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Algorithm for neuropathic pain treatment: An evidence based proposal

N.B. Finnerup[a,*], M. Otto[b,1], H.J. McQuay[c,2], T.S. Jensen[a,3], S.H. Sindrup[b,4]

[a]*Department of Neurology, Danish Pain Research Centre, Aarhus University Hospital, Aarhus Sygehus, Noerrebrogade 44, Aarhus 8000, Denmark*
[b]*Department of Neurology, Odense University Hospital, Sdr. Boulevard 29, Odense 5000, Denmark*
[c]*Pain Relief Unit, Churchill Hospital, Oxford OX3 7LJ, UK*

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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

* Corresponding author. Tel.: +45 8949 3455; fax: +45 8949 3269.
E-mail addresses: finnerup@akhphd.au.dk (N.B. Finnerup), maritotto@dadlnet.dk (M. Otto), henry.mcquay@balliol.ox.ac.uk (H.J. McQuay), tsj@akhphd.au.dk (T.S. Jensen), s.sindrup@dadlnet.dk (S.H. Sindrup).
[1] Tel.: +45 6541 2433; fax: +45 6541 3389.
[2] Tel.: +44 1865 225404; fax: +44 7092 160948.
[3] Tel.: +45 8949 3380; fax: +45 8949 3269.
[4] Tel.: +45 6541 2471; fax: +45 6541 3389.

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available treatments for neuropathic pain using NNT values (McQuay et al., 1995; Sindrup and Jensen, 1999, 2000). 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.

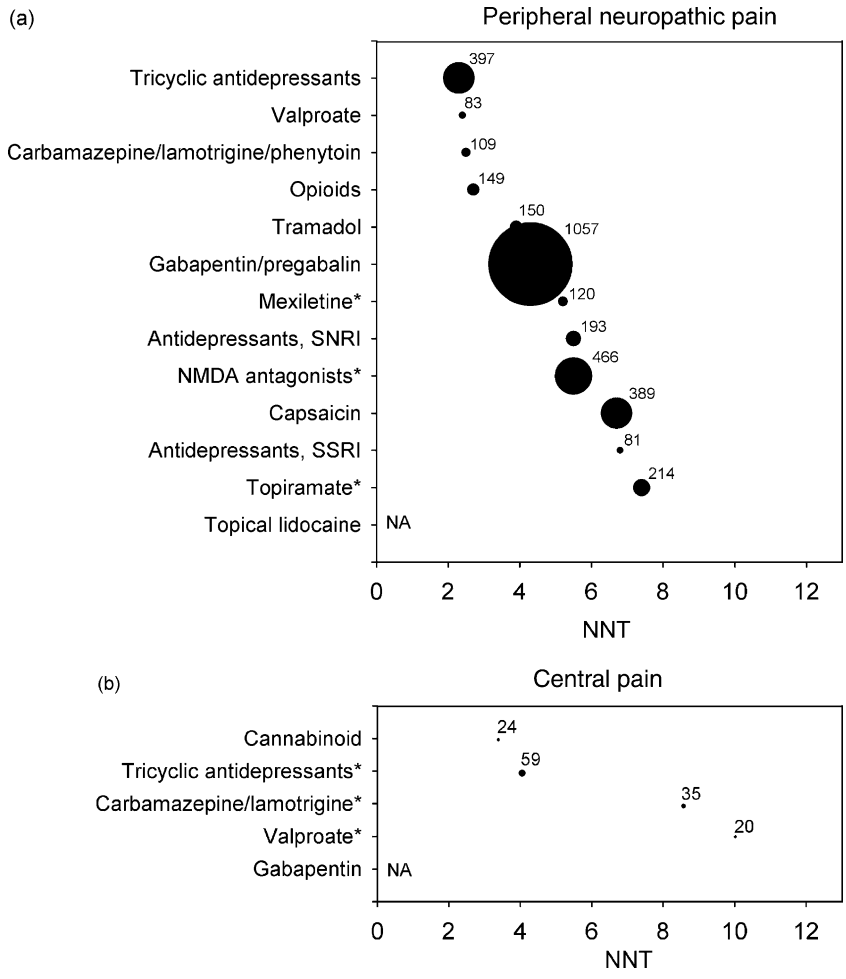

Fig. 1. Numbers needed to treat in peripheral and central neuropathic pain. Combined numbers needed to treat (NNT) to obtain one patient with more than 50% pain in (a) peripheral neuropathic pain (painful polyneuropathy, postherpetic neuralgia, and peripheral nerve injury pain) and (b) central pain (central 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 $\geq$ tramadol $\geq$ 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

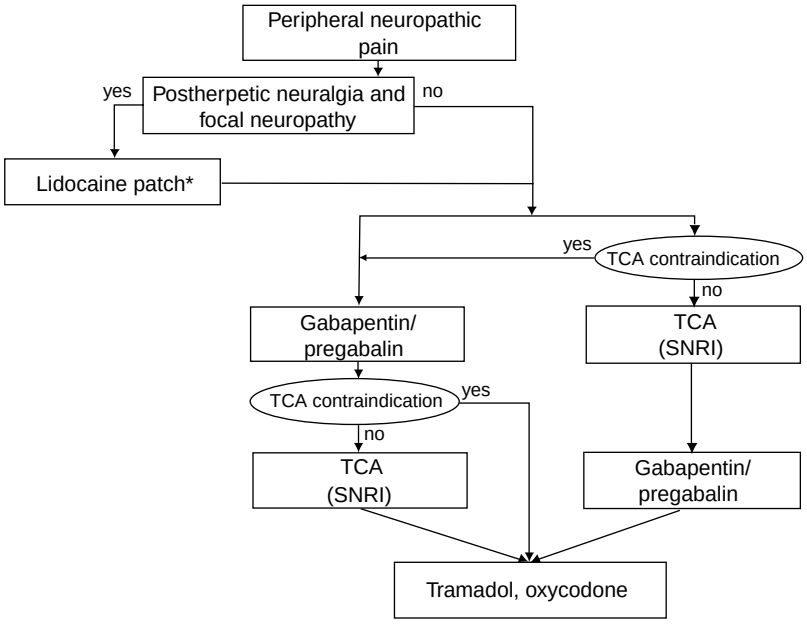

Fig. 2. Treatment algorithm. Proposed algorithm for the treatment of peripheral neuropathic pain. TCA, tricyclic antidepressants; SNRI, serotonin noradrenaline reuptake inhibitors. *Pain relieving effect of topical lidocaine has been shown in patients with allodynia.

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
Anticonvulsants									
Central post-stroke pain									

(*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	
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 Methadone, average 15 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)
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
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

(*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	
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	[n]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	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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