European Journal of Neurology 2010, **17:** 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

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Keywords:
neuropathic pain, painful diabetic polyneuropathy, post-herpetic neuralgia, trigeminal neuralgia, central neuropathic pain, evidence-based recommendations, pharmacological treatment, randomized clinical trials

Received 13 October 2009
Accepted 2 February 2010

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

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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 dysesthesia 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., alphalipoic 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], nitrate derivatives [36,37] and a new nicotinic

Table 1 Classification of evidence for drug treatments in commonly studied neuropathic pain (NP) conditions and recommendations for use. Treatments are presented in alphabetical order. Only drugs used at repeated dosages are shown here (with the exception of treatments with long-lasting effects such as capsaicin patches). Drugs marked with an asterisk were found effective in single class II or III studies and are generally not recommended. Drugs marked with two asterisks are not yet available for use.

Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
Diabetic NP[a]	Duloxetine Gabapentin-morphine TCA Gabapentin Nicotine agonist** Nitrate derivatives** Oxycodone Pregabalin TCA[b] Tramadol alone or with acetaminophen Venlafaxine ER	Botulinum toxin* Dextromethorphan Gabapentin/venlafaxine* Levodopa*	Carbamazepine Phenytoin	Capsaicin cream Lacosamide Lamotrigine Memantine Mexiletine Mianserin NK1 antagonist** Oxcarbazepine SSRI Topical clonidine Topiramate Valproate Zonisamide	Duloxetine Gabapentin Pregabalin TCA Venlafaxine ER	Opioids Tramadol[c]
PHN	Capsaicin 8% patch** Gabapentin Gabapentin ER** Lidocaine plasters Opioids (morphine, oxycodone, methadone) Pregabalin TCA[b]	Capsaicin cream Valproate*		Benzydamide topical Dextromethorphan Fluphenazine Memantine Lorazepam Mexiletine COX-2 inhibitor** Tramadol	Gabapentin Pregabalin TCA Lidocaine plasters[d]	Capsaicin Opioids
Classical trigeminal neuralgia	Carbamazepine	Oxcarbazepine	Baclofen* Lamotrigine* Pimozide* Tizanidine*		Carbamazepine Oxcarbazepine	Surgery
Central pain[e]	Cannabinoids (oro-mucosal **, oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)* Opioids		Carbamazepine Gabapentin Lamotrigine (SCI) Levetiracetam Mexiletine S-ketamine iont. Valproate	Gabapentin Pregabalin TCA	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI)

[a]Diabetic neuropathy was the most studied. Only TCA, tramadol and venlafaxine were studied in non-diabetic neuropathies. [b]Amitriptyline, clomipramine (diabetic neuropathy), nortriptyline, desipramine, imipramine. [c]Tramadol may be considered first line in patients with acute exacerbations of pain especially for the tramadol/acetaminophen combination. [d]Lidocaine is recommended in elderly patients (see section 2). [e]Cannabinoids (positive effects in MS) and lamotrigine (positive effects in CPSP but negative results in MS and SCI except in patients with incomplete lesion and brush-induced allodynia in one study based on post hoc analysis) are proposed for refractory cases. iont., iontophoresis; CPSP, central post-stroke pain; ER, extended release; MS, multiple sclerosis; PHN, post-herpetic neuralgia; SCI, spinal cord injury; TCA, tricyclic antidepressants; SSRI, Selective serotonin reuptake inhibitor.

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

(1–8% tetrahydrocannabinol for 5 days) on pain intensity but not mood or functioning [44,45]. A one-off application of high concentration (8%) capsaicin patch applied to the feet for 30, 60 or 90 min was superior to low concentration (0.04%) in the 30- and 90-minute group from weeks 2 to 12 without detectable changes in sensory thresholds [46]. However, another study reported in a systematic review [47] was negative on the primary outcome.

Recommendation. We recommend TCA, gabapentin, pregabalin and SNRI (duloxetine, venlafaxine) as first-line treatment in PPN (notably related to diabetes) (level A). Tramadol (level A) is recommended second line except for patients with exacerbations of pain (for the tramadol/acetaminophen combination) or those with predominant coexisting non-neuropathic pain (in view of its largely established efficacy in nociceptive pain). Third-line therapy includes strong opioids because of concerns regarding their long-term safety including addiction potential and misuse, which warrants further RCTs [4,48]. Treatments with drug with no or equivocal effect are listed in Table 1. In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment) (level B), smoking cannabis (level A) and capsaicin patches (level A) were found moderately useful.

Post-herpetic neuralgia

Post-herpetic neuralgia is a common aftermath of herpes zoster in the elderly.

Antidepressants
Systematic reviews concur that TCA are effective in PHN [9,49] with superiority over SSRI [7,50]. No studies were found on the efficacy of SNRI.

Antiepileptics
Gabapentin and pregabalin have established efficacy in PHN with no difference shown between gabapentin and nortriptyline in a further comparative study [20,49] An extended release formulation of gabapentin was more effective than placebo [51]. Good efficacy was reported with divalproex sodium in a small RCT, but only results from completers were reported [52].

Opioids
Oxycodone, morphine and methadone are effective in PHN [49] and have similar or slightly better efficacy compared to TCA in one comparative trial but are associated with more frequent discontinuation due to side effects [7,49]. Tramadol was negative on the primary outcome in one class I trial [7].

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 inefficacy of valproate [7,76,77]. *Traumatic NP*: Gabapentin was reported to be ineffective

Table 2 Classification of evidence for drug treatments in less commonly studied neuropathic pain (NP) conditions. Treatments are presented in alphabetical order. Drugs marked with an asterisk were found effective in single class II studies

Aetiology of NP	Level A rating for efficacy	Level B rating for efficacy	Level A/B rating for inefficacy/poor efficacy or discrepant results
HIV neuropathy	Capsaicin 8% patch Smoked cannabis	Lamotrigine	Amitriptyline Capsaicin cream Gabapentin Lidocaine plasters Memantine
Post-traumatic or post-surgical NP		Amitriptyline* Botulinum toxin-A*	Cannabinoids Capsaicin Gabapentin Levetiracetam Propranolol Venlafaxine ER
Chronic radiculo-pathy			Morphine* Nortriptyline* Nortriptyline-morphine * Pregabalin (unpublished) Topiramate
Cancer NP	Gabapentin	Amitriptyline* Tramadol*	Valproate
Phantom pain	Morphine Tramadol		Amitriptyline Gabapentin Memantine Mexiletine
Multi-aetiology NP	Bupropion Cannabinoids (oromucosal, synthetic analogue) Levorphanol	Methadone TCA (nortriptyline, clomipramine)	Amitriptyline/ketamine topical CCK2 antagonists Dextromethorphan Dihydrocodeine Gabapentin[a] Venlafaxine ER[a] Lidocaine plasters Lamotrigine Lidocaine plasters Mexiletine[a] Nabilone Riluzole

[a]These drugs were found effective in some spontaneous NP symptoms (gabapentin) or only on brush-induced or static mechanical allodynia (mexiletine, venlafaxine) in single trials. ER, extended release; TCA, tricyclic antidepressants.

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].

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, contra-indications, 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 Mérieux. RB: Pfizer, Genzyme, Grünenthal, 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.

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Appendix 1

Treatments	Authors	Methods	Main results	Primary outcomes	Secondary outcomes	Results on secondary outcomes	EFNS Class
Diabetic Neuropathy							
Antidepressants							
Duloxetine 60 mg QD or BID vs. placebo	Raskin *et al.* 2005	Parallel groups 12 weeks, $n = 348$	Duloxetine QD or BID > placebo	NRS pain intensity (average) (diary) baseline to endpoint	Worst pain, night pain, PGIC, CGIC, BPI, SF-MPQ sensory, dynamic allodynia (examination)	All outcome measures similarly improved except allodynia (weak at baseline) but modest difference/placebo (0.87–0.9/10 on average pain intensity)	I
Duloxetine 20, 60, 120 mg vs. placebo	Goldstein *et al.* 2005	Parallel groups, 12 weeks, $n = 457$	Duloxetine > placebo for 60 and 120 mg	NRS pain intensity (average) (diary) baseline to endpoint	Analgesic use, worst pain, night pain, PGIC, CGIC, BPI, SF-MPQ sensory, dynamic allodynia	All outcome measures similarly improved except allodynia (weak at baseline)	I
Duloxetine 60 BID or QD mg vs. placebo	Wernicke *et al.* 2006	Parallel groups 12 weeks, $n = 334$	Duloxetine > placebo	NRS pain intensity (average) (diary) baseline to endpoint	Analgesic use, worst pain, night pain, PGIC, CGIC, BPI, SF-MPQ sensory, dynamic allodynia	All outcome measures similarly improved except allodynia (weak at baseline)	I
Meta-analyses of 3 duloxetine trials	Kajdascz *et al.* 2007	$N = 1139$ patients (800 duloxetine, 339 placebo) 12 weeks	NNT 5.2 (3.8–8.3) for 60 mg/day NNT 4.9 (3.6–7.6) for 120 mg/day	NNT 50% pain relief LOCF and BOCF; NNH based on discontinuation			SR class I
Venlafaxine ER 75–150 mg (flexible) vs. vitamin combination (B1B6)	Kadiroglu *et al.* 2008	Parallel groups, 8 weeks, $n = 60$	Venlafaxine > placebo	VAS pain intensity at visits (SFMPQ); NRS pain intensity; SFMPQ Categorical response	No specification of primary and secondary outcomes	Significant effects on all outcome measures	II
Escitalopram 20 mg vs. placebo	Otto *et al.* 2008	Cross over, 5 weeks per treatment $n = 48$ (37 completers)	Escitalopram > placebo	6 point categorical Pain relief	NRS of total and NP symptoms; paracetamol use: QST, SF36, MDI, NNT, sleep	Symptoms equally improved but not analgesic uses and sleep, SF36 and MDI	I
Antiepileptics							
Meta-analysis of gabapentin trials in NP including diabetic NP (Cochrane)	Wiffen *et al.* 2009	4 placebo controlled studies and 3 active controlled studies	Gabapentin > placebo NNT 2.9 (CI 2.2–4.3)	NNT 50% pain relief Relative risk			SR class I
Treatments (diabetic neuropathy)	Authors	Method	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	EFNS Class
Oxcarbazepine (OXC) 1200 mg vs. placebo	Grosskopf *et al.* 2006	Parallel groups 12 weeks, $n = 141$	OXC = placebo	VAS pain intensity (average) (electronic diary)	Global assessment of therapeutic effects, sleep, SF36, POMS	Only one measure of pain No effect on any measure	I

Appendix 1 (Continued)

Treatments	Authors	Methods	Main results	Primary outcomes	Secondary outcomes	Results on secondary outcomes	EFNS Class
Oxcarbazepine 300–1800 mg vs. placebo	Dogra *et al.* 2005	Parallel groups 12 weeks, $n = 146$	OXC > placebo	VAS pain intensity (average) (electronic diary) NNT	Global assessment of therapeutic effects (GATE), sleep, SF36, POMS	VAS, GATE similar effects; sleep improved but not SF36	I
Pregabalin, 150, 600 mg vs. placebo	Richter *et al.* 2005	Parallel groups 6 weeks, $n = 246$	Pregabalin > placebo	NRS pain intensity (average) (diary) NNT (50% pain relief)	Sleep, SF-MPQ (sensory, affective total), VAS pain intensity, PPI(MPQ),SF36, POMS, CGI	All measures improved except SF36 less sensitive (1 domain improved only)	I
Pregabalin 600 mg/day vs. placebo	Arezzo *et al.* 2008	Parallel groups, 13 weeks, $n = 167$	Pregabalin > placebo	NRS pain intensity (average) (diary) at endpoint + weekly pain scores, responders	Sleep interference (NRS), SFMPQ, VAS and PPI (SFMQP) PGIC, CGIC, + safety parameters (Nerve conduction)	Significant effects on all outcome measures No effect on nerve conduction	I
Pregabalin 150, 300, 600 mg/day vs. placebo	Tölle *et al.* 2008	Parallel groups 12 weeks, $n = 396$	Pregabalin > placebo (highest dosage)	NRS pain intensity (average) (diary) (endpoint, weekly, 8 weeks)	Sleep interference (NRS), PGIC, CGIC, EQ-5D, NNT	Effects on all outcomes of the highest dosage only except EQ-5D more sensitive to all dosages; centre effect	I
Pregabalin flexible 150–600 mg vs. fixed 600 mg vs. placebo (including PHN patients)	Freynhagen *et al.* 2005	Parallel groups 12 weeks, $n = 338$	Pregabalin (fixed, flexible) > placebo	NRS pain intensity (average) (diary) NNT: 30%, 50%	MOS-sleep, PGIC	All measures equally sensitive	I
Meta-analysis of 7 pregabalin trials in diabetic PN	Freeman *et al.* 2008	$N = 1510$ (ITT population, 7 studies)	Reduction in endpoint least squares mean pain scores	Pregabalin > placebo all doses -correlation with doses; 150 mg not effective in single trials but effective in pooled analysis	PGIC, safety measures, time to onset of pain relief, NNT 30–50% pain relief, proportion of responders, sleep	Discontinuation rates: absent (150 mg) to 20% (600 mg); other outcome measures improved; Side effects dose-dependent	SR class I
Lamotrigine, 200, 300, 400 mg (2 RCTs) vs. placebo	Vinik *et al.* 2007	Parallel groups, 19 weeks, $n = 360$ per study	Lamotrigine = placebo (LOCF) > placebo (observed scores)	NRS pain intensity (average) (diary) Responders (30%, 50%); Large placebo effect	Sleep, pain intensity (walking) SF-MPQ, Neuropathic pain scale (NPS), CGI, Rescue analgesics	End of trt (observed scores): PGIC, walking pain intensity, NPS:significant for some doses; No effect on other outcomes	I
Lamotrigine up to 200 mg vs. amitriptyline up to 75 mg	Jose *et al.* 2007	Cross over, 6 weeks per trt, $n = 53$	Lamotrigine = amitriptyline	Pain relief, overall improvement	McGill pain questionnaire, Likert pain scale	No difference in secondary outcome but lamotrigine had less side effects (43% vs. 75%)	II

Appendix 1 (Continued)

Treatments	Authors	Methods	Main results	Primary outcomes	Secondary outcomes	Results on secondary outcomes	EFNS Class
Lacosamide 400 mg vs. placebo	Rauck *et al.* 2007	Parallel groups, 10 weeks, $n = 119$ (94 completers)	Lacosamide > placebo	NRS pain intensity (average) (diary) Effect size	SF-MPQ including VAS-PPI, NPS, sleep (NRS), SF36, POMS, pain free days, CGI	Measures of pain equally improved; No effect on POMS; SF36 only 2 domains improved including pain	I
Lacosamide 200, 400 and 600 mg vs. placebo	Wymer *et al.* 2009	Parallel groups 18 weeks, $n = 370$ (64% completers)	Lacosamide 400 mg > placebo; 600 mg > placebo observed cases	NRS pain intensity last 4 weeks (diary)	Sleep NRS), PGIC, activity (diary)	40% discontinuation in the 600 mg group for adverse effects; 23% in the 400 mg (9% placebo)	I
Lacosamide 200, 400 and 600 mg vs. placebo	Shaibani *et al.* 2009	Parallel groups, 12 weeks, $n = 468$	Lacosamide 400 mg approached significance; 600 mg ns	NRS pain intensity last 4 weeks (diary)	PGIC, responders (50% and 30% pain relief), pain free days	Responders ns improvement; no significant effect on sleep	I
Zonisamide 540 mg vs. placebo	Atli and Dogra 2005	Parallel groups, 12 weeks, $n = 25$	Zonisamide = placebo	VAS/NRS pain intensity (average) (diary)-responders	Sleep, daily functioning, pain interference	No effect on any outcome measures	II
Opioids and tramadol							
CR Oxycodone, mean 37 mg (10–99) vs. placebo	Gimbel *et al.* 2003 Jensen *et al.* 2006 (post hoc analysis of NPS)	Parallel groups, 6 weeks, $n = 159$	Oxycodone > placebo	NRS pain intensity (average) (diary)	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	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	I
CR Oxycodone (Oxy) 10–80 mg + gabapentin (gaba) (100–3600 mg) vs. placebo + gabapentin	Hanna *et al.* 2008	Parallel groups, 12 weeks, $n = 338$	Oxy-gaba > gabapentin-placebo	NRS pain intensity (box scale) at each visit	Rescue analgesics, sleep (n of disturbed night sleeps, quality of sleep), SF- BPI, SF-MPQ, EuroQol	All measures of pain equally improved; Sleep disturbance improved but not quality of sleep-No statistics for EuroQol	I
Tramadol 37.5 acetaminophen 325 vs. placebo (up to 1–2 tablets 4 times daily)	Freeman *et al.* 2009	Parallel groups, 8 weeks, $n = 311$	Tramadol/APAP > placebo	NRS pain intensity (average) (diary) from baseline to final week	Sleep interference, PGIC, QoL, mood	All outcome measures significantly improved Nausea:the only adverse effect; similar discontinuation rates (8.1% for active; 6.5% for placebo)	I
Other treatments							
SC Botulinum toxin-A (max 300 U) vs. saline	Yuan *et al.* 2009	Cross over, 12 weeks, $n = 20$ (18 completers)	BTX-A > placebo	VAS pain intensity, Pittsburgh sleep quality index, SF36		No primary outcome specified; effects on VAS and sleep (4 weeks) but not SF36	II

Appendix 1 (Continued)

Treatments	Authors	Methods	Main results	Primary outcomes	Secondary outcomes	Results on secondary outcomes	EFNS Class
Glyceryl trinitrate spray (feet) vs. placebo	Agrawal *et al*. 2007	Cross over, 4 weeks per trt, $n = 48$ (43 completers)	GTN spray > placebo	VAS pain intensity at visits	SFMPQ (total score) NRS pain intensity, PPI, NNT for pain relief	All outcome measures equally sensitive	II
NK-1 receptor antagonist TKA731 vs. placebo	Sindrup *et al*. 2006	Parallel groups 2 weeks, $n = 87$	TKA = placebo	VAS pain intensity (average) (diary)	CGI, rescue medication, sleep questionnaire, VAS for neuropathic symptoms	No effect on any outcome measure	I
ABT-594 (150, 225, 300 mg BID) vs. placebo	Rowbotham *et al*. 2009	Parallel groups, 7 weeks (1 week titration)	ABT > placebo for all dosages without dose response	NRS pain intensity final week (diary)	NRS pain intensity each week, Proportion of responders, NPS score and symptoms, SF36, rescue medication	Responders improved but too many side effects and dropouts (up to 66%) NPS ns; SF36 only physical subscore improved but mental component deteriorated	I
Combination (in diabetic PN and PHN)							
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 Morphine > placebo Combination > mor > gaba And > 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 > gabapentin or nor Gabapentin > placeboNor > 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 > with nor and weight gain > for gabapentin	I

Appendix 1 (Continued)

Treatments	Authors	Method	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	EFNS Class
Post-Herpetic Neuralgia (PHN)							
Antidepressants							
Fluoxetine 60 mg vs. imipramine 150 mg vs. amitriptyline 150 mg	Rowbotham *et al.* 2005	Parallel groups, 6 weeks, $n = 38$	Similar effects of the 3 drugs	VAS pain intensity (average) at visits	Pain relief scale (6 items) BDI, QST (allodynia to brush)	VAS and pain relief scale similarly improved Allodynia sensitive to TCAs	I
Nortriptyline 25–100 mg vs. gabapentin 300–1200 mg vs. placebo	Chandra *et al.* 2006	Parallel groups, 8 weeks, $n = 76$ (70 as intent to treat)	Nortriptyline = Gabapentin	NRS pain intensity (diary) from baseline to end of study	VAS sleep, VAS pain SF-MPQ, disability (categorical scale) pain categorical (0–5) CGI (0–4); proportion responders (50%)	No difference in outcome measure between active treatments Categorical scales not commonly used (some not validated)	II
Antiepileptics							
Meta-analysis of gabapentin in NP including PHN (Cochrane)	Wiffen *et al.* 2009	2 RCTs of gabapentin vs. placebo	Gabapentin > placebo NNT 3.9 (95% CI 3–5.7)	NNT Relative risk			SR class I
Gabapentin ER 1800 mg/day twice daily or once daily vs. placebo	Irving *et al.* 2009 Jensen *et al.* 2009 (posthoc analysis of NPS)	Parallel groups, $n = 158$, 4 weeks Enrichment design	Gabapentin ER > placebo for twice daily administration only	NRS pain intensity (diary) from baseline to endpoint	Sleep interference score NPS	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)	I
Pregabalin 150, 300, 600 mg vs. placebo	Van Seventer *et al.* 2006	Parallel groups, 13 weeks $n = 370$	Pregabalin > placebo	NRS pain intensity (average) (diary) NNT 30–50% relief	Sleep CGI (patient)	All measures equally sensitive	I
Pregabalin 150–600 vs. 300 mg vs. placebo	Stacey *et al.* 2008	Parallel groups 4 weeks, $n = 269$	Pregabalin > placebo	NRS pain intensity (diary) (criteria:time to onset of pain relief)	% responders (≥30% or 50%); PGIC; VAS (SFMPQ, anxiety); VAS allodynia to brush Daily interference scores	Pain/allodynia correlated; more severe baseline allodynia:less response to PGB; odds ratio for ≥50% PR: 1.30 (0.71–2.36)	I

Appendix 1 (Continued)

Treatments (PHS)	Authors	Method	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	EFNS Class
Meta-analysis of pregabalin studies in PHN (Cochrane)	Moore *et al.* 2009	5 RCTs, $n = 1417$	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	NNT 50% PR, NNH			SR class I
Valproate 1000 mg vs. placebo	Kochar *et al.* 2005	Parallel groups 8 weeks, $n = 45$	Valproate > placebo	SF-MPQ, VAS (PPI), NRS, NNT	CGI (patient)	All measures equally sensitive	II (only results from completers)
Opioids vs. antidepressants							
Morphine 91 mg or methadone 15 mg vs. nortriptyline 89 mg or desipramine 63 mg vs. placebo	Raja *et al.* 2002 Edwards *et al.* 2006 (predictors for response)	Cross over, 8 weeks per trt, $n = 76$ (44 completers of 3 periods)	Opioids = tricyclics > placebo	NRS pain intensity Pain relief (0%–100%) Cognitive function	Preference with treatment; MPI (physical, sleep) Beck; Treatment preference, NNT (50% PR), QST	All pain measures improved; effects on sleep and preference with trts; Predictors for response:higher heat pain thresholds at baseline, higher baseline pain, younger age	I
Topical agents							
Lidocaine patch, 5% (max 3/day) vs. placebo in PHN patients	Binder *et al.* 2009	Parallel groups, enriched enrolment, 2 weeks per trt after 8 weeks open label run-in phase, $n = 265$ (71 randomized)	No difference in the full analysis set in the primary outcome but only in perprotocol population ($n = 34$)	Time to exit	Allodynia to brush, pain relief, SF-MPQ, mean pain intensity	Significant in the perprotocol population; no direct statisti cal 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)	II (groups not balanced, many early withdrawals)
High concentration capsaicin patch NGX-4010 (8%) vs. low concentrations (0.04%) 60 min in PHN	Backonja *et al.* 2008	Parallel groups, Assessment up to 12 weeks $N = 402$	NGX-4010 > placebo	NRS average pain intensity (diary) from week 2–8	Proportion of responders (30% pain relief); Gracely pain scale, SFMPQ, PGIC, CGIC; BPI; SF36, Self assessment of treatment (SAT); concomitant treatments	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	I
Others							
COX-2 inhibitor (GW40381) 25 or 50 mg vs. placebo	Shackelford *et al.* 2009	Parallel groups, 3 weeks $N = 209$	COX-2 = placebo but duration of trial may be too short	NRS average pain intensity (diary) from baseline to last week	NPS; allodynie severity (brush) SF-MPQ; PGIC; CGIC; PR score; discon tinuation due to lack of effect:rescue medication	No statistical effect on primary and secondary endpoints except for the NPS in the 25 mg group	II
Meta-analysis of drug treatments	Hempestall *et al.* 2005	25 analysable RCTs	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)	NNT, NNH, ratio NNT/NNH			SR class I

Appendix 1 (Continued)

Treatments	Authors	Method	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	EFNS Class
Trigeminal Neuralgia							
Systematic review and guidelines of diagnosis and treatment including drug treatments in trigeminal neuralgia	Cruccu *et al.* 2009 Gronseth *et al.* 2008	SR of all treatments in TN including drugs; 12 RCTs analysed	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	Efficacy on number of attacks, paroxysmal pain, brush-evoked pain, and global assessment	Adverse events		SR class I
Central Pain							
Amitriptyline 150 mg vs. gabapentin 3600 mg vs. placebo (diphenhydramine) SCI pain	Rintala *et al.* 2007	Cross over 8 week per trt n = 38 (22 completers)	Amitriptyline > gabapentin Gabapentin = placebo	VAS pain intensity (average) at visits	Proportion responders (30%) VAS pain intensity (worst) Rescue analgesics	VAS and proportion responders responsive to trts No effect on rescue trts	II
Tramadol 150 mg vs. placebo SCI pain	Norrbrink and Lunderberg 2009	Cross over, 4 weeks, = 36 (35 analysable)	Tramadol > placebo	NRS pain intensity	Multidimensional Pain Inventory; HAD; sleep questionnaire; PGIC; Brush induced allodynia (tooth-brush); pain unpleasantness, maximal and minimal pain (NRS)	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	II
Pregabalin, 150–600 mg vs. placebo (SCI pain)	Siddal *et al.* 2006	Parallel groups, 8 weeks n = 137	Pregabalin > placebo	NRS pain intensity (average) (diary)	SF-MPQ, % responders (30, 50%), sleep, POMS, CGI	All measures of pain equally sensitive 21% discontinuation for adverse events vs. 13% placebo	I
Pregabalin, 150–600 mg vs. placebo (SCI, brain)	Vranken *et al.* 2008	Parallel groups 4 weeks n = 40	Pregabalin > placebo	VAS pain intensity (average) at weekly visits	SF36, EuroQol, PDI	Only one measure of pain; PDI and SF36 less sensitive than EQD5 (SF36 -pain improved)	I
Lamotrigine up to 400 mg vs. placebo (multiple sclerosis)	Breuer *et al.* 2007	Cross over, 11 weeks per trt n = 12	Lamotrigine = placebo Inclusion criteria 4/10 on any NPS item	NRS pain intensity from the BPI (worst, least, average pain) (diary) Responders from BPI average pain (>30%)	Rescue analgesics, NPS Multiple sclerosis QOL-54 BPI-interference	Pain responses similar but NS; Carryover effect for the item «sensitive» of the NPS; underpowered study	II

Appendix 1 (Continued)

Treatments	Authors	Method	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	Class
Levetiracetam 500–3000 mg/day vs. placebo (SCI pain)	Finnerup *et al.* 2009	Cross over, 5 weeks per tret, washout 1 week $n = 36$ (24 completers)	Levetiracetam = placebo	Average pain intensity (NRS)	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	No effect on any outcome measure Possibly underpowered for secondary outcome measures (evoked pain, spasms)	II
S-ketamine iontophoretic transdermal 50 and 75 mg vs. placebo (NP screened with LANSS)	Vranken *et al.* 2005	Parallel groups 7 days $n = 33$	Ketamine = placebo (primary outcome)	VAS pain intensity at each visit	Measures of quality of life and disability:PDI, EuroQol, SF 3	No effect on pain but effects on all measures of QOL with the high dosage	I
THC/cannabidiol (CBD) 2.7/2.5 oromucosal vs. placebo max 48 sprays/day	Rog *et al.* 2005	Parallel groups 5 weeks $n = 64$	THC/CBD > placebo	NRS pain intensity (average) (diary)	Sleep NRS NPS cognitive function HADS-Multiple sclerosis related disability CGI (patient)	Pb with NP screening (some had spasticity) Similar effects on NRS, total score NPS and sleep NPS:signifi cant effect for some items (intense, dull, sensitive)	I
Tramadol 1–1.5 mg/kg per 6 h	Arbaiza *et al.* 2007	Parallel groups 6 weeks $n = 36$	Tramadol > placebo	NRS pain intensity at each visit	Karnovsky scale, ADL including sleep and appetite (yes/no), Zung depression, Beck anxiety, SEPs, AED use on a scale (0–5)	Non validated scales (AED use, ADL) Similar effects on pain, AED rescue, Karnovski, ADL, but not mood	II
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 mn; 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

Appendix 1 (Continued)

Treatments	Authors	Method	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	Class
Smoked cannabis (1 and 8% THC) vs. placebo	Ellis *et al.* 2009	Cross over 5 days $n = 34$	Smoked cannabis > placebo	Pain intensity (Descriptor Differential Scale)	Mood and functioning Proportion of responders (30% pain relief)	Significant effects on pain but no difference on mood and functioning	II
High concentration capsaicin patch NGX-4010 (8%) vs. low concentrations (during 30, 60, 90 mn) in HIV neuropathy	Simpson *et al.* 2008	Parallel groups, Assessment up to 12 weeks $n = 307$ (274 completers)	NGX-4010 > placebo	NRS average pain intensity (diary) from week 2–12	% 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	All measures equally sensitive to treatment No effect on sensory function	I
Nerve trauma							
Gabapentin up to 2400 mg vs. placebo	Gordh *et al.* 2008	Cross over 5 weeks per trt, $n = 120$ VAS ≥ 3 at inclusion	Gabapentin = placebo on the primary outcome Placebo effect superior during the first period	VAS pain intensity (present pain twice a day) (electronic diary % responders (30%, 50% pain relief)	Pain relief (categorical), sleep interference (VAS electronic diary), SF36, CGI, rescue analgesics	PR and PGIC more improved than VAS; sleep significant; 3 items of the SF36 improved; NNT depends on the measure	I

Treatments (other conditions)	Authors	Methods	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	EFNS Class
Levetiracetam 3000 mg/day vs. placebo	Vilholm *et al.* 2008	Parallel groups, 4 weeks $n = 27$ (25 completers)	Levetiracetam = Placebo	NRS pain intensity, relief, NP symptoms; rescue analgesics; QST	No specification of primary and secondary endpoints	No effect on any outcome	II
SC Botulinum toxin A (BTX-A) (max 200 U) vs. saline in peripheral neuropathic pain (traumatic, PHN) with allodynia	Ranoux *et al.* 2008	Parallel groups 6 months $n = 29$	BTX-A > placebo	NRS pain intensity (average) (diary)	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	Effect on global pain/pain relief and CGI similar Better effect on NPSI symptoms/ dimensions (burning, paroxysmal pain, allodynia); Only 2 items of BPI-inter ference improved Predictors of response based on QST (patients with severe thermal deficits less improved)	I

Appendix 1 (Continued)

Treatments (other conditions)	Authors	Methods	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	EFNS Class
Phantom pain							
Gabapentin, 300–3600 mg vs. placebo	Smith *et al*., 2005	Cross over, 6 weeks, $n = 24$	Gabapentin = placebo	NRS Pain intensity	Categorical pain relief scale, benefit and side effects; BPI; blinding; SF-MPQ; CES-D; FIM; SWLS; CHART	No effect on any outcome measures Categorical scales not validated	II
Morphine 112 mg vs. mexiletine 933 mg vs. placebo	Wu *et al*. 2008	Cross over 6 weeks per trt wash out 1 week $n = 60$	Morphine > placebo and mexiletine	NRS pain intensity (averagediary) throughout the study (stump and phantom mixed)	% pain relief (0–100%) NNT for 50 and 33% pain relief, functional activity (MPI) (general and ntererence scales)	Effects on pain but not on self reported levels of activity	I
Cancer NP							
Gabapentin 600–1800 mg vs. placebo (cancer NP)	Caraceni *et al*. 2005	Parallel groups, 10 days $n = 121$	Gabapentin > placebo	NRS pain intensity (average) (diary)	Neuropathic symptoms NNT 33% pain relief Allodynia at examination Rescue analgesics	Effects on pain intensity but not on analgesic use or on neuropathic symptom	I
Radiculopathies							
Nortriptyline 25–100 mg vs. morphine 15–90 mg vs. combination vs. placebo	Khoromi *et al*. 2007	Cross over 7 weeks per trt $n = 55$ (28 completers)	No effect of treatments	NRS pain intensity (average and maximal) (diary)	Global pain relief (categorical) Oswestry disability scale BDI, SF-36, NNT (pain relief) Blinding	Average pain: ns -Combination > placebo for worst pain and pain relief/placebo (chance effect?) No blinding	II
Topiramate 200 mg vs. diphenhydramine 40 mg	Khoromi *et al*. 2005	Cross over 6 weeks per trt $n = 41$ (29 completers)	Topiramate marginally > placebo (primary outcome)	NRS pain intensity (average) (diary) for leg pain	NRS pain intensity (back, global pain), worst pain, Pain relief (categorical) Oswestry, BDI, SF36	Average leg pain less improved than global assessment or worst pain	II
Pregabalin 150–600 mg vs. placebo	Pfizer, protocol A0081007 –20 may 2008	Single blind run in phases with placebo then pregabalin, then 5 weeks double blind period, $n = 217$ (187 completers)	Pregabalin = placebo	Increase in pain over the double blind treatment period in patients randomized to placebo compared to pregabalin	PGIC, sleep interference, HADS, EQ-5D, MOS, pain treatment satisfaction scale, Roland Morris disability	No effect on any outcome measure	II (numerous protocol violations)
Multiaetiology NP							
Gabapentin 600–1800 mg vs. placebo	Yelland *et al*. 2009	N of 1 method, 3 double-blind RCT cross over trials $N = 73$ (48 completes)	Only 29% patients showed a positive response to gabapentin, 69% no difference	Aggregate measure for: VAS for pain intensity, sleep-VAS, functional limitation VAS, treatment preference,side effects			II many withdrawals (35%)

Appendix 1 (Continued)

Treatments (other conditions)	Authors	Methods	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	EFNS Class
Lamotrigine 200, 300, 400 mg. vs. placebo	Silver *et al.* 2007	Parallel group, 14 weeks $n = 220$	Lamotrigine = placebo Large placebo effect	NRS pain intensity (average) (diary), responders (30%, 50%)	Sleep interference SF-MPQ, NPS total score Rescue analgesics, CGI	No difference/placebo, No outcome measure more sensitive -No predictors – dizziness, rash, somnolence in > 5% of patients	I
Lidocaine patch, 5% (max 4/day) vs. placebo in patients with allodynia (PHN, postsurgical, peripheral neuropathy)	Meier *et al.* 2003 Wasner *et al.* 2005 (subgroup analysis)	Cross over 7 days per trt $n = 40$	Lidocaine > placebo	VAS spontaneous pain and allodynia intensity (diary)	Descriptors partially derived from the MPQ QOL (how did you sleep) on a 5-point categ scale; NNT for 50% pain relief and allodynia relief; effect size QST and QSART in a subgroup of 18 PHN patients	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	I (II for Wasner *et al.*)
Lidocaine patch 5% vs. topical amitripty-line (ami) 5% vs. placebo	Ho *et al.* 2008	Cross over 1 week per trt, $n = 35$	Amitriptyline = lidocaine = placebo; Lido-caine > ami	VAS pain intensity at the end of trt period	Daily NRS, MPQ, rescue analgesics, patient satisfaction(categorical), degree of pain relief	Outcome measures equally improved	II
Topical amitriptyline 2% vs. topical keta mine 1% vs. combi nation vs. placebo	Lynch *et al.* 2005	Parallel groups 3 weeks $n = 92$	Ami = ketamine = combination = placebo	NRS pain intensity (average) (diary)	SF-MPQ, dynamic allodynia, pinprick hyperalgesia, PDI, patient satisfaction	No effect on any outcome measure	I
Venlafaxine 75 mg vs. 150 mg vs. placebo	Yucel *et al.* 2004	Parallel groups 8 weeks $n = 55$	Venlafaxine = placebo	VAS pain intensity (VAS-PI) (average) at visits	Patient satisfaction (categorical) Effect on daily activities Rescue analgesics Global efficacy QST (allodynia)	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 allodynia (QST) > PI	II
Nabilone 2 mg vs. dihydrocodeine 240 mg	Frank *et al.* 2009	Cross over, 6 weeks (2 weeks washout) $n = 96$ (73 available)	Nabilone < Dihydrocodeine	VAS pain intensity	Anxiety and depression (HAD), SF36, sleep (numbers of hours slept each night)	Dihydrocodeine > nabilone on all outcomes but effect moderate in all cases Effect of nabilone on the role physical of SF36	I

Appendix 1 (Continued)

Treatments (other conditions)	Authors	Methods	Main results	Primary outcome	Secondary outcome	Results on secondary outcomes	EFNS Class
THC/CBD oromucosal 2.7/2.5 vs. placebo-max 8 sprays/2 h self-titration (peripheral NP)	Nurmikko *et al.* 2007	Parallel groups, 5 weeks, $n = 125$	Sativex > placebo	NRS pain intensity (average) (diary)	NPS, PDI, PGIC pain and allodynia, GHQ-12 (mood, anxiety); NRS sleep; Cognitive tests; allodynia (dynamic, punctate); NNT ongoing pain, allodynia	All measures of pain improved – no change in pain threshold but decrease in pain evoked by punctate stimuli No effect on CHG-Q	I

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, Mc Gill 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 Mc Gill 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

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