Biennial Review of Pain

PAIN®

Pharmacotherapy of neuropathic pain: which drugs, which treatment algorithms?

Nadine Attal*, Didier Bouhassira

Abstract

Neuropathic pain (NP) is a significant medical and socioeconomic burden. Epidemiological surveys have indicated that many patients with NP do not receive appropriate treatment for their pain. A number of pharmacological agents have been found to be effective in NP on the basis of randomized controlled trials including, in particular, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitor antidepressants, pregabalin, gabapentin, opioids, lidocaine patches, and capsaicin high-concentration patches. Evidence-based recommendations for the pharmacotherapy of NP have recently been updated. However, meta-analyses indicate that only a minority of patients with NP have an adequate response to drug therapy. Several reasons may account for these findings, including a modest efficacy of the active drugs, a high placebo response, the heterogeneity of diagnostic criteria for NP, and an inadequate classification of patients in clinical trials. Improving the current way of conducting clinical trials in NP could contribute to reduce therapeutic failures and may have an impact on future therapeutic algorithms.

Keywords: Neuropathic pain, Pharmacotherapy, Clinical trials, Therapeutic algorithms, Phenotypic subgrouping

1. Introduction

Neuropathic pain (NP) is estimated to affect as much as 7% of the general population in European countries[19,83] and induces a specific disease burden in patients.[6,30,83] It is now considered as a clinical entity regardless of the underlying etiology.[4] Epidemiological surveys have indicated that many patients with NP do not receive appropriate treatment for their pain.[6,33,86] This finding may not only be due to lack of diagnostic accuracy and relatively ineffective drugs but also due to insufficient knowledge about effective drugs and their appropriate use in clinical practice.[65] Evidence-based recommendations for pharmacotherapy of NP are therefore essential and have recently been updated.[41]

However, meta-analyses and systematic reviews in NP or of specific NP conditions indicate that only a minority of patients with NP have an adequate response to drug therapy.[2,3,10,21,31,41,45,67,68,69,84] Furthermore, many recent trials using drugs expected to be effective in NP are negative on the primary outcome (eg, Ref. 47). Beyond the problem of drug failure or high placebo effect, 1 major reason could be due to trial failure: thus many negative trials failed to identify responder populations because they did not take into account the heterogeneity of NP syndromes, probably reflecting various mechanisms.[1,11,15,17]

Here, we briefly present the major pharmacological treatments studied in NP and the latest therapeutic recommendations for their use. We then outline the difficulties associated with pharmacotherapy of NP in clinical trials and draw prospects for future drug trials and therapeutic algorithms.

2. Which drugs?

A number of drug classes alone or in combination have been evaluated in NP based on randomized controlled trials (RCTs).[41,45] We will only present the drugs used at repeated dosages or those used at single administrations but with long-term efficacy. Practical recommendations, side effects, and precautions for use for recommended drugs are indicated in **Table 1**.

2.1. Antidepressants

The analgesic efficacy of antidepressants is independent of their antidepressant effect. It is probably largely mediated by their action on descending modulatory inhibitory controls, but other mechanisms, such as blockade of sodium channels and glutamate receptors, and the effect on β2 adrenergic receptors have been proposed.[61,97] Two antidepressant classes have been found to be beneficial in NP: tricyclic antidepressants (TCAs), particularly amitriptyline (the effects of other TCAs being generally similar in direct comparative trials) and serotonin–norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine. In particular, recent studies have indicated that duloxetine, which has been found to be initially beneficial in painful diabetic neuropathy, is effective in various other NP conditions.[82,91,93] Somnolence and constipation are the most common side effects of antidepressants in clinical trials, whereas dry mouth is more common with TCA and nausea is more common with duloxetine. However, tertiary amine TCAs (imipramine, amitriptyline, and clomipramine) have a poorer side effect profile with major anticholinergic effects including postural hypotension and cardiac conduction slowing, sedative side effects, and consequently risk of falls.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

INSERM U-987, Centre d'Evaluation et de Traitement de la Douleur, CHU Ambroise Paré, APHP, F-92100 Boulogne-Billancourt, France and Université Versailles Saint-Quentin, Versailles, F-78035, France

**Corresponding author. Address: INSERM U 987 and Centre d'Evaluation et de Traitement De La Douleur, 9 Avenue Charles De Gaulle, Boulogne-Billancourt 92104, France. Tel.: +33 1 49 09 44 34; fax: +33 1 49 09 44 35.*
E-mail address: nadine.attal@apr.aphp.fr (N. Attal).

PAIN 156 (2015) S104–S114

http://dx.doi.org/10.1097/01.j.pain.0000460358.01998.15

Table 1

Summary of evidence-based recommendations for pharmacotherapy of neuropathic pain.

Drug	Main mechanisms of action	Common major side effects	Precautions for use	Other benefits beyond NP	Initial/maximum dosage/effective dosages	Titration	Level of GRADE recommendation for NP*
Tricyclic antidepressants Nortriptyline Desipramine Amitriptyline† Clomipramine† Imipramine†	Inhibition of reuptake of monoamines, blockade of sodium channels, anticholinergic effects	Somnolence, anticholinergic effects, weight gain	Cardiac disease, glaucoma, prostatic adenoma, seizure, use of tramadol. Tertiary amines should be avoided at dosages >75 mg in older adults	Improvement of depression, although at generally higher dosages than pain (75 mg/h) and sleep (amitriptyline)	10-25 mg at bedtime/150 mg daily. Effective doses vary from one patient to another	Increase by 10-25 mg every 3-7 d up to efficacy and side effects	Strong for; recommended as first line
Serotonin–norepinephrine reuptake inhibitors							Strong for; recommended as first line
Duloxetine	Inhibition of serotonin and norepinephrine reuptake	Nausea	Hepatic disorder, use of tramadol, hypertension	Improvement of depression and generalized anxiety, improvement of sleep	30 mg once daily/60 mg twice daily. Effective doses: 60-120 mg daily	May start at 30 mg once daily and then increase by 30 mg after 1 wk as tolerated up to 120 mg daily	
Venlafaxine	Inhibition of serotonin and norepinephrine reuptake	Nausea, hypertension at high dosages	Cardiac disease, hypertension, use of tramadol	Improvement of depression and generalized anxiety, improvement of sleep	37.5 mg once or twice daily/225 mg daily. Effective doses 150-225 mg daily	Increase by 37.5-75 mg each week as tolerated	
Calcium channel alpha-2-delta ligands							Strong for; recommended as first line
Gabapentin Gabapentin ER/enacarbil	Acts on alpha-2-delta subunit of voltage-gated calcium channels, which decreases central sensitization	Sedation, dizziness, peripheral edema, weight gain	Reduce dosages in renal insufficiency	No significant drug interactions, improvement of generalized anxiety and sleep	100-300 mg once to 3 times daily/1200 mg 3 times daily. Effective doses 1200-3600 mg daily	Increase by 100-300 mg 3 times daily every 3-7 d as tolerated	
Pregabalin	Acts on alpha-2-delta subunit of voltage-gated calcium channels, which decreases central sensitization	Sedation, dizziness, peripheral edema, weight gain	Reduce dosages in renal insufficiency	No significant drug interactions, improvement of generalized anxiety and sleep	25-75 mg once daily/300 mg twice daily. Effective doses 150-600 mg daily	Increase by 75 mg daily after 3-7 d and then by 150 mg every 3 to 7 d as tolerated	
Topical lidocaine Lidocaine 5% plasters	Block of sodium channels	Local erythema, itch rash	None	No systemic side effects	1-3 patches/3 patches for 12 h to cover the painful area	None	Weak for in peripheral NP; recommended as second line; first line in frail and ederly patients
Capsaicin high-concentration patches (8%)	TRPV1 agonist	Pain, erythema, itching. Rare cases of high blood pressure (initial increase in pain)	No overall impairment of sensory evaluation after repeated applications, caution in progressive neuropathy	No systemic side effects	1-4 patches to cover the painful area, repeat every 3 mo; 30-minute application to the feet; 60 minutes for the rest of the body; avoid the face; hospital use in several countries	None	Weak for in peripheral NP: recommended as second line

(*continued on next page*)

Table 1 (*continued*)

Drug	Main mechanisms of action	Common major side effects	Precautions for use	Other benefits beyond NP	Initial/maximum dosage/effective dosages	Titration	Level of GRADE recommendation for NP*
Opioids							
Tramadol	Mu receptor agonist and inhibition of monoamine reuptake	Nausea and vomiting, constipation, dizziness, somnolence	History of substance abuse, suicide risk, use of antidepressant in elderly patients	Rapid onset of analgesic effect, effect on inflammatory pain	50 mg once or twice daily/400 mg daily as long-acting drug	Increase by 50-100 mg every 3 to 7 d	Weak for; recommended as second line
Morphine, oxycodone	Mu receptor agonists; oxycodone may also act as k-receptor agonist	Nausea and vomiting, constipation, dizziness, somnolence	History of substance abuse, suicide risk, risk of misuse on long-term use	Rapid onset of analgesic effect, effect on inflammatory pain weak for second line	10-15 mg morphine every 4 h or as needed (equianalgesic doses for other opioids)/up to 300 mg morphine has been used in neuropathic pain	After 1 to 2 wk, convert to long-acting opioids, use short-acting drugs as needed and as tolerated	Weak for; recommended as third line
Botulinum toxin type A	Acetylcholine release inhibitor and neuromuscular blocking agent. Potential effects on neurogenic inflammation	Pain at injection site	Known hypersensitivity, infection of the painful area	No systemic side effects	50-300 units subcutaneously adapted to the painful area—repeat every 3 mo	None	Weak for; recommended as third line

Data modified from Refs. 2, 10, 32.
* Based on updated NeuPSIG recommendations[41].
† Tertiary amines.
ER, extended release; NP, neuropathic pain.

2.2. Antiepileptics

2.2.1. Pregabalin and gabapentin

In preclinical studies, the analgesic effects of pregabalin and gabapentin are mainly related to a decrease in central sensitization and nociceptive transmission through the action on the alpha-2-delta subunit of calcium channels.[60,63] Their efficacy is established in peripheral or central NP, but the number of weak or negative trials has increased over the last 5 years (eg, Refs. 58 and 81). Extended-release formulations of gabapentin (gabapentin extended release or enacarbil) have similar efficacy as gabapentin in clinical trials and can be used twice daily.[41,73] Similar efficacy as compared to TCA has been reported.[9,48] Common side effects include somnolence, dizziness, and weight gain. These agents have a good safety profile with no drug–drug interaction.

2.2.2. Other antiepileptics

Antiepileptics other than pregabalin and gabapentin (eg, topiramate, oxcarbazepine, carbamazepine, valproate, zonisamide, lacosamide) have weak or inconsistent results in NP, with the notable exception of carbamazepine in trigeminal neuralgia.[41] However, some of these antiepileptics are possibly effective in subgroups of patients (see section 4.4.5). All the studies of levetiracetam were negative in NP.

2.3. Opioids

2.3.1. Strong opioids

Opioid agonists (particularly oxycodone and morphine) have been reported to be moderately effective in peripheral NP.[37] Most common adverse effects are constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch. After several years, opioid use may be associated with risk of abuse, particularly with high doses in young patients, as well as potential cognitive impairment, and endocrine and immunologic changes.[23,35,78] There are concerns about an increase in prescription opioid–associated overdose mortality, diversion, misuse, and other opioid-related morbidity.[14,46] It is therefore recommended to track the daily dose in morphine equivalence and monitor more closely when patients require higher daily doses.

2.3.2. Tramadol and tapentadol

Tramadol is a weak opioid with serotonin and norepinephrine reuptake inhibition, and tapentadol is an opioid with norepinephrine reuptake inhibition. Both drugs have a lower potential for misuse, abuse, and dependency than strong opioids. Tramadol has been found to be moderately effective in peripheral NP. The drug should be used with caution in the elderly (risk of confusion) and in combination with antidepressants (risk of serotonin syndrome). In contrast with other painful conditions such as low-back pain,[38] the evidence for efficacy of tapentadol is still weak in NP, with 1 negative RCT (unpublished here) and 2 positive large-scale enrichment withdrawal studies, but with potential bias related to their enrichment design (risk of unblinding in particular) and a modest therapeutic gain in the subgroup of patients participating in the double-blind period (eg, in 65%-80% of the patients included in the trial).[79,90]

2.4. Cannabinoids

Oromucosal cannabinoids (2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol) have been found to be effective in 2 trials in multiple sclerosis–associated pain and for refractory peripheral NP associated with allodynia,[71,75] but several published and unpublished trials in the same NP conditions were negative in the primary outcome.[41,59] Common side effects included dizziness, fatigue, somnolence, and nausea. However, cannabis may potentially exacerbate psychiatric conditions, and therefore cannabinoids are not recommended for patients with psychiatric disorders.[27,52,80]

2.5. Topical or focal therapy

2.5.1. Lidocaine patches

Lidocaine may reduce ectopic discharges through its sodium channel–blocking properties. The efficacy of lidocaine 5% patches has been assessed mainly in postherpetic neuralgia in small duration trials (less than 3 weeks). The therapeutic gain is modest as compared with placebo. However, given their excellent safety profile and lack of alternative safe and well tolerated medications, lidocaine patches are recommended as second line in peripheral NP especially in the elderly.

2.5.2. Capsaicin cream and high-concentration patches

Capsaicin activates TRPV1 ligand-gated channels on nociceptive fibers. This activation causes depolarization, initiation of an action potential, and transmission of pain signals to the spinal cord.[94] After several days of application, TRPV1-containing sensory axons are desensitized, a process also referred to as "defunctionalization." Standard capsaicin-containing creams (0.075%) have been found to be moderately effective in postherpetic neuralgia, but they require many applications per day and cause burning sensation for many days before the analgesic effect starts. The efficacy of single application of high-concentration capsaicin patch (8%) for up to 3 months compared with a low concentration patch (0.04%) has been demonstrated in postherpetic neuralgia and HIV neuropathy. Better results were noted for the 60-minute application in postherpetic neuralgia and 30-minute application in HIV-related painful polyneuropathy.[29,41] Training is required for application, and in some countries, such as France and United Kingdom, the drug must be administered in a hospital setting. Common adverse effects include local pain and erythema, but there is a potential risk of blood pressure elevation because of the immediate pain caused by the application. The long-term safety of repeated applications in patients has not been clearly established particularly with respect to degeneration of epidermal nerve fibers,[70] which may be a concern in progressive neuropathy.

2.5.3. Botulinum toxin type A

It has been suggested that botulinum toxin type A (BTX-A), a potent neurotoxin commonly used for the treatment of focal muscle hyperactivity, may have analgesic effects independent of its action on muscle tone, possibly by acting on neurogenic inflammation.[72] Such mechanisms may be involved in some peripheral NP conditions. Five independent single-center RCTs reported the long-term efficacy of BTX-A (1 single set of subcutaneous injections into the painful area) in peripheral NP and were characterized by a high response rate, and 1 unpublished study (sponsored by Allergan) was negative in postherpetic neuralgia.[41] In published studies, the onset of efficacy (about 1 week) and duration of effects (3 months) was remarkably similar.

2.6. Combination therapy

Two RCTs suggested the additional benefit of gabapentin combined with nortriptyline or to morphine with lower dosages compared with monotherapy without an increase in side effects in patients with peripheral NP.[48,49] However, these results were not confirmed in a larger study (Combo-DN study) of a different drug combination of pregabalin and duloxetine with a distinct trial design.[85] This study showed similar efficacy and side effect profile of monotherapy at high dosages (eg, 600 mg pregabalin or 120 mg duloxetine) compared with combination therapy at moderate dosages (pregabalin 300 mg daily and duloxetine 60 mg daily) in patients with diabetic NP not responding to monotherapy at moderate dosages. Other studies of combination therapy generally had inconclusive results.

2.7. Comparative studies

Few comparative RCTs have been conducted in NP, and most used limited sample sizes, with generally unknown assay sensitivity.[41] Neither individual studies nor their statistical combination demonstrated significant differences in efficacy or safety between drugs. This phenomenon makes it difficult to conclude regarding the potential superiority of one drug over another.

2.8. Miscellaneous

Results for a number of drugs (eg, SSRI antidepressants, NMDA antagonists, Δ-9-tetrahydrocannabinol, mexiletine, and newer topical or oral drugs) have generally been inconsistent or negative except possibly in subgroups of patients for some of these treatments (see section 4.4.5).

3. Which treatment algorithms?

Over the past 10 years, several recommendations have been proposed for the pharmacological management of NP or specific NP conditions, particularly painful diabetic neuropathies and postherpetic neuralgia[2,3,21,31,32,45,68,69,84] These recommendations sometimes came to discrepant conclusions because of inconsistencies in methods of assessment of the quality of evidence. Furthermore, systematic reviews generally did not consider unpublished large trials. These trials can now be identified on the web (clinicaltrials.gov, pharmaceutical industry Web sites), and this, together with analysis of publication bias, may limit the risk of bias in reporting data.

Recently, the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain updated the evidence-based recommendations for oral and topical pharmacotherapy of NP.[41] They conducted a systematic review and meta-analysis of all drug studies published since 1966, including unpublished trials, and selected randomized, double-blind, placebo-controlled studies of at least 3 weeks duration considering NP as the primary outcome. In these recommendations, NP was considered as an entity based on results of updated and previous meta-analyses showing that the efficacy of systemic drug treatments was generally not dependent on the etiology of the underlying disorder.[41,45] However, some neuropathic conditions such as HIV neuropathy and lumbar radiculopathy seem less likely to yield positive RCTs compared with others. Publication bias was assessed and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the recommendations.[50] This system is based on a *sequential* assessment of the final quality of evidence (taking into account the risks of bias), the balance between advantages and disadvantages (including the values and preferences for patients, the balance between desirable and undesirable effects, and the cost), and judgment about the strength of recommendation. Final recommendations are generally graded into weak and strong for or against the treatment, but "inconclusive" recommendations were added here, based on the high number of inconclusive or discrepant results from RCTs.

Pregabalin, gabapentin, SNRI antidepressants, particularly duloxetine, and TCAs received strong GRADE recommendations

for use because of moderate or high quality of evidence, established efficacy in most trials, generally good safety profile (except for TCAs), and low cost for TCAs. These drugs are therefore recommended as the first line for peripheral or central NP, although with caution regarding TCAs: in particular, doses higher than 75 mg daily are not recommended for tertiary amines (amitriptyline, imipramine, clomipramine) because of anticholinergic and sedative effects particularly in the elderly.

Capsaicin high-concentration patches, lidocaine patches, and tramadol received a weak GRADE recommendation for use mainly because of moderate to high quality of evidence (except for lidocaine), high values and preferences (for topical agents), excellent safety profile (for lidocaine), and low cost (for tramadol). These drugs are therefore recommended as generally the second line, topical agents being specifically recommended for peripheral NP and local pain generator (eg, postherpetic neuralgia, traumatic nerve injury, painful neuropathies).

Strong opioids and BTX-A received weak GRADE recommendations for use mainly because of efficacy in most trials but safety concerns (opioids) or lower quality of evidence (BTX-A). These drugs are recommended as the third line (for peripheral NP by specialist use regarding BTX-A).

There was a weak GRADE recommendation against the use of oromucosal cannabinoids (Sativex) and valproate because of generally negative studies (for cannabinoids), discrepant studies and poor quality of evidence (for valproate), and safety concerns. There were strong GRADE recommendations against the use of levetiracetam and mexiletine because of generally negative results and safety concerns (mexiletine). Other drug treatments (eg, other antiepileptics, antidepressants, topical treatments, tapentadol, and NMDA antagonists) or combination therapy received inconclusive GRADE recommendations because of generally discrepant findings, although some of these drugs might be effective in subgroups of patients (see section 4.4.5).

4. Problems associated with neuropathic pain treatment and recommendations for future trials in neuropathic pain

Despite newer drugs and the increased use of rational polypharmacy, the outcome of clinical trials in NP is generally modest. In particular, the numbers needed to treat (NNT) for 50% pain relief (the number of patients necessary to treat to obtain 1 responder as compared with placebo) have been recently estimated to range from 6 to 8 in most positive trials,[41] whereas they were generally lower (4-6) in the latest published meta-analysis for pharmacotherapy of NP.[45] This recent increase in NNT may be due to the consideration of unpublished (generally negative) trials and the use of stringent criteria for inclusion in the updated meta-analysis. However, other reasons may account for such a modest outcome. These include in particular weak or modest efficacy of active drugs, a high placebo response, diagnostic issues, and inadequate classification of patients in NP clinical trials.

4.1. Modest efficacy of active drug treatments in neuropathic pain

Although many drugs have been found to be effective in NP on the basis of RCTs, response rates to the active treatment arms are generally low. It is generally accepted that 30% or 50% pain relief corresponds to a good clinical outcome in NP,[40] although this is only a very incomplete response, which does not even concern the majority of painful patients. For example 46% to 48% of patients in most duloxetine and pregabalin trials in diabetic NP achieve a 50% reduction of pain relief.[41] Updated meta-analyses suggest that very few patients are excellent responders to any active drug in NP when such information is available. For example, only 7% of the patients receiving pregabalin in a recent randomized positive trial in spinal cord injury pain were very much improved, whereas 38% were minimally improved.[25] This finding suggests that most available drug therapies fail to target the complexity of peripheral or central mechanisms involved in NP. Drugs acting on novel targets (eg, Ref. 74) and with better efficacy/safety profile are therefore highly needed.

4.2. High placebo response

The placebo response has been found to be high in several recent trials of NP,[57] particularly those conducted in HIV neuropathy, and this finding may lead to underestimation of drug effects.[62] In contrast, placebo response seems to be lower in postherpetic neuralgia.[26] Several analyses from recent trials in NP have reported that the placebo response was also higher in patients with low or variable pain scores at inclusion.[34,39] Other studies are needed to further explore the potential reasons for such a high placebo response in NP.

4.3. Diagnostic issues

Analysis of RCTs in NP shows that most trials used heterogenous diagnostic criteria, particularly in conditions such as postsurgical NP or central pain. In some trials, central pain could not be differentiated from pain related to spasms (eg, Ref. 75). The use of diagnostic algorithms for NP and validated screening tools,[18,51,87] which were introduced recently, might contribute to reduce diagnostic heterogeneity. For example, a trial of transcutaneous electrical stimulation for the treatment of low-back pain was negative against placebo on the primary outcome but positive only in the subgroup of patients with neuropathic component, as assessed with the validated DN4 questionnaire.[22] In the same line, although this was an open-label prospective trial, it has been suggested that the efficacy of pregabalin (alone or combined with celecoxib) on low-back pain was related to the neuropathic status of patients based on the LANSS score.[76] Further systematic studies are warranted to confirm whether the use of diagnostic algorithms or screening tools for NP indeed increases the assay sensitivity of clinical trials.

4.4. Classification of patients in clinical trials

4.4.1. The concept

One reason for the difficulties to treat patients with NP also stems from the fact that the pharmacological treatments are used in a uniform fashion, whatever the clinical phenotypes and underlying mechanisms are, the latter being highly heterogenous.[15,17] For these reasons, it has been proposed as early as in 1998 that a preferable therapeutic approach to NP should be based on the specific mechanisms underlying NP rather than on the etiological condition, leading to targeted treatments of these mechanisms (eg, Refs. 95 and 96). However, this approach has been debated, mainly because of difficulties of translating in the clinic the pathophysiological mechanisms identified essentially in animals.[17,43,53,66,77] Because specific pain symptoms or their combinations provide with relevant information about mechanisms (eg, Ref 88, Refs in 89 and 92), it has been proposed that a more realistic therapeutic approach should focus mainly on clinical phenotypes (symptoms and signs).[1,11,15,89,92]

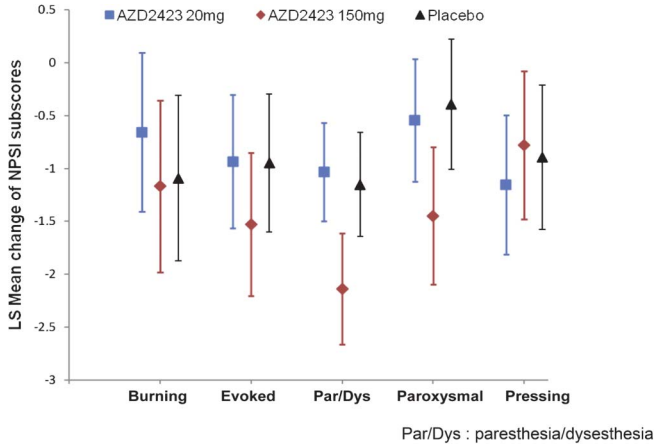

Figure 1. Effects of the chemokine CCR2-receptor antagonist (AZD2423) and placebo on the 5 Neuropathic Pain Symptom Inventory (NPSI) dimensions from baseline to the end of treatment. Data are presented as least square mean Neuropathic Pain Symptom Inventory (NPSI) change and 80% confidence intervals from treatment day 1 to day 29 (ITT analysis). Efficacy was noted on 2 dimensions of the NPSI: paroxysmal pain ($P = 0.05$) and paresthesia/dysesthesia ($P = 0.04$) with the highest dosages of the drug. Reproduced from Ref. 56 (with permission).

4.4.2. Assessment of clinical phenotypes in trials of neuropathic pain

The assessment of symptoms and signs in clinical trials can be best achieved with validated and specific NP questionnaires such as the Neuropathic Pain Scale or the Neuropathic Pain Symptom Inventory (NPSI) regarding symptoms,[18] and with an extension of the clinical examination such as quantitative sensory testing (QST) for sensory signs.[8,51] Quantitative sensory testing is now increasingly used in large-scale RCTs.[24,28,71] Both methods are complementary: only questionnaires provide information about the quality of spontaneous pain, whereas only QST provides information about the severity of sensory deficits. Both QST and questionnaires may be relevant to quantify evoked pains: interestingly, significant correlations have been reported between the presence and severity of various symptoms of evoked pains using the NPSI and that of allodynia or hyperalgesia as assessed blindly in the same patients using QST.[4] These data suggest that questionnaires may also be valid to assess evoked pains particularly for large cohorts of patients in clinical trials.

4.4.3. Initial results: differential effects of drugs on symptoms/signs

Initial pioneer small single-center studies using QST have contributed to characterize the effects of treatments on sensory signs and symptoms of NP. These studies suggested differential efficacy of intravenous tests of the sodium channel blocker lidocaine, opioids, or the NMDA antagonist ketamine on various types of evoked pains to mechanical or thermal stimuli, although most of their results have not been replicated (refs in[1]). For example, 2 studies of intravenous (i.v.) lidocaine in patients with peripheral or central NP found that in both conditions, lidocaine was more effective on mechanical allodynia/hyperalgesia than cold allodynia.[5,7] More recent single-center studies using the NPSI, a specific NP questionnaire,[16] have found that drugs such as BTX-A relieved only some dimensions of NP (burning pain, paroxysmal pain, evoked pains) but not deep pain or paresthesia.[72] A recent large-scale study using a new chemokine antagonist in patients with postsurgical NP was negative on the primary

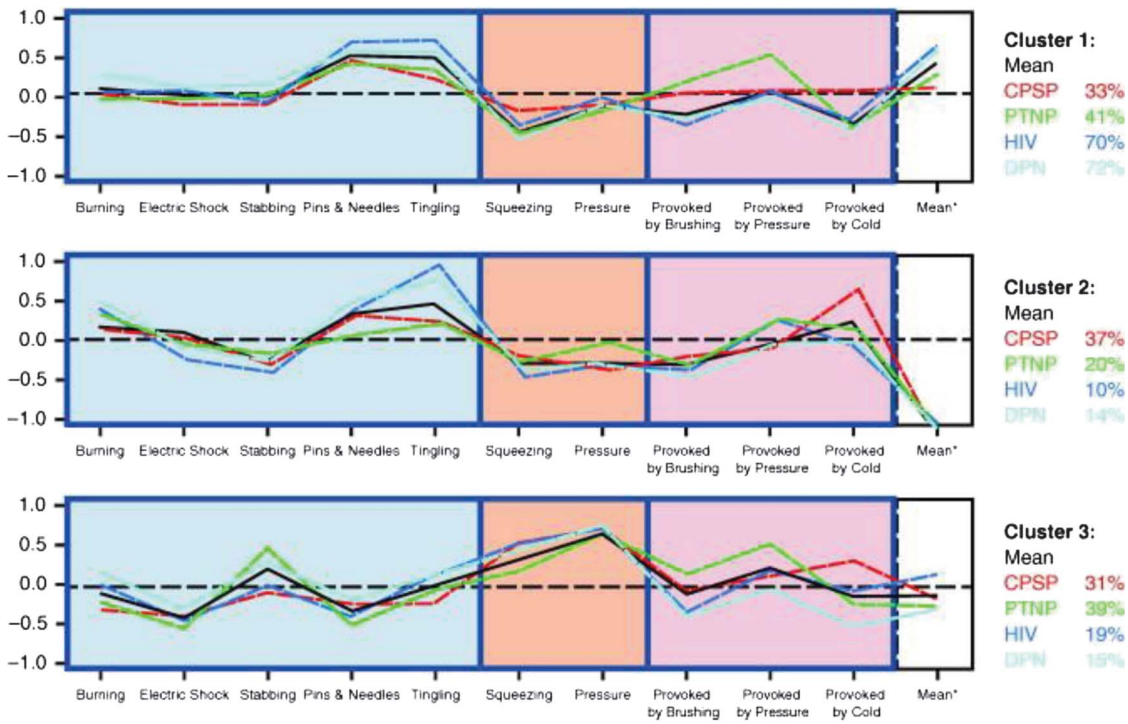

Figure 2. Neuropathic Pain Symptom Inventory (NPSI) cluster means by disease and individual pain dimension. Cluster 1 includes patients with severe paresthesia/dysesthesia ("pins and needles" or "tingling") and the highest pain severity (mean NPSI score: 5.54/10). Cluster 2 includes patients with severe burning pain and paresthesia/dysesthesia, moderate evoked pain (to pressure and cold), and the lowest pain severity (NPSI 2.41/10). Cluster 3 includes patients with severe deep pain ("pressure" or "squeezing") and moderate evoked pain (to pressure). CPSP, central poststroke pain; DPN, painful diabetic peripheral neuropathy; HIV, painful HIV neuropathy; PTNP, posttraumatic peripheral neuropathic pain. Reproduced from Ref. 47 (with permission).

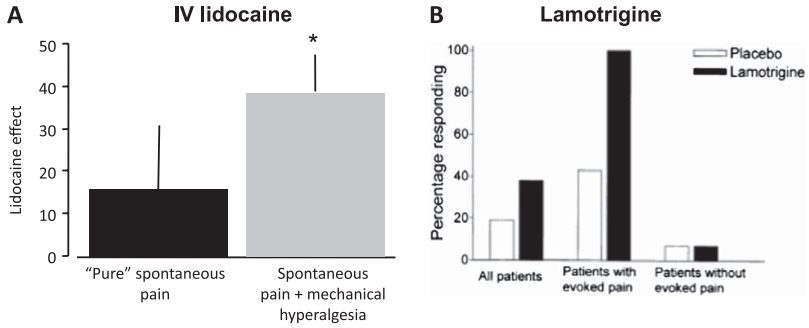

Figure 3. Effects of 2 distinct sodium channel blockers in patients classified according to the presence or absence of evoked pains (post hoc classification) in 2 pioneer studies using quantitative sensory testing. (A), Effects of intravenous (i.v.) lidocaine (5 mg/kg) on spontaneous pain in patients with peripheral nerve lesions (n = 24). The effect of i.v. lidocaine was significant only in patients with spontaneous pain and mechanical hyperalgesia (to punctate stimuli). (B), Proportion of patients with spinal cord injury responding (pain reduction ≥2/10 on a 0-10 NRS) to placebo and lamotrigine (400 mg daily) (n = 21). The effects of lamotrigine were significant only in those with spontaneous and evoked pains (brush-evoked pain and temporal summation) in the painful area (n = 7). Reproduced from Refs. 7 and 44 (with permission).

outcome; however, the drug relieved 2 dimensions of NP with an apparent dose–response efficacy: paresthesia/dysesthesia and paroxysmal pain[56] (**Fig. 1**).

4.4.4. Identification of relevant criteria for patients subgrouping

A second and probably more important contribution of phenotypic profiling is to increase therapeutic prediction. This implies identification of relevant clinical criteria allowing classification of patients into several subgroups, with the assumption that these groups have different underlying pain mechanisms and hence will respond differentially to treatments. Several studies have suggested the relevance of phenotypic subgrouping in patients with NP. Based on the PainDetect questionnaire, Baron et al.[12] identified 5 different clusters of patients corresponding to various symptom combinations in 2100 patients with postherpetic neuralgia or painful diabetic polyneuropathy. All clusters occurred in both diagnoses. Using QST in 1236 patients with NP, Maier et al.[64] also found that QST profiles (ie, loss of mechanoreception, thermoreception, or nociception, gain in nociception) were heterogenous across the spectrum of NP conditions. Finally, in a recent post hoc analysis of 4 large-scale negative trials of pregabalin, a hierarchical cluster analysis based on the NPSI identified 3 distinct clusters of patients with distinct pain characteristics profiles independent of NP syndrome and presumably responding differentially to pregabalin[47] (**Fig. 2**).

4.4.5. Phenotypic subgrouping in trials of neuropathic pain and prediction of the response to therapy

Initial RCTs used phenotypic subgrouping as post hoc analyses to identify potential predictors of the response to treatments. These studies suggested that patients with mechanical (static or dynamic) allodynia/hyperalgesia were better responders to the systemic sodium channel blockers i.v. lidocaine or oral lamotrigine than those without such evoked pains (eg, Refs. 7 and 44)

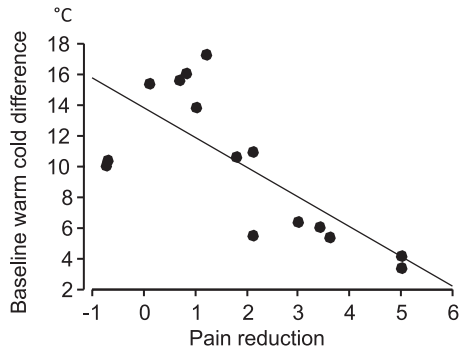

Figure 4. Inverse correlation between thermal deficits at baseline as assessed by quantitative sensory testing (warm and cold difference limen on the painful side) and the effects of botulinum toxin type A (BTX-A) and pain reduction at 12 weeks (as assessed by the difference in numerical scores between values obtained at 12 weeks and baseline values) in 31 patients with peripheral neuropathic pain (painful mononeuropathy and allodynia). The more thermal deficits at baseline, the less the efficacy of BTX-A and conversely. Reproduced from Ref. 72 (with permission).

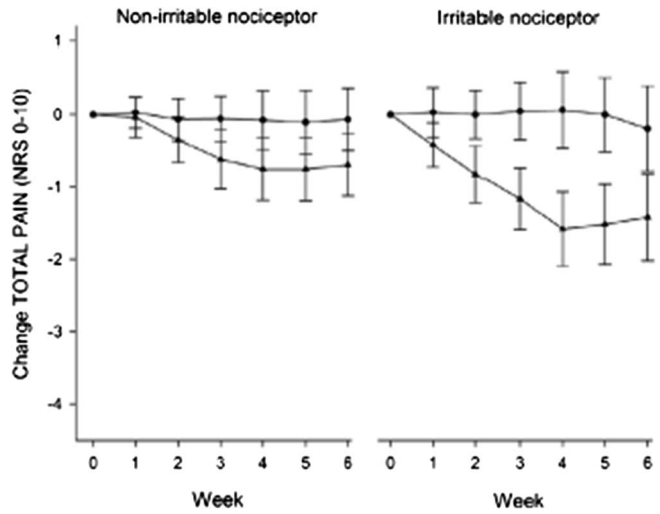

Figure 5. Change in total pain intensity for placebo and oxcarbazepine from baseline by 6 weeks of treatment (end of study). Patients were subdivided into irritable and nonirritable nociceptor phenotypes based on the results of quantitative sensory testing before treatment. Patients with the irritable nociceptor phenotype were characterized as having normal thermal detection thresholds and at least one sign suggestive of hypersensitivity in the painful area (dynamic mechanical allodynia, allodynia to mechanical, warm, or cold stimuli, or hyperalgesia to mechanical stimuli). Patents with the nonirritable nociceptor phenotype were characterized by the presence of at least on sign suggestive of hyposensitivity in the painful are (warm, cold, or mechanical deficit). There was a significant effect of oxcarbazepine only in the subgroup of patients classified into irritable nociceptive subtypes. Reproduced from Ref. 28 (with permission).

(**Fig. 3**). Similarly, in a negative trial of pregabalin in HIV neuropathy, the drug was superior to placebo in patients with severe mechanical punctate hyperalgesia.[81] Despite discrepant findings in other studies of i.v. or topical lidocaine,[42,55] these results suggest that patients with evoked pains are more responsive to sodium channel blockers than those with spontaneous pain only. These data are in keeping with various pathophysiological studies showing that different mechanisms are at play in neuropathic patients with spontaneous pain only and those with superimposed allodynia (eg, Ref. 54).

Furthermore, exploratory analyses from the recent COMBO-DN trial[85] showed that specific clinical phenotypes predicted the response to duloxetine, pregabalin, or their combination.[20] In patients not responding to initial 60 mg/d duloxetine, adding 300 mg/d pregabalin for combination treatment was particularly effective regarding 2 neuropathic dimensions (pressing pain and evoked pain), whereas maximizing the duloxetine dose to 120 mg daily seemed to be more beneficial on paresthesia/dysesthesia.

Finally, it has also been found that the preservation of thermal sensation was correlated to the response to botulinum toxin A in patients with peripheral NP, eg, the less severe the thermal deficits in these patients at baseline, the higher the therapeutic response (eg, Ref. 72) (**Fig. 4**); these data suggested that the best responders to BTX have preserved nociceptive function. They were recently confirmed by the same group in a more recent study using repeated administrations of BTX-A in a larger sample of patients with peripheral NP (manuscript in preparation). In the same study, the effects of BTX were also correlated to the severity of mechanical allodynia (manuscript in preparation). Conversely, other studies have found that loss of heat pain sensitivity predicted the response to opioids in patients with postherpetic neuralgia.[36]

Two recent large-scale randomized placebo-controlled studies using a prespecified classification of patients tend to support the relevance of phenotypic subgrouping. The first study explored the efficacy of clonidine gel, an alpha-2 adrenergic agonist in patients with diabetic NP.[24] In this study, all patients had an assessment of nociceptor function as measured by the response to topical capsaicin applied to the pretibial area of each subjects. The study was negative on the primary outcome, but seemed to be positive in subjects who felt pain in response to capsaicin particularly those with significant pain rating. Despite potential limitations (eg, there was no correction for multiple significance tests, and the placebo response was lower in patients who felt pain in response to capsaicin), this study suggests that subjects with functional (and possibly sensitized) nociceptors in the affected skin may be best responders to clonidine gel, which presumably acts on sensitized nociceptors.[24] The second study used the sodium channel blocker oxcarbazepine in patients with peripheral NP. This study used another type of classification based on QST, which was mainly based on the severity of sensory deficits rather than pain. In any case, results showed similarly that only patients with preserved nociceptive function were significantly responsive to oxcarbazepine[28] (**Fig. 5**).

Altogether, these data indicate that sensory phenotyping could lead to a more stratified treatment and to personalized pain therapy in the future. Of note, 2 often combined phenotypes, eg, presence of mechanical allodynia and preserved nociceptive function seem to predict the response to sodium channel blockers, botulinum toxin A and clonidine gel. However, the use of such phenotypic approach in clinical practice still faces a number of issues. Thus, based on the above trials, it is still difficult to determine to what extent a treatment would be more effective in a particular clinical profile as compared with any patient with neuropathy. Furthermore, a classification based on QST would be difficult to apply in routine: prediction based on specific questionnaires should be easier, but has been explored in limited large-scale trials thus far (see Ref. 20).

5. Conclusions

In the last decade, several evidence-based recommendations have appeared for the pharmacological treatment of NP and have very recently been updated. However, systematic review of RCTs in NP particularly shows that the current way to classify patients in clinical trials is generally inadequate. New clinical trials should now include patients with carefully characterized clinical phenotypes regardless of the etiology of NP. This is now greatly facilitated by the use of validated NP assessment questionnaires and standardization of sensory testing for large-scale trials. Hence, rather than using simple algorithms such as those currently proposed, it could become possible to use more elaborate therapeutic algorithms based on patients clinical phenotypes. Results obtained with these therapeutic approaches may be crucial to improve the prediction of therapeutic responses and should contribute to reduce therapeutic failures in NP, which represents a highly unmet need and a substantial burden for the community.

Conflict of interest statement

The authors have no conflicts of interest to declare.

N. Attal has received honoraria from Astra Zeneca, Astellas Pharma, Adir Servier, Eli Lilly, Grunenthal, Johnson & Johnson, Pfizer, and Sanofi Pasteur Mérieux, for advisory boards, speaker panels, or investigation studies. D. Bouhassira has received honoraria from Astra Zeneca, Astellas Pharma, Eli Lilly, Sanofi Pasteur Mérieux, Grunenthal, Johnson & Johnson, and Pfizer for advisory boards, speaker panels, or investigation studies.

Acknowledgements

The authors thank the Special Interest Group of the International Association for the Study of Pain (NeuPSIG) for supporting this work.

Article history:
Received 2 December 2014
Received in revised form 24 December 2014
Accepted 30 December 2014

References

[1] Attal N, Bouhassira D, Baron R, Dostrovsky J, Dworkin RH, Finnerup N, Gourlay G, Haanpaa M, Raja S, Rice AS, Simpson D, Treede RD. Assessing symptom profiles in neuropathic pain clinical trials: Can it improve outcome? Eur J Pain 2011;15:441–3.

[2] Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T; European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain. 2010 revision. Eur J Neurol 2010;17:1113–e88.

[3] Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P; EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13:1153–69.

[4] Attal N, Fermanian C, Fermanian J, Lanteri-Minet M, Alchaar H, Bouhassira D. Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion? PAIN 2008;138:343–53.

[5] Attal N, Gaudé V, Brasseur L, Dupuy M, Guirimand F, Parker F, Bouhassira D. Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. Neurology 2000;54:564–74.
[6] Attal N, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: Results of a French nationwide survey. PAIN 2011;152:2836–43.
[7] Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology 2004;62:218–25.
[8] Backonja MM, Attal N, Baron R, Bouhassira D, Drangholt M, Dyck PJ, Edwards RR, Freeman R, Gracely R, Haanpaa MH, Hansson P, Hatem SM, Krumova EK, Jensen TS, Maier C, Mick G, Rice AS, Rolke R, Treede RD, Serra J, Toelle T, Tugnoli V, Walk D, Walalce MS, Ware M, Yarnitsky D, Ziegler D. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. PAIN 2013;154:1807–19.
[9] Bansal D, Bhansali A, Hota D, Chakrabarti A, Dutta P. Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. Diabet Med 2009;26:1019–26.
[10] Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010;9: 807–19.
[11] Baron R, Forster M, Binder A. Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach. Lancet Neurol 2012;11:999–1005.
[12] Baron R, Tölle TR, Gockel U, Brosz M, Freynhagen R. A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: Differences in demographic data and sensory symptoms. PAIN 2009;146:34–40.
[13] Binder A, Bruxelle J, Rogers P, Hans G, Bösl I, Baron R. Topical 5% lidocaine (lignocaine) medicated plaster treatment for post-herpetic neuralgia: results of a double-blind, placebo-controlled, multinational efficacy and safety trial. Clin Drug Investig 2009;29:393–408.
[14] Bohnert AS, Ilgen MA, Trafton JA, Kerns RD, Eisenberg A, Ganoczy D, Blow FC. Trends and regional variation in opioid overdose mortality among veterans health administration patients, fiscal year 2001 to 2009. Clin J Pain 2013;30:605–12.
[15] Bouhassira D. Neuropathic pain: the clinical syndrome revisited. Acta Neurol Belg 2001;101:47–52.
[16] Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the Neuropathic Pain Symptom Inventory. PAIN 2004; 108:248–57.
[17] Bouhassira D, Attal N. Novel strategies for neuropathic pain. In: Villanueva L, Dickenson A, Ollat H, editors. The pain system in normal and pathological states: a primer for clinicians. Progress in Pain Research and Management, Volume 31, Seattle: IASP Press, 2004.
[18] Bouhassira D, Attal N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. PAIN 2011;152:S74–83.
[19] Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. PAIN 2008;136:380–7.
[20] Bouhassira D, Wilhelm S, Schacht A, Perrot S, Kosek E, Cruccu G, Freynhagen R, Tesfaye S, Lledó A, Choy E, Marchettini P, Micó JA, Spaeth M, Skljarevski V, Tölle T. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study. PAIN 2014;155: 2171–9.
[21] Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011;76:1758–65.
[22] Buchmuller A, Navez M, Milletre-Bernardin M, Pouplin S, Presles E, Lantéri-Minet M, Tardy B, Laurent B, Camdessanché JP; Lombotens Trial Group. Value of TENS for relief of chronic low back pain with or without radicular pain. Eur J Pain 2012;16:656–65.
[23] Buss T, Leppert W. Opioid-induced endocrinopathy in cancer patients: an underestimated clinical problem. Adv Ther 2014;31:153–67.
[24] Campbell CM, Kipnes MD, Stouch BC, Brady KL, Kelly M, Schmidt WK, Petersen KL, Rowbotham MC, Campbell JN. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. PAIN 2012; 153:1815–23.
[25] Cardenas DD, Nieshoff EC, Suda K, Goto S, Sanin L, Kaneko T, Sporn J, Parsons B, Soulsby M, Yang R, Whalen E, Scavone JM, Suzuki MM, Knapp LE. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. Neurology 2013;5:533–9.
[26] Cepeda MS, Berlin JA, Gao CY, Wiegand F, Wada DR. Placebo response changes depending on the neuropathic pain syndrome: results of a systematic review and meta-analysis. Pain Med 2012;13:575–95.
[27] Davis GP, Compton MT, Wang S, Levin FR, Blanco C. Association between cannabis use, psychosis, and schizotypal personality disorder: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Schizophr Res 2013;151:197–202.
[28] Demant DT, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup NB, Jensen TS, Sindrup SH. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. PAIN 2014;155:2263–73.
[29] Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2013;2:CD007393.
[30] Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: a systematic review and meta-analysis of health utilities. PAIN 2010; 149:338–44.
[31] Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004;63:959–65.
[32] Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence evidence-based recommendations. PAIN 2007;132:237–51.
[33] Dworkin RH, Panarites CJ, Armstrong EP, Malone DC, Pham SV. Is treatment of postherpetic neuralgia in the community consistent with evidence-based recommendations? PAIN 2012;153:869–75.
[34] Dworkin RH, Turk DC, Peirce-Sandner S, He H, McDermott MP, Farrar JT, Katz NP, Lin AH, Rappaport BA, Rowbotham MC. Assay sensitivity and study features in neuropathic pain trials: an ACTTION meta-analysis. Neurology 2013;81:67–75.
[35] Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. Clin J Pain 2014;30:557–64.
[36] Edwards RR, Haythornthwaite JA, Tella P, Max MB, Raja S. Basal heat pain thresholds predict opioid analgesia in patients with postherpetic neuralgia. Anesthesiology 2006;104:1243–8.
[37] Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA 2005; 293:3043–52.
[38] Etropolski M, Kuperwasser B, Flügel M, Häufel T, Lange B, Rauschkolb C, Laschewski F. Safety and tolerability of tapentadol extended release in moderate to severe chronic osteoarthritis or low back pain management: pooled analysis of randomized controlled trials. Adv Ther 2014;31:604–20.
[39] Farrar JT, Troxel AB, Haynes K, Gilron I, Kerns RD, Katz NP, Rappaport BA, Rowbotham MC, Tierney AM, Turk DC, Dworkin RH. Effect of variability in the 7-day baseline pain diary on the assay sensitivity of neuropathic pain randomized clinical trials: an ACTTION study. PAIN 2014;155: 1622–31.
[40] Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. PAIN 2001;94:149–58.
[41] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SR, Rice ASC, Rowbotham M, Sena E, Siddall P, Smith B, Wallace M. Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and NeuPSIG recommendations. Lancet Neurol 2015. Jan 6. [epub ahead of print].
[42] Finnerup NB, Biering-Sorensen F, Johannesen IL, Terkelsen AJ, Juhl GI, Kristensen AD, Sindrup SH, Bach FW, Jensen TS. Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. Anesthesiology 2005;102:1023–30.
[43] Finnerup NB, Jensen TS. Mechanisms of disease: mechanism-based classification of neuropathic pain-a critical analysis. Nat Clin Pract Neurol 2006;2:107–15.
[44] Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. PAIN 2002;96:375–83.
[45] Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. PAIN 2010;150:573–81.
[46] Fischer B, Jones W, Urbanoski K, Skinner R, Rehm J. Correlations between prescription opioid analgesic dispensing levels and related

mortality and morbidity in Ontario, Canada, 2005-2011. Drug Alcohol Rev 2014;33:19–26.
[47] Freeman R, Baron R, Bouhassira D, Cabrera J, Emir B. Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. PAIN 2014;155:367–76.
[48] Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet 2009; 374:1252–61.
[49] Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol 2013;12:1084.
[50] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
[51] Haanpaa M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, Cruccu G, Hansson P, Haythornthwaite JA, Iannetti GD, Jensen TS, Kauppila T, Nurmikko TJ, Rice AS, Rowbotham M, Serra J, Sommer C, Smith BH, Treede RD. NeuPSIG guidelines on neuropathic pain assessment. PAIN 2011;152:14–27.
[52] Hall W, Degenhardt L. Cannabis and the increased incidence and persistence of psychosis. BMJ 2011;342:d719.
[53] Hansson P. Difficulties in stratifying neuropathic pain by mechanisms. Eur J Pain 2003;7:353–7.
[54] Hatem SM, Attal N, Ducreux D, Gautron M, Parker F, Plaghki L, Bouhassira D. Clinical, functional and structural determinants of central pain in syringomyelia. Brain 2010;133:3409–22.
[55] Herrmann DN, Pannoni V, Barbano RL, Pennella-Vaughan J, Dworkin RH. Skin biopsy and quantitative sensory testing do not predict response to lidocaine patch in painful neuropathies. Muscle Nerve 2006;33: 42–8.
[56] Kalliomäki J, Attal N, Jonzon B, Bach FW, Huizar K, Ratcliffe S, Eriksson B, Janecki M, Danilov A, Bouhassira D; AZD2423 PTN Study Group. A randomized, double-blind, placebo-controlled trial of a chemokine receptor 2 (CCR2) antagonist in posttraumatic neuralgia. PAIN 2013;154: 761–7.
[57] Katz J, Finnerup NB, Dworkin RH. Clinical trial outcome in neuropathic pain: relationship to study characteristics. Neurology 2008;70:263–72.
[58] Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. PAIN 2011;152:1018–23.
[59] Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, Ratcliffe S. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol 2013;260:984–97.
[60] Li CY, Zhang XL, Matthews EA, Li KW, Kurwa A, Boroujerdi A, Gross J, Gold MS, Dickenson AH, Feng G, Luo ZD. Calcium channel alpha2delta1 subunit mediates spinal hyperexcitability in pain modulation. PAIN 2006; 125:20–34.
[61] Liang J, Liu X, Zheng J, Yu S. Effect of amitriptyline on tetrodotoxin-resistant Nav1.9 currents in nociceptive trigeminal neurons. Mol Pain 2013;9:31.
[62] Lund K, Vase L, Petersen GL, Jensen TS, Finnerup NB. Randomised controlled trials may underestimate drug effects: balanced placebo trial design. PLoS ONE 2014;9:e84104.
[63] Luo ZD, Chaplan SR, Higuera ES, Sorkin LS, Stauderman KA, Williams ME, Yaksh TL. Upregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. J Neurosci 2001;21:1868–75.
[64] Maier C, Baron R, Tölle TR, Binder A, Birbaumer N, Birklein F, Gierthmühlen J, Flor H, Geber C, Huge V, Krumova EK, Landwehrmeyer GB, Magerl W, Maihöfner C, Richter H, Rolke R, Scherens A, Schwarz A, Sommer C, Tronnier V, Uçeyler N, Valet M, Wasner G, Treede RD. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. PAIN 2010;150:439–50.
[65] Martinez V, Attal N, Vanzo B, Vicaut E, Gautier JM, Bouhassira D, Lantéri-Minet M. Adherence of French GPs to Chronic Neuropathic Pain Clinical Guidelines: results of a cross-sectional, randomized, "e" case-vignette survey. PLoS ONE 2014;9:e93855.
[66] Max MB. Is mechanism-based pain treatment attainable? Clinical trial issues. J Pain 2000;1(3 suppl):2–9.
[67] Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014;4:CD007938.
[68] Moulin D, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA, Furlan A, Gilron I, Gordon A, Morley-Forster PK, Sessle BJ, Squire P, Stinson J, Taenzer P, Velly A, Ware MA, Weinberg EL, Williamson OD. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014;19:328–35.
[69] NICE. clinical guideline: Neuropathic pain-pharmacological management. 2013. Available at: http:/guidance nice org uk/CG173. Accessed June 24, 2014.
[70] Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. PAIN 1999;81:135–45.
[71] Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. PAIN 2007; 133:210–20.
[72] Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain: a double blind placebo controlled study. Ann Neurol 2008;64:274–83.
[73] Rauck R, Makumi CW, Schwartz S, Graff O, Meno-Tetang G, Bell CF, Kavanagh ST, McClung CL. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. Pain Pract 2013;13:485–96.
[74] Rice AS, Dworkin RH, McCarthy TD, Anand P, Bountra C, McCloud PI, Hill J, Cutter G, Kitson G, Desem N, Raff M; EMA401-003 study group. EMA401, an orally administered highly selective angiotensin II type 2 receptor antagonist, as a novel treatment for postherpetic neuralgia: a randomised, double-blind, placebo-controlled phase 2 clinical trial. Lancet 2014;383:1637–47.
[75] Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812–9.
[76] Romanò CL, Romanò D, Bonora C, Mineo G. Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. J Orthop Traumatol 2009;10:185–91.
[77] Rowbotham MC. Mechanisms of neuropathic pain and their implications for the design of clinical trials. Neurology 2005;65(12 suppl 4):S66–73.
[78] Schiltenwolf M, Akbar M, Hug A, Pfüller U, Gantz S, Neubauer E, Flor H, Wang H. Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids. Pain Physician 2014;17:9–20.
[79] Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, Rauschkolb C. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2011;27: 151–62.
[80] Semple DM, McIntosh AM, Lawrie SM. Cannabis as a risk factor for psychosis: systematic review. J Psychopharmacol 2005;19:187–94.
[81] Simpson DM, Schifitto G, Clifford DB, Murphy TK, Durso-De Cruz E, Glue P, Whalen E, Emir B, Scott GN, Freeman R; 1066 HIV Neuropathy Study Group. 1066 HIV Neuropathy Study Group. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology 2010;74:413–20.
[82] Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL; Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013;309: 1359–67.
[83] Smith BH, Torrance N. Epidemiology of neuropathic pain and its impact on quality of life. Curr Pain Headache Rep 2012;16:191–8.
[84] Tan T, Barry P, Reken S, Reken S, Baker M; Guideline Development Group. Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance. Br Med J 2010;340: c1079.
[85] Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, Cruccu G, Skljarevski V, Freynhagen R. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. PAIN 2013;154: 2616–25.
[86] Torrance N, Ferguson JA, Afolabi E, Bennett MI, Serpell MG, Dunn KM, Smith BH. Neuropathic pain in the community: more under-treated than refractory? PAIN 2013;154:690–9.
[87] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008; 70:1630–5.
[88] Truini A, Biasiotta A, La Cesa S, Di Stefano G, Galeotti F, Petrucci MT, Inghilleri M, Cartoni C, Pergolini M, Cruccu G. Mechanisms of pain in distal

symmetric polyneuropathy: a combined clinical and neurophysiological study. PAIN 2010;150:516–21.
[89] Truini A, Garcia-Larrea L, Cruccu G. Reappraising neuropathic pain in humans–how symptoms help disclose mechanisms. Nat Rev Neurol 2013;9:572–82.
[90] Vinik AI, Shapiro DY, Rauschkolb C, Lange B, Karcher K, Pennett D, Etropolski MS. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. Diabetes Care 2014;37:2302–9.
[91] Vollmer TL, Robinson MJ, Risser RC, Malcolm SK. A randomized, double-blind, placebo-controlled trial of duloxetine for the treatment of pain in patients with multiple sclerosis. Pain Pract 2014;14: 732–44.
[92] von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron 2012;73:638–52.
[93] Vranken J, Hollmann MW, van der Vegt MH, et al. Duloxetine in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. PAIN 2010;152:267–73.
[94] Wong GY, Gavva NR. Therapeutic potential of vanilloid receptor TRPV1 agonists and antagonists as analgesics: recent advances and setbacks. Brain Res Rev 2009;60:267–77.
[95] Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. Life Sci 2004; 74:2605–10.
[96] Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? PAIN 1998;77:227–9.
[97] Yalcin I, Choucair-Jaafar N, Benbouzid M, Tessier LH, Muller A, Hein L, Freund-Mercier MJ, Barrot M. Beta(2)-adrenoceptors are critical for antidepressant treatment of neuropathic pain. Ann Neurol 2009;65: 218–25.