

EFNS guidelines on pharmacological treatment of neuropathic pain

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Neuropathic pain treatment remains unsatisfactory despite a substantial increase in the number of trials. This EFNS Task Force aimed at evaluating the existing evidence about the pharmacological treatment of neuropathic pain. Studies were identified using first the Cochrane Database then Medline. Trials were classified according to the aetiological condition. All class I and II controlled trials (according to EFNS classification of evidence) were assessed, but lower-class studies were considered in conditions that had no top level studies. Only treatments feasible in an outpatient setting were evaluated. Effects on pain symptoms/signs, quality of life and comorbidities were particularly searched for. Most of the randomized controlled trials included patients with postherpetic neuralgia (PHN) and painful polyneuropathies (PPN) mainly caused by diabetes. These trials provide level A evidence for the efficacy of tricyclic antidepressants, gabapentin, pregabalin and opioids, with a large number of class I trials, followed by topical lidocaine (in PHN) and the newer antidepressants venlafaxine and duloxetine (in PPN). A small number of controlled trials were performed in central pain, trigeminal neuralgia, other peripheral neuropathic pain states and multiple-aetiology neuropathic pains. The main peripheral pain conditions respond similarly well to tricyclic antidepressants, gabapentin, and pregabalin, but some conditions, such as HIV-associated polyneuropathy, are more refractory. There are too few studies on central pain, combination therapy, and head-to-head comparison. For future trials, we recommend to assess quality of life and pain symptoms or signs with standardized tools.

Background and objectives

Despite the considerable increase in the number of randomized placebo-controlled trials in neuropathic pain over the last few years, the medical treatment of neuropathic pain is still far from being satisfactory, with less than half of the patients achieving significant benefit with any pharmacological drug [1,2]. Randomized controlled trials (RCTs) have generally been per-

formed in patients categorized according to their aetiologies. Most RCTs have been conducted in postherpetic neuralgia (PHN) and painful polyneuropathy, whereas there are very few trials in other peripheral neuropathic pains – including trigeminal neuralgia (TN) – and central pain (CP), and no RCTs in painful radiculopathies. Recently, therapeutic strategies aiming at selecting treatments by targeting the putative mechanisms of pain (mechanism-based strategies) have been proposed [3,4]; yet, this approach remains difficult to apply in clinical practice [5–7].

Although well-conducted meta-analyses or systematic reviews (SR) on medical treatment of neuropathic pain have been recently published [1,2,8–11], there is still a lack of expert consensus on guidelines regarding the medical treatment of neuropathic pain. This may be mainly due to the heterogeneity of such pain in terms of aetiologies, symptoms, signs and underlying mechanisms.

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The objectives of our Task Force were: (1) to examine all the RCTs performed in the various neuropathic pain conditions; (2) to evaluate the drug effects on pain symptoms, quality of life, and sleep, and the adverse events; (3) to propose recommendations based on the results of these trials aiming at helping clinicians in their treatment choice for most neuropathic pain conditions; (4) to propose new studies that may help clarify unsolved issues.

Methods

We conducted an initial search through the central database in the Cochrane Library. Whenever the Cochrane search failed to find top level studies for a given neuropathic pain condition or a drug which was supposedly active on neuropathic pain, we expanded the search using Medline and other electronic databases (1966–to date), and checking reference lists published in meta-analyses, review articles, and other clinical reports. Furthermore, to get the most updated information, we also asked all the pharmaceutical companies producing drugs in this field to provide us with studies not yet published (Appendix A). Any reports retrieved from these contacts were pooled with the others for selection.

In order to provide the neurologist with clear indications regarding drug treatment for the most studied neuropathic pains, the Task Force decided to produce individual chapters for painful polyneuropathies, PHN, TN, and CP [spinal cord injury (SCI), post-stroke pain and multiple sclerosis (MS)], but to search and report also for the other less studied neuropathic conditions (post-traumatic/post-surgical nerve lesions, phantom limb pain, Guillain–Barré syndrome) and for neuropathic pains with multiple aetiology. Each chapter was assigned to two Task Force participants.

Classification of evidence

Classification of evidence and recommendation grading adhered to the EFNS standards [12]. In particular, class I refers not only to adequate prospective RCTs, but also to adequately powered SR.

Inclusion and exclusion criteria

Included studies complied with the following criteria: (1) randomized or non-randomized but controlled class I or II trials (lower-class studies were evaluated in conditions in which no higher-level studies were available); (2) pain relief considered as a primary outcome and measured with validated scales; (3) minimum sample of 10 patients; (4) treatment duration and follow up clearly specified; (5) treatment assessed in repeated dose settings for at

least 1 week; (6) treatment feasible in an outpatient setting (i.v., subcutaneous, or intrathecal therapy or nerve blocks were not considered); (7) evaluating currently used drugs or drugs under clinical phase-III development; (8) including patients with pain secondary to a definite nervous system lesion/disease [13] or idiopathic TN; (9) full paper citations in English, Danish, French, Finnish, German, Italian, Portuguese or Spanish.

Exclusion criteria were duplicated patient series, uncontrolled studies, pain without evidence of a nerve lesion, such as atypical facial pain, CRPS type I or low back pain, non-validated or unconventional outcome measures, non-pharmacological intervention, treatments acting directly on the disease or pre-emptive treatments.

Information selected from the trials

From articles meeting our search criteria, we extracted information regarding the efficacy not only on overall pain and main side-effects, but also effects on pain symptoms or signs, quality of life and mood, whenever available. We also referred to recent well-conducted meta-analyses when analysis of these studies did not provide with additional information regarding these end-points. We used the NNT (the number of patients needed to treat to obtain one responder to the active drug) with 95% confidence intervals (CI) for class I/II studies in order to gain information regarding the overall efficacy of a drug. Unless otherwise specified, we used the NNT for 50% pain relief. These values were calculated for newer trials or extracted from recent meta-analyses performed by members of this Task Force [2,9,14] or the Cochrane database [11,15–17]. We did not use the Number Needed to Harm because of lack of uniform criteria for assessing harmful events [2].

Results

Painful polyneuropathy

Painful polyneuropathy (PPN) is a common neuropathic pain condition. Diabetic polyneuropathy is the most classical example. Patients usually present with spontaneous and stimulus-evoked pains with a distal and symmetrical distribution [18]. Although one or more of the pain symptoms characteristics of neuropathic conditions are seen in the majority of the patients, the most frequent single pain symptom is deep aching pain [18]. Diabetic and non-diabetic PPN are similar in symptomatology and with respect to treatment response [class I SR: 19]. The only exceptions seem to concern HIV- and chemotherapy-induced neuropathy which are described separately.

Antidepressants

Antidepressants have recently been reviewed in two class I meta-analyses in neuropathic pain including PPN [11,14]. Evidence for the efficacy of tricyclic antidepressants (TCA: amitriptyline, clomipramine, desipramine, imipramine, Table 1) has compiled since they were first introduced in PPN about 30 years ago. Most data stem from relatively small cross-over class I or II trials, which may overestimate efficacy. The NNT for TCA in painful polyneuropathy is 2.1 (CI 1.8–2.6) for drugs with balanced serotonin and noradrenalin reuptake inhibition and 2.5 (CI 1.9–3.6) for drugs that mainly inhibit noradrenaline reuptake [14]. In one trial, amitriptyline was slightly but significantly more effective than maprotiline [class I: 20] whereas another trial failed to observe significant differences between clomipramine and desipramine [class I: 21].

Selective serotonin reuptake inhibitors (SSRI) or mianserin cause minor and clinically insufficient pain relief in four class I trials [class I SR: 11,14], whereas serotonin-noradrenaline reuptake inhibitors (SNRI) such as venlafaxine (150–225 mg/day) [class I: 22,23] and duloxetine (60–120 mg/day) [class I: 24,25] are effective, although their effects appear generally moderate. In a head-to-head comparative study of 33 patients, venlafaxine was less effective than imipramine on the proportion of responders [class I: 23]. With adequate dosing, the NNT is 4.6 (CI 2.9–10.6) for

venlafaxine (150–225 mg/day) and 5.2 (CI 3.7–8.5) for duloxetine (60–120 mg/day).

Antiepileptics

Two small crossover double-blind trials, published some 30 years ago, reported significant effects of carbamazepine (CBZ) in diabetic PPN, but their methods and reporting do not live up to current standards [class III: 26,27]. One small double-blind study ($n = 16$) reported similar efficacy of CBZ and nortriptyline-fluphenazine, but the small sample size might prevent showing a difference [class II: 28].

Oxcarbazepine (OXC) data were equivocal in PPN as judged by abstracts from the EFNS congress in 2004, with several still unpublished negative trials. However, in a recent double-blind parallel-group placebo trial of 16-week duration, OXC (300–1800 mg/day) had a modest although significant efficacy in diabetic PPN with NNT = 5.9 (CI 3.2–42.2) [class II: 29].

Lamotrigine (LTG) has shown significant efficacy with NNT = 4.0 (CI 2.1–42) in diabetic PPN [class I: 30].

Topiramate failed to relieve diabetic PPN in three large controlled trials [class I SR: 31] and one later study found a marginal effect with NNT = 7.4 (4.3–28.5) [class I: 32].

Because data about valproate are controversial, with two very positive studies from the same group

Table 1 Predominant mechanism of action of main drugs

Drug	Predominant mechanism
Amitriptyline	TCA, balanced monoamine reuptake inhibition
Capsaicin (topical)	Depolarizes the nervous membrane via vanilloid receptor type 1, initially stimulates then blocks skin nerve fibres
Carbamazepine	Voltage-gated sodium-channel block
Clomipramine	TCA, balanced monoamine reuptake inhibition
Desipramine	TCA, predominantly noradrenaline reuptake inhibition
Dextromethorphan	NMDA-receptor antagonist
Duloxetine	SNRI, serotonin-noradrenaline reuptake inhibition
Gabapentin	Binding to the $\alpha_{2\delta}$ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters
Imipramine	TCA, balanced monoamine reuptake inhibition
Lidocaine (topical)	Block of peripheral sodium channels and thus of ectopic discharges
Lamotrigine	Presynaptic voltage-gated sodium-channel inhibition and thus reduced release of presynaptic transmitters
Memantine	NMDA-receptor antagonist
Nortriptyline	Predominantly noradrenalin reuptake inhibition
Oxcarbazepine	Voltage-gated sodium- and calcium-channel block
Oxycodone	μ -opioid-receptor agonist
Pregabalin	Binding to the $\alpha_{2\delta}$ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters
Tetrahydrocannabinol	Agonist to the CB1 and the CB2 subtype of cannabinoid receptors
Topiramate	Voltage-gated sodium-channel block and inhibition of glutamate release by an action on AMPA/kainate receptors
Tramadol	μ -opioid-receptor agonist and monoamine reuptake inhibitor
Valproate	Increase of GABA levels in brain and potentiation of GABA-mediated responses
Venlafaxine	SNRI, serotonin-noradrenaline reuptake inhibition

(NNT = 1.5; CI 1.2–2.2) [33,34, class II] and one negative study [35, class I], its potential in PPN needs further scrutiny.

The antiepileptics with best evidence for efficacy to date in PPN are gabapentin (GBP) 1200–3600 mg/day and pregabalin 150–600 mg/day [class I: 36–39]. These drugs relieve diabetic PPN consistently across trials (overall NNT = 3.9, CI 3.2–5.1). Most of the initial pregabalin trials were flawed by exclusion of GBP non-responders, resulting in an enriched enrolment, but two recent class I RCTs without this criterion still reported a similar efficacy [40,41]. Only one head-to-head controlled study compared GBP (1800 mg/day) with amitriptyline (75 mg/day). Because of an insufficient sample size, the order of efficacy and tolerability between these drugs could not be settled [class II: 42]. In one unpublished parallel group trial comparing pregabalin and amitriptyline to placebo, amitriptyline, but not pregabalin, was significantly better than placebo on the primary end-point, but the study may be biased by significant differences in baseline characteristics between the two active treatment groups (class II: Pfizer, data on file).

Opioids

Oxycodone (average doses 37–60 mg/day, range 10–99 mg/day), the only pure opioid assessed in PPN, is effective with a combined NNT = 2.6 (CI 1.9–4.1) [class I: 43,44]. Patients previously receiving opioids were allowed to participate in these trials, which may enhance the proportion of opioid responders and reduce the incidence of side-effects (see ‘Adverse events and indications for use’). Tramadol 200–400 mg/day, with opioid and monoaminergic effects, also relieves PPN effectively with an NNT = 3.4 (CI 2.3–6.4) [class I: 45,46].

Others

The antiarrhythmic drug mexiletine did not yield significant pain relief in four class I–II trials in PPN [class I SR: 2]. Topical capsaicin gave discrepant results across five class I–II studies that do not provide evidence for a clinically noticeable pain relief in PPN [class I SR: 2]. Furthermore, the intense burning sensation caused by this agent decreases compliance and may cause unblinding. The NMDA-antagonist memantine has not shown convincing efficacy in PPN [class I: 47], whilst pain relief was found for the weak NMDA-antagonist dextromethorphan in two small trials [47, class II: 48]. Efficacy of levodopa has been reported in one small RCT [class II: 49]. Other drugs assessed in PPN (aspirin, NSAIDs, topical clonidine) have either limited or lack of efficacy on the basis of class I–II trials or are not available for use [class I SR: 19].

HIV-associated neuropathy and chemotherapy-induced neuropathy

In HIV-associated neuropathy, two parallel-group RCTs did not show benefit from LTG (300–600 mg/day) except in subgroups of patients depending on their use of concomitant antiretroviral therapy (ART) [class I/II: 50,51]: the study with the largest sample (227 patients), which used stratified randomization, showed efficacy in the group receiving ART and had a high placebo response in the group not receiving ART “51”, whereas the smaller study showed better effects in the group not receiving ART [50].

In one crossover RCT GBP (titrated to 2400 mg/day) improved pain and sleep with no significant difference from placebo [class II: 52].

There is evidence, from class I/II studies, that amitriptyline [53,54], topical lidocaine patches [55], mexiletine [54,56] and capsaicin [57] lack efficacy.

One class II RCT performed in cisplatin-induced neuropathy reported little benefit from nortriptyline (100 mg/day) on pain or paresthesias (except during the second period of treatment probably due to carryover effect), but the major limitation of this study is the lack of distinction between pain and paresthesia [58].

Combination therapy

The usefulness of combination therapy has been assessed in two RCTs. The largest one, which also included patients with PHN, demonstrated synergistic effects of GBP–morphine combination, with better analgesia at lower doses of each drug than either as a single agent, but the additional effect of the combination was low [class I: 59]. Another parallel-group study showed the superiority of GBP–venlafaxine combination on pain, mood and quality of life when compared with GBP plus placebo, but the study sample was very small (11 patients) [class II: 39].

Recommendations

Treatments with established efficacy on the basis of class I trials in PPN (with the exception of HIV-associated polyneuropathy) are TCA, duloxetine, venlafaxine, GBP, pregabalin, opioids and tramadol (level A). The balanced TCA (amitriptyline and imipramine) at adequate dosages seem to have the highest efficacy on the basis of NNT, but most data stem from small trials which may overestimate efficacy. We recommend TCA or GBP/pregabalin as first choice. The SNRI duloxetine and venlafaxine are considered second choice because of moderate efficacy, but are safer and have less contraindications than TCAs and should be preferred to TCA particularly in patients with cardiovascular risk factors (see ‘Adverse events

and indications for use'). Second/third-line therapy includes opioids (potential safety concerns in non-cancer pain; see 'Adverse events and indications for use') and LTG (level B). Treatments with weaker/lack of efficacy include capsaicin, mexiletine, OXC, SSRI, topiramate (level A), memantine, mianserin and topical clonidine (level B). There is low strength of evidence and safety concerns for CBZ (see 'Adverse events and indications for use') (level C) and limited support for the use of dextrometorphan and levodopa. Discrepant results have so far been obtained with valproate.

HIV-associated polyneuropathy has been found refractory to most currently assessed drugs. This may be due to particular mechanisms of pain in this often progressive condition and/or to a high placebo response, observed in many trials. Only LTG has been reported efficacious in a subgroup of patients receiving ART in one class I trial, but a smaller class II trial reported totally opposite results (level B).

Postherpetic neuralgia

Postherpetic neuralgia is a painful aftermath of herpes zoster. The most important risk factors for PHN are old age and severe acute pain. Patients with PHN commonly describe a constant generally burning pain, an intermittent pain with lancinating or shooting quality, and brush-induced allodynia is observed in nearly 90% of cases. In an individual patient, any component can be the most distressing feature of the pain [60].

Antidepressants

The TCAs amitriptyline (average dosages 65–100 mg/day), nortriptyline (average 89 mg), desipramine (average 65–73 mg) are effective in PHN on the basis of three class I–II placebo-controlled trials with a combined NNT = 2.6 (CI 2.1–3.5) [class I SR: 8,9]. In two small head-to-head comparative trials, the antidepressant maprotiline has been found slightly less effective than amitriptyline [class II: 61] and nortriptyline as effective as amitriptyline, but better tolerated [class II: 62]. There are no RCTs of the efficacy of SSRIs or SNRIs in PHN.

Antiepileptics

Gabapentin 1800–3600 mg/day [class I: 63,64] and pregabalin 150–600 mg/day [class I: 65,66] have consistently shown efficacy in PHN, with an NNT of 4.4 (CI 3.3–6.1) for GBP and 4.9 (3.7–7.6) for pregabalin [class I SR: 9]. Very good results have recently been reported with valproate 1000 mg in one study with an NNT = 2.1 (1.4–4.2) [66, class II].

Topical treatments

Repeated application of lidocaine patches (5%) has shown efficacy in PHN patients with allodynia in three placebo-controlled studies, all with short duration (up to 3 weeks) [class II: 68–70]. One crossover study (in 32 patients) did not report baseline levels of pain and used an enriched enrolment (i.e. only patients with clinical open-label improvement with topical lidocaine were recruited) [68]. Two studies [69,70] were *post-hoc* analyses from larger trials performed in multiple-aetiology neuropathic pain group [class II: 71] or in PHN patients [68].

Topical capsaicin 0.075% has been found effective, though to a small degree, in two parallel group RCTs and caused burning sensation in most subjects [class I: 72,73].

Opioids

Oxycodone, morphine and methadone have shown efficacy on PHN in two crossover placebo-controlled RCTs [class I: 74,75]. One non-placebo-controlled parallel group study reported better efficacy of high versus low dosages of levorphanol in PHN patients (extracted from a larger group of patients with multiple-aetiology neuropathic pains) [class I: 76]. The combined NNT for strong opioids in PHN is estimated 2.7 (CI 2.1–3.7) [class I SR: 9]. In one trial comparing slow-release morphine (91 mg/day, range 15–225) and methadone (15 mg/day) with TCAs and placebo, pain relief was significantly greater with morphine than with nortriptyline, whereas the analgesic efficacy of methadone was comparable with that of TCAs [75]. There were significantly more withdrawals during the opioid treatment than during the TCA treatment, but cognitive deterioration was seen only with TCAs.

Tramadol (mean dosage 275 mg/day, up to 400 mg/day) was shown moderately effective only on some measures of spontaneous pain intensity in PHN, with an NNT = 4.8 (CI 2.6–26.9) [class I: 77]; in this study, only patients with pain lasting for less than 1 year were included, thus several patients tended to recover spontaneously during the trial, which accounts for the high rate of placebo response.

Other treatments

The NMDA-antagonists dextrometorphan and memantine, as well as the benzodiazepine lorazepam, are inefficacious in PHN [class I/II: 47,48,78,79].

Recommendations

In PHN, drugs with established efficacy include TCAs, GBP, pregabalin and opioids (level A, class I trials). Drugs with lower efficacy or limited strength of

evidence include capsaicin, tramadol, topical lidocaine and valproate (level B). We recommend TCAs or GBP/pregabalin as first line. Topical lidocaine has been evaluated only in patients with allodynia in short-term studies which used an enrichment phase or were *post-hoc* analyses from larger trials. However, due to excellent tolerability, this treatment may be preferred in the elderly, particularly in patients with allodynia and small area of pain. Despite established efficacy, strong opioids should be recommended as second choice (see 'Adverse events and indications for use'). Drugs with weak efficacy or inefficacy include mexiletine, lorazepam and NMDA antagonists (level A).

Trigeminal neuralgia

Trigeminal neuralgia typically presents with paroxysmal pain, with sudden, very brief attacks of pain (electric-shocks). Pain may be spontaneous or evoked by innocuous stimuli in specific facial or intraoral areas (trigger zones). TN is divided into 'classical' (idiopathic) when secondary to vascular compression of the trigeminal nerve in the cerebellopontine angle or when no cause can be found, or 'symptomatic', when secondary in particular to cerebellopontine-angle benign masses or MS. Patients with symptomatic TN are considered to be less responsive to treatment [80].

Antiepileptics

Phenytoin was the first drug used for TN, with positive effects, but there are only class IV studies for this condition [class I SR: 81].

Carbamazepine (200–1200 mg/day), the treatment of choice for TN, has been studied 40 years ago in three placebo-controlled trials including a total of 150 patients, with an NNT = 1.8 (1.3–2.2) from one class II and one class III trial [class I SR: 16,81] and an effect on both the frequency and intensity of paroxysms in the largest study [class II: 82]. The use of CBZ is complicated by pharmacokinetic factors and sometimes severe adverse events, particularly in elderly patients (see 'Adverse events and indications for use'). However, it seems that in TN excellent efficacy compensates its poor tolerability.

Oxcarbazepine is commonly used as initial treatment for TN [83]. Its preference over CBZ is mainly related to its documented efficacy in epilepsy and accepted greater tolerability [class I: 84]. Three double-blind RCTs compared OXC (average dose 1038 mg/day) versus CBZ (average dose 734 mg/day; Novartis, Basel, Switzerland). Only one of them was published in extenso [class II: 85]. In meta-analyses of these trials, including a total of 130 patients, the reduction in number of attacks and global assessment were equally

good for both CBZ and OXC (88% of patients achieving a reduction of attacks by > 50%), with no significant difference [SR class II: 86; Novartis, Basel, Switzerland]. These studies are not placebo controlled, which impedes NNT calculations, and only the one published in extenso can be rated according to EFNS criteria.

The efficacy of both CBZ and OXC decreases over time [SR class I: 81].

Lamotrigine (400 mg/day) has been found effective as add-on therapy on a composite index of efficacy in 14 patients [class II: 87]. However, no statistical results are available on the intensity and frequency of paroxysms.

Several other antiepileptics (clonazepam, GBP, valproate) have been reported effective in small class IV uncontrolled studies.

Other drugs

Small class II trials (10–15 patients) have shown that baclofen alone reduces the number of attacks [88,89]. Both tocainide and pimozone, reported to be as effective as or more effective than CBZ [class II: 90,91] are no longer used.

Ineffective therapy

RCT-documented inefficacy in TN includes topical ophthalmic anaesthesia [class I: 92] and topical capsaicin [class III: 93]. Tizanidine is less effective than CBZ [class II/III: 94,95].

Combination therapy

Considering the relatively narrow mechanism of action of the available drugs, combination treatments might be useful, but there are no published studies comparing polytherapy with monotherapy [96].

Symptomatic TN

Only class IV studies have reported beneficial effects of LTG, GBP or topiramate on TN associated with MS [class I SR: 81]. All studies in TN secondary to cerebellopontine-angle tumours or other posterior fossa masses only deal with surgical treatment.

Recommendations

The two most widely used drugs in idiopathic TN are CBZ (200–1200 mg/day) (level A) and OXC (600–1800 mg/day) (level B). OXC has a lower strength of evidence than CBZ, but poses less safety concerns. Baclofen and LTG have only level C evidence. We recommend CBZ or OXC as first line. Because TN typically lasts forever with periods of partial or complete remission and recurrence, the patients should be taught to adapt the dosage to the frequency of attacks. There is no evidence that combination therapies are

advantageous. In patients non-responsive to medical treatment, surgical interventions have given excellent results. In fact, many patients cannot withstand several weeks of pharmacological testing and need prompt neurosurgical attention. Baclofen or LTG may be proposed as add on in patients refractory to CBZ or OXC, particularly if the patient cannot undergo or refuses surgery.

We encourage controlled studies in symptomatic TN.

Central pain

Central pain or central neuropathic pain is pain due to a lesion in the central nervous system. CP can be a consequence of stroke, SCI, MS, but also other aetiologies [97]. Pain may be burning, shooting, aching, or pricking and is often accompanied by dysesthesia, hyperalgesia or allodynia, particularly to brush or cold [97,98].

Tricyclic antidepressants

Amitriptyline has been assessed in post-stroke and SCI pain. In 15 patients with post-stroke pain, amitriptyline 75 mg daily was superior to placebo (NNT = 1.7; CI 1.2–3.1) and to CBZ (800 mg), the latter being similar to placebo [class I: 99]. In a large study of patients with SCI pain ($n = 84$), amitriptyline (average dose 55 mg/day) was found to be ineffective, but the lack of effect might be due to inadequate assessment of neuropathic pain [class I: 100]: the primary outcome was overall pain, and only regression analyses were used to determine if the effect of amitriptyline was influenced by the presence of neuropathic pain.

Antiepileptics

In a class I study of 30 patients with post-stroke pain, LTG (200 mg/day) significantly reduced pain intensity compared with placebo [101]. In patients with traumatic SCI, LTG up to 400 mg/day failed to induce a significant effect on spontaneous and evoked pain, but an effect was observed in a *post hoc* analysis in patients with incomplete SCI [class I: 102].

In a small cross-over trial of 20 patients with SCI pain, GBP up to 3600 mg was significantly effective [class II: 103]. Pregabalin (average dose 460 mg/day) was significantly efficacious in a large ($n = 137$) class I parallel-group RCT in SCI (Pfizer, data on file).

In an RCT in SCI, there was no difference between valproate (up to 2400 mg/day for 3 weeks) and placebo [class II: 104].

Opioids

There is only one RCT on opioids, in multiple-aetiology peripheral or CP: levorphanol at high dose (8.9 mg/day) was more effective than levorphanol at low dose

(2.7 mg/day) in patients with CP, but there was no placebo group [class I: 76]. There was no difference in response between patients with SCI, MS, PHN, or PPN, but patients with brain lesions had more early dropouts due to side-effects compared with the others.

Others

In a small cross-over trial involving 11 SCI patients, mexiletine 450 mg/day was no better than placebo [class II: 105]. Low doses and small number of patients might play a role for lack of efficacy.

Cannabinoid treatment has recently been assessed in two RCTs on pain associated with MS. In one trial in 24 patients, the oral cannabinoid dronabinol (tetrahydrocannabinol, THC) 5–10 mg/day for 3 weeks, was superior to placebo with an NNT = 3.4 (CI 1.8–23.4) [class I: 106]; dronabinol was effective on ongoing and paroxysmal pain, but not on mechanical allodynia. Cannabinoids delivered via an oromucosal spray (2.7 mg of THC, 2.5 mg of cannabidiol) are under clinical phase III development for pain due to MS. One parallel group placebo-controlled trial including 66 patients showed beneficial effects on pain and sleep (mean number of sprays 9.6, range 2–25), with an NNT = 3.7 (CI 2.2–13) [class I: 107]. The patients included either had neuropathic or spasm-related pain and *post hoc* analyses indicated a trend towards better effects in patients with painful muscle spasms.

Recommendations

Considering the small number of RCTs in CP and the generally small sample sizes, the treatment may be based on general principles for peripheral neuropathic pain treatment and for side-effect profile. There is level B evidence for the use of LTG, GBP, pregabalin (unpublished study) or tricyclic antidepressants for post-stroke or SCI pain. The level of evidence is lower for opioids in the lack of placebo-controlled studies (level C). There is level B evidence for inefficacy of valproate and mexiletine in SCI pain. In CP associated with MS, cannabinoids have shown significant efficacy (level A), but may raise safety concerns (see 'Adverse events and indications for use'). Therefore, we recommend initially a trial with other drugs found effective on other CP conditions.

Less studied neuropathic pain conditions

RCTs in less studied neuropathic conditions encompassed pain due to cancer infiltration, phantom limb, post-surgical/post-traumatic nerve lesions, Guillain-Barré syndrome, or multiple-aetiology neuropathic pains.

Although many RCTs were performed in low back pain, no trial considered radiculopathy pain as a primary outcome. Regarding CRPS, most trials included patients with CRPS I or used sympathetic nerve blocks [class I SR: 108].

Neuropathic pain due to cancer infiltration

Gabapentin (up to 1800 mg/day) in addition to opioids induced modest benefit on pain and dysesthesia in one large ($n = 121$) class I RCT [109]; GBP was generally well tolerated, with no difference in dropouts compared with placebo. One RCT on low-dose amitriptyline (30–50 mg/day) for 10 days only, reported a modest effect on maximal but not average pain, combined with opioids [class II: 110].

Post-traumatic/post-surgical neuropathic pain

Three studies were performed in post-mastectomy pain and one in mixed post-surgical pain related to cancer. One small ($n = 15$) class II study showed efficacy of amitriptyline (25–100 mg) on pain, sleep and daily activities [111]; side-effects caused four early dropouts and most patients discontinued treatment after the study.

In one small ($n = 13$) class II RCT, characterized by a remarkably high response to placebo, low-dose venlafaxine (37.5–75 mg/day) was effective on maximal pain and pain relief, but not on average pain [112]. Topical capsaicin (0.075%) was reported generally efficacious in a large class I trial in post-surgical pain [113], whereas in a small class II study in post-mastectomy pain it gave negative effects on steady pain and positive effects on jabbing pain, category pain intensity and pain relief [114]. Both studies used a neutral placebo, which may induce a bias due to the burning sensation engendered by capsaicin.

There is evidence regarding the inefficacy of propranolol in post-traumatic nerve lesions [class II: 115] or cannabinoid spray on pain after brachial plexus avulsion [class I: 116].

Phantom limb pain

In a small ($n = 19$) class II RCT, GBP titrated to 2400 mg/day was effective on pain but had no effect on mood, sleep, or activities of daily living [117]. Morphine sulphate (70–300 mg/day) was effective in one small ($n = 12$) class II RCT, but most patients and therapists recognized the active treatment, which might unmask the blinding; there was a significant reduction of attention in morphine-treated patients [118].

There is evidence regarding the inefficacy of meamantine 30 mg/day [class I: 119] or amitriptyline 125 mg/day [class II: 120].

Guillain–Barré syndrome

Two short-duration (7 days) class II RCTs used GBP combined with opioids on demand. Gabapentin was superior to placebo in one study [$n = 18$; 121] and superior to CBZ in another [$n = 36$; 122], with rapid (day 2–3) reduction of both pain and opioid consumption. A systematic search by a consensus group on Guillain–Barré syndrome supports the use of GBP or CBZ in the intensive care unit in the acute phase, whilst appropriate opioids may be used but require careful monitoring of adverse effects in the setting of autonomic denervation [SR: 123].

Multiple-aetiology neuropathic pains

Trials in multiple-aetiology neuropathic pain included a large proportion of patients with CRPS or radiculopathy. In patients with peripheral neuropathic pain, there is evidence for the efficacy of the antidepressants bupropion 150 mg [class I: 124], clomipramine [class II: 125,126], nortriptyline [class II: 125], CBZ [class II: 127], and for topical lidocaine [71, discussed in ‘Effects on pain symptoms and signs’]. Discrepant results were reported for mexiletine [class I: 128,129] with positive effects only on mechanical allodynia in one study [129]. Results with the NMDA-antagonist riluzole were negative [class II: 130] and one study was also negative with fixed dose morphine [class II: 127].

Four RCTs examined the effects of opioids [76, see ‘Central pain’], dextromethorphan [negative results, class II: 131] GBP [class II: 132] or the cannabinoid CT3 (positive results, class I: 133) in patients with multiple-aetiology peripheral or CP. The GBP study was positive only at some time points on burning pain and hyperalgesia, but not on shooting pain; these poor results are possibly due to the inclusion of a large group of patients without evidence of nerve lesion (CRPS type I), who may be more refractory to the drug.

In two class III trials, the aetiology was not mentioned at all, one with LTG 200 mg/day was negative and the other with capsaicin alone or combined with topical doxepine was positive on several pain symptoms [134,135].

Recommendations

Several less studied neuropathic conditions, such as phantom limb pain, post-surgical neuropathic pain and Guillain–Barré syndrome, appear to be similarly responsive to most current drugs used in other neuropathic conditions (e.g. TCAs, GBP, opioids), but results are based on a limited number of generally class II RCTs with small sample sizes (level B). Neuropathic pain due to cancer infiltration seems to be more

refractory to drug treatment, probably because it is a progressive condition.

Effects on pain symptoms and signs

Although most initial trials have considered neuropathic pain as a uniform entity, some newer trials have assessed various pain symptoms and signs of evoked pain. TCAs and SNRIs have been found similarly active on ongoing and paroxysmal pain in PPN or PHN [class I/II: 23,24,61,62]. The effect of antidepressants on symptoms or signs of evoked pain are controversial, with weak effects on brush-evoked allodynia compared with spontaneous pain [class I/II: 23,25,136,137] but positive effects on the subjective report of pains elicited by to brush [class II: 61,62] or pressure [class I: 23].

The opioids oxycodone and tramadol have been found to relieve continuous pain, paroxysmal pain and symptoms of evoked pain (to touch) in three placebo-controlled trials in PPN and PHN [class I: 43,46,74].

Lamotrigine has been reported effective on cold-evoked allodynia, although not on mechanical allodynia, in central post-stroke pain [class I: 101]. GBP effects on distinct pain symptoms were investigated in a large group of patients with multiple-aetiology neuropathic pain, but this study had several limitations (see 'Less studied neuropathic pain conditions'). In TN, CBZ was efficacious both on spontaneous and evoked attacks [class II: 82], and CBZ and OXC were found equally effective in reducing pain triggered by eating or drinking [class I SR: 138]. However, a SR of RCTs reports that, although OXC reduced the number of spontaneous paroxysms in most patients, it did not succeed in suppressing the trigger-evoked pain in 42% of patients [class I SR: 139].

Efficacy of topical lidocaine has been reported on various symptoms (i.e. burning pain, dull pain, pain evoked by touch) [class II: 69], with a less prominent effect on signs of mechanical allodynia than ongoing pain [class II: 71]. Surprisingly this drug has recently been found more effective in allodynic PHN patients with major impairment of nociceptor function compared with those with no sensory loss [class II: 70].

Hence many drugs appear to have different efficacy on the various symptoms and signs of neuropathic pain; however, because these trials had generally small sample sizes and used methods of assessment that often were not tested for reliability, these data need confirmation from large trials using standardized and validated measures [140].

Effects on quality of life and comorbidities

Quality of life is usually impaired in patients with neuropathic pain, and this contributes to enhance the

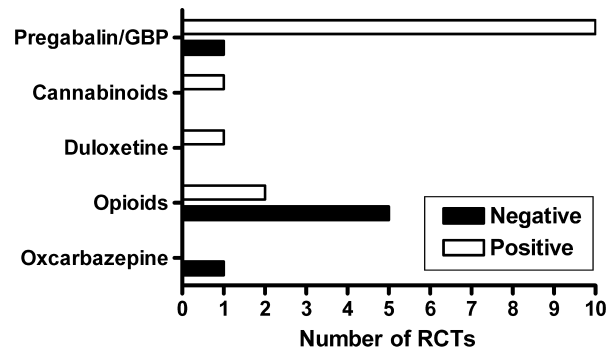


Figure 1 Quality of life/comorbidities. Number of class I or II randomized controlled trials reporting positive (white) or negative (black) effects on most measures of quality of life/mood. Two studies with pregabalin [40] or oxcarbazepine [29] had negative results on most measures of quality of life and mood, but found positive effects on sleep. Three additional studies with topical lidocaine [71], pregabalin [41] or cannabinoids [107] assessed sleep only (not shown here).

burden of pain. Notwithstanding previous EFNS guidelines that stressed its importance and detailed apt tools for assessment [140], only some of the recent trials have adequately examined the effects of drug treatment on quality of life, sleep and comorbidities (Fig. 1). Significant effects on several measures of quality of life including commonly sleep have been reported for pregabalin and GBP in large class I trials in PPN, PHN or SCI pain [36–39,59,63–66,132; Pfizer, data on file], for duloxetine in PPN [24, class I] and for cannabinoids in MS [106, class I] (level A). One study found no significant effects of pregabalin on most measures of quality of life, but positive effects on sleep [40, class I]. Pregabalin and GBP have also been found to improve some measures of mood [class I: 36,38,63,66] (level A).

In contrast, strong opioids or tramadol have not shown significant effects on most measures of quality of life or mood in RCTs [class I: 44,45,74,76,77] with the exception of two studies [class I: 43,59] (level B). No effect on quality of life or mood has been reported for OXC in one trial in PPN, but the drug had positive effects on sleep [29, class II]. Finally one trial with topical lidocaine [71, class II] found no effects on quality of sleep in multiple-aetiology peripheral neuropathic pain (level B).

Adverse events and indications for use

In this section, we present the main side-effects observed with drugs with established efficacy in several trials of neuropathic pain and propose practical indications for use.

TCA

The most common side-effects of TCA are dry mouth, constipation, sweating, dizziness, disturbed vision, drowsiness, palpitation, orthostatic hypotension, sedation and urinary hesitation. More selective TCA such as nortriptyline are better tolerated than the non-selective ones, with less anticholinergic effects and sedation [class II: 62]. A suspected association between TCA treatment and sudden cardiac death has raised concern; a recent epidemiological study found a slight increase in sudden cardiac death with TCA doses superior to 100 mg/day [141]. Therefore caution is recommended for older patients, particularly those with cardiovascular risk factors [1,14]. TCAs should be initiated at low dosages (10–25 mg in a single dose taken at bedtime) and then slowly titrated, as tolerated. Effective dosages are highly variable from one subject to another, the average dosage for amitriptyline being 75 mg/day. Whether TCA blood concentrations should be measured is still controversial [class I SR: 14,137, class II: 142].

SNRI

Serotonin-noradrenaline reuptake inhibitors (duloxetine, venlafaxine) are safer to use than TCAs and are a better option in patients with cardiac disease. The relative risk for withdrawal due to side-effects is weak and there is no need for drug level monitoring. The most frequently observed adverse events with duloxetine are nausea, vomiting, constipation, somnolence, dry mouth, increased sweating, loss of appetite and weakness [24,25, class I]. Although immediate release *venlafaxine* is associated with adverse CNS and somatic symptoms such as agitation, diarrhoea, increased liver enzymes, hypertension and hyponatremia [class I SR: 143], the extended release formulation seems to be far more tolerable, the main side-effects being gastrointestinal disturbances [class I: 22,23]. However, in a head-to-head comparison, venlafaxine 225 mg/day was not superior than imipramine 150 mg/day with respect to tolerability and withdrawal rate for side-effects [23].

The optimal dosage of duloxetine is 60 mg/day; 120 mg/day are no better than 60 mg, 20 mg/day are ineffective [24,25]. High doses of venlafaxine (150–225 mg/day) have been reported to be effective whilst lower doses (75 mg/day) are weakly or not effective [class I/II: 76,112].

Carbamazepine/oxcarbazepine

Carbamazepine entails frequent adverse events, which include sedation, dizziness, gait abnormalities. Liver enzymes, blood cells, platelets and sodium levels must be monitored for at least during 1 year, because of possible risk for hepatitis-anaplastic effects or hypo-

natremia. Induction of microsomal enzyme systems may influence the metabolism of several drugs.

In contrast to CBZ, OXC does not entail enzymatic induction and there is little risk for crossed cutaneous allergy. In the first months of treatment, sodium levels must be monitored because OXC, like CBZ induces hyponatraemia, particularly in the elderly (6% in a cohort of 54 patients) [class I SR: 84]. As regards other side-effects, although a better tolerance has been claimed with OXC compared with CBZ [86,138,139], this notion lacks consistent evidence from class I trials. In a recent trial in diabetic PPN, 27.5% of the OXC group discontinued treatment due to central or gastrointestinal side-effects versus 8% with the placebo [class II: 29].

Both drugs should be initiated with low dosages and slowly increased up to efficacy or intolerable side-effects. Effective dosages range 200–1200 mg/day for CBZ and 600–1800 mg/day for OXC.

Gabapentin/pregabalin

The most common side-effects of GBP and pregabalin include dizziness, somnolence, peripheral oedema, and dry mouth, with a similar frequency for both drugs. Whilst GBP is widely accepted as highly tolerable even at high dosages (> 2400 mg) [class I SR: 15,17], the reports on pregabalin change remarkably with the daily dose: with 150–300 mg there is almost no difference with placebo [class I: 37,40], whilst the withdrawal rate reaches 20% with 600 mg [class I: 42,65]. Effective dosages range 1200–3600 mg/day for GBP and 150–600 mg/day for pregabalin. Gabapentin needs slow individual titration with initial dosages of 300 mg/day (or less in elderly patients) whilst pregabalin can be titrated more rapidly and has a short onset of action (< 1 week). Whereas GBP should be administered t.i.d., pregabalin can be administered b.i.d.

Lamotrigine

Lamotrigine is generally well tolerated. Side-effects include dizziness, nausea, headache and fatigue [class I: 30,39,101,102]. However, it may induce potentially severe allergic skin reactions. In a meta-analysis collecting data from 572 patients, 9% of patients were withdrawn because of major adverse events, most commonly rash [class I: 144]. To minimize the occurrence of cutaneous rashes, a very slow dose titration is recommended and lamotrigine should not be used in combination with valproate: treatment should be initiated with 25 mg daily and increased by 25 mg every other week. The analgesic dosages of LTG range 200–400 mg/day.

Opioids/tramadol

The most common side-effects of opioids in RCTs are constipation, sedation, nausea, dizziness and vomiting.

The risk of cognitive impairment has been reported to be negligible [class I: 75,76], although morphine may impair attention at very high dosages (up to 300 mg/day) [class II: 118]. In RCTs on neuropathic pain, the side-effect profile of opioids has been reported to be good, particularly for oxycodone [class I: 43,44,74–76], sometimes with-surprisingly – a similar degree of side-effects and number of dropouts in the active and placebo groups [43; see also ‘Painful polyneuropathy’]. However, less than 20% of patients continue with opioids after 1 year, because of an unfavourable balance between side-effects and efficacy [class I SR: 5] and the available RCTs may have been too short to address the issues of tolerance and addiction, which, although probably low, may represent a concern with their long-term use in chronic non-cancer pain. According to recent European recommendations, opioids should be considered for chronic non-cancer pain as second line, if other reasonable therapies fail to provide adequate analgesia [145]. Dosages of opioids should be titrated individually up to efficacy and side-effects. Effective doses range 10–120 mg/day for oxycodone and 15–300 mg/day for morphine.

Tramadol has been reported to induce dizziness, dry mouth, nausea, constipation and somnolence with significantly more dropouts compared with placebo [class I: 46,76]. There is an increased risk of seizures in patients with a history of epilepsy or receiving drugs which may reduce the seizure threshold. Serotonergic syndrome (various combinations of myoclonus, rigidity, hyperreflexia, shivering, confusion, agitation, restlessness, coma, autonomic instability, fever, nausea, diarrhoea, flushing, and rarely, rhabdomyolysis and death) may occur if tramadol is used as an add-on treatment to other serotonergic medications (particularly SSRIs). Tramadol should be initiated at low dosages, particularly in the elderly patient (50 mg once daily) and then titrated as tolerated. The effective dosages range 200–400 mg/day.

The use of *lidocaine patches* is very safe with a very low systemic absorption and only local adverse effects (mild skin reactions) have been reported in RCTs [class II: 68,69]. Up to four patches per day for a maximum of 12 h may be used to cover the painful area [class II: 71]. Titration is not necessary.

Cannabinoids have been found generally well tolerated with low dosages (10 mg/day for dronabinol) and slow titration. Adverse events are mainly dizziness, dry mouth and sedation [class I: 106,107]. One study found significant memory impairment with cannabinoids in spray [107]. The potential risk of physical dependence and tolerance warrants consideration with long-term use.

Final recommendations and issues for future trials

Selecting a first-line medication in neuropathic pain should take into account not only the relative efficacy based at best on direct drug comparisons, but also the ratio efficacy/safety. The effect on different pain symptoms, comorbidities and quality of life should also be documented. So far, such assessment has been performed in a small number of studies for a few drugs only, and the evaluation of symptoms and signs used sometimes inadequate or non-validated methods [140].

The effects of drugs on distinct peripheral neuropathic conditions share many similarities, with the exceptions of HIV-polyneuropathy and TN. Central pain has been much less studied. For this reason, the following recommendations concern mainly peripheral neuropathic pain. Recommendations pertaining to other conditions can be found in the above sections and Table 2.

Drugs with best established efficacy in various neuropathic conditions and recommended as first line include TCA, GBP and pregabalin (level A, several class I trials). TCA seem to be more efficacious on the basis of NNT, but these values may have been overestimated and their superiority has generally not been confirmed by substantial head-to-head comparative trials. These drugs have cardiac effects and should be used cautiously in elderly patients. Drugs with less established efficacy in various neuropathic conditions and recommended as second line include topical lidocaine, the SNRI venlafaxine and duloxetine, LTG and tramadol. However, topical lidocaine may be preferred in patients with PHN or focal neuropathy and small area of pain, particularly in the elderly. Contrary to common notion about their poor efficacy in neuropathic pain [147], opioids have been found efficacious in several class I trials in various neuropathic conditions (level A) but should only be proposed second to third line in chronic non-cancer pain [145]. There is insufficient support for the use of CBZ and OXC (with the noteworthy exception of TN), capsaicin (with the exception of PHN), mexiletine, NMDA antagonists, SSRI, topiramate, because of weak efficacy, discrepant results or safety concerns. Despite long-term use of valproate for epilepsy, RCTs have only recently appeared with this drug in peripheral neuropathic pain with good efficacy in several class II studies from the same group, but negative results from another group. This drug needs further trials by other groups before its level of recommendation is settled.

Regarding comorbidities or quality of life, only GBP, pregabalin and duloxetine have been adequately studied with positive effects, and may therefore be preferred in patients with severe impact of pain on quality of life or significant comorbidities (level A), whilst lack of effects

Table 2 Classification of evidence for drug treatments in painful polyneuropathy (PPN), postherpetic neuralgia (PHN), trigeminal neuralgia (TN), and central pain, with recommendations for first- and second-line treatments

Pain condition	Level A rating	Level B rating	Level C rating or weak/discrepant results with level A/B evidence	Recommendations for first line	Recommendations for second/or third line
PPN	Gabapentin Opioids ¹ Pregabalin SNRI TCA Tramadol	Lamotrigine	Capsaicin, topical CBZ Levodopa Mexiletine NMDA antagonists OXC SSRI ² Topiramate Valproate	Gabapentin Pregabalin TCA	Lamotrigine Opioids SNRI Tramadol
PHN	Gabapentin Opioids ³ Pregabalin TCA	Capsaicin, topical Lidocaine, topical Tramadol Vaproate	NMDA antagonists Lorazepam Mexiletine	Gabapentin Pregabalin Lidocaine, topical (<i>in pts with small area of pain-allodynia</i>) TCA	Capsaicin Opioids Tramadol Valproate
TN	CBZ	OXC	Baclofen Lamotrigine	OXC CBZ	Surgery
Central pain		Cannabinoids ⁴ (<i>in MS</i>) Gabapentin (<i>in SCI</i>) Pregabalin ⁵ (<i>in SCI</i>) Amitriptyline (<i>in CPSP</i>) Lamotrigine (<i>in CPSP</i>)	Mexiletine Opioids ⁶ (<i>in multiple -aetiology pains</i>) Valproate	Amitriptyline Gabapentin Pregabalin ⁵	Cannabinoids ⁴ Lamotrigine Opioids

Recommendations take into account not only the efficacy assessed in class I or II trials (see Methods), but also the side-effect profile and safety issues (drugs appear in alphabetical order).

TCA have level A evidence for efficacy but should be used cautiously in elderly patients particularly with cardiac risks. Opioids (level A evidence for use in several neuropathic pain conditions) are recommended second/third line because of potential safety concerns in chronic neuropathic non-cancer pain, particularly for long-term use [111]. SNRI (duloxetine and venlafaxine, level A in PPN) are recommended second line because of a comparatively lower efficacy, but may be preferred to TCA particularly in patients with cardiovascular risk factors. Lidocaine patches (level B evidence) may be proposed first line in patients with small area of pain and allodynia, particularly in the elderly, because of excellent tolerability. Lamotrigine, due to potentially severe cutaneous rashes, is recommended second/third line. Oxcarbazepine (OXC, level B evidence) is proposed first line in trigeminal neuralgia, because of lower safety concerns than for carbamazepine (CBZ). Very few trials have been performed in central pain and recommendations are generally based on level B evidence for most treatments.

1. Oxycodone.

2. On the basis of one RCT each, paroxetine has been found moderately effective and citalopram and fluoxetine ineffective.

3. Oxycodone, morphine and methadone.

4. Cannabinoids, due to potential safety concerns, should be used after a negative trial with other drugs found beneficial in other central pain conditions.

5. Pregabalin has been studied in a still unpublished trial in SCI.

6. Levorphanol (controlled study, but no placebo group).

of opioids on these outcomes have been reported in most trials. Regarding pain symptoms or signs, only antidepressants and opioids/tramadol have so far been shown effective on ongoing and paroxysmal pain, whilst effects on brush-induced allodynia have been reported for topical lidocaine and opioids/tramadol (level B). The use of topical lidocaine may be preferred in patients with mechanical allodynia.

Combination therapy may be proposed in cases of insufficient efficacy with monotherapy and should preferably use drugs with complementary mechanisms

of action. It has been shown useful so far for GBP/morphine (level A).

We propose the following strategy for new trials: (1) Efficacy should be based on standardized and preferably internationally accepted end-points and use standardized sets of tests for assessing efficacy [138]; in establishing such efficacy, not only overall pain, but also multiple pain symptoms or signs should be assessed; (2) universal and identical criteria for assessing harmful events should be obtained; (3) comparative trials of different drugs for specific pain

conditions/mechanisms permit a solid way for presenting an algorithm for pain therapy; (4) the rationale for a combination therapy needs to be established.

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Revision

As we commented in the text, we know that several important trials are currently in progress and expect that some new drugs will be soon provided with adequate evidence. Hence we plan to update these guidelines in 2 years.

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Appendix A: Survey of pharmaceutical companies (see Methods)

Companies that were contacted: Cephalon, Elan, Endo, Forest Pharmaceuticals, GSK, GW Pharma, Janssen & Johnson, Lilly, Lundbeck, Newron, Novartis, Pfizer, Schwarz Pharma, SigmaTau, UCB Pharma, Wallace Laboratories, Wyeth.

Companies that had relevant material and sent it to us: Cephalon, Endo, Forest Pharmaceuticals, Janssen & Johnson, Lundbeck, Novartis, Pfizer, Schwarz Pharma, UCB Pharma, Wyeth.

Appendix B: List of acronyms

AIDS, acquired immunodeficiency syndrome; CBZ, carbamazepine; CI, confidence intervals; CP, central pain; CRPS, complex regional pain syndrome; EMLA, eutectic mixture of local anaesthetics (lidocaine and prilocaine); GABA, gamma-aminobutyric acid; GBP, gabapentin; LTG, lamotrigine; MS, multiple sclerosis; NMDA, *N*-methyl-*D*-aspartate; NNH, number needed to harm; NNT, number needed to treat; NSAID, non-steroidal anti-inflammatory drug; OXC, oxcarbazepine; PHN, postherpetic neuralgia; PPN, painful polyneuropathy; RCT, randomized controlled trial; SCI, spinal cord injury; SNRI, serotonin-noradrenalin reuptake inhibitor antidepressants; SR, systematic review or meta-analysis; SSRI, selective serotonin reuptake inhibitor antidepressants; TCA, tricyclic antidepressants; TN, trigeminal neuralgia; VAS, visual analogue scale.