EFNS guidelines on the pharmacological treatment of neuropathic pain: 2009 revision

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Background and objectives: This second European Federation of Neurological Societies Task Force aimed at updating the existing evidence about the pharmacological treatment of neuropathic pain since 2005.

Methods: Studies were identified using the Cochrane Database and Medline. Trials were classified according to the aetiological condition. All class I and II randomized controlled trials (RCTs) were assessed; lower class studies were considered only in conditions that had no top-level studies. Treatments administered using repeated or single administrations were considered, provided they are feasible in an outpatient setting.

Results: Most large RCTs included patients with diabetic polyneuropathies and post-herpetic neuralgia, while an increasing number of smaller studies explored other conditions. Drugs generally have similar efficacy in various conditions, except in trigeminal neuralgia, chronic radiculopathy and HIV neuropathy, with level A evidence in support of tricyclic antidepressants (TCA), pregabalin, gabapentin, tramadol and opioids (in various conditions), duloxetine, venlafaxine, topical lidocaine and capsaicin patches (in restricted conditions). Combination therapy appears useful for TCA-gabapentin and gabapentin-opioids (level A).

Conclusions: There are still too few large-scale comparative studies. For future trials, we recommend to assess comorbidities, quality of life, symptoms and signs with standardized tools and attempt to better define responder profiles to specific drug treatments.

Background and objectives

Neuropathic pain (NP) may be caused by a lesion or a disease of the somatosensory system [1] and is estimated to afflict as high as 7–8% of the general population in Europe [2,3]. The management of NP is challenging because the response to most drugs remains unpredictable [4] despite attempts to develop a more rationale therapeutic approach [5,6]. In 2006, the European Federation of Neurological Societies (EFNS) produced the first guidelines on pharmacological treatment of NP [7]. Since 2006, new randomized controlled trials (RCTs) have appeared in various NP conditions, justifying an update.

The objectives of our revised Task Force were (i) to examine all the RCTs performed in various NP conditions since 2005, (ii) to propose recommendations aiming at helping clinicians in their treatment choice for most NP conditions, and (iii) to propose studies that may clarify unresolved issues.

Methods

We conducted an initial search of the Cochrane Library from 2005. Whenever the Cochrane search failed to
identify top-level study for a given NP condition or a potentially effective drug, we expanded the search to Medline and other electronic databases including Web results from major unpublished company trials (January 2005–September 2009). As in the first guidelines, we produced individual chapters and guidelines based on aetiological conditions. Each chapter was assigned to two or more Task Force participants. Classification of evidence and recommendation grading adhered to the EFNS standards [8].

Inclusion criteria were the following: controlled class I or II trials (lower class studies were evaluated in conditions in which no higher level studies were available); trials including patients with probable or definite NP [1] or trigeminal neuralgia; chronic NP (≥3 months); pain considered as the primary outcome (e.g. studies in which dyesthesias were the primary outcome, as in chemotherapy-induced neuropathy, were excluded); minimum sample of 10 patients; treatment duration and follow-up specified; treatment feasible in an outpatient setting; studies evaluating currently used drugs or drugs under clinical phase-III development: full paper citations in English.

Exclusion criteria included duplicated patient series, conditions with no evidence of lesion in the somatosensory system (e.g. CRPS I, fibromyalgia, low-back pain), studies using non-validated primary outcome measures, disease modifying treatments (i.e., alphabetic acid for diabetes) and pre-emptive treatments.

We extracted information regarding the efficacy on pain, symptoms/signs, quality of life, sleep and mood and side effects (see Appendices 1 and 2).

Results
Our search strategy identified 64 RCTs since January 2005 using placebo or active drugs as comparators and three subgroup or post hoc analyses of prior RCTs.

Painful polyneuropathy
Painful polyneuropathy (PPN) is a common NP condition. Diabetic and non-diabetic PPN are similar in symptomatology and with respect to treatment response, with the exception of HIV-induced neuropathy.

Antidepressants
The efficacy of tricyclic antidepressants (TCA) is largely established in PPN (notably diabetic), although mainly based on single centre class I or II trials [7,9,10]. Three RCTs reported the efficacy of venlafaxine ER in PPN, although this seems lower than imipramine on responders and quality of life in a comparative trial [7,11]. Side effects are mainly gastrointestinal, but elevated blood pressure and clinically significant ECG changes were reported in 5% of patients. The efficacy of duloxetine is established by three large-scale trials in diabetic PPN [12], with similar efficacy to that of gabapentin/pregabalin based on one industry-funded meta-analysis [13], although direct comparisons are lacking; the effect is reported to persist for one year [14]. Frequent adverse events are nausea, somnolence, dry mouth, constipation, diarrhoea, hyperhidrosis and dizziness; discontinuation rates are 15–20% [15,16]. Duloxetine induces no/little cardiovascular side effects, but rare cases of hepatotoxicity have been reported [15]. Selective serotonin reuptake inhibitor (SSRI) or mianserin provides little or no pain relief [7,17].

Antiepileptics
Gabapentin and pregabalin are effective in diabetic PPN [18,19], with dose-dependent effects for pregabalin (several negative studies for 150 mg/day, mainly positive studies for 300–600 mg/day) [19] and similar efficacy between gabapentin and the TCA nortriptyline in a recent class I study [20]. Side effects include dizziness, somnolence, peripheral oedema, weight gain, asthenia, headache and dry mouth. In a recent comparative trial, only two side effects differentiated gabapentin and nortriptyline: dry mouth (more frequent with nortriptyline) and concentration disorders (more frequent with gabapentin) [20]. Discontinuation rates for pregabalin range from 0 (150 mg/day) to 20% (600 mg/day) [19,21]. All the other trialled antiepileptics show variable and sometimes discrepant results. Smaller class III trials (carbamazepine) suggest efficacy [7], while larger placebo-controlled studies usually show no or limited benefit (Table 1) [7,22–29]. One reason for this variability could be a large placebo effect [30].

Opioids
Oxycodone, tramadol [31,32] and tramadol/acetaminophen combination [33] reduce pain in diabetic PPN. Side effects include mainly nausea and constipation, but long-term use of opioids may be associated with misuse (2.6% in a recent 3-year registry study of oxycodone in mainly diabetic NP, although higher rates were also reported) [4,34]. Tramadol should be used with caution in elderly patients because of risk of confusion and is not recommended with drugs acting on serotonin reuptake such as SSRIs [7,32]. The tramadol/acetaminophen combination appears better tolerated [33].

Others
Recent studies reported efficacy of botulinum toxin type A [35], nitrates derivatives [36,37] and a new nicotinic
agonist [38]. Of the other drugs trialled in PPN, one reported a positive outcome (levodopa), another showed discrepant results (NMDA antagonists), while the rest had limited or no efficacy (Table 1) [10,39].

**Combination**

Three class I studies found a superiority of the gabapentin-opioids (morphine, oxycodone) and gabapentin/nortriptyline combinations compared to each drug alone in patients with diabetic PN including Post-Herpetic Neuralgia (PHN) in two studies [20,40,41], while a small study suggested superiority of the gabapentin/venlafaxine combination compared with gabapentin and placebo [7].

**HIV neuropathy**

Most initial trials of HIV neuropathy were negative (Table 1) [7,42]. Only lamotrigine was moderately effective in patients receiving antiretroviral treatment [43]. Recent RCTs found efficacy of smoked cannabis
Topical agents

Lidocaine plasters (5%) are effective based on 5 class I or II RCTs in PHN with brush-induced allodynia, but the therapeutic gain is modest against placebo, and the level of evidence is lower than for systemic agents [7, 53]. The largest recent trial including patients with or without allodynia (with enriched enrolment design) was negative on the primary outcome (time-to-exit), but the groups were not balanced at baseline, and many patients withdrew prematurely from the study [54]. In an enriched-design open-label trial, lidocaine plaster was better tolerated than pregabalin [55]. Lidocaine plasters are safe because of their low systemic absorption and well tolerated with local adverse effects only (mild skin reactions) [54–56].

Randomized controlled trials have reported benefit from topical capsaicin 0.075% [7], but as a result of the burning effect of capsaicin, blinding was probably compromised. A one-off application of high concentration (8%) capsaicin patch applied to the skin for 60 min was more effective than a low concentration patch (0.04%) during 12 weeks [57]. Although a post hoc analysis suggests that blinding was successful, patient randomized to the high concentration patch required more rescue medication immediately after application. Adverse effects were primarily attributable to local capsaicin-related reactions at the application site (pain, erythema). Efficacy of capsaicin patches was demonstrated in two other studies reported in a systematic review [47].

Others

NMDA antagonists, lorazepam and a selective Cox2 inhibitor do not provide pain relief in PHN (Table 1) [7, 58].

Recommendation

We recommend TCA or gabapentin/pregabalin as first-line treatment in PHN (level A). Topical lidocaine (level A, less consistent results) with its excellent tolerability may be considered first line in the elderly, especially if there are concerns regarding the CNS side effects of oral medications. In such cases, a trial of 2-4 weeks before starting other therapy is justified [54]. Strong opioids (level A) and capsaicin cream are recommended as second choice (see section 1). Capsaicin patches are promising (level A), but the long-term effects of repeated applications particularly on sensation are not clarified.

Trigeminal neuralgia

Trigeminal neuralgia (TN) typically presents with very brief attacks of pain (electric shocks) and is divided into ‘classic’ when secondary to vascular compression of the
trigeminal nerve in the cerebellopontine angle or when no cause is found, or ‘symptomatic’ when secondary in particular to cerebellopontine angle masses or multiple sclerosis [59].

Carbamazepine, oxcarbazepine
Carbamazepine is the drug of choice in TN, but its efficacy may be compromised by poor tolerability and pharmacokinetic interactions. Two class II RCTs found similar effects of oxcarbazepine compared to carbamazepine on the number of attacks and global assessment [60,61].

Others
Several drugs (i.e., lamotrigine, baclofen) have been reported efficacious in TN based on small single trials each [61,62] (Table 1), but a Cochrane review [63] concludes that there is insufficient evidence to recommend them in TN. Small open-label studies also suggested therapeutic benefit from botulinum toxin A and some antiepileptics [62,64,65] (Table 1).

Symptomatic TN
There are only small open-label class IV studies in symptomatic TN associated with multiple sclerosis [62].

Recommendation
In agreement with previous guidelines [7,61,62], carbamazepine (level A) and oxcarbazepine (level B) are confirmed first line for classical TN. Oxcarbazepine may be preferred because of decreased potential for drug interactions. Patients with intolerable side effects may be prescribed lamotrigine (level C) but should also be considered for a surgical intervention. We deplore the persistent lack of RCTs in symptomatic TN.

Central neuropathic pain
The most frequent central neuropathic pain (CP) states are caused by stroke (central post-stroke pain, CPSP), spinal cord injury (SCI) or multiple sclerosis (MS).

Antidepressants
The beneficial effects of TCA were suggested in CPSP, but one large-scale study was negative in SCI pain probably because of low doses and lack of specific evaluation of NP [7,66]. A recent RCT in SCI pain showed that high doses of amitriptyline (150 mg/day) relieved pain more effectively than diphenhydramine and gabapentin (3600 mg) in depressed patients [67]. Despite its limitations (small study, high dose of amitriptyline), it suggests that TCA can justifiably be considered for SCI patients particularly those with depression. No RCT has evaluated the efficacy of SNRI in CP.

Antiepileptics
The efficacy of pregabalin was demonstrated in a multicentre study of traumatic SCI pain [68] and confirmed in various CP conditions in a single centre study [20,69]. Discrepant results were reported with gabapentin and lamotrigine [7,43,67,70]. Negative results were obtained with other antiepileptics (Table 1) [7,71].

Opioids
Evidence for efficacy of opioids in CP is based on only one study comparing high and low doses of levorphanol in which patients with peripheral or central NP participated [72]. A recent RCT showed beneficial effect of tramadol on pain intensity, but not pain affect but many side effects were observed and caused attrition in 43% of cases (17% for the placebo) [73].

Cannabinoids
Cannabinoids (tetrahydrocannabinol, oromucosal sprays 2.7 mg delta-9-tetrahydrocannabinol/2.5 mg cannabidiol) were effective in MS-associated pain in two class I trials [7]. Adverse events (dizziness, dry mouth, sedation, fatigue, gastrointestinal effects, oral discomfort) were reported by 90% of patients in long-term extension study (up to 3 years), but no tolerance was observed [74].

Others
Negative results were obtained with low-dose mexiletine in SCI pain and S-ketamine iontophoretic transdermal in CP [7,75].

Recommendation
We recommend pregabalin (level A), amitriptyline (level B, level A in other NP conditions) or gabapentin (level A in other NP conditions) as first line in CP (Table 1). Tramadol (level B) may be considered second line. Strong opioids (level B) are recommended second or third line if chronic treatment is not an issue. Lamotrigine may be considered in CPSP or SCI pain with incomplete cord lesion and brush-induced allodynia (level B) and cannabinoids in MS (level A) only if all other treatments fail.

Other NP conditions
The level of evidence for drugs in other NP conditions is reported in Table 2.

Cancer NP: There is level A evidence for the efficacy of gabapentin (one study), level B for TCA and tramadol and ineffectiveness of valproate [7,76,77]. Traumatic NP: Gabapentin was reported to be ineffective.
on the primary outcome in a large multicentre trial but improved several secondary outcomes and may be beneficial in a subgroup of patients (level A) although predictors of the response need to be identified [78]; antidepressants have level B evidence, good results were reported for botulinum toxin A, and discrepant or negative results were obtained with other drugs [79,80].

**Radiculopathy:** Pregabalin (level A), TCA and opioids and their combination (level B) are ineffective or slightly effective (the combination TCA/opioids was effective on maximal pain only in one study) [81–83].

**Phantom pain:** Efficacy of tramadol and morphine was reported (level A), while gabapentin induced discrepant results [84,85].

Results in **multi-aetiology NP** are positive mainly for antidepressants (bupropion, TCA), opioids (levorphanol, methadone) and cannabinoids [7,86–92].

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**Effects on pain symptoms and signs and predictors of the response**

Randomized controlled trials increasingly assess symptoms and signs [60] and suggest that drugs (gabapentin, oxycodone, topical lidocaine, cannabinoids) have differential effects on the quality of NP (i.e., burning, deep, paroxysmal) [7,93,94] and that some may alleviate brush-induced and/or static mechanical allodynia based on single trials (TCA, pregabalin, cannabinoids, topical lidocaine, venlafaxine, NMDA antagonists but not lamotrigine) [7,50,87,88,95].
Although predictors of response to some drugs (e.g., opioids, lidocaine plasters) were identified in post hoc analyses [79,96,97], no RCT has yet been designed to detect predictive factors of the response based on baseline phenotypic profile (level C).

**Effects on Quality of Life (QoL), sleep and mood**

Quality of Life, sleep and mood are frequently impaired in patients with NP [98,99]. Generally, the effects on pain are related to improvement in QoL [100; however see 75]. Beneficial effects of duloxetine, pregabalin and gabapentin were reported on these outcomes in class I trials [7,40,99,101]. However, the most consistent effects were observed with pregabalin and gabapentin on sleep quality [40,98], and poor results were reported with pregabalin on QoL or mood in 6 trials. Three trials reported the efficacy TCA on QoL [40,99,102]. Opioids and tramadol improve pain impact on sleep but have discrepant effects on QoL [99], cannabinoids alleviate QoL or sleep [44,45,87], but these drugs generally do not improve mood [32,72,73,76,87].

**Final recommendations and issues for future trials**

The present revised EFNS guidelines confirm TCA (25–150 mg/day), gabapentin (1200–3600 mg/day) and pregabalin (150–600 mg/day) as first line for various NP conditions (except for trigeminal neuralgia, section 3) and lidocaine plasters (up to 3 plasters/day) first line in PHN particularly in the elderly (section 2). We now are able to recommend SNRI (duloxetine 60–120 mg/day, venlafaxine 150–225 mg/day) first line in painful diabetic polyneuropathies based on their more established efficacy. TCA raise safety issues at high doses and in the elderly, they are not more effective than gabapentin based on one comparative trial [20], but they are less costly [98]. Pregabalin has pharmacokinetic advantages compared to gabapentin (bid dosing, dose-dependent efficacy) but has similar efficacy and tolerability based on meta-analyses. Second-line treatments include tramadol (200–400 mg/day) except in select conditions (section 1) and capsaicin cream in PHN. Strong opioids are recommended as second/third line despite established efficacy in neuropathic non-cancer pain because of potential risk for abuse on long-term use, as there are still too few long-term safety trials in neuropathic pain [48]. Capsaicin patches are promising for painful HIV neuropathies or PHN (level A). Cannabinoids (level A in MS and peripheral NP) are proposed for refractory cases. Combination therapy (level A for gabapentin combined with opioids or TCA) is recommended for patients who show partial response to drugs administered alone.

To date, the choice between these different treatments is mainly in their ratio efficacy/safety and in the patients’ clinical condition (e.g. comorbidities, contraindications, concomitant treatments). However, in a recent study investigating more than 2000 patients with neuropathic pain caused by diabetic neuropathy and post-herpetic neuralgia, Baron and colleagues [103] found that patients with these conditions could be subgrouped according to specific sensory profiles. A classification per sensory profiles rather than based merely on aetiology could contribute to minimize pathophysiological heterogeneity within study groups and increase the positive treatment responses [104,105].

We propose the following strategy for future trials: (i) Efficacy should be based on standardized end-points [60]; in establishing such efficacy, symptoms/signs and QoL in addition to overall pain should be identified; (ii) Identification of responder profiles based on a detailed characterization of symptoms and signs using sensory examination and specific pain questionnaires should contribute to more successful neuropathic pain management; (iii) Identical criteria for assessing harmful events should be obtained; (iv) Large-scale comparative trials of drugs should be conducted; (v) More large-scale trials are needed to determine the value of combination therapy.

**Conflicts of interest**

The following authors (initials) did trials or have been consultants for the following pharmaceutical companies:

- NA: Grunenthal, Novartis, Pfizer, Eli Lilly/Boehringer, Pierre Fabre, Sanofi-Pasteur Merieux.
- RB: Pfizer, Genzyme, Grunenthal, Mundipharma, Allergan, Sanofi Pasteur, Medtronic, Eisai, UCB, Lilly.
- GC: Boehringer Ingelheim, Eli Lilly, Medtronic, Pfizer.
- MH: Boehringer-Ingelheim, Janssen-Cilag, GlaxoSmithKline, EMEA, Merck, Mundipharma, Orion, Pfizer, Sanof-Pasteur.
- PH: Bioschwartz, GlaxoSmithKline, Eli Lilly/Boehringer Ingelheim, Grunenthal, Lundbeck, Neurosearch, Pfizer.
- TSJ: Eli Lilly, GlaxoSmithKline, Grunenthal, Pierre Fabre Takeda Pfizer.
- TN: Allergan, AstraZeneca, GlaxoSmithKline, GWPharma, Napp, Novartis, Pfizer, Renovis, SchwarzPharma.

**References**


gesia in patients with postherpetic neuralgia. *Anesthesiology* 2006; **104**: 1243–1248. (class II).


### Appendix 1

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<td>All outcome measures similarly improved except allodynia (weak at baseline)</td>
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<td>NNT 50% pain relief Relative risk</td>
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<td>Only one measure of pain No effect on any measure</td>
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<td>Global assessment of therapeutic effects (GATE), sleep, SF-36, POMS</td>
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<td>All measures improved except EQ-5D more sensitive to all doses; centre effect improved</td>
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<td>Discontinuation rates: absent (150 mg) to 20% (600 mg); other outcome measures improved; Side effects dose-dependent</td>
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<td>No difference in secondary outcomes. Lamotrigine had less side effects (4% vs. 17%)</td>
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<td>Primary outcomes</td>
<td>Secondary outcomes</td>
<td>Results on secondary outcomes</td>
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<td>Oxcarbazepine 300–1800 mg vs. placebo</td>
<td>Dogra et al. 2005</td>
<td>Parallel groups</td>
<td>12 weeks, n = 146</td>
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<td>OXC &gt; placebo</td>
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<td>VAS pain intensity (average) (diary) NNT</td>
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<td>Global assessment of therapeutic effects (GATE), sleep, SF-36, POMS</td>
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<td>Significant effects on all outcome measures. No effect on nerve conduction</td>
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<td>All measures improved except EQ-5D more sensitive to all doses; centre effect improved</td>
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<td>Discontinuation rates: absent (150 mg) to 20% (600 mg); other outcome measures improved; Side effects dose-dependent</td>
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<td>No difference in secondary outcomes. Lamotrigine had less side effects (4% vs. 17%)</td>
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<td>Pregabalin, 150, 300, 600 mg/day vs. placebo</td>
<td>Richter et al. 2005</td>
<td>Parallel groups</td>
<td>6 weeks, n = 246</td>
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<td>Pregabalin &gt; placebo</td>
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<td>NRS pain intensity (average) (diary) at endpoint + weekly pain scores, responders</td>
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<td>Sleep, SF-MPQ (sensory, affective total), VAS, PPI (MPQ), SF36, POMS, CGI</td>
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<td>All measures improved except SF36 less sensitive (1 domain improved only)</td>
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<td>Pregabalin, 150, 300, 600 mg/day vs. placebo</td>
<td>Arezzo et al. 2008</td>
<td>Parallel groups, 13 weeks, n = 167</td>
<td>Pregabalin &gt; placebo</td>
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<td>NRS pain intensity (average) (diary) at endpoint + weekly pain scores, responders</td>
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<td>Sleep interference (NRS), SFMPQ, VAS and PPI (SFMPQ) PGIC, CGIC, + safety parameters (Nerve conduction)</td>
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<td>Pregabalin, 150, 300, 600 mg/day vs. placebo</td>
<td>To¨lle et al. 2008</td>
<td>Parallel groups</td>
<td>12 weeks, n = 396</td>
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<td>Pregabalin &gt; placebo (highest dosage)</td>
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<td>Pregabalin flexible 150–600 mg vs. fixed 600 mg vs. placebo (including PHN patients)</td>
<td>Freynhagen et al. 2005</td>
<td>Parallel groups</td>
<td>12 weeks, n = 338</td>
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<td>Pregabalin (fixed, flexible) &gt; placebo</td>
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<td>NRS pain intensity (average) (diary) at endpoint + weekly pain scores, responders</td>
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<td>Sleep interference (NRS), PGIC, CGIC, EQ-5D, NNT</td>
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<td>Effects on all outcomes of the highest dosage only except EQ-5D more sensitive to all doses; centre effect improved</td>
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<td>All measures equally sensitive</td>
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<td>Lamotrigine, 200, 300, 400 mg vs. placebo</td>
<td>Vinik et al. 2007</td>
<td>Parallel groups, 19 weeks, n = 360 per study</td>
<td>Lamotrigine = placebo (LOCF) &gt; placebo (observed scores)</td>
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<td>NPS pain intensity (average) (diary) at endpoint + weekly pain scores, responders</td>
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<td>Sleep intensity (NRS), SF-MPQ, VAS, PPI (SF-MPQ) PGIC, CGIC, + safety parameters (Nerve conduction)</td>
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<td>Lamotrigine flexible 150–600 mg vs. fixed 600 mg vs. placebo</td>
<td>Jose et al. 2007</td>
<td>Cross over, 6 weeks per trt, n = 55</td>
<td>Lamotrigine = amitriptyline (observed scores)</td>
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<td>NPS pain intensity (average) (diary) at endpoint + weekly pain scores, responders</td>
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<td>Sleep intensity (NRS), SF-MPQ, VAS, PPI (SF-MPQ) PGIC, CGIC, + safety parameters (Nerve conduction)</td>
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<td>Treatments</td>
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<td>Methods</td>
<td>Main results</td>
<td>Primary outcomes</td>
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<td>Lacosamide 400 mg vs. placebo</td>
<td>Rauck et al. 2007</td>
<td>Parallel groups, 10 weeks, n = 119 (94 completers)</td>
<td>Lacosamide &gt; placebo</td>
<td>NRS pain intensity (average) (diary) Effect size</td>
<td>SF-MPQ including VAS-PPI, NPS, sleep (NRS), SF36, POMS, pain free days, CGI</td>
<td>Measures of pain equally improved; No effect on POMS; SF36 only 2 domains improved including pain</td>
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<td>Lacosamide 200, 400 and 600 mg vs. placebo</td>
<td>Wymer et al. 2009</td>
<td>Parallel groups, 18 weeks, n = 370 (64% completers)</td>
<td>Lacosamide 400 mg &gt; placebo; 600 mg &gt; placebo observed cases</td>
<td>NRS pain intensity last 4 weeks (diary)</td>
<td>Sleep NRS, PGIC, activity (diary)</td>
<td>40% discontinuation in the 600 mg group for adverse effects; 23% in the 400 mg (9% placebo)</td>
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<td>Lacosamide 200, 400 and 600 mg vs. placebo</td>
<td>Shaibani et al. 2009</td>
<td>Parallel groups, 12 weeks, n = 468</td>
<td>Lacosamide 400 mg approached significance; 600 mg ns</td>
<td>NRS pain intensity last 4 weeks (diary)</td>
<td>PGIC, responders (50% and 30% pain relief), pain free days</td>
<td>Responders ns improvement; no significant effect on sleep</td>
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<td>Zonisamide 540 mg vs. placebo</td>
<td>Ali and Dogra 2005</td>
<td>Parallel groups, 12 weeks, n = 25</td>
<td>Zonisamide = placebo</td>
<td>VAS/NRS pain intensity (average) (diary)-responders</td>
<td>Sleep, daily functioning, pain interference</td>
<td>No effect on any outcome measures</td>
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<td>Opioids and tramadol</td>
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<td>CR Oxycodone, mean 37 mg (10–99) vs. placebo</td>
<td>Gimbel et al. 2003, Jensen et al. 2006 (post hoc analysis of NPS)</td>
<td>Parallel groups, 6 weeks, n = 159</td>
<td>Oxycodone &gt; placebo</td>
<td>NRS pain intensity (average) (diary)</td>
<td>NRS current/worst pain (diary), satisfaction, sleep scale, BPI interference, Rand Mental Health Inventory, SIP, SF 36, NPS, discontinuation, time to mild pain, days of mild pain</td>
<td>Effective on all measures of pain but only 2 items of BPI interference and no effect on SF36, Rand, SIP except ambulation NPS:effects on deep, sharp, dull not sensitive</td>
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<td>CR Oxycodone (Oxy) 10–80 mg + gabapentin (gaba) (100–3600 mg) vs. placebo + gabapentin</td>
<td>Hanna et al. 2008</td>
<td>Parallel groups, 12 weeks, n = 338</td>
<td>Oxy-gaba &gt; gaba-pentin-placebo</td>
<td>NRS pain intensity (box scale) at each visit</td>
<td>Rescue analgesics, sleep (n of disturbed night sleeps, quality of sleep), SF- BPI, SF-MPQ, EuroQol</td>
<td>All measures of pain equally improved; Sleep disturbance improved but not quality of sleep-No statistics for EuroQol</td>
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<td>Tramadol 37.5 acetaminophen 325 vs. placebo (up to 1–2 tablets 4 times daily)</td>
<td>Freeman et al. 2009</td>
<td>Parallel groups, 8 weeks, n = 311</td>
<td>Tramadol/APAP &gt; placebo</td>
<td>NRS pain intensity (average) (diary) from baseline to final week</td>
<td>Sleep interference, PGIC, QoL, mood</td>
<td>All outcome measures significantly improved Nausea: the only adverse effect; similar discontinuation rates (8.1% for active; 6.5% for placebo)</td>
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<td>Other treatments</td>
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<td>SC Botulinum toxin-A (max 300 U) vs. saline</td>
<td>Yuan et al. 2009</td>
<td>Cross over, 12 weeks, n = 20 (18 completers)</td>
<td>BTX-A &gt; placebo</td>
<td>VAS pain intensity, Pittsburgh sleep quality index, SF36</td>
<td>No primary outcome specified; effects on VAS and sleep (4 weeks) but not SF36</td>
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<td>Treatments</td>
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<td>Main results</td>
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<td>Glyceryl trinitrate spray (feet) vs. placebo</td>
<td>Agrawal et al. 2007</td>
<td>Cross over, 4 weeks per trt, n = 48 (43 completers)</td>
<td>GTN spray &gt; placebo</td>
<td>VAS pain intensity at visits</td>
<td>SFMPQ (total score) NRS pain intensity, PPI, NNT for pain relief</td>
<td>All outcome measures equally sensitive</td>
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<td>NK-1 receptor antagonist TKA731 vs. placebo</td>
<td>Sindrup et al. 2006</td>
<td>Parallel groups 2 weeks, n = 87</td>
<td>TKA = placebo</td>
<td>VAS pain intensity (average) (diary)</td>
<td>CGI, rescue medication, sleep questionnaire, VAS for neuropathic symptoms</td>
<td>No effect on any outcome measure</td>
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<td>ABT-594 (150, 225, 300 mg BID) vs. placebo</td>
<td>Rowbotham et al. 2009</td>
<td>Parallel groups, 7 weeks (1 week titration)</td>
<td>ABT &gt; placebo for all dosages without dose response</td>
<td>NRS pain intensity final week (diary)</td>
<td>NRS pain intensity each week, Proportion of responders, NPS score and symptoms, SF36, rescue medication</td>
<td>Responders improved but too many side effects and dropouts (up to 66%) NPS ns; SF36 only physical subscore improved but mental component deteriorated</td>
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Combination (in diabetic PN and PHN)

<p>| Gabapentin, 2207 mg vs. morphine 45 mg vs. combination (morphine 34 mg + gaba 1705 mg) vs. placebo | Gilron et al. 2005 | Cross over 5 weeks per trt, n = 57 (41 completers) | Gabapentin = placebo Morphone &gt; placebo Combination &gt; mor &gt; gaba And &gt; pbo | NRS pain intensity (average) (diary) | SF-MPQ (sensory affective total, VAS-PPI), BDI, BPI (interference), SF36, MMSE, global pain relief, blinding | SFMPQ, BPI, SF36, BDI significant for gabapentin, morphine and combination; NRS less sensitive to gabapentin | I |
| Gabapentin 2433 mg vs. nortriptyline 61.6 mg vs. combination 2180 + 50.1 | Gilron et al. 2009 | Cross over, 6 weeks per trt, n = 56 (45 completers) | Combination &gt; gabapentin or nor Gabapentin &gt; placebo Nor &gt; placebo | NRS pain intensity (average) (diary) | BPI, SF-MPQ, blinding, SF36 | Better effects of the combination on BPI, BPI interference with sleep, mood (/nor), SFMPQ, SF36; dry mouth &gt; with nor and weight gain &gt; for gabapentin | I |</p>
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<th>Treatments</th>
<th>Authors</th>
<th>Method</th>
<th>Main results</th>
<th>Primary outcome</th>
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<th>Results on secondary outcomes</th>
<th>EFNS Class</th>
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<td><strong>Post-Herpetic Neuralgia (PHN)</strong></td>
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<td><strong>Antidepressants</strong></td>
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<td>Fluoxetine 60 mg vs. imipramine 150 mg vs. amitriptyline 150 mg</td>
<td>Rowbotham et al. 2005</td>
<td>Parallel groups, 6 weeks, n = 38</td>
<td>Similar effects of the 3 drugs</td>
<td>VAS pain intensity (average) at visits</td>
<td>Pain relief scale (6 items BDI, QST (alldynia to brush))</td>
<td>VAS and pain relief scale similarly improved Allodynia sensitive to TCAs</td>
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<td>Nortriptyline 25–100 mg vs. gabapentin 300–1200 mg vs. placebo</td>
<td>Chandra et al. 2006</td>
<td>Parallel groups, 8 weeks, n = 76 (70 as intent to treat)</td>
<td>Nortriptyline = Gabapentin</td>
<td>NRS pain intensity (diary) from baseline to end of study</td>
<td>VAS sleep, VAS pain SF-MPQ, disability (categorical scale) pain categorical (0–5) CGI (0–4); proportion responders (50%)</td>
<td>No difference in outcome measure between active treatments Categorical scales not commonly used (some not validated)</td>
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<td><strong>Antiepileptics</strong></td>
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<tr>
<td>Meta-analysis of gabapentin in NP including PHN (Cochrane)</td>
<td>Wiffen et al. 2009</td>
<td>2 RCTs of gabapentin vs. placebo</td>
<td>Gabapentin &gt; placebo NNT 3.9 (95% CI 3.5–7.9)</td>
<td>NNT Relative risk</td>
<td></td>
<td>Effects on sleep for twice daily and once daily administration; dizziness and somnolence most common AE Differential effects of gabapentin on NP symptoms (hot, cold, deep) SR class I</td>
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<tr>
<td>Gabapentin ER 1800 mg/day twice daily or once daily vs. placebo</td>
<td>Irving et al. 2009 Jensen et al. 2009 (posthoc analysis of NPS)</td>
<td>Parallel groups, n = 158, 4 weeks Enrichment design</td>
<td>Gabapentin ER &gt; placebo for twice daily administration only</td>
<td>NRS pain intensity (diary) from baseline to endpoint</td>
<td>Sleep interference score NPS</td>
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<tr>
<td><strong>Pregabalin 150, 300, 600 mg vs. placebo</strong></td>
<td>Van Seventer et al. 2006</td>
<td>Parallel groups, 13 weeks n = 370</td>
<td>Pregabalin &gt; placebo</td>
<td>NRS pain intensity (average) (diary) NNT 30–50% relief</td>
<td>Sleep CGI (patient)</td>
<td>All measures equally sensitive</td>
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<tr>
<td><strong>Pregabalin 150–600 vs. 300 mg vs. placebo</strong></td>
<td>Stacey et al. 2008</td>
<td>Parallel groups, 4 weeks, n = 269</td>
<td>Pregabalin &gt; placebo</td>
<td>NRS pain intensity (diary) (criteria: time to onset of pain relief)</td>
<td>% responders (≥30% or 50%); PGIC; VAS (SFMPQ, anxiety); VAS allodynia to brush Daily interference scores</td>
<td>Pain/allodynia correlated; more severe baseline allodynia; less response to PGB; odds ratio for ≥50% PR: 1.30 (0.71–2.36)</td>
<td>I</td>
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<tr>
<td>Treatments (PHS)</td>
<td>Authors</td>
<td>Method</td>
<td>Main results</td>
<td>Primary outcome</td>
<td>Secondary outcome</td>
<td>Results on secondary outcomes</td>
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<tr>
<td>Meta-analysis of pregabalin studies in PHN (Cochrane)</td>
<td>Moore et al. 2009</td>
<td>5 RCTs, n = 1417</td>
<td>NNT 50% PR: 6.9 (4.8–13) for 150 mg; 5.5 (3.8–8.1) for 300 mg and 4.0 (3.1–5.5) for 600 mg</td>
<td>NNT 50% PR, NNT</td>
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<td>SR class I</td>
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<tr>
<td>Valproate 1000 mg vs. placebo</td>
<td>Kochar et al. 2005</td>
<td>Parallel groups 8 weeks, n = 45</td>
<td>Valproate &gt; placebo</td>
<td>SF-MPQ, VAS (PP), NRS, NNT</td>
<td>CGI (patient)</td>
<td>All measures equally sensitive</td>
<td>II (only results from completers)</td>
</tr>
<tr>
<td>Opioids vs. antidepressants</td>
<td>Raja et al. 2002, Edwards et al. 2006 (predictors for response)</td>
<td>Cross over, 8 weeks per trt, n = 76 (44 completers of 3 periods)</td>
<td>Opioids = tricycles &gt; placebo</td>
<td>Preference with treatment; MPI (physical, sleep) Beck; Treatment preference, NNT (50% PR), QST</td>
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<tr>
<td>Topical agents</td>
<td>Binder et al. 2009</td>
<td>Parallel groups, enriched enrolment, 2 weeks per trt after 8 weeks open label run-in phase, n = 265 (71 randomized)</td>
<td>No difference in the full analysis set in the primary outcome but only in perprotocol population (n = 34)</td>
<td>Time to exit</td>
<td>Allodynia to brush, pain relief, SF-MPQ, mean pain intensity</td>
<td>Significant in the perprotocol population; no direct statistical comparisons of secondary endpoints between lidocaine and placebo; only 2.8% adverse events in the double blind phase (13.8% for lidocaine in the study including run in period)</td>
<td>II (groups not balanced, many early withdrawals)</td>
</tr>
<tr>
<td>High concentration capsacin patch NGX-4010 (8%) vs. low concentrations (0.04%) 60 min in PHN</td>
<td>Backonja et al. 2008</td>
<td>Parallel groups, Assessment up to 12 weeks N = 402</td>
<td>NGX-4010 &gt; placebo</td>
<td>NRS average pain intensity (diary) from week 2–8</td>
<td>Proportion of responders (30% pain relief); Gracely pain scale, SFMPQ, PGIC, CGIC; BPI; SF36, Self assessment of treatment (SAT); concomitant treatments</td>
<td>Effects on pain, PGIC, SAT but no significant effects on BPI, SFMPQ, SF36, ≥50% reduction pain (not shown); no effect on rescue medication – blinding perhaps compromised due to more initial pain in the high concentration patch</td>
<td>I</td>
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<tr>
<td>Others</td>
<td>Shackelford et al. 2009</td>
<td>Parallel groups, 3 weeks N = 209</td>
<td>COX-2 = placebo but duration of trial may be too short</td>
<td>NRS average pain intensity (diary) from baseline to last week</td>
<td>NPS; allodynie severity (brush) SF-MPQ; PGIC; CGIC; PR score; discontinuation due to lack of effect: rescue medication</td>
<td>No statistical effect on primary and secondary endpoints except for the NPS in the 25 mg group</td>
<td>II</td>
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<tr>
<td>Meta-analysis of drug treatments</td>
<td>Hempestaff et al. 2005</td>
<td>25 analyseable RCTs</td>
<td>NNT for TCA combined 2.64 (2.43–7.99); NNT for gabapentin 4.39 (3.34–6.07) NNT for opioids 2.67 (2.07–3.77); NNT for tramadol 4.76 (2.61–26.97)</td>
<td>NNT, NNH, ratio NNT/NNH</td>
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<td>SR class I</td>
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<tr>
<td>Treatments</td>
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<td><strong>Trigeminal Neuralgia</strong></td>
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<tr>
<td>Systematic review and guidelines of diagnosis and treatment including drug treatments in trigeminal neuralgia</td>
<td>Cruccu <em>et al.</em> 2009</td>
<td>SR of all treatments in TN including drugs; 12 RCTs analysed</td>
<td>CBZ: NNT = 1.8 (1.3–2.2) one class II and 1 class II trial (n = 147); OXC 600–1800 mg similar effect as CBZ on number of attacks and global assessment in 2 class II RCTs (n = 130); other drugs have poor efficacy or effective in single trials</td>
<td>Efficacy on number of attacks, paroxysmal pain, brush-evoked pain, and global assessment</td>
<td>Adverse events</td>
<td>SR class I</td>
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<tr>
<td><strong>Central Pain</strong></td>
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<tr>
<td>Amitriptyline 150 mg vs. gabapentin 3600 mg vs. placebo (diphenhydramine) SCI pain</td>
<td>Rintala <em>et al.</em> 2007</td>
<td>Cross over 8 week per trt n = 38 (22 completers)</td>
<td>Amitriptyline &gt; gabapentin Gabapentin = placebo</td>
<td>VAS pain intensity (average) at visits</td>
<td>Proportion responders (30%) VAS pain intensity (worst) Rescue analgesics</td>
<td>VAS and proportion responders responsive to trts No effect on rescue trts</td>
<td>II</td>
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<tr>
<td>Tramadol 150 mg vs. placebo SCI pain</td>
<td>Norrbrink and Lunderberg 2009</td>
<td>Cross over, 4 weeks, = 36 (35 analyzable)</td>
<td>Tramadol &gt; placebo</td>
<td>NRS pain intensity</td>
<td>Multidimensional Pain Inventory; HAD; sleep questionnaire; PGIC; Brush induced allodynia (tooth-brush); pain unpleasantness, maximal and minimal pain (NRS)</td>
<td>Diff./placebo on pain intensity, PGIC, anxiety, sleep but not mood, pain unpleasantness, pain interference, distress. 43% of withdrawal due to side effects with tramadol vs. 17% placebo</td>
<td>II</td>
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<tr>
<td>Pregabalin, 150–600 mg vs. placebo (SCI pain)</td>
<td>Siddal <em>et al.</em> 2006</td>
<td>Parallel groups, 8 weeks n = 137</td>
<td>Pregabalin &gt; placebo</td>
<td>NRS pain intensity (average) (diary)</td>
<td>SF-MPO, % responders (30, 50%), sleep, POMS, CGI</td>
<td>All measures of pain equally sensitive 21% discontinuation for adverse events vs. 13% placebo</td>
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<tr>
<td>Pregabalin, 150–600 mg vs. placebo (SCI, brain)</td>
<td>Vranken <em>et al.</em> 2008</td>
<td>Parallel groups 4 weeks n = 40</td>
<td>Pregabalin &gt; placebo</td>
<td>VAS pain intensity (average) at weekly visits</td>
<td>SF36, EuroQol, PDI</td>
<td>Only one measure of pain; PDI and SF36 less sensitive than EQD5 (SF36 -pain improved)</td>
<td>I</td>
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<tr>
<td>Lamotrigine up to 400 mg vs. placebo (multiple sclerosis)</td>
<td>Breuer <em>et al.</em> 2007</td>
<td>Cross over, 11 weeks per trt n = 12</td>
<td>Lamotrigine = placebo Inclusion criteria 4/10 on any NPS item</td>
<td>NRS pain intensity from the BPI (worst, least, average pain) (diary) Responders from BPI average pain (&gt; 30%)</td>
<td>Rescue analgesics, NPS Multiple sclerosis QOL-54 BPI-interference</td>
<td>Pain responses similar but NS; Carryover effect for the item ‘sensitivess of the NPS; underpowered study</td>
<td>II</td>
</tr>
<tr>
<td>Treatments</td>
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<td>Levetiracetam 500-3000 mg/day vs. placebo (SCI pain)</td>
<td>Finnerup et al. 2009</td>
<td>Cross over, 5 weeks per tret, washout 1 week n = 36 (24 completers)</td>
<td>Levetiracetam = placebo</td>
<td>Average pain intensity (NRS)</td>
<td>Pain relief (categorical), MPQ, NPSI, proportion of pain relief (33%), sleep interference, use of rescue analgesics, evoked pain (pinprick, brush, cold evoked), PGIC, spasm (NRS, Penn), Ashworth, blindness</td>
<td>No effect on any outcome measure Possibly underpowered for secondary outcome measures (evoked pain, spasms)</td>
<td>II</td>
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<tr>
<td>S-ketamine iontophoretic transdermal 50 and 75 mg vs. placebo (NP screened with LANSS)</td>
<td>Vranken et al. 2005</td>
<td>Parallel groups 7 days n = 33</td>
<td>Ketamine = placebo (primary outcome)</td>
<td>VAS pain intensity at each visit</td>
<td>Measures of quality of life and disability: PDI, EuroQol, SF 3</td>
<td>No effect on pain but effects on all measures of QOL with the high dosage</td>
<td>I</td>
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<tr>
<td>THC/cannabidiol (CBD) 2.7/2.5 oromucosal vs. placebo max 48 sprays/day</td>
<td>Rog et al. 2005</td>
<td>Parallel groups 5 weeks n = 64</td>
<td>THC/CBD &gt; placebo</td>
<td>NRS pain intensity (average) (diary)</td>
<td>Sleep NRS NPS cognitive function HADS-Multiple sclerosis related disability CGI (patient)</td>
<td>Pb with NP screening (some had spasticity) Similar effects on NRS, total score NPS and sleep NPS: significant effect for some items (intense, dull, sensitive) Non validated scales (AED use, ADL) Similar effects on pain, AED rescue, Karnovski, ADL, but not mood</td>
<td>I</td>
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<tr>
<td>Tramadol 1–1.5 mg/kg per 6 h</td>
<td>Arbaiza et al. 2007</td>
<td>Parallel groups 6 weeks n = 36</td>
<td>Tramadol &gt; placebo</td>
<td>NRS pain intensity at each visit</td>
<td>Karnovsky scale, ADL including sleep and appetite (yes/no), Zung depression, Beck anxiety, SEPs, AED use on a scale (0–5)</td>
<td>Similar effects on pain, AED rescue, Karnovski, ADL, but not mood</td>
<td>II</td>
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Other Neuropathic Pain Conditions

HIV neuropathy

| Memantine 40 mg/day or max tolerated dose vs. placebo | Schiffito et al. 2006 | Parallel groups 16 weeks n = 45 | Memantine = placebo | VAS pain and paresthesia intensity at 16 weeks | No effects on pain or paresthesia | II |

Smoked cannabis (3.56% THC) vs. placebo cigarettes; 1 cig TID | Abrams et al. 2007 | Parallel groups 5 days n = 55 | Smoked cannabis > placebo | VAS pain intensity (average) (diary) | Current pain VAS (immediate effect) NNT 30% pain relief Pain intensity (VAS) induced by 45°C for 1 mm; Heat/capsaicin sensitization; POMS | Measures of pain improved No effect on pain induced by heat but attenuation of heat/capsaicin hyperalgesia at day 1 No effect on the POMS | I |
<table>
<thead>
<tr>
<th>Treatments</th>
<th>Authors</th>
<th>Method</th>
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<th>Secondary outcome</th>
<th>Results on secondary outcomes</th>
<th>Class</th>
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<tbody>
<tr>
<td>Smoked cannabis (1 and 8% THC) vs. placebo</td>
<td>Ellis et al. 2009</td>
<td>Cross over 5 days $n = 34$</td>
<td>Smoked cannabis &gt; placebo</td>
<td>Pain intensity (Descriptor Differential Scale)</td>
<td>Mood and functioning</td>
<td>Significant effects on pain but no difference on mood and functioning</td>
<td>H</td>
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<tr>
<td>High concentration capsaicin patch NGX-4010 (8%) vs. low concentrations (during 30, 60, 90 min) in HIV neuropathy</td>
<td>Simpson et al. 2008</td>
<td>Parallel groups, Assessment up to 12 weeks $n = 307$ (274 completers)</td>
<td>NGX-4010 &gt; placebo</td>
<td>NRS average pain intensity (diary) from week 2–12</td>
<td>% change in NRS present, worst pain intensity (diary) % change from baseline of average NRS; proportion responder (30% pain relief); Gracely pain scale, SFMPQ, PGIC, CGIC; BPI composite score; QST</td>
<td>All measures equally sensitive to treatment No effect on sensory function</td>
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<tr>
<td>Nerve trauma</td>
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<td>Gabapentin up to 2400 mg vs. placebo</td>
<td>Gordh et al. 2008</td>
<td>Cross over 5 weeks per trt, $n = 120$ VAS ≥ 3 at inclusion</td>
<td>Gabapentin = placebo on the primary outcome Placebo effect superior during the first period</td>
<td>VAS pain intensity (present pain twice a day) (electronic diary) % responders (30%, 50% pain relief)</td>
<td>Pain relief (categorical), sleep interference (VAS electronic diary), SF36, CGI, rescue analgesics</td>
<td>PR and PGIC more improved than VAS; sleep significant; 3 items of the SF36 improved; NNT depends on the measure</td>
<td>I</td>
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<tr>
<td>Treatments (other conditions)</td>
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<td>Main results</td>
<td>Primary outcome</td>
<td>Secondary outcome</td>
<td>Results on secondary outcomes</td>
<td>EFNS Class</td>
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<tr>
<td>Levetiracetam 3000 mg/day vs. placebo</td>
<td>Vilholm et al. 2008</td>
<td>Parallel groups, 4 weeks $n = 27$ (25 completers)</td>
<td>Levetiracetam = Placebo</td>
<td>NRS pain intensity, relief, NP symptoms; rescue analgesics; QST</td>
<td>No specification of primary and secondary endpoints</td>
<td>No effect on any outcome</td>
<td>H</td>
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<tr>
<td>SC Botulinum toxin A (BTX-A) (max 200 U) vs. saline in peripheral neuropathic pain (traumatic, PHN) with allodynia</td>
<td>Ranoux et al. 2008</td>
<td>Parallel groups 6 months $n = 29$</td>
<td>BTX-A &gt; placebo</td>
<td>NNT 50% pain relief PGIC, % pain relief, NPSI, average pain VAS at each visit, QST (area of allodynia to brush and punctate, thermal testing) BPI-interference, HAD Blinding assessment</td>
<td>Effect on global pain/pain relief and CGI similar Better effect on NPSI symptoms/dimensions (burning, paroxysmal pain, allodynia); Only 2 items of BPI-interference improved Predictors of response based on QST (patients with severe thermal deficits less improved)</td>
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<td><strong>Phantom pain</strong></td>
<td><strong>Gabapentin, 300–3600 mg vs. placebo</strong>&lt;br&gt;Smith <em>et al.</em>, 2005</td>
<td>Cross over, 6 weeks, <em>n = 24</em>&lt;br&gt;Gabapentin = placebo</td>
<td>NRS Pain intensity</td>
<td>Categorical pain relief scale, benefit and side effects; BPI; blinding; SF-MPQ; CES-D; FIM; SWLS; CHART</td>
<td>No effect on any outcome measures</td>
<td>Categorical scales not validated</td>
<td>II</td>
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<tr>
<td><strong>Morphine 112 mg vs. mexiletine 933 mg vs. placebo</strong>&lt;br&gt;Wu <em>et al.</em>, 2008</td>
<td>Cross over 6 weeks per trt wash out 1 week <em>n = 60</em>&lt;br&gt;Morphine &gt; placebo and mexiletine</td>
<td>NRS pain intensity (averagediary) throughout the study (stump and phantom mixed)</td>
<td>% pain relief (0-100%)&lt;br&gt;NNT for 50 and 33% pain relief, functional activity (MPI) (general and interference scales)</td>
<td>Effects on pain but not on self reported levels of activity</td>
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<td><strong>Cancer NP</strong></td>
<td><strong>Gabapentin 600–1800 mg vs. placebo (cancer NP)</strong>&lt;br&gt;Caraceni <em>et al.</em>, 2005</td>
<td>Parallel groups, 10 days <em>n = 121</em>&lt;br&gt;Gabapentin &gt; placebo</td>
<td>NRS pain intensity (average) (diary)</td>
<td>Neuropathic symptoms&lt;br&gt;NNT 33% pain relief&lt;br&gt;Allodynia at examination&lt;br&gt;Rescue analgesics</td>
<td>Effects on pain intensity but not on analgesic use or on neuropathic symptom</td>
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<tr>
<td><strong>Radiculopathies</strong></td>
<td><strong>Nortriptyline 25–100 mg vs. morphine 15–90 mg vs. combination vs. placebo</strong>&lt;br&gt;Khoromi <em>et al.</em>, 2007</td>
<td>Cross over 7 weeks per trt <em>n = 55</em> (28 completers)</td>
<td>No effect of treatments</td>
<td>Global pain relief (categorical) Ossewrty disability scale BDI, SF-36, NNT (pain relief)</td>
<td>Average pain: ns - Combination &gt; placebo for worst pain and pain relief/placebo (chance effect?) No blinding</td>
<td>II</td>
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<tr>
<td><strong>Topiramate 200 mg vs. diphenhydramine 40 mg</strong>&lt;br&gt;Khoromi <em>et al.</em>, 2005</td>
<td>Cross over 6 weeks per trt <em>n = 41</em> (29 completers)</td>
<td>Topiramate marginally &gt; placebo (primary outcome)</td>
<td>NRS pain intensity (average) (diary) for leg pain</td>
<td>NRS pain intensity (back, global pain), worst pain, Pain relief (categorical) Ossewrty, BDI, SF36</td>
<td>Average leg pain less improved than global assessment or worst pain</td>
<td>II</td>
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<tr>
<td><strong>Pregabalin 150–600 mg vs. placebo</strong>&lt;br&gt;Pfizer, protocol A0081007 –20 may 2008</td>
<td>Single blind run in phases with placebo then pregabalin, then 5 weeks double blind period, <em>n = 217</em> (187 completers)</td>
<td>Pregabalin = placebo</td>
<td>Increase in pain over the double blind treatment period in patients randomized to placebo compared to pregabalin</td>
<td>PGIC, sleep interference, HADS, EQ-SD, MOS, pain treatment satisfaction scale, Roland Morris disability</td>
<td>No effect on any outcome measure</td>
<td>II (numerous protocol violations)</td>
<td></td>
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<tr>
<td><strong>Multiaetiology NP</strong></td>
<td><strong>Gabapentin 600–1800 mg vs. placebo</strong>&lt;br&gt;Yeland <em>et al.</em>, 2009</td>
<td>N of 1 method, 3 double-blind RCT cross over trials&lt;br&gt;<em>N = 73</em> (48 completers)</td>
<td>Only 29% patients showed a positive response to gabapentin, 69% no difference</td>
<td>Aggregate measure for: VAS for pain intensity, sleep-VAS, functional limitation VAS, treatment preference, side effects</td>
<td></td>
<td>II many withdrawals (35%)</td>
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<tr>
<td>Lamotrigine 200, 300, 400 mg. vs. placebo</td>
<td>Silver et al. 2007</td>
<td>Parallel group, 14 weeks ( n = 220 )</td>
<td>Lamotrigine = placebo Large placebo effect</td>
<td>NRS pain intensity (average) (diary), responders (30%, 50%)</td>
<td>Sleep interference SF-MPQ, NPS total score Rescue analgesics, CGI</td>
<td>No difference/placebo, No outcome measure more sensitive -No predictors – dizziness, rash, somnolence in &gt;5% of patients</td>
<td>I</td>
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<tr>
<td>Lidocaine patch, 5% (max 4/day) vs. placebo in patients with allodynia (PHN, postsurgical, peripheral neuropathy)</td>
<td>Meier et al. 2003, Wasner et al. 2005 (subgroup analysis)</td>
<td>Cross over 7 days per trt ( n = 40 )</td>
<td>Lidocaine &gt; placebo</td>
<td>VAS spontaneous pain and alldynia intensity (diary)</td>
<td>Descriptors partially derived from the MPQ QOL (how did you sleep) on a 5-point categ scale; NNT for 50% pain relief and alldynia relief; effect size QST and QSART in a subgroup of 18 PHN patients</td>
<td>Short period assessment (7 days)- Non validated scales (symptoms, sleep); Better effect on ongoing pain/allodynia (NNT) - ES 0.4; Reduction in number of symptoms only; sleep ns, Better effects of lidocaine in patients with impairment of nociceptor function</td>
<td>I (II for Wasner et al.)</td>
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<tr>
<td>Lidocaine patch 5% vs. topical amitriptyline (ami) 5% vs. placebo</td>
<td>Ho et al. 2008</td>
<td>Cross over 1 week per trt, ( n = 35 )</td>
<td>Amitriptyline = lidocaine = placebo; Lido-caine &gt;ami</td>
<td>VAS pain intensity at the end of trt period</td>
<td>Daily NRS, MPQ, rescue analgesics, patient satisfaction (categorical), degree of pain relief</td>
<td>Outcome measures equally improved</td>
<td>H</td>
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<tr>
<td>Topical amitriptyline 2% vs. topical ketamine 1% vs. combination vs. placebo</td>
<td>Lynch et al. 2005</td>
<td>Parallel groups 3 weeks ( n = 92 )</td>
<td>Ami = ketamine = combination = placebo</td>
<td>NRS pain intensity (average) (diary)</td>
<td>SF-MPQ, dynamic alldynia, pinprick hyperalgesia, PDI, patient satisfaction</td>
<td>No effect on any outcome measure</td>
<td>I</td>
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<tr>
<td>Venlafaxine 75 mg vs. 150 mg vs. placebo</td>
<td>Yucel et al. 2004</td>
<td>Parallel groups 8 weeks ( n = 55 )</td>
<td>Venlafaxine = placebo</td>
<td>VAS pain intensity (VAP-PI) (average) at visits</td>
<td>Patient satisfaction (categorical) Effect on daily activities Rescue analgesics Global efficacy QST (alldynia)</td>
<td>VAS-PI reduced in the 3 groups (placebo effect); No effect on rescue analgesics- Slight effect on satisfaction and daily activity (75 mg); Effects on brush-induced alldynia (QST) &gt; PI</td>
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<tr>
<td>Nabilone 2 mg vs. dihydrocodeine 240 mg</td>
<td>Frank et al. 2009</td>
<td>Cross over, 6 weeks (2 weeks washout) ( n = 96 ) (73 available)</td>
<td>Nabilone &lt; Dihydrocodeine</td>
<td>VAS pain intensity Anxiety and depression (HAD), SF36, sleep (numbers of hours slept each night)</td>
<td>Anxiety and depression (HAD), SF36, sleep (numbers of hours slept each night)</td>
<td>Dihydrocodeine &gt; nabilone on all outcomes but effect moderate in all cases Effect of nabilone on the role physical of SF36</td>
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<td>Treatments (other conditions)</td>
<td>Authors</td>
<td>Methods</td>
<td>Main results</td>
<td>Primary outcome</td>
<td>Secondary outcome</td>
<td>Results on secondary outcomes</td>
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<td>THC/CBD oromucosal 2/2.5 vs. placebo-max 8 sprays/2 h self-titration (peripheral NP)</td>
<td>Numikko et al. 2007</td>
<td>Parallel groups, 5 weeks, n = 125</td>
<td>Sativex &gt; placebo</td>
<td>NRS pain intensity (average) (diary)</td>
<td>NPS, PDI, PGIC pain and allodynia, GHQ-12 (mood, anxiety); NRS sleep; Cognitive tests; allodynia (dynamic, punctate); NNT ongoing pain, allodynia</td>
<td>All measures of pain improved – no change in pain threshold but decrease in pain evoked by punctate stimuli No effect on CHG-Q</td>
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</tbody>
</table>

BDI, Beck depression inventory; BOCF, baseline observation carried forward; BPI, Brief pain inventory; CGIC, clinical global impression of change; HDRS, Hamilton depression rating scale; LANSS, Leeds assessment of neuropathic symptoms and signs; LOCF, last observation carried forward; MDI, major depression inventory; MMSE, mini mental scale examination; MPI, Multidimensional Pain inventory; MPQ, McGill Pain questionnaire; NIS, Neuropathy impairment score; NNT, number needed to treat; NPS, neuropathic pain scale; NPSI, neuropathic pain symptom inventory; NRS, numerical rating scale (or Likert scale); NS, not significant; NWC, number of words chosen; PDI, Pain disability index; PHN, post herpetic neuralgia; PN, polyneuropathy; PGIC, patient clinical global impression; POMS, profile of mood scale; PPI, present pain intensity; PR, pain relief; QOL, quality of life; QST, quantitative sensory testing; RCT, randomized controlled trial; SF-MPQ, short form McGill pain questionnaire; SIP, Sickness Impact Profile; SF36, Short Form 36 (QoL measure); STAI, Spielberger trait anxiety inventory; Trt, treatment; VAS, visual analogue scale; VRS, Verbal rating scale; vs., versus.
Appendix 2

General references


Meta-analyses, guidelines and systematic reviews


**RCTs and meta-analyses in painful polyneuropathies**


Kochar DK, Rawat N, Agrawal RP, Vyas A, Beniwal R, Kochar SK, et al. Sodium valproate for painful...


**Systematic reviews and RCTs in postherpetic neuralgia**


Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Clin J Pain 2002; 18: 297–301 (class II).


Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled


Systematic reviews and RCTs in trigeminal neuralgia


Systematic reviews and RCTs in central pain


Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic


**RCTs in other NP conditions**


Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 1996; 64: 293–302 (class II).


Lynch ME, Clark AJ, Sawynok J. A pilot study examining topical amitriptyline, ketamine, and a com-


McCleane GJ. 200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: a randomised, double-blind, placebo controlled trial. Pain 1999; 83: 105–107 (class II).


Wilder-Smith CH, Hill LT, Laurent S. Postamputation pain and sensory changes in treatment-naive patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. Anesthesiology 2005; 103: 619–628 (class II).
