075% qid	[ar]Low et al., 1995, 3	Parallel, 40	Caps = pla	23/40	26/40	ns	NA	NA	NA
Postherpetic neuralgia									
Capsaicin, 0.075% tid/qid	Bernstein et al., 1989, 4	Parallel, 32	Caps > pla	7/16	1/16	2.7 (1.5–9.6)	0/16	0/16	ns
Capsaicin, 0.075% qid	Watson et al., 1993, 4	Parallel, 143	Caps > pla	44/74	21/69	3.4 (2.2–7.4)	18/74	2/69	4.7 (3.1–9.2)
Postmastectomy pain									
Capsaicin, 0.075% qid	[s]Watson and Evans, 1992, 3	Parallel, 25	Caps = pla	8/14	3/11	ns	1/14	0/11	ns
Post-surgical pain									
Capsaicin, 0.075% qid	Ellison et al., 1997, 4	Parallel, 99	Caps > pla	10/49	5/50	ns	4/49	4/50	ns
HIV-neuropathy									
Capsaicin, 0.075% qid	Paice et al., 2000, 3	Parallel, 26	Caps = pla	NA	NA	NA	0/15	0/11	ns
Mixed patients									
Capsaicin, 0.075% qid	McCleane, 2000, 4	Parallel, 74	Caps > pla	NA	NA	NA	0/33	0/41	ns
Glycine antagonist									
Mixed patients									
Glycine antagonist, 300 mg	[o]Wallace et al., 2002b, 4	Parallel, 63	Gly = pla	7/32	4/31	ns	1/32	2/31	ns

Combinations									
Painful polyneuropathy									
Gabapentin 3600 mg + venlafaxine 150 mg	Simpson, 2001, 2	Parallel, 11	Gab + ven > gab + pla	NA	NA	NA	NA	NA	NA
Mixed patients									
Gabapentin 2400 mg + morphine 60 mg	Gilron et al., 2005, 5	Cross-over, 41	Gab + mor > pla Gab + mor > gab Gab + mor > mor	32/41	13/42	2.1 (1.5–3.5)	6/47	1/44	ns

Pla = placebo, subl = sublingual, NA: dichotomized data are not available, ns: relative risk not significant.

[a] Additional data provided by author.
[b] Study include questionable neuropathic pain conditions.
[c] Data limited and difficult to interpret.
[d] 30 patients on multiple cross-over.
[e] 900 mg/day of gabapentin may be too low a dose for achieving an analgesic effect.
[f] Patients failing to respond to pre-study gabapentin excluded, which may cause an overestimation of the efficacy of pregabalin and gabapentin.
[g] For trigeminal neuralgia only.
[h] Partial cross-over.
[i] Add on therapy to carbamazepine or phenytoin.
[j] Pretreated with spinal cord stimulation, alternating drug/placebo administration, (NNT therefore not calculated).
[k] 200 mg/day of lamotrigine may be too low a dose for achieving an analgesic effect.
[l] Criteria for neuropathic pain inadequate.
[m] Methadone only superior in a dose of 20 mg.
[n] Mexiletine superior to placebo for highest dose.
[o] Patients with allodynia.
[p] Focal peripheral neuropathy, add-on therapy.
q Cannabinoid superior to placebo only 3 h after intake.
r Capsaicin on one leg and placebo on the other.
s No effect on steady pain.

strengthens the arguments for more head-to-head comparisons, and making such comparisons a regulatory requirement will help to make them happen.

Note added in proof

By September 2005, additional two large randomized trails have been published. Duloxetine had a significant pain relieving effect in painful diabetic neuropathy, with a NNT of 4.1 (2.9–7.2) for the highest doses of 60 and 120 mg/day (Goldstein et al., 2005). Pregabalin in flexible- or fixed-dose regimens had a significant pain relieving effect in postherpetic neuralgia and painful diabetic neuropathy with a NNT of 3.8 (2.6–7.3) (Freynhagen et al., 2005).

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Supplementary data

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Review and recommendations

Pharmacologic management of neuropathic pain: Evidence-based recommendations

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Abstract

Patients with neuropathic pain (NP) are challenging to manage and evidence-based clinical recommendations for pharmacologic management are needed. Systematic literature reviews, randomized clinical trials, and existing guidelines were evaluated at a consensus meeting. Medications were considered for recommendation if their efficacy was supported by at least one methodologically-sound, randomized clinical trial (RCT) demonstrating superiority to placebo or a relevant comparison treatment. Recommendations were based on the amount and consistency of evidence, degree of efficacy, safety, and clinical experience of the authors. Available RCTs typically evaluated chronic NP of moderate to severe intensity. Recommended first-line treatments include certain antidepressants (i.e., tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel α2-δ ligands (i.e., gabapentin and pregabalin), and topical lidocaine. Opioid analgesics and tramadol are recommended as generally second-line treatments that can be considered for first-line use in select clinical circumstances. Other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances include certain antiepileptic and antidepressant medications, mexiletine, *N*-methyl-D-aspartate receptor antagonists, and topical capsaicin. Medication selection should be individualized, considering side effects, potential beneficial or deleterious effects on comorbidities, and whether prompt onset of pain relief is necessary. To date, no medications have demonstrated efficacy in lumbosacral radiculopathy, which is probably the most common type of NP. Long-term studies, head-to-head comparisons between medications, studies

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involving combinations of medications, and RCTs examining treatment of central NP are lacking and should be a priority for future research.

Keywords: Neuropathic pain; Evidence-based recommendations; Pharmacologic management; Randomized clinical trials

1. Introduction

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" [74]. It is estimated to afflict millions of people worldwide, although precise figures are not available [7,9,12,44,102]. Many common diseases, injuries, and interventions cause NP by producing lesions in somatosensory pathways in the peripheral or central nervous system.

The management of patients with chronic 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. Evidence-based consensus treatment recommendations exist [25], but additional medications have become available since their publication [31]. Because of gaps and controversies in the literature, considerable interpretation of available evidence, judgment, and experience are required to develop treatment approaches that can be used in clinical practice.

The objectives of this article are to: (1) briefly review the results of RCTs examining medications for the treatment of NP; (2) present up-to-date, evidence-based guidelines for the pharmacologic management of NP that take into account clinical efficacy, adverse effects, impact on health-related quality of life, convenience, and costs; and (3) provide specific recommendations for the use of these medications.

2. Methods

The consensus meeting on which these treatment recommendations are based and the preparation of this article were conducted under the auspices of the IASP Neuropathic Pain Special Interest Group with additional support provided by the Neuropathic Pain Institute, both of which have received unrestricted support for their activities from multiple pharmaceutical companies. No individuals employed by pharmaceutical companies were involved in the consensus meeting on which these recommendations are based or in the preparation of this article. Prior to the consensus meeting, all participants were provided with copies of existing treatment guidelines [25,58], systematic reviews and meta-analyses, and recently published RCTs. This literature and the authors' clinical and research experience were reviewed during the consensus meeting. Systematic reviews and RCTs published after the meeting were reviewed subsequently. The treatment recommendations included in this article have been endorsed by the American Pain Society, Canadian Pain Society, Finnish Pain Society, Latinamerican Federation of IASP Chapters, and Mexican Pain Society.

2.1. Search strategy and selection criteria

Relevant publications were identified through Medline searches (1966–2007), examination of reference lists of relevant published articles and book chapters, and personal knowledge of the authors. Only studies of oral or topical pharmacotherapy in adults were considered, and our recommendations do not apply to the treatment of pediatric neuropathic pain. The treatment of trigeminal neuralgia (tic douloureux), for which there are distinct treatment recommendations [3,65], was not considered. On the basis of recent recommendations for the diagnosis of NP [115], conditions for which there is no evidence of lesions affecting nervous system somatosensory pathways (e.g., fibromyalgia, irritable bowel syndrome) were also not considered.

In evaluating the literature and developing recommendations, the Cochrane Database and other recent systematic reviews were emphasized [27,31,33,50,53,68,100,109,119,129]. Efficacy was considered to have been demonstrated if the results of an RCT found statistically significantly greater pain reduction vs. placebo for the primary outcome measure [31] and was evaluated according to the Oxford Centre for Evidence-based Medicine levels of evidence [78]. All medications with efficacy supported by at least one systematic review or positive placebo-controlled or dose-response RCT (levels of evidence criterion 1b or better), [78] in which reduction of chronic NP was a primary or co-primary endpoint were considered for inclusion. Published data, unpublished data (when available), and the clinical experience of the authors were used to evaluate each of these medications in terms of degree of efficacy, safety, tolerability, drug interactions, ease of use, and impact on health-related quality of life.

Recommendations for first-line treatments are consistent with the results of multiple RCTs (Oxford Centre for Evidence-based Medicine grade A recommendation), [78] and the clinical experience of the authors. Recommendations for opioid analgesics and tramadol as generally second-line treatments are consistent with the results of multiple RCTs (grade A recommendation), the clinical experience of the authors, and published guidelines and recommendations for their use. Recommendations for other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances are based on a single positive RCT or inconsistent results from multiple trials (grade B recommendation) and the authors' clinical experience.

3. General management considerations and recommendations

Appropriate diagnosis and assessment are critical to the successful treatment of NP. The diagnosis of NP can often be challenging, diagnostic criteria are evolving, and NP commonly coexists with other types of pain (e.g., low back pain associated with both radiculopathy and musculoskeletal abnormalities). Assessment of NP should focus on identifying and treating the underlying disease processes and peripheral or central nervous system lesions, response to prior therapies, and comorbid conditions that can be affected by therapy. Particular attention should be paid to identifying coexisting depression, anxiety, sleep disturbances, and other adverse impacts of NP on health-related quality of life [56,75], and both pain and its adverse effects should be reassessed frequently. Patient education and support are critical components of the successful management of NP. Careful explanation of the cause of NP and the treatment plan are essential. Patient and provider expectations regarding treatment effectiveness and tolerability must be discussed, and realistic treatment goals should be established with patients. Non-pharmacologic methods of coping with pain should be discussed, including the importance of stress reduction, good sleep hygiene, physical therapy, and other potentially useful interventions. Additional information about the diagnosis of NP and recommendations for its assessment can be found elsewhere [20,25,47,85].

The majority of the RCTs of patients with NP have examined either PHN or painful diabetic peripheral neuropathy (DPN). Although the extent to which the results of RCTs of one type of NP apply to other types is unknown, the extrapolation of efficacy from first-line medications that have demonstrated efficacy in one or more types of NP to other types of NP is reasonable and often clinically necessary. Medications that have demonstrated efficacy in several different NP conditions may have the greatest probability of being efficacious in additional, as yet unstudied, conditions [46]. However, it is possible that some types of NP respond differently to treatment [3]. Although few clinical trials have been conducted, no medications have demonstrated efficacy in patients with lumbosacral radiculopathy, which is probably the most common type of NP.

The methodology used in RCTs of NP varies, and there are few head-to-head comparisons of different medications, making it difficult to compare the relative efficacy and safety of many medications. Little is known regarding the treatment response of patients with mild-to-moderate NP because RCTs have typically evaluated chronic NP of moderate to severe intensity. Moreover, treatment duration has generally not exceeded three months in the RCTs of any treatments for NP, and knowledge of the long-term benefits and risks of treatment is therefore inadequate. Unfortunately, there is insufficient evidence to rank first-line medications for NP by their degree of efficacy or safety. Given these limitations, clinicians must consider several other factors when selecting a specific medication for a patient with NP, including: (1) the potential for adverse outcomes associated with medication-related side effects; (2) potential drug interactions; (3) comorbidities that may also be relieved by the non-analgesic effects of the medication (e.g., sleep disturbance, depression, anxiety); (4) costs associated with therapy; (5) the potential risks of medication abuse; and (6) the risks of intentional and unintentional overdose. These potentially competing factors must be prioritized according to the specific needs of each patient with NP.

Individual variation in the response to the medications used to treat NP is substantial and unpredictable. Although evidence-based recommendations encourage the use of specific medications, the overall approach should be recognized as a stepwise process intended to identify the medication, or medication combination, that provides the greatest pain relief and fewest side effects for a given patient (Table 1). If an adequate trial of one medication fails to adequately relieve pain or causes intolerable side effects, treatment should be discontinued and a different medication should be selected for a trial. If a medication is well tolerated and provides partial pain relief, it should be continued and a second medication with a distinct mechanism of action added.

In addition to potential additive analgesic benefits, combination therapy may provide analgesia more quickly by combining a medication with a rapid onset of effect with one that requires several weeks of treatment before maximum benefit is achieved. These potential advantages of combination therapy must be weighed against the possibility of additive adverse effects, drug interactions, increased cost, and reduced adherence to a more complex treatment regimen. In one of the first RCTs of combination therapy in NP, gabapentin and morphine in combination provided superior pain relief to either medication alone and to placebo [36]. However, a recent RCT evaluating nortriptyline, morphine, and their combination in patients with chronic lumbar root pain found no greater efficacy with the combination than with either medication alone or placebo [60].

4. First-line medications

Three medications or medication classes are recommended as first-line treatment for patients with NP (grade A recommendation). Table 2 summarizes treatment selection considerations. Prescribing information for each of these medications – including starting dosage, titration requirements, target dosage, and duration of an adequate trial – is provided in Table 3.

Table 1
Stepwise pharmacologic management of neuropathic pain (NP)

Step 1

Assess pain and establish the diagnosis of NP [25,20]; if uncertain about the diagnosis, refer to a pain specialist or neurologist

Establish and treat the cause of NP; if uncertain about availability of treatments 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:

- A secondary amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, venlafaxine)
- A calcium channel $\alpha 2$-δ ligand, either gabapentin or pregabalin
- For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the other first-line therapies
- For patients with acute neuropathic pain, 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 one of the first-line therapies

Evaluate patient for non-pharmacologic 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 $\leqslant 3/10$) and tolerable side effects, continue treatment

If partial pain relief (e.g., average pain remains $\geqslant 4/10$) after an adequate trial (see Table 3), add one of the other first-line medications

If no or inadequate pain relief (e.g., $< 30\%$ reduction) at target dosage after an adequate trial (see Table 3), switch to an alternative first-line medication

Step 4

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

TCA, tricyclic antidepressant; SSNRI, selective serotonin and norepinephrine reuptake inhibitor.

Table 2
Treatment selection considerations for first-line medications and for opioid agonists

Medication class	Therapeutic index[a]	Major side effects	Precautions	Other benefits	Cost[b]
Secondary amine TCAs					
Nortriptyline, desipramine (use a tertiary amine TCA only if a secondary amine TCA is not available)	+	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol	Improvement of depression, improvement of insomnia	$
SSNRIs					
Duloxetine[c]	++	Nausea	Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol	Improvement of depression	$$
Venlafaxine	+	Nausea	Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation	Improvement of depression	$/$$
Calcium channel α2-δ ligands					
Gabapentin	++	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, no clinically significant drug interactions	$/$$
Pregabalin[c]	++	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, improvement of anxiety, no clinically significant drug interactions	$$
Topical lidocaine	++	Local erythema, rash	None	No systemic side effects	$$ (patch) $ (gel)
Opioid agonists[d]					
Morphine, oxycodone, methadone, levorphanol	+	Nausea/vomiting, constipation, drowsiness, dizziness	History of substance abuse, suicide risk, driving impairment during treatment initiation	Rapid onset of analgesic benefit	$/$$
Tramadol	+	Nausea/vomiting, constipation, drowsiness, dizziness seizures	History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SSNRI, TCA	Rapid onset of analgesic benefit	$/$$

TCA, tricyclic antidepressants; SSNRI, selective serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] Refers to the likelihood of pain relief relative to the likelihood of side effects, with "++" being more favorable.
[b] Cost varies by region but is estimated on the basis of availability and cost of generic formulations, with "$$" being relatively more expensive.
[c] Lack long-term clinical experience and safety data because new to market.
[d] First-line only in certain circumstances; see text.

4.1. Tricyclic antidepressants (TCAs) and selective serotonin and norepinephrine reuptake inhibitors (SSNRIs)

Systematic reviews have consistently concluded that placebo-controlled trials have provided support for the efficacy of TCAs in the treatment of patients with NP, especially PHN and painful DPN [31,50,100,109]. A substantial percentage of patients do not respond favorably to treatment with TCAs, as is also true of the other medications recommended for the treatment of NP, with no more than 40–60% of patients obtaining partial relief of their pain. TCAs have not differed significantly from placebo in RCTs of patients with HIV neuropathy [62,105], spinal cord injury [15], cisplatin neuropathy [45], neuropathic cancer pain [73], phantom limb pain [91], and chronic lumbar root pain [60].

Table 3
Prescribing recommendations for first-line medications and for opioid agonists

Medication class	Starting dosage	Titration	Maximum dosage	Duration of adequate trial
Secondary amine TCAs				
Nortriptyline, desipramine[a] (use a tertiary amine TCA only if a secondary amine TCA is not available)	25 mg at bedtime	Increase by 25 mg daily every 3–7 days as tolerated	150 mg daily; if blood level of active medication and its metabolite is below 100 ng/ml (mg/ml), continue titration with caution	6–8 weeks with at least 2 weeks at maximum tolerated dosage
SSNRIs				
Duloxetine	30 mg once daily	Increase to 60 mg once daily after one week	60 mg twice daily	4 weeks
Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg each week	225 mg daily	4–6 weeks
Calcium channel α2-δ ligands				
Gabapentin[a]	100–300 mg at bedtime or 100–300 mg three times daily	Increase by 100–300 mg three times daily every 1–7 days as tolerated	3600 mg daily (1200 mg three times daily); reduce if impaired renal function	3–8 weeks for titration plus 2 weeks at maximum dosage
Pregabalin[a]	50 mg tid or 75 mg bid	Increase to 300 mg daily after 3–7 days, then by 150 mg/d every 3–7 days as tolerated	600 mg daily (200 mg three times or 300 mg twice daily); reduce if impaired renal function	4 weeks
Topical lidocaine				
5% lidocaine patch	Maximum of 3 patches daily for a maximum of 12 h	None needed	Maximum of 3 patches daily for a maximum of 12–18 h	3 weeks
Opioid agonists[b]				
Morphine, oxycodone, methadone, levorphanol[a]	10–15 mg morphine every 4 h or as needed (equianalgesic dosages should be used for other opioid analgesics)	After 1–2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed	No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (e.g., 120–180 mg morphine daily; equianalgesic dosages should be used for other opioid analgesics)	4–6 weeks
Tramadol[c]	50 mg once or twice daily	Increase by 50–100 mg daily in divided doses every 3–7 days as tolerated	400 mg daily (100 mg four times daily); in patients older than 75, 300 mg daily	4 weeks

TCA, tricyclic antidepressants; SSNRI, selective serotonin and norepinephrine reuptake inhibitor.
[a] Consider lower starting dosages and slower titration in geriatric patients.
[b] First-line only in certain circumstances; see text.
[c] Consider lower starting dosages and slower titration in geriatric patients; dosages given are for short-acting formulation.

TCAs are typically inexpensive and usually administered once daily. The presence of depression is not required for the analgesic effects of these medications [69], although they may be particularly useful in patients with inadequately treated depression. The most common side effects of TCAs include sedation, anticholinergic effects (e.g., dry mouth, constipation, and urinary retention), and orthostatic hypotension. Secondary amine TCAs (nortriptyline and desipramine) are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) but have comparable analgesic efficacy [70,98,126]. Amitriptyline in particular should be avoided in elderly patients.

The decision to start a TCA should also consider the possibility of cardiac toxicity. Nortriptyline was associated with sinus tachycardia and increased ventricular ectopy in an RCT that examined patients with a history of depression and ischemic heart disease [92].

An increased risk of myocardial infarction with TCAs compared to selective serotonin reuptake inhibitors (SSRIs) has been reported [19], but subsequent, larger studies did not confirm this finding [51,113]. Finally, a large, retrospective cohort analysis found an increased risk of sudden cardiac death at dosages of 100 mg/day or higher [86].

Taken together, these data suggest that the lowest effective dosage of a TCA should be used in all patients with NP, and that TCAs should be avoided in patients who have ischemic heart disease or an increased risk of sudden cardiac death. A screening electrocardiogram (ECG) is recommended before beginning treatment with TCAs in patients over 40 years of age [25]. TCAs should be used cautiously in patients at risk for suicide or accidental death from overdose. They can cause or exacerbate cognitive impairment and gait disturbances in elderly patients, and may predispose to falls. Toxic TCA levels may result if TCAs are administered together with medications that inhibit cytochrome P450 2D6, such as SSRIs.

Starting doses of TCAs should be low, and the dosage should be titrated slowly until pain is adequately controlled or side effects limit continued titration (Table 3). Although monitoring medication levels is not usually necessary, it may reduce the risk of cardiac toxicity at dosages greater than 150 mg/day.

Duloxetine is an SSNRI that inhibits the reuptake of both serotonin and norepinephrine. It has demonstrated significantly greater pain relief compared with placebo in three RCTs in patients with painful DPN [38,82,128], but it has not been studied in other types of NP. Although duloxetine is also an efficacious antidepressant and anxiolytic, these effects do not account for its analgesic benefits in painful DPN [38]. Safety and effectiveness have also been demonstrated in open-label treatment of patients with painful DPN extending over 52 weeks [83], and meta-analyses showed modest increases in fasting plasma glucose in the patients with DPN [49] but no clinically meaningful ECG changes relative to placebo in depressed patients [116].

Duloxetine has a generally favorable side effect profile and dosing is simple. Nausea is the most common side effect, but it occurs less frequently if treatment is initiated at 30 mg/day and titrated after one week to 60 mg/day [23], an efficacious dosage at which pain relief can occur within one week (Table 3). In RCTs in painful DPN, 60 mg once daily appears to be as efficacious as 60 mg twice daily and is associated with fewer side effects. As a new medication, there is limited long-term safety information and efficacy data are limited to studies of painful DPN.

Venlafaxine is an SSNRI that inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages. RCTs in patients with painful DPN [96] and painful polyneuropathies of various types including DPN [108] demonstrated efficacy at dosages of 150–225 mg/day. RCTs in other populations, including those with post-mastectomy pain [112], various peripheral and central NP conditions [133], and PHN [42], demonstrated inconsistent or negative results. Two of these trials used lower dosages of venlafaxine [112,133], which may account for some of the differences in efficacy.

In one RCT, 5% of venlafaxine-treated patients developed ECG changes [96], and monitoring is therefore recommended in patients with cardiovascular risk factors. Venlafaxine is available in both short- and long-acting formulations. Two-to-four weeks is often required to titrate to an effective dosage, and patients should be tapered gradually from venlafaxine because of the risk of discontinuation syndrome (Table 3) [29].

4.2. Calcium channel α2-δ ligands

Gabapentin and pregabalin both bind to the α2-δ subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine, and substance P [114]. Pain reduction has been greater with gabapentin than with placebo in RCTs of PHN, painful DPN, phantom limb pain, diverse peripheral NP conditions, Guillain-Barré syndrome, neuropathic cancer pain, and acute and chronic spinal cord injury pain [4,10,14,39,64,79,87,97,104,111]. In some RCTs, treatment with gabapentin was also associated with improvement in sleep and various components of mood and health-related quality of life. Negative trials of gabapentin include an unpublished study in painful DPN [5] and recent studies of complex regional pain syndrome, type I [121], painful HIV neuropathy [43], chronic phantom and residual limb pain [110], and chemotherapy-induced neuropathy [132].

Gabapentin is generally safe, has no clinically important drug interactions, and is available in generic formulations. The main dose-limiting side effects are somnolence and dizziness, which are reduced by gradual dosage titration, and peripheral edema. In some patients, particularly the elderly, gabapentin can cause or exacerbate cognitive or gait impairment.

Several weeks can be required to reach an effective dosage, which is usually between 1800 and 3600 mg/day (administered in three divided doses, increasing the night-time dose preferentially). Dosage reduction is necessary in patients with renal insufficiency. The onset of activity can be seen as early as the second week of therapy when titration is rapid, but peak effect usually occurs approximately two weeks after a therapeutic dosage is achieved. Therefore, an adequate trial may require two months or more (Table 3).

Pregabalin has demonstrated efficacy in three RCTs in PHN [26,101,122], in three RCTs in painful DPN [63,93,89], and in one RCT that enrolled patients with

either of these types of NP [32]. An RCT in patients with spinal cord injury neuropathic pain also demonstrated greater pain relief with pregabalin than with placebo [106]. An unpublished trial in patients with DPN also showed evidence of efficacy, but in two unpublished trials, pregabalin did not differ significantly from placebo in patients with PHN and with DPN [24].

Pregabalin produces dose-dependent side effects similar to those of gabapentin. It has also demonstrated anxiolytic effects in RCTs of generalized anxiety disorder [76,90], which may provide additional benefit in patients with chronic pain. Like gabapentin, it has no clinically important drug interactions but requires dosage reduction in patients with renal impairment. Studies indicate that treatment can be initiated at 150 mg/day (in either two or three divided doses), although a starting dose of 75 mg at bedtime is used by some clinicians to reduce the likelihood of early side effects in elderly patients and in others especially prone to side effects (Table 3). The potential for twice daily dosing and the linear pharmacokinetics of pregabalin may contribute to relatively greater ease of use compared with gabapentin, but the overall efficacy and tolerability of these two medications appear similar. However, onset of pain relief with pregabalin can be more rapid than with gabapentin because its starting dosage of 150 mg/day is efficacious [26]. Upward dosage titration can reach 300 mg/day within one to two weeks, and the maximum benefits typically occur after two weeks of treatment at target dosages of 300–600 mg/day. Because it is a new medication, long-term safety of pregabalin is not as well established as it is for gabapentin.

4.3. Topical lidocaine

RCTs have demonstrated significantly greater pain relief with lidocaine patch 5% than with vehicle-controlled patches in patients with PHN and allodynia [34,95] and in patients with diverse peripheral NP conditions and allodynia [72], including a subgroup without PHN [71]. As a topical preparation, it is recommended for patients with localized peripheral NP but not for patients with central NP.

When used as recommended, the only side effects that occur with the lidocaine patch 5% are mild skin reactions (e.g., erythema and localized rash). Blood levels are minimal with the approved maximum dosing of three patches/day applied for 12 h and also when four patches/day are applied for 18 h [35]. Nonetheless, use of the lidocaine patch 5% should be avoided in patients receiving oral Class I antiarrhythmic medications (e.g., mexiletine) and in patients with severe hepatic dysfunction, in whom excessive blood concentrations are theoretically possible.

The efficacy of lidocaine gel was demonstrated in patients with PHN and allodynia [94], but not in patients with HIV neuropathy [28]. Because of its safety and ease of use, lidocaine gel can be considered when the lidocaine patch 5% is not available, application of a patch is problematic, or the cost of the lidocaine patch 5% precludes its use.

5. Second-line medications that can be used for first-line treatment in select clinical circumstances

Opioid analgesics and tramadol have demonstrated efficacy in multiple RCTs in patients with NP, and when patients do not have a satisfactory response to the first-line medications alone or in combination, opioid agonists can be used as second-line treatment alone or in combination with the first-line medications (grade A recommendation).

In select clinical circumstances, opioid analgesics and tramadol can also be considered for first-line use (Table 4). These circumstances include when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, and for episodic exacerbations of severe pain, acute neuropathic pain, and neuropathic cancer pain.

5.1. Opioid analgesics

Oral opioid analgesics have demonstrated efficacy in RCTs ranging from eight days to eight weeks in duration in patients with a variety of peripheral and central NP conditions, including painful DPN, PHN, and phantom limb pain [37,54,77,80,99,124,125]; however, morphine did not differ from placebo in a recent RCT for chronic nerve root pain [60]. These trials have examined different opioids, including oxycodone, morphine, methadone, and levorphanol. The magnitude of pain reduction associated with opioid analgesics is at least as great as that obtained with other treatments for NP [27,31,36,80].

Although opioid analgesics have demonstrated efficacy in multiple RCTs in patients with NP, they are generally considered a second-line treatment for several reasons. First, in head-to-head comparisons, opioids have produced side effects more frequently than TCAs [60,80] and gabapentin [36], and some of these side effects can persist throughout long-term treatment [127]. Second, the long-term safety of opioid treatment has not been systematically studied [27,33], and evidence

Table 4
Circumstances in which opioid analgesics and tramadol can be considered for first-line treatment of neuropathic pain

During titration of a first-line medication to an efficacious dosage for prompt pain relief
Episodic exacerbations of severe pain
Acute neuropathic pain
Neuropathic cancer pain

that long-term opioid use is associated with the development of immunologic changes and hypogonadism [21,81,120] suggests that clinicians should not be guided by the assumption that safety is intrinsically better for opioids than other medications. Third, experimental data suggest that opioid treatment can be associated with hyperalgesia [2,16,17,131]; like tolerance, opioid-induced hyperalgesia could potentially alter the risk-benefit ratio of long-term therapy in patients with various types of acute and chronic pain. There are no studies of opioid-induced hyperalgesia in patients with chronic NP, however, and future studies must evaluate the clinical significance of this phenomenon and also systematically distinguish opioid-induced hyperalgesia from tolerance [2,17] and from exacerbation of the underlying pain condition.

Finally, the results of recent studies using a variety of methods and patient samples have provided estimates of the frequency of opioid analgesic misuse or addiction that range widely from less than 5% to as much as 50% [1,6,52,55,66,67]. Although the risk that opioid analgesics will be misused or abused has not been determined for patients with chronic NP, these recent estimates cannot be ignored when initiating opioid treatment. Recent recommendations have emphasized the need for clinical skills in risk assessment and management as a prerequisite to safe and effective opioid prescribing [6,52,59].

Because of these problematic aspects of opioid treatment, and given the efficacy of the first-line medications discussed above, treatment of chronic NP with opioid agonists should generally be reserved for patients who have failed to respond to or cannot tolerate the first-line medications. This recommendation is consistent with published guidelines for the use of opioids in chronic non-cancer pain that have been prepared by various groups [52]. Of existing medications with efficacy in NP, however, opioid analgesics may be most likely to provide prompt pain relief. For this reason, and because of their established efficacy in NP, opioids can be considered for first-line use in select clinical circumstances (see Table 4). Typically, such first-line use of opioids should be reserved for circumstances in which suitable alternatives cannot be identified and should be on a short-term basis to the extent possible.

Before initiating treatment with opioid analgesics, clinicians should identify and address risk factors for abuse, which include active substance abuse, prior history of opioid or other drug abuse, other major psychiatric pathology, and family history of substance abuse [6,52,135]. Response to treatment, side effects, and signs of opioid misuse or abuse should be monitored on a regular basis, as has been described in guidelines for opioid use in chronic non-cancer pain [6,52,57,58,117]. It is recommended that clinicians without opioid expertise obtain consultation from appropriate specialists in developing a treatment plan for challenging patients.

The most common opioid-related side effects are nausea, constipation, and sedation [27,33]. Although nausea and sedation typically decrease after several weeks of treatment, constipation may not; it usually requires concurrent management, especially in the elderly or other groups with risk factors for this problem. Opioids should be used cautiously in patients at risk for suicide or accidental death from overdose. In elderly patients, opioids can also cause or exacerbate cognitive impairment and gait disturbances, increasing the risk of falls. In contrast to abuse or addiction, physical dependence develops in all patients chronically treated with opioid analgesics, and patients must be advised that they should not discontinue these medications on their own.

The effective opioid dosage varies widely among patients, and either of two strategies for the initiation of treatment can be used depending on the specific clinical circumstances. For opioid-naïve patients, treatment can be initiated with an oral immediate-release opioid at a dose equivalent to 10–15 mg of morphine every 4 h or on an as needed basis, with conversion to a long-acting opioid after a few days, when the approximate daily dosage has been identified (Table 3). Treatment can also be initiated with a long-acting opioid (e.g., extended-release oral morphine or oxycodone, or transdermal fentanyl). Fixed-schedule dosing with a long-acting opioid is generally preferred, although RCTs in patients with NP are needed to compare the efficacy and safety of short- vs. long-acting opioids. Titration should continue until satisfactory pain relief is achieved or unacceptable side effects persist despite attempts to improve tolerability (e.g., laxatives for constipation). Treatment with a short-acting opioid on an as needed basis may be appropriate to continue in selected patients with NP who have episodes of markedly increased pain; until the role of such ''rescue'' treatment has been more adequately characterized for patients with NP, treatment approaches used for patients with other types of chronic pain, including cancer pain, can be followed [57,58,117]. As with all of the medications recommended for NP, the lowest effective dosages of opioid analgesics should be used. If an adequate trial of therapy has not produced clinically meaningful pain relief, patients should be tapered off their opioid analgesic and an alternative treatment administered.

5.2. Tramadol

Tramadol is a weak μ-opioid agonist that also inhibits the reuptake of norepinephrine and serotonin. The results of RCTs in patients with PHN, painful DPN, painful polyneuropathies of different etiologies, and post-amputation pain demonstrated that tramadol reduced pain and improved some aspects of health-related quality

of life [11,48,53,107,130]. As with opioids, tramadol is associated with abuse potential; although rates of tramadol abuse have remained very low despite new branded and generic formulations [18], some recent reports suggest that the rate of recreational tramadol use may be rising [134].

The most common side effects of tramadol are somnolence, constipation, dizziness, nausea, and orthostatic hypotension, which occur more frequently with rapid dosage escalation. Tramadol can cause or exacerbate cognitive impairment and gait disturbances in elderly patients. It can also precipitate seizures in patients with a history of seizures or in those receiving medications that reduce seizure threshold. Concurrent use of other serotonergic medications (including SSRIs and SSNRIs) may increase the risk of serotonin syndrome, and combination therapy with these medications must be undertaken cautiously.

Tramadol may be somewhat less efficacious than stronger opioid analgesics in patients with NP [31]. As for opioid analgesics, tramadol is recommended primarily for patients who have not responded to the first-line medications but it can also be considered for first-line use in select clinical circumstances (Table 4). Tramadol is available in both short- and long-acting formulations; for the short-acting formulation, the starting dosage is 50 mg once or twice daily, with gradual titration to a maximum of 400 mg/day. Dosage reduction is necessary in patients with renal or hepatic disease and in the elderly (Table 3).

6. Generally third-line medications

There are a number of other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances (e.g., when treatment with an opioid agonist is not indicated or when the patient's treatment history suggests greater potential for their effectiveness). These medications – for which there is substantially less evidence of efficacy than exists for TCAs, SSNRIs, calcium channel α2-δ ligands, topical lidocaine, opioid analgesics, and tramadol – include certain other antiepileptic (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid) and antidepressant (bupropion, citalopram, paroxetine) medications, mexiletine, *N*-methyl-D-aspartate (NMDA) receptor antagonists, and topical capsaicin. Recommendations for their use are based on efficacy in a single RCT or inconsistent results from multiple RCTs and the clinical experience of the authors (grade B recommendation).

6.1. Antiepileptic medications

In contrast to its established efficacy in trigeminal neuralgia, carbamazepine has yielded inconsistent results in RCTs of other types of neuropathic pain [31]. These studies generally had limited methodological quality. Three positive trials of valproic acid in painful DPN or PHN were reported from a single center but an RCT conducted in patients with painful polyneuropathies by a different research group was negative [31].

In several relatively small RCTs, lamotrigine showed evidence of efficacy in several types of NP or in subgroups of patients with these conditions [31]. However, intention-to-treat analyses were negative in three large recent RCTs, two of which were in painful DPN [40,123]. Slow titration from a low initial dosage is required with lamotrigine to reduce the risk of potentially serious cutaneous hypersensitivity reactions.

Three placebo-controlled RCTs have been published of oxcarbazepine in patients with painful DPN, one of which was positive [22], but two of which were negative [8,41]. In patients with painful DPN, topiramate showed efficacy in one RCT [84] but not in three others [118], and its efficacy was equivocal in a trial of chronic lumbar radicular pain [61]. Based on the results of these studies of first- and second-generation antiepileptic medications, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid can be considered options for patients who have not responded to the first- and second-line medications.

6.2. Antidepressant medications

The SSRIs citalopram and paroxetine showed limited evidence of efficacy in RCTs in painful DPN but fluoxetine did not [31]. Bupropion, which inhibits the reuptake of norepinephrine and dopamine, was efficacious in various peripheral and central NP conditions [31]. Based on the results of these trials, bupropion, citalopram, and paroxetine are options for patients who have not responded to an adequate trial of a TCA or SSNRI when additional treatment with a medication with analgesic and antidepressant effects is being considered.

6.3. Mexiletine, NMDA receptor antagonists, and topical capsaicin

Mexiletine is an orally administered lidocaine analogue, and RCTs in patients with painful DPN and other types of NP have shown either modest benefits or no differences compared to placebo [31,119]. When evidence of efficacy was found in these trials, it was at higher dosages, which are often poorly tolerated because of side effects.

Dextromethorphan and memantine block the NMDA receptor. A few early RCTs showed evidence of efficacy, but later trials have provided limited or no evidence of efficacy [31].

The results of RCTs that compared topical capsaicin with placebo in patients with painful DPN, PHN, and

post-mastectomy pain have been inconsistent [31,68]. Interpretation of efficacy is problematic in these studies because the burning associated with capsaicin use may have compromised blinding in the trials in which superiority to placebo was found.

7. Additional recommendations for central NP

Based on the results of a small number of RCTs [30,31,88], the following specific medications should be considered for patients with central NP: TCAs for central post-stroke pain; calcium channel α2-δ ligands for spinal cord injury pain; and cannabinoids for NP associated with multiple sclerosis (grade B recommendation). Lack of long-term follow-up data, limited availability, and concerns over precipitating psychosis or schizophrenia, especially in individuals with environmental or genetic risk factors [103], restrict the use of cannabinoids to second-line therapy for patients with multiple sclerosis NP at present, and additional trials are needed to further establish their efficacy and safety.

Many patients with central NP either do not have one of these diagnoses or require alternative therapy. In these situations, the first- and second-line medications recommended for peripheral NP can be considered for the treatment of central NP (except for topical lidocaine). However, it must be acknowledged that the evidence base for such treatment is limited.

8. Conclusions

TCAs, SSNRIs, calcium channel α2-δ ligands, and topical lidocaine have demonstrated efficacy in NP and are recommended as first-line medications. In patients who have failed to respond to these first-line medications alone and in combination, opioid analgesics or tramadol can be used as a second-line treatment alone or in combination with one of the first-line medications. Opioid analgesics and tramadol can also be considered for first-line use in select clinical circumstances (Table 4).

Patients who have not responded adequately to these medications used alone and in combination can be treated with one or more other recommended medications. For patients who have not responded adequately to pharmacologic management or those who have pain that is associated with challenging comorbidities or with a high level of disability or distress, prompt consultation with a pain specialist or multidisciplinary pain management center is recommended, including consideration of a broad array of non-pharmacologic therapies and invasive treatments.

It is important to emphasize that pharmacologic management of the patient with chronic NP should be considered an integral component of a more comprehensive approach that also includes non-pharmacologic treatments. Non-pharmacologic treatments for NP require increased attention and evaluation in controlled trials in which they are administered alone and also in combination with pharmacologic therapies.

Existing pharmacologic treatments for NP are limited, with no more than 40–60% of patients obtaining partial relief of their pain. Continued development of new medications for NP, additional trials involving existing medications alone and in combination to identify characteristics of treatment responders, identification of efficacious non-pharmacologic treatments for NP, and the development of strategies to prevent NP are therefore needed to advance the management of NP [13]. The management of NP is expected to rapidly evolve because of ongoing translational studies, and these evidence-based management recommendations should be updated within five years.

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Topical review

On the definitions and physiology of back pain, referred pain, and radicular pain

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1. Introduction

Despite the efforts of the International Association for the Study of Pain [6,21], confusion still persists amongst clinicians about the definitions of back pain, referred pain, radicular pain, and radiculopathy. Basic scientists now stand to inherit this confusion as they develop animal models of back pain [7].

Pivotal to the definition of these entities are seminal studies undertaken 50, 60, and 70 years ago. The legacy of this pioneering work has not properly permeated medical education, publications or clinical practice.

2. Nociceptive back pain

By definition, nociceptive back pain must be pain that is evoked by noxious stimulation of structures in the lumbar spine. The quality of pain so evoked has been determined in studies of normal volunteers, in whom discrete noxious stimuli were delivered to selected lumbar structures. In the original studies, muscles of the back [17] or the interspinous ligaments [18] were stimulated, using injections of hypertonic saline. Others replicated these studies [2,13]. Later, the lumbar zygapophysial joints [22,23] and the sacroiliac joints [14] were stimulated with injections of contrast medium that evoked pain by distending these joints. The dura mater has been stimulated mechanically [27] and chemically [10]. Surgeons who have operated on patients under local anaesthesia have probed various structures mechanically, and showed that the posterior surface of the lumbar intervertebral discs are the most potent source of experimentally-induced back pain [12,20,29]. Uniformly, these experimental studies showed that noxious stimulation causes dull, aching pain in the back. Consequently, when it occurs clinically, this type of pain that should be inferred to be nociceptive back pain.

3. Somatic referred pain

Noxious stimulation of structures in the lumbar spine can produce referred pain in addition to back pain. The pain spreads into the lower limbs, and is perceived in regions innervated by nerves other than those that innervate the site of noxious stimulation – the core of the definition of referred pain [21]. Since the source of spinal referred pain lies in the somatic tissues of the lumbar spine it has been named somatic referred pain [3,5], in order to distinguish it both from visceral referred pain and radicular pain. Somatic referred pain does not involve stimulation of nerve roots. It is produced by noxious stimulation of nerve endings within spinal structures such as discs, zygapophysial joints, or sacroiliac joints. The proposed mechanism of referral is convergence of nociceptive afferents on second-order neurons in the spinal cord that happen also to subtend regions of the lower limb [21]. As a general rule, somatic referred pain is perceived in regions that share the same segmental innervation as the source. Since somatic referred pain is not caused by compression of nerve roots, there are no neurological signs.

Somatic referred pain is dull, aching and gnawing, and is sometimes described as an expanding pressure. It expands into wide areas that can be difficult to localize [2,13,18]. Once established, it tends to be fixed in location. Subjects often find it difficult to define the boundaries of the affected area, but can confidently identify its centre or core. The earliest studies depicted segmental maps of the referred pain patterns [13,18] (Fig. 1). However, although pain from different segments in the lumbar spine refers to different regions in the lower limb, patterns are not consistent amongst subjects or between studies. Most significantly, however, the pattern is not dermatomal. If anything, the pattern corresponds to the segmental innervation of deep tissues in the lower limb, such as muscles and joints. Moreover, although somatic referred pain tends most often to centre over the gluteal region and proximal thigh, it can also extend as far as the foot (Fig. 1). Such distributions have been evoked in normal volunteers and patients by stimulating the lumbar zygapophysial joints [22,23] or intervertebral discs [25], and relieved in patients by anaesthetizing their zygapophysial joints [11,23,26]. To be consistent with these experimental data, when dull aching pain that spreads into the lower limb and settles into a relatively fixed location occurs in patients, it should be recognized as somatic referred pain, when it occurs in patients.

4. Radicular pain

Radicular pain differs from somatic referred pain both in mechanism and clinical features. Physiologically, it is pain evoked by ectopic discharges emanating from a dorsal root or its ganglion [21]. Disc herniation is the most common cause, and inflammation of the affected nerve seems to be the critical pathophysiological process [3]. The clinical features of radicular pain were established in studies of patients who underwent surgery for disc herniation. In

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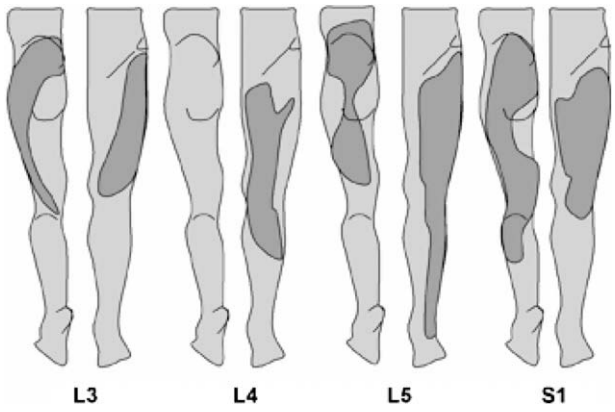

Fig. 1. Patterns of somatic referred pain evoked by noxious stimulation of the interspinous ligaments at the segments indicated. Based on Kellgren [18].

one study, the affected nerves and adjacent nerves were challenged by squeezing them with forceps in awake patients [24]. In another study, sutures were placed around the nerves, during surgery, and led out through the wound, so that they could be pulled on the following day [27]. The pain evoked was distinctive. It had a lancinating quality, and traveled along the length of the lower limb, in a band no more than 2–3 inches wide (see Fig. 2). This is the only type of pain that has been produced by stimulating nerve roots. So, reciprocally, it is only this type of pain that should be interpreted as radicular pain.

Significantly, squeezing or pulling normal nerve roots does not produce radicular pain. Only if nerve roots have previously been inflamed does mechanical stimulation evoke radicular pain [27]. For compression alone to be painful, it seems that it must involve the dorsal root ganglion. Although this has not been verified in experiments on human volunteers, it is borne out in animal studies.

Studies in laboratory animals have provided a neurophysiologic correlate of radicular pain. Squeezing normal nerve roots evokes only a momentary discharge, but squeezing a dorsal root ganglion, or squeezing an inflamed dorsal root, evokes discharges in Aβ as well as Aδ and C fibers [15,16]. Radicular pain, therefore, is not due to a discharge exclusively in nociceptive afferents; it is due to a heterospecific discharge in the affected nerve. The evoked sensation is very unpleasant but is not exactly pain, in a classical, nociceptive sense. The qualities of lancinating, shocking, or electric are consonant with more than nociceptive afferents discharging. Since the English language lacks a more precise word, this sensation is, nevertheless, by default, called pain.

Fig. 2. An illustration of the lancinating quality of radicular pain traveling into the lower limb along a narrow band.

The term – sciatica, is arcane. It stems from an era when the mechanisms of referred pain were not understood, and any referred pain was attributed to irritation of the peripheral nerve that passed through the region of pain. The taxonomy of the IASP recommends replacement by the term – radicular pain [21].

5. Radiculopathy

Radiculopathy is yet another, distinct entity [21]. It is a neurological state in which conduction is blocked along a spinal nerve or its roots. When sensory fibers are blocked, numbness is the symptom and sign. When motor fibers are blocked weakness ensues. Diminished reflexes occur as a result of either sensory or motor block. The numbness is dermatomal in distribution and the weakness is myotomal. However, radiculopathy is not defined by pain. It is defined by objective neurological signs. Although radiculopathy and radicular commonly occur together, radiculopathy can occur in the absence of pain, and radicular pain can occur in the absence of radiculopathy.

Careful clinical examination remains the best tool for diagnosing a radiculopathy. Electrophysiological testing should rarely be necessary. The indications and validity of electrophysiological testing are beyond the scope if this review, but they have been addressed elsewhere [1,4,9].

A common maxim is that the segmental origin of radicular pain can be determined from its distribution. This is not true. The patterns of L4, L5, and S1 radicular pain cannot be distinguished from one another [24,28]. Segments can be estimated only when radiculopathy occurs in combination with radicular pain. In that event, it is the dermatomal distribution of numbness – not the distribution of pain – that allows the segment of origin to be determined.

6. Discussion

Failure to distinguish radicular pain from somatic referred pain may lead to misdiagnosis and thereby mismanagement. Back pain and somatic referred pain are common, but radicular pain is not. When radicular pain has been strictly defined, its prevalence is only about 12% or less [8]. Mistaking somatic referred pain for radicular pain creates the erroneous impression that radicular pain is more common. Because of the strong possibility that somatic referred pain has been mistaken for radicular pain in the past, studies of the prevalence of radicular pain are not reliable [19].

With respect to clinical management, imaging is justified for the investigation of radicular pain and radiculopathy because imaging can often establish the causative lesion. The same does not apply for somatic referred pain. Plain radiographs, MRI scan, or CT scan are unable to reveal the cause of somatic pain, in the majority of cases. Moreover, they carry the risk of false-positive interpretations. Finding degenerative changes, disc bulges and possible nerve root compression is immaterial to the diagnosis if the patient has somatic referred pain, but can lead to unnecessary surgery if somatic referred pain is mistaken for radicular pain.

Since nociceptive back pain and somatic referred pain do not involve nerve injury, there are no grounds for expecting neurological symptoms or signs. In particular, allodynia should not be a feature; and, indeed, allodynia has never been recorded in cases of nociceptive back pain. In contrast, since radicular pain and radiculopathy do involve pathology of a nerve trunk, allodynia is a theoretical possibility, provided that the nerve suffers an appropriate injury. However, allodynia is not a typical feature of radicular pain or radiculopathy, unless there is true nerve damage and neuropathy rather than simply compression or inflammation.

Clinical practice is straightforward when presentations are unambiguous. A patient who is distressed by pain shooting down the lower limb, cannot lie comfortably, and on examination has numbness or weakness in the leg, clearly has radicular pain and radiculopathy. A patient with aching pain in the back, which spreads into the buttock and thigh, but no lancinating pain and no neurological symptoms, has nociceptive back pain and somatic referred pain.

Difficulties arise when patients have combinations. It is possible for a patient to have nociceptive back pain, due to internal disc disruption, for instance. This pain may be referred into the lower limb, in which case it is somatic referred pain. However, the disc may also herniate, or leak inflammatory chemicals onto the nearby nerve root. Chemical irritation of the nerve root will cause radicular pain. Radiculopathy may ensue as the nerve root becomes swollen and conduction block occurs. Each feature, then, has a separate cause and a separate mechanism; and invites separate investigation and treatment. Discectomy might remove the disc herniation and relieve the radicular pain; but it will not relieve the back pain and any somatic referred pain. Indeed, this is the common experience of surgeons: discectomy is highly successful for leg pain, but patients are left with their back pain.

Certain terms are misleading and unhelpful. There is no singular condition called "low back pain – sciatica". This term implies that the patient has a single condition that causes both symptoms, which is not correct. Patients can have back pain; they can also have sciatica; but the two symptoms have separate mechanisms and causes. Features, causes, and mechanisms of one entity cannot be attributed to the other. Thus, although disc herniation is the most common cause of radicular pain, it is not a common cause of back pain. The vast majority of patients with nociceptive back pain does not have radicular pain, and do not have a disc herniation. Nor is it necessary to invoke terms such as pseudo-sciatica or pseudo-radicular pain. There is nothing false about these symptoms. These terms are superfluous synonyms for somatic referred pain or, at times, peripheral nerve entrapment distal to the spine, neither of which has anything in common with radicular pain, other than being perceived in the lower limb. Indeed, because somatic referred pain is far more common than radicular pain, radicular pain should be regarded as the exception rather than somatic referred pain being relegated to some irregularity of radicular pain.

If clinicians ceased to confuse somatic referred pain and radicular pain, fewer patients would be mismanaged, and fewer would sustain iatrogenic problems. If basic scientist understand the distinction, animal models of nociceptive back pain would be developed that do not include neurological abnormalities.

Conflict of interest

The author has no conflicts of interest regarding this article.

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