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# The evidence for pharmacological treatment of neuropathic pain

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ABSTRACT

Randomized, double-blind, placebo-controlled trials on neuropathic pain treatment are accumulating, so an updated review of the available evidence is needed. Studies were identified using MEDLINE and EMBASE searches. Numbers needed to treat (NNT) and numbers needed to harm (NNH) values were used to compare the efficacy and safety of different treatments for a number of neuropathic pain conditions. One hundred and seventy-four studies were included, representing a 66% increase in published randomized, placebo-controlled trials in the last 5 years. Painful poly-neuropathy (most often due to diabetes) was examined in 69 studies, postherpetic neuralgia in 23, while peripheral nerve injury, central pain, HIV neuropathy, and trigeminal neuralgia were less often studied. Tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors, the anticonvulsants gabapentin and pregabalin, and opioids are the drug classes for which there is the best evidence for a clinical relevant effect. Despite a 66% increase in published trials only a limited improvement of neuropathic pain treatment has been obtained. A large proportion of neuropathic pain patients are left with insufficient pain relief. This fact calls for other treatment options to target chronic neuropathic pain. Large-scale drug trials that aim to identify possible subgroups of patients who are likely to respond to specific drugs are needed to test the hypothesis that a mechanism-based classification may help improve treatment of the individual patients.



## 1. Introduction

Damage to the somatosensory system represents a potential risk for the development of neuropathic pain, and such damage to the nervous system can be caused by a variety of disorders ranging from simple nerve cuts to complex genetic disorders compromising axonal transport [85]. The sites of the disorders giving rise to neuropathic pain are likewise multiple and dispersed, extending from the boutons of terminal nerve fibers to the highest centers in the cerebral cortex. Neuropathic pain, which was recently suggested to be defined as "*pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system*" [105], constitutes a rather well-described symptom constellation despite diversities in causes and anatomy.

Pharmacological management remains the most important therapeutic option for chronic neuropathic pain, but results are still unsatisfactory and far from all patients obtain sufficient pain relief. So there is a considerable and unmet need for finding improved treatment of these patients. A series of guidelines have been proposed based on the published meta-analyses [29,31,83,115,116]. Subsequent recommendations (e.g., [26]) have added other aspects based mainly on consensus statements. The recommendations usually depend on the simple assessments of the patients' pain intensity and functionality without taking the possible underlying mechanisms into account. These global measures of pain and functionality may therefore disregard the underlying mechanisms responsible for the pain. As a result, our possibility to optimally target mechanisms of pain with specific therapies may be obscured. However, despite our ignorance of the underlying pain-generating mechanisms in individual neuropathic pain patients and despite the general lack of disease-modifying drugs, there is a need to find the best possible evidence for symptom control. Without head-to-head comparisons between different compounds, numbers needed to treat (NNT) and numbers needed to harm (NNH) collected either retrospectively or prospectively are alternative methods for determining efficacy across both compounds and conditions.

Following our review in 2005 [31], the number of randomized controlled trials has increased considerably, and the question is if this changes the picture of treatment recommendation. This paper provides up-to-date calculations of NNT and NNH values in neuropathic pain, and the advantages and disadvantages of these measures for advocating treatment strategies will be discussed.

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## 2. Methods

### 2.1. Search strategy

The full reports of randomized, placebo-controlled, double-blind studies published in peer-reviewed journals were identified using free-text searches of MEDLINE (April 2005 – April 30, 2010) and EMBASE (April 2005 – April 30, 2010). Additional papers were identified from published reviews and the reference lists of retrieved papers. The PhRMA Clinical Study Results Website (www.clinicalstudyresults.org) was searched by going through the list of drug names and retrieving all information for the drugs that have been used for neuropathic pain (up to May 2009) [19]. Letters were sent to the corresponding authors of papers that did not provide dichotomous data to ask if they could provide us with such data. All retrieved data were added to the results of our previous review, which included publications up to April 2005 [31].

### 2.2. Selection criteria

Randomized, double-blind, placebo-controlled studies in neuropathic pain conditions including at least 10 patients with no minimum follow-up time were included. Studies not written in English and studies where pain was not the primary outcome measure as well as enrich-enrollment and preemptive studies were excluded. We included the following neuropathic pain conditions: central post-stroke pain, neuropathic pain due to spinal cord injury and multiple sclerosis, painful poly-neuropathy, HIV neuropathy (including HIV-associated and antiretroviral treatment-associated peripheral and central neuropathies), postherpetic neuralgia (PHN), post-amputation pain (including stump and phantom pain), peripheral nerve injury pain, brachial plexus avulsion, trigeminal neuralgia, and mixed neuropathic pain. The studies on radiculopathies, complex regional pain syndrome, and cancer neuropathic pain were excluded because of the mixed pain etiology. Well-defined postmastectomy pain syndromes and postsurgical pain with postoperative pain compatible with a nerve cut were included. In addition comparative randomized double-blind trials of first-line drugs (tricyclic antidepressants (TCAs), serotonin noradrenaline reuptake inhibitors (SNRIs), topical lidocaine, gabapentin, and pregabalin [5,25] for neuropathic pain conditions were included.

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

From each study we extracted information as described earlier [31]. NNT for 50% pain intensity reduction (alternatively, 30% pain reduction or at least good pain relief) was the primary effect measure [61], and NNH was calculated as the number of patients that needed to be treated for one patient to drop out due to adverse effects. When the studies included only the percentage of patients with 50% pain relief, the actual numbers were calculated based on the assumption that it was the percentage of the intention-to-treat population. The 95% confidence interval (CI) of NNT and NNH values was calculated as the reciprocal value of the 95% CI for the absolute risk difference using the normal approximation. NNT values are expressed in the text as NNT (95% CI). Pooled raw data were used to obtain the combined measures of NNT values, assuming clinically homogeneous trials [63]. An instrument suggested by Jadad et al. was used as a measure of quality, and a minimum score of two (randomized and double-blind) was required [48]. The outcome of a trial (positive or negative) was judged by the reviewers in those cases where the authors' conclusions were at odds with the change in the primary outcome measure.

## 3. Results

### 3.1. Study and patient characteristics of included trials

Eligible randomized placebo-controlled trials (No. = 174) with references, study characteristics, and quality scores are listed in Supplementary Table 1. In addition to the 105 randomized, double-blind, placebo-controlled studies included in the 2005 review [31], 69 placebo-controlled studies (an 66% increase) met the inclusion and exclusion criteria. The number of studies with a cross-over design increased from 59 to 80, and those using a parallel design increased from 46 to 94. Painful poly-neuropathy (most often due to diabetes) was examined in 69 studies, PHN in 23, peripheral nerve injury in 19, HIV neuropathy in 16, central pain in 15, trigeminal neuralgia in 7, and mixed neuropathic pain (including studies on PHN or painful poly-neuropathy) in 25 studies. There was no statistically significant change in the average Jadad score from 2005 (3.9 (sd 0.9)) to 2010 (4.1 (sd 0.9)) ($p = 0.20$, $t$-test)).

### 3.2. Antidepressants

Tricyclic antidepressants (TCAs) have been shown to relieve various neuropathic pain conditions in many, often small, trials (review in [31]). In agreement with this, one recent study has confirmed the efficacy of TCAs in central pain [78] (Supplementary Table 1), although two studies with a high effect size during placebo treatment found no effect of amitriptyline in HIV neuropathy compared with placebo [56,89]. Two studies also failed to find effect of amitriptyline or nortriptyline in chemotherapy-induced neuropathic symptoms, where pain was not the primary outcome measure [43,54]. TCAs are generally reasonable well-tolerated but high doses may be a matter of concern [77].

The serotonin noradrenaline reuptake inhibitors (SNRIs) duloxetine and venlafaxine have a well-documented efficacy in painful poly-neuropathy [40,74,80,95,114], but venlafaxine failed to relieve postmastectomy in a low dose [102] and neuropathic pain of different etiologies in one small study [123](Supplementary Table 1).

SSRIs have been studied in a few trials which have demonstrated a weak analgesic effect [67,96,97] (Supplementary Table 1), but the clinical relevance of these compounds is questionable.

### 3.3. Anticonvulsants

The alpha-2-delta binding agents pregabalin and gabapentin are studied in large clinical trials. A clinical relevant effect of pregabalin has been shown in several trials across different peripheral and central neuropathic pain conditions (Supplementary Table 1), although it failed to relieve HIV neuropathy [93]. None of the trials published within the last 5 years [4,35,90,93,100,104,107,108,113] excluded patients failing to respond to prestudy gabapentin. The efficacy of gabapentin is also well-documented (Supplementary Table 1). Recently, extended release gabapentin relieved painful poly-neuropathy [84], but other recently published studies on gabapentin have been negative [41,73,78,99]. However, there is no overall evidence for superior efficacy of either of these two drugs in neuropathic pain (Supplementary Table 1), although the lower cost may favor the use of gabapentin.

Lamotrigine was effective in relieving central post-stroke pain [109] and painful diabetic poly-neuropathy [28], but recent larger studies have failed to show a pain-relieving effect in mixed neuropathic pain [91], pain in multiple sclerosis [15], and painful poly-neuropathy [72,111] although some of these studies had a high placebo response (Supplementary Table 1).

Oxcarbazepine relieved pain in a study of 146 patients with painful diabetic neuropathy [22], but failed to relieve such pain in two subsequent large studies [14,42]. One of these studies did, however, include a low dose of oxcarbazepine [42] and the other study was a dose-ranging study [14].

Valproate has an unsettled role in neuropathic pain treatment with three studies from one group reporting high efficacy [57–59] and others failing to find an effect [3,23,68].

Topiramate, an anticonvulsant with multiple modes of action and anorexic properties, failed to produce an analgesic response in three large studies of painful diabetic neuropathy involving more than 1200 patients [103]. A marginal effect was found in one additional study [75].

Lacosamide, a new anticonvulsant drug had a small but significant pain-relieving effect on painful diabetic neuropathy [76], while subsequent trials have failed to find an effect [88,121,125], except for the efficacy of a 400 mg dose in subgroup analyses. These studies had a high placebo response.

Levetiracetam, despite some promising experimental and open-label studies, has failed to relieve postmastectomy syndrome [110] and spinal cord injury pain [32] with no tendency towards better efficacy than placebo.

### 3.4. Opioids

Opioids, including tramadol, have a consistent efficacy in neuropathic pain (Refs. in [31] and [34,44,65,117,120]) (Supplementary Table 1). In a non-placebo-controlled study, Rowbotham and colleagues also demonstrated a dose-dependent pain relief with the opioid levorphanol in patients with peripheral and central neuropathic pain [82].

### 3.5. Miscellaneous

Lidocaine patch has been recommended as another first-line drug for patients with PHN or focal neuropathy with allodynia based on three published positive trials [31]. Recently, lidocaine spray produced a short-term effect in peripheral nerve injury and trigeminal neuralgia [50,51], but two trials with lidocaine cream or patch 5% failed to find efficacy in patients with peripheral nerve injury [17] or mixed neuropathic pain [47]. Therefore, at present, the results of placebo-controlled trials of topical lidocaine (cream or path) are conflicting. In an open-label study, a comparable efficacy of topical lidocaine and pregabalin was suggested in patients with painful poly-neuropathy and PHN [12]. In a subgroup analysis of a trial which is not published in full, lidocaine patch relieved pain intensity and various pain qualities, including non-allodynic pain qualities, in PHN [36].

Cannabinoids have a modest effect on central pain in multiple sclerosis [79,101]. Cannabinoids, including Sativex spray, have also been shown to relieve peripheral neuropathic pain [13,52,66] (Supplementary Table 1), but the effect size is small, and there was no effect in a small study in painful poly-neuropathy [87]. Smoked cannabis has been shown to be superior to placebo in HIV neuropathy and mixed neuropathic pain [1,30,118] (Supplementary Table 1).

NMDA antagonists and mexiletine have no consistent clinically relevant efficacy in neuropathic pain (Refs. in [31] and [86,120]) (Supplementary Table 1).

### 3.6. New drug classes

Until recently, studies on topical capsaicin have only shown consistent efficacy in PHN (Table 1 and Supplementary Table 1). However, two new studies found at least a 12-week modest pain reduction following the application of a single high-concentration capsaicin patch (NGX-4010) in patients with painful poly-neuropathy and HIV neuropathy [8,92]. Application of NGX-4010 is painful and requires prior application of a local anesthetic, but the treatment has long-term effect (12 weeks) and no or only limited systemic exposure and systemic side effects [7], suggesting that it may be a safe treatment option. A 4-week randomized trial with an open-label extension up to 48 weeks where PHN patients could receive up to three additional treatments supports the long-term efficacy [9]. Although epidermal nerve fiber density has shown nearly full recovery 24 weeks after a high dose capsaicin exposure in healthy volunteers [55], the long-term effect on epidermal fibers of repeated applications in patients with neuropathic pain is unknown. Qutenza, a cutaneous patch of capsaicin 8%, has been given marketing authorization in Europe with the indication: "treatment of peripheral neuropathic pain in non-diabetic adults" and FDA approval for PHN.

Botulinum toxin has been found to have antihyperalgesic effects and may thus be of potential value in treating chronic pain conditions. Botulinum toxin type A was injected intradermally in the painful area in 29 patients with focal painful neuropathy and relieved spontaneous pain and allodynia with a low placebo response and a low NNT [71]. There was sustained improvement in pain from weeks 2 to 14. Subsequently, the effect of botulinum toxin A was confirmed in painful diabetic neuropathy [122], again with a low placebo response. Besides pain upon application, the treatment had no further local or systemic side effects. Future studies are needed to determine if the long-term effect is consistent.

Three studies have also found the effect of isosorbide dinitrate or glyceryl trinitrate spray in painful diabetic neuropathy [2,3124], but the primary outcome was not clearly defined and the complete blinding questionable in two of these studies [2,3].

Single studies have suggested some efficacy of a neuronal nicotinic acetylcholine receptor (NNR) agonist in painful poly-neuropathy [81] and subcutaneous sumatriptan in trigeminal neuralgia [49], while other studies with more specific treatments have been negative (Supplementary Table 1).

It has recently been advocated that NSAIDs, which are generally considered non-effective in neuropathic pain, deserve to be examined in randomized controlled trials [112], although their use in chronic pain states are limited by their side-effect profiles.

### 3.7. PhRMA Clinical Study Results Database

The Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database is an open electronic database, which urges companies to post unpublished study summaries [19]. In addition to the published trials, this database presented one trial examining gabapentin 3600 mg, which relieved painful poly-neuropathy with an NNT of 7.0 (4.3–20), and four positive and three negative trials with pregabalin, revealing a combined NNT of 9.5 (6.8–16.0) (Supplementary Table 2). The outcome of lacosamide in one trial was not clearly stated and one trial failed to find an effect of levetiracetam in PHN (Supplementary Table 2).

### 3.8. Drug combinations

Due to the limited efficacy of available treatments, drug combinations are often used. In a placebo-controlled trial, a combination of morphine and gabapentin provided better pain relief than each drug given alone [38], but the gain was modest and in that particular study, gabapentin alone failed to reduce pain significantly. A combination of gabapentin and an opioid was supported in another study where patients with moderate to severe painful diabetic neuropathy despite receiving their maximum tolerated dose of gabapentin were administered prolonged release oxycodone or placebo [44]. Co-administration with oxycodone was associated

**Table 1**
Published randomized placebo-controlled trials in neuropathic pain excluding trigeminal neuralgia, radiculopathies, complex regional pain syndrome, and cancer-related neuropathic pain. The table indicates the number of positive (+) and negative (−) trials, combined numbers needed to treat (NNT) (with 95% confidence interval) to obtain one patient with more than 50% pain relief for drugs or drugs classes where the majority of studies show a pain-relieving effect, and the combined numbers needed to harm (NNH) for one drop out due to adverse effects. Please note that the differences in study design and patient populations preclude a direct comparison of NNT values across drug classes (see text).

| | Painful poly-neuropathy | Postherpetic neuralgia | Peripheral nerve injury[a] | HIV neuropathy | Central pain | Mixed neuropathic pain | Combined NNH |
|---|---|---|---|---|---|---|---|
| **Antidepressants** | | | | | | | |
| TCAs | **11+** 2.1 (1.9-2.6) | **4+** 2.8 (2.2-3.8) | **1+/1**− | **2**− | **2+** 2.7 (1.7-6.1) | **2+** NA | 15.9 (11-26) |
| SNRIs | **5+** 5.0 (3.9-6.8) | | **1**− | | | **1**− | 13.1 (9.6-21) |
| SSRIs | **3+/1**− 6.8 (3.9-27) | | | | | | ns |
| **Anticonvulsants** | | | | | | | |
| Gabapentin | **3+/1**− 6.4 (4.3-12) | **2+** 4.3 (3.3-6.1) | **1+/2**− | **1**− | **1+/1**− | **1+/1**− | 32.5 (18-222) |
| Pregabalin | **5+** 4.5 (3.6-5.9) | **4+** 4.2 (3.4-5.4) | **1+** ns | **1**− | **2+** 5.6 (3.5-14) | **1+** 3.8 (2.6-7.3) | 10.6 (8.7-14) |
| Lacosamide | **1+/3**− | | | | | | 7.8 (5.9-12) |
| Valproate | **2+/2**− | **1+** 2.1 (1.4-4.2) | | | **1**− | | ns |
| Lamotrigine | **1+/3**− | | | **1+/1**− | **1+/2**− | **2-** | 11.7 (8.5-19) |
| Topiramate | **1+/3**− | | | | | | 6.3 (5.1-8.1) |
| Levetiracetam | | | **1**− | | **1**− | | ns |
| Carbamazepine/ Oxcarbazepine | **3+/2**− 3.7 (2.6-6.4) | | | | **1**− | **1+** NA | 6.6 (4.9-10) |
| **Opioids** | | | | | | | |
| Opioids | **2+** 2.6 (1.7-6.0) | **2+** 2.6 (2.0-3.8) | **2+** 5.1 (2.7-36) | | | **2+/1**− 2.1 (1.5-3.3) | 17.1 (9.9-66) |
| Tramadol | **3+** 4.9 (3.5-8.0) | **1+** 4.8 (2.6-27) | **1+** NA | | **1+** ns | | 13.3 (8.8-27) |
| **Various** | | | | | | | |
| Cannabinoids | **1**− | | **1+** ns | | **2+** 3.4 (1.8-23) | **2+** 8.3 (4.5-45) | ns |
| Topical lidocaine | | **2+** NA | **1+/1**− | **1**− | | **1+/1**− | ns |
| NMDA antagonists | **2+/1**− 3.4 (2.1-9.0) | **4**− | **2**− | **1**− | | **3**− | 12.5 (7.5-36) |
| Mexiletine | **1+/3**− | | **1+/1**− | **2**− | **1**− | **1**− | ns |
| Topical capsaicin | **3+/2**− 11 (5.5-316) | **2+** 3.2 (2.2-5.9) | **1+/1**− | **1**− | | **1+** NA | 11.5 (8-20) |
| NGX capsaicin | | **2+** ns | | **1+** 6.5 (3.9-20) | | | ns |
| BTX-A | **1+** 2.3 (1.5-4.7) | | | | | **1+** 3.0 (1.6-22) | ns |
| Nitrate spray | **3+** NA | | | | | | ns |

TCAs: tricyclic antidepressants; SNRIs: serotonin noradrenaline reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; BTX-A: Botulinum Toxin Type A; NA: dichotomized data are not available; ns: absolute risk difference not significant.
[a] Includes postamputation pain and brachial plexus avulsion.

with significant pain relief and improved sleep, and the opioid-induced adverse events were not exacerbated by the combination with gabapentin. However, the interpretation of these results is compromised by inadequate doses of gabapentin in a substantial proportion of the patients. A small dose of oxycodone (10 mg) did not enhance the pain-relieving effect of pregabalin in a mixed blind-open-label study [126]. In a recent non-placebo-controlled study, the combination of nortriptyline and gabapentin at maximum tolerated doses produced greater pain relief and lesser pain interference with sleep and mood than when each drug was administered alone [37].

### 3.9. Comparative drug trials

A few comparative trials of first-line drugs (tricyclic antidepressants (TCAs), serotonin noradrenaline reuptake inhibitors (SNRIs), topical lidocaine, gabapentin, and pregabalin) [5,25] exist(Supplementary Table 3). There was no difference between venlafaxine and imipramine in a small study [95] and no differences between a TCA and gabapentin/pregabalin in six comparative trials (Supplementary Table 3). Combining these trials, equal number of patients had a 50% pain relief or a moderate pain relief during TCA (49% (128/261)) and during gabapentin or pregabalin (43% (110/254)) treatments ($p = 0.19$, $X^2$) [10,16,20,37,64,78]. There was also no difference in the combined number of patients withdrawn due to side effects in these studies (14.3% for TCAs and 10.5% for pregabalin/gabapentin, $p = 0.23$).

### 3.10. Quantitative data synthesis and homogeneity/heterogeneity

Combined NNT and NNH values for different drug classes and neuropathic pain conditions are shown in Table 1 and Fig. 1. Fig. 1 illustrates that despite new trials on NGX-capsaicin and intradermal BTX-A, the NNT values have changed only little during the past 5 years. As can be seen, drugs are only able to provide partial pain relief, leaving many patients with a minimal or no effect. Heterogeneity was examined visually using L'Abbé plots, showing pain relief for the major drug classes (Supplementary Fig. 1), while other measures such as calculating statistical heterogeneity [46] were not done. Differences in drug classes, drug doses, and placebo responses seem to be responsible for part of the heterogeneity in NNT, while the type of neuropathic pain diagnosis (Table 1) seems to be less important. It was not possible to retrieve data for 50% pain intensity reduction in all papers. In most studies where values for both 30% and 50% pain reduction were available the NNT was slightly lower for 30%, e.g. in four pregabalin studies in PHN and painful diabetic neuropathy [24,60,100,108] the combined NNT for 30% is 3.2 (2.7–3.9) and for 50% 3.9 (3.2–4.9). Thus, the variance in outcome measure may also be an important source of heterogeneity.

Fig. 2 shows the NNT values for the different drug classes against specific disease etiologies. As can be seen, the effect of the alpha-2-delta binding agents, TCAs, and opioids are almost similar in painful poly-neuropathy and PHN. For other conditions, the efficacy is less consistent, but these NNT values are often based on single studies. Thus, across the disease categories, the NNT values change very little (Table 1 and Fig. 2). Exceptions include lack of efficacy of amitriptyline and pregabalin in HIV neuropathy [56,89,93], which may in part be explained by extremely high effects during placebo treatment, lack of effect of gabapentin and TCAs in chemotherapy-induced painful poly-neuropathy [43,54,73], and limited efficacy in a few trials in phantom limb pain and peripheral nerve injury (Supplementary Table 1).

Fig 3 shows the relationship between NNT and NNH values. The comparison of NNH values is, however, difficult due to the differ-

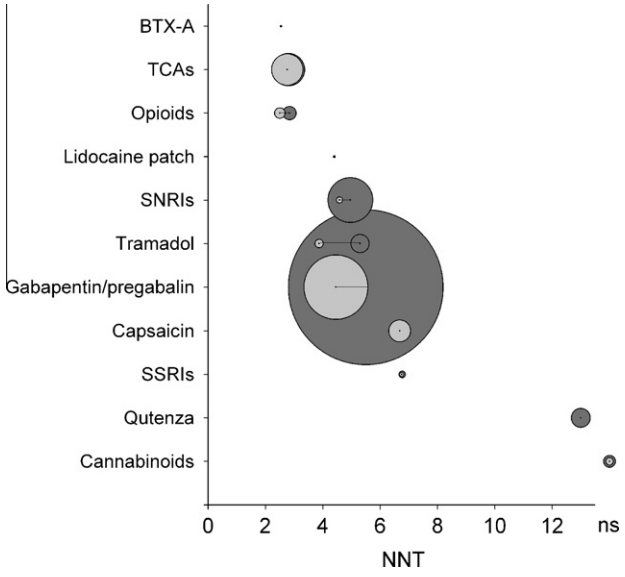


**Fig. 1.** It shows the combined numbers needed to treat (NNT) values for various drug classes in all central and peripheral neuropathic pain conditions (not including trigeminal neuralgia). The figure illustrates the change from 2005 values in light grey to 2010 values in dark grey. The circle sizes indicate the relative number of patients who received active treatment drugs in trials for which dichotomous data were available. Please note that the differences in study design and the patient populations preclude a direct comparison of NNT values across drug classes (see text). BTX-A: botulinum toxin type A; TCAs: tricyclic antidepressants; SNRIs: serotonin noradrenaline reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitor.

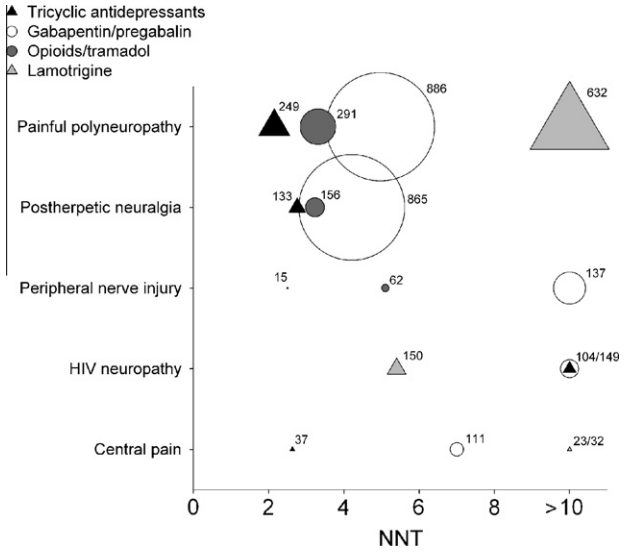


**Fig. 2.** It shows the combined numbers needed to treat (NNT) values for different drug classes against specific disease etiologies. The symbol sizes indicate the relative number of patients who received active treatment drugs in the trials for which dichotomous data were available.

ences in designs. TCA and opioid trials, e.g., are short lasting and studies on BTX-A and NGX-capsaicin do not include repeated treatments, which tend to reduce the number of dropouts as opposed to longer lasting trials (e.g., some pregabalin, gabapentin, and SNRI trials).

### 3.11. Effects during placebo treatment

Drug trials sometimes suffer from high placebo effect rates, which may preclude a positive outcome of possible efficacious

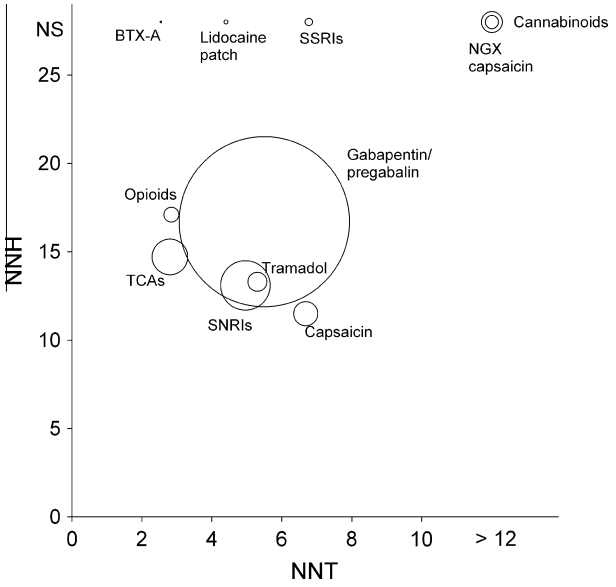


**Fig. 3.** It shows the relationship between the combined numbers needed to treat (NNT) values for 50% pain relief and numbers to harm (NNH) values for the number of patients to drop out of the study due to side effects. Please note that there are differences in study design and placebo responses that may influence NNH and NNT values, e.g. short-term trials and single drug applications may have higher NNH values (fewer dropouts due to side effects) than the long-term trials. The circle sizes and the related numbers indicate the number of patients who received active treatment drugs in trials for which the dichotomous data were available.

treatments [53]. Combining all the trials, the NNT values correlate to the percentage responding to the placebo treatment ($p < 0.001$, Pearson correlation coefficient 0.37); i.e. the higher the effect during placebo treatment, the higher the NNT value. Fig 4 shows how this may affect the conclusions for single drugs/drug classes, e.g. high average placebo effects and NNT values in lacosamide trials and low placebo values and NNT values in botulinum toxin A trials. Large pain reductions in the placebo treatment period may cause a ceiling effect, and the genuine efficacy of the tested drug may be difficult to show. In addition, the effect during active treatment is not necessarily additive to the effect during placebo treatment. The high effect sizes during placebo treatment are likely to influence the outcome of, e.g., the lacosamide trials with an average of 41% responding to placebo (Fig. 4) and the two negative topiramate trials with a 38% and 48% pain reduction during placebo [103]. Similar high placebo effects have been seen in some of the trials in HIV neuropathy [56,89,93]. Likewise, variability in the NNT values between the published (overall NNT 5.3 (4.5–6.3)) and the unpublished (overall NNT 9.5 (6.8–16)) pregabalin trials may also be explained partly by the variability in the placebo effect. In the 12 published trials, 39% responded to pregabalin and 20% to placebo, while in the still unpublished trials, 42% responded to pregabalin and 31% to placebo. On the otherhand, low NNT values may reflect very low placebo responses rather than a particularly high efficacy of the drug (e.g. in botulinum toxin A trials [71,122]) (Fig. 4).

## 4. Discussion

### 4.1. Meta-analyses: a useful measure for judging drug efficacy?

The use of NNT and NNH values instead of head-to-head comparisons is not without problems. In our previous review [31], different reasons were listed why the NNT calculations may be criticized as a method to compare efficacy of different drug classes. These critical points include: (a) exclusion of non-placebo-controlled studies, (b)

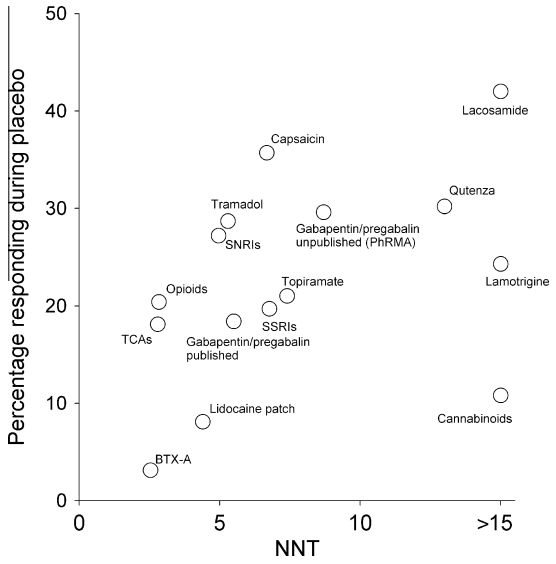


**Fig. 4.** It shows the combined numbers needed to treat (NNT) values for various drug classes and the corresponding percentage of patients reporting at least 50% pain relief during placebo treatment.

different cut-off points for pain relief, (c) drug efficacy based on one-dimensional measures such as pain intensity or pain relief, (d) NNT calculation requires dichotomization of data resulting in loss of information, and (e) difference in study design across drug classes. The neuropathic pain syndrome in a particular patient is a result of a series of factors reflecting the disease etiology, location of nerve damage, mechanisms of the symptoms and signs seen, and intraindividual factors. It is unlikely that this complexity can be squeezed into a "crude rating scale of global pain intensity" [21]. This means that a statistically significant effect between two compounds does not necessarily represent a clinically meaningful difference. For that reason it has been recommended that additional outcome domains rather than anchor-based methods such as pain intensity are used to evaluate the importance of improvement or the opposite [27]. It is also important that the emphasis in treatment guidelines are not based only on the amount of evidence, since we then risk a bias towards drugs that are pushed forward in clinical trials by the pharmaceutical industry. A drawback of the present study is the free-text search which precludes a proper list of primary included and secondary excluded papers. Another limitation is the possible lack of sufficient power in some of the included studies; many negative trials based on a few patients are likely to suffer from a type-2 error.

#### 4.1.1. Heterogeneity

As discussed above, the variability in response during the placebo treatment is important to acknowledge as a critical factor when comparing the efficacy across different trials. Identifying the methods for reducing the placebo response is important for future trials [69,70]. Cross-over trials are likely to have lower NNT values than parallel-group trials since NNT values in cross-over designs are calculated on the basis of the completed population (as opposed to intention-to-treat analyses) [31] and cross-over trials have lower placebo responses [53]. Also, the many small cross-over trials in, e.g., TCA trials may have been more prone to publication bias, which was demonstrated to have a major influence on apparent effect size of antidepressants in depression [106].

Therefore, due to the heterogeneity of the studies, particularly in drug dose, design (cross-over versus parallel-group designs), and placebo response, the use of NNT (and other meta-analysis measures) for comparing the drug efficacy should be done cautiously. Nevertheless, because of lack of large long-term comparative drug trials, meta-analyses can provide some guidance to a treatment algorithm, provided comparisons are used with caution.

#### 4.1.2. The role of NNH for treatment recommendations

Adverse effects represent an important limiting factor for recommending treatments but are often reported in an unsystematic manner so that the only measure that can be calculated retrospectively is the number of dropouts due to adverse effects from a particular trial. The issue of NNH is complex because adverse effects are likely to differ in their severity and relevance in patients. For example, weight gain, which is seen with TCAs and gabapentin/pregabalin, is an important side-effect in diabetes, while this may be less important in PHN, and a beneficial sedative effect of gabapentin in the elderly with PHN may be a disadvantageous effect in a patient with traumatic nerve injury who is still working. So side effects cannot be recorded in a general fashion across different conditions. Another limitation of the use of NNH is that the dropout rates are likely to be influenced by the duration of the trial and to be low in single dose settings (e.g. botulinum toxin A and NGX-capsaicin trials), and they do not provide information of long-term side effects.

#### 4.1.3. A disease-based classification: fact or fiction?

Since (1) there are no clear indications that specific diseases should be treated with specific treatments, (2) symptoms and signs overlap in various neuropathic pain conditions [6], and (3) currently available drugs act with unspecific neurodepressant actions rather on pivotal pathophysiological mechanisms, at present there is no good rationale for a treatment algorithm that discriminates between underlying etiologies [45]. Nevertheless, the vast majority of trials have been done in painful diabetic neuropathy and PHN and few, if any, in certain other conditions (e.g. Guillain–Barré syndrome and small-fiber neuropathy), and recommending a treatment for other conditions may seem to be an unjustified jump.

### 4.2. Treatment recommendations

Despite an increase of 66% in new randomized placebo-controlled trials in neuropathic pain since 2005 (Fig. 1), there seems to be no evidence for major changes of the treatment algorithm proposed before [31]. The present findings indicate that for any algorithm it is necessary not only to consider the evidence but also take effect size and potential long-term side effects into account.

### 4.3. Future challenges in improving neuropathic pain treatment

With the clear increase in the number of trials in neuropathic pain seen in the last 5 years, it is noteworthy that the NNTs have not decreased, so the current principles for treating neuropathic pain still seem to be insufficient. There may be several reasons for this rather disappointing fact, 5 years after the last meta-analysis: (1) limited number of trials on new drugs and lesser studied diseases. (2) Use of a disease-based classification in all trials. (3) Available drugs do not target the various mechanisms underlying the pain, since many of these drugs act mainly by reducing neuronal hyperexcitability, but not the more distinct pain-generating mechanisms. (4) The primary outcome measure in most pain trials is based on a one-dimensional recording of pain intensity, which does not encapsulate the complex spectrum of the pain experience such as the emotional and socioeconomic aspects of long-lasting pain. (5) Previous trials have not looked at agents attempting to prevent the maladaptive changes in the pain process, i.e., those processes where the underlying disease or the long-standing pain cause irreversible changes in the nervous system that are beyond any type of modulation.

The minor effects found in large-scale "low-intensity" trials may reflect no effect at all in most patients and a superb effect in small subgroups. Therefore, large-scale drug trials including thorough patient characterizations are needed to improve our algorithm so that possible subgroup specificity of efficacy can be determined for both drugs with a high overall efficacy and drugs with only a minor effect [94,98]. Such classification is in line with strategies directed at pain mechanisms, which are currently being explored [11,33,119]. It is possible that a mechanism-based classification will improve treatment by specifying specific pain phenotypes that respond to, e.g., sodium channel blockers, SSRIs, topical capsaicin, etc. Particularly with the focused development of more selective drugs [39], subgroup analyses may be of particular importance [94]. In other words, more trials are needed to establish guidelines for whom to treat and with which drug [18,62]. Future trials – despite the so far discouraging stage – are needed to evaluate the usefulness of a mechanism-based classification and whether neuropathic pain can be relieved by highly specific pain treatment or the complexity of pain transmission and modulation will require treatments that address several targets.

## 5. Conclusion

Pharmacological treatment still represents the main option for treating chronic neuropathic pain. Our understanding of neuropathic pain-generating mechanisms has grown considerably within the last few decades, but unfortunately this research has not been matched by a similar improvement in treatment efficacy. We are still limited in our efforts in managing neuropathic pain by relying on treating the symptoms of pain rather than identifying the underlying disease mechanisms causing the pain. Although 69 new randomized controlled trials have been published in the past 5 years compared with 105 published trials published in the preceding 39 years, only a marginal improvement in the treatment of the patients with neuropathic pain has been achieved.

## Conflict of interest

Nanna B. Finnerup has received honoraria in the past year from Grunenthal. Troels S Jensen has received honoraria or consultancy fee from Pfizer, Eli Lilly, Grunenthal, Takeda, PharmaEste. Søren H Sindrup is paid to participate in advisory boards with Eli Lilly/Boehringer Ingelheim, Grünenthal, Nycomed Group and Pierre Fabre within the last year.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.06.019.

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