Neuropathic Pain

Colloca L[1], Ludman T[1], Bouhassira D[2], Baron R[3], Dickenson AH[4], Yarnitsky D[5], Freeman R[6], Truini A[7], Attal N[8], Finnerup NB[9], Eccleston C[10], Kalso E[11], Bennett DL[12], Dworkin RH[13], Raja SN[14]

[1]Department of Pain and Translation Symptom Science School of Nursing and Department of Anesthesiology School of Medicine, University of Maryland Baltimore, USA
[2] INSERM, Unit 987, mbroise Paré Hospital, UVSQ, Boulogne Billancourt, France
[3]Department of Neurology, Division of Neurological Pain Research and Therapy, Klinik fur Neurologie Christian-Albrechts-Universität Kiel, Kiel, Germany
[4]Department of Neuroscience, Physiology and Pharmacology University College London, UK
[5]Department of Neurology, Rambam Health Care Campus, Technion Faculty of Medicine, Haifa, Israel
[6]Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[7]Department of Neurological Science, University of Sapienza, Italy
[8,2]Pain Evaluation and Treatment Centre of Hôpital Ambroise Paré, Paris, France
[9]Department of Clinical Medicine - The Danish Pain Research Center, Aarhus University, Denmark
[10] Centre for Pain Research, University of Bath, United Kingdom and Department of Clinical and Health Psychology, Ghent University, Belgium
[11] Department of Anesthesiology, Division of Pain Medicine, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Finland
[12] Nuffield Department of Clinical Neuroscience, University of Oxford, UK
[13] Department of Anesthesiology, School of Medicine and Dentistry, Rochester, NY, USA
[14]Department of Anesthesiology and Critical Care Medicine Johns Hopkins University School of Medicine, Baltimore, USA

Correspondence to: Luana Colloca, University of Maryland, 655 W. Lombard Street 21201 Baltimore, MD; Phone: +1 410-706-8244; fax: +1 410-706-5427; email: colloca@son.umaryland.edu

Word Count – Abstract (198); Text (7,947); Reference Count – 190; Figures: 8; Tables: 2

ABSTRACT

Neuropathic pain is caused by a lesion or disease of the somatosensory system and affects 7-10% of the general population. Neuropathic pain will likely become more common because of the ageing of the global population, increased incidence of diabetes and survival from cancer. The burden of chronic neuropathic pain appears to be related to the number of neuropathic symptoms more than the intensity or duration of pain, highlighting the peculiarity of this chronic pain disorder. A significant increase of drug prescriptions and visits to health care providers is observed and the quality of life is more impaired in patients suffering from neuropathic chronic pain than in those with non-neuropathic chronic pain.

Progress in our understanding of the pathophysiology of neuropathic pain provides enthusiasm for the development of new diagnostic procedures and personalized interventions.

We critically provide a current update about the epidemiology, mechanisms, pathophysiology, classification, diagnosis, screening, prevention and management of neuropathic pain. We present the recent up-to-date diagnostic criteria and describe the advances in targeted pharmacological and non-pharmacological treatments. Finally, we describe approaches which will lead to better personalized therapeutic strategies and incorporate evidence emphasizing the need for a multidisciplinary approach to the management of neuropathic pain.

INTRODUCTION

Distinct definitions of neuropathic pain have been used over the years, leading researchers to call for a unified nomenclature. Recently, neuropathic pain has been defined as "pain caused by a lesion or disease of the somatosensory system", a definition that has since been widely accepted[1]. Importantly, neuropathic pain may be mechanistically dissimilar to other chronic pain conditions and is therefore diagnosed and treated differently.

Neuropathic pain will likely become more common because of the ageing of the global population, increased incidence of diabetes, and cancer survival. Neuropathic pain is associated with a significant increase of drug prescriptions and visits to health care providers [2, 3]. Sleep disturbances, anxiety and depression are frequent and severe in patients suffering from neuropathic pain and quality of life is more impaired in patients with chronic neuropathic pain than in those with chronic non-neuropathic pain [2, 4]. The burden of chronic neuropathic pain appears to be related to the number of neuropathic symptoms more than the intensity or duration of pain, highlighting the peculiarity of this chronic pain disorder [2, 4].

Recent progress in our understanding of the pathophysiology of neuropathic pain provides optimism for the development of new diagnostic procedures and personalized interventions with favorable therapeutic outcomes despite an increased failure rate of randomized clinical trials in the past ten years [5, 6, 7,8].

This review critically presents a current update about the presentation, causes, diagnosis, and treatment of neuropathic pain. We provide up-to-date diagnostic criteria, describe the recent advance in targeted treatments that may lead to better personalized therapeutic strategies and incorporate evidence indicating that the management of neuropathic pain should be based upon a multidisciplinary approach.

EPIDEMIOLOGY

The estimation of the incidence and prevalence of neuropathic pain has been difficult because of the variety of diagnostic tools and definitions. Furthermore, the epidemiology of neuropathic pain has not been carefully studied until recently. The prevalence of neuropathic pain in the chronic pain population has been mainly estimated on the basis of retrospective and prospective studies [9] conducted by specialized centers with a focus on specific conditions such as post-

herpetic neuralgia [10, 11], painful diabetic polyneuropathy [12-15], post-surgery neuropathic pain [16], multiple sclerosis [17, 18], spinal cord injury [19], stroke [20] and cancer [21, 22].

Another approach to estimating the prevalence of neuropathic pain is based on the use of validated screening tools in the form of simple questionnaires [23]. Despite some limitations, inherent to the variety of definitions and diagnostic criteria of neuropathic pain, several large epidemiological surveys conducted in different countries (UK, France, US and Brazil), using these tools, have provided valuable new information on the general prevalence of neuropathic pain [3]. Using similar methodologies and screening tools such as the Douleur Neuropathique 4 (DN4) or the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale [24, 25] the population prevalence of chronic neuropathic pain has been estimated to range from 7% to 10% [3, 26-28]. Chronic neuropathic pain is more frequent in women and in older patients and, most commonly affects the lower back and lower limbs, neck and upper limbs. Lumbar and cervical painful radiculopathies are the most frequent cause of chronic neuropathic pain. Consistent with these data, a survey of more than 12,000 chronic pain patients with both nociceptive and neuropathic pain types, referred to pain specialists in Germany[29] , revealed that 40% of all patients experience at least some characteristics of neuropathic pain (especially patients with chronic back pain and radiculopathy).

PATHOPHYSIOLOGY/MECHANISMS

Translational research: from basic science to clinical studies

A lesion or disease of the peripheral somatosensory nervous system leads to altered and disordered transmission of sensory signals into the spinal cord (Figure 1). Preclinical science has described a number of changes from the periphery through to higher centers of the central nervous system (CNS) that appears to relate to neuropathic pain in patients. These changes result from alterations in ion channels within the affected nerve with increased function of sodium channels leading to increased excitability coupled with a loss of potassium channels which normally modulate neural activity. At the spinal central ending of the sensory nerves, there is increased expression and function of calcium channels leading to increased transmitter release. If a fiber is disconnected from the periphery there will be sensory loss but the fibers at the injury site can generate ectopic activity, e.g., neuroma afferents, and so pain from a numb area results [30]. The remaining intact fibers are hyperexcitable, so called “irritable nociceptors” [31]. Overall,

there is a combination of ongoing pain, numbness and evoked pains. Altered sodium channel function within damaged peripheral nerves is the rationale for the use of drugs such as lidocaine and carbamazepine for neuropathic pain. Recently, oxcarbazepine was shown to be more effective in patients with "irritable nociceptor" phenotype, where abnormal sodium channel activity could be assumed [32]. The altered inputs into the spinal cord coupled with increased calcium channel function, best understood by enhanced expression of their alpha-2 delta subunit which causes greater expression of the channel in the terminal, now results in increased transmitter release and enhanced excitability of spinal neurons. This subunit is the site of action of the drugs, gabapentin and pregabalin [33]. The spinal cord outputs to the brain with projections to the thalamus and cortex and parallel pathways to the limbic brain. Thus patients report high pain ratings as a consequence of the former projections and anxiety, depression and sleep problems as painful messages start to dominate limbic function. The main substrate for the central sensitization is activation of the NMDA receptor for glutamate. Hyperexcitable spinal neurons exhibit increased responses to many sensory modalities and expand their receptive fields, central sensitization [34, 35]. This is the most plausible explanation for dynamic, static and cold allodynia and is reflected by enhanced thalamic neuronal coding [36]. Hyperexcitability is compounded by a loss of GABA mediated inhibitions at spinal levels [37] and there are less well understood functional changes in non-neuronal cells within the spinal cord such as microglia which contribute to the development of hypersensitivity [38]. Consequently, the brain receives altered and abnormal sensory messages. Areas such as the cingulate cortex and amygdala have been implicated in the ongoing aversive state and comorbidities associated with neuropathic pain [39]. Projections from these forebrain areas now alter descending controls running from the periaqueductal grey to the brain stem. Under normal conditions, there is a balance between descending inhibitions and excitations, but after peripheral neuropathy, the latter now dominate. A number of studies have shown that the brainstem excitatory pathways are more important in the maintenance rather than induction of the pain state.

Noradrenergic inhibitions, through spinal alpha-2 receptors are attenuated and enhanced 5HT facilitations through 5HT2 and 3 receptors gain the upper hand [40]. Descending inhibitions can be assessed through Diffuse Noxious Inhibitory controls (DNIC) the animal counterpart of the human Conditioned Pain Modulation (CPM, Figure 2A), where one pain inhibits another through

descending pathways. DNIC is mediated by the noradrenergic inhibitory system and both DNIC and CPM are lost after neuropathy. Animals that recruit noradrenergic inhibitions have markedly reduced hypersensitivity after neuropathy despite identical levels of nerve damage. Thus at peripheral, spinal and central levels there is a gain of excitation and facilitation and a loss of inhibition. These shift the sensory pathways to a state of hyperexcitability. It appears that there may be a sequence of changes over time from the periphery to the brain as the neuropathic pain state becomes chronic.

These events have been deduced from the use of animal models of neuropathy, the majority of which use surgical lesions of peripheral sensory nerves [41]. The animal models use ligation of parts or branches of peripheral nerves, constriction and transection. The majority of animals show hypersensitivity (most often mechanical as assessed with von Frey testing, but which also can include hot and cold) which contrasts to patients but this is most likely due to the homogeneity of the genetic strain of animal. Models of diabetic neuropathy have been bedeviled by ill health of the animals but these are improving.

Recently, clinical research is revealing ectopic activity in primary afferents as having a key role in the maintenance of neuropathic pain following peripheral nerve injury. Patients with painful diabetic polyneuropathy and traumatic peripheral nerve injury showed a complete abolition of ipsilateral spontaneous and evoked pain when treated with a peripheral nerve block with lidocaine [42]. Similarly, a blockade of the dorsal root ganglion by intraforaminal epidural administration of lidocaine resulted in relief of painful and non-painful sensations in patients with phantom pain [43]. Microneurography studies have also indicated a spontaneous activity in C-nociceptors related to pain supporting a peripheral mechanism for neuropathic pain [44, 45].

Human pain modulation mechanisms

Individuals experience and cope with chronic neuropathic pain differently; some are mildly affected, while others suffer debilitating dysfunction. Individuals also vary substantially in their responses to therapeutic interventions; for some, pharmacological treatments are highly efficacious and in others only modest reductions in pain occur. A key factor in this variability may be the way the pain message is modulated in the CNS. While ascending from its entry port, the dorsal horn, into the CNS, until arriving at the cerebral cortex, the area critical for consciousness, the signal may be augmented or reduced, modifying the assumed correlation

between the extent of the peripheral pathology, and the extent of the pain syndrome. Most pain patients express a pro-nociceptive pain modulation profile, i.e. pain messages are augmented in their central system [46]. Pronociception can be inhibitory due to less efficient CPM, facilitatory due to enhanced summation, or both, less efficient CPM and enhanced temporal summation (Figure 2B). The temporal summation is augmented in neuropathic and non-neuropathic pain. Neuropathic pain patients present with a higher slope of increase [46]. CPM has been shown to be less efficient in a variety of pain syndromes compared to healthy controls [47].

Studies have shown that the pain modulation profile predicts the development and extent of chronic post-operative pain [48-50]. The prospect of harnessing pain modulation seems promising for a more individualized approach to pain management. A 'fix the dysfunction' principle has been advocated, suggesting that patients who express a facilitatory pro-nociceptive profile could be treated by a drug that reduces the facilitation, e.g., gabapentinoids, and patients who express an inhibitory pro-nociceptive profile could be treated with an SNRI, that is expected to enhance the inhibitory capacity by reuptake inhibition of noradrenaline [48]. It is likely that patients expressing both less efficient CPM and enhanced temporal summation may need a combination of treatments. Indeed, the level of CPM predicts the efficacy of duloxetine in patients and is restored by both duloxetine and tapentadol, both having norepinephrine reuptake inhibition (NRI) actions. Actions on these descending controls underlie the actions of TCA and SNRI in neuropathic pain patients [40]. Moreover, an altered patient's pain modulation profile can be reversed towards normality when pain is treated such as in osteoarthritis patients treated with arthroplasty surgery. In the case when the diseased joint is replaced, the majority of patients will be free of pain and the central and peripheral processes normalize [42, 51, 52].

Notably, pain modulation is highly influenced by expectancy-induced analgesia, referring to changes due to patients and providers' beliefs and desires [53, 54] affecting response to treatment for neuropathic pain. In laboratory settings, expectancy-induced analgesia influences clinical pain in Irritable Bowel Syndrome [55-57], idiopathic and neuropathic pain [58]. Recently, Petersen et al. tested expectancy-induced analgesia in patients who developed neuropathic pain after thoracotomy [59, 60]. Patients received lidocaine in an open (e.g. patients were told: 'The agent you have just been given is known to powerfully reduce pain in some patients) and hidden ("This is a

control condition for the active medication) fashion in accordance with a previously described protocol [61] showed large significant reduction of ongoing pain, maximum wind-up-like pain and area of hyperalgesia (Figure 3) [58, 59]. These findings point to a clinically relevant endogenous pain inhibitory mechanism with relevant implications for clinical trial designs and practices. These effects should be reduced in clinical trials and intentionally enhanced in daily clinical practices as a strategy to optimize pain management.

Classification of central and peripheral neuropathic pain

The pathology of the peripheral disorders causing neuropathic pain predominantly involves the small lightly or unmyelinated peripheral nerves, namely the A delta and C fibers [4] (Figure 4). An approach to classifying these peripheral disorders is to subdivide them into those that have a generalized (usually symmetrical) and those that have a focal (usually asymmetrical) distribution (Table 1).

The most clinically important painful generalized peripheral neuropathies include those due to diabetes, pre-diabetes and other metabolic dysfunctions, human immunodeficiency virus, chemotherapeutic agents, immune-system and inflammatory disorders, inherited neuropathies and channelopathies. No definite cause is found in many patients with a painful peripheral neuropathy – a disorder called idiopathic small fiber neuropathy. The topography of the pain in these disorders typically encompasses the distal extremities, often called a "glove and stocking" distribution. This pattern is characteristic of dying-back, length-dependent, distal peripheral neuropathies. Less frequently, the pain has a proximal distribution. This pattern occurs when the pathology involves the sensory ganglia. Painful *focal* peripheral disorders are due to pathological processes that involve one or more peripheral nerves or nerve roots. These disorders include post-herpetic neuralgia, post-traumatic neuropathy, post-surgical neuropathy, cervical and lumbar polyradiculopathies, complex regional pain syndrome type 2 and trigeminal neuralgia [62].

Central neuropathic pain is due to a lesion or disease of the spinal cord or brain. Cerebrovascular disease affecting the central somatosensory pathways (post-stroke pain) and neurodegenerative diseases, most notably Parkinson' disease, are brain disorders that often cause central neuropathic pain [63]. Spinal cord lesions or diseases that cause neuropathic pain include spinal

cord injury, syringomyelia and demyelinating diseases such as multiple sclerosis, transverse myelitis and neuromyelitis optica [64].

DIAGNOSIS/SCREENING AND PREVENTION

Grading system and screening tools to assess sensory symptoms

Chronic neuropathic pain is characterized by a lesion or a disease of the nervous system and should be distinguished from other chronic pain syndromes. This distinction is of particular importance since specific treatment recommendations exist for neuropathic pain.

A grading system was proposed which is intended for determining the level of certainty with which the pain in question is neuropathic [4] (Figure 5A). If the patient's history suggests that there is a neurological lesion or disease and the pain could be related to such (e.g. by using validated screening tools, see below) and the pain distribution is neuroanatomically plausible the pain is termed *possible* neuropathic pain. *Probable* neuropathic pain requires supporting evidence obtained by a clinical examination of sensory signs (e.g. bed-side testing, quantitative sensory testing, see below). *Definite* neuropathic pain requires that an objective diagnostic test confirms the lesion or disease of the somatosensory nervous system (e.g. neurophysiological tests, skin biopsies as detailed below). The separation of neuropathic pain from other chronic pain syndromes is relevant for using the correct treatment. A grading system should be used to determine the certainty with which the pain in question is neuropathic. A finding of probable neuropathic pain in a given individual patient should lead to treatment according to the neuropathic pain treatment guidelines.

Based on the assumption that characteristic qualities of sensory perceptions exist, that are indicative of neuropathic pain, several screening tools have been developed to identify neuropathic pain conditions or neuropathic components to chronic pain syndromes [65].These simple to use patient-reported questionnaires, e.g. DN4 or painDETECT [25, 66] assess characteristic neuropathic pain symptoms (e.g., burning, tingling, sensitivity to touch, pain caused by light pressure, electric shock like pain, pain to cold or heat, numbness) and can distinguish between neuropathic and non-neuropathic pain with high specificity and specificity.

Psychophysical and objective diagnostic tests to demonstrate nerve damage

Different psychophysical and diagnostic tests are available for investigating somatosensory pathway function, including bedside evaluation and assessment of sensory signs as well as neurophysiological techniques, skin biopsy, and corneal confocal microscopy (Figure 5B).

- *Bedside sensory assessment of sensory signs*

In addition to sensory symptoms patients with neuropathic pain also demonstrate a variety of distinct sensory symptoms and signs that can coexist in combinations [67]. Diagnostic sensory bed-side examinations should include the following modalities: touch, pinprick, pressure, cold, heat, vibration, temporal summation and after sensations [68]. To assess either a loss (negative) or a gain of somatosensory function (positive sensory signs) the responses can be graded as normal, decreased or increased. The stimulus-evoked (positive) pain types are classified as hyperalgesic or allodynic, and according to the dynamic or static character of the stimulus.

- *Quantitative sensory testing*

A psychophysical technique to test the afferent nociceptive and non-nociceptive systems in the periphery and the central nervous system is quantitative sensory testing (QST) which uses standardized mechanical and thermal stimuli (graded v. Frey hairs, several pinprick stimuli, pressure algometers, quantitative thermotesting). An advantage of QST is that it assesses a loss as well as a gain of function of the whole spectrum of different afferent fiber classes [69]. A standardized protocol for QST was proposed by the nationwide German Network on Neuropathic Pain [70] including 13 parameters of sensory testing procedures for the analysis of the exact somatosensory phenotype of neuropathic pain patients. To evaluate plus or minus signs in patients, an age- and gender-matched database for absolute and relative QST reference data was established for healthy human subjects. For most variables pathological values of positive and negative signs can be detected on the basis of reference data.

- *Neurophysiological techniques*

The Aβ-fiber mediated standard neurophysiological techniques (i.e. nerve conduction studies, trigeminal reflexes and somatosensory evoked potentials) do not provide information on nociceptive pathway. However, they are still useful to identify damage along the somatosensory pathways and are widely used for assessing peripheral and central nervous system diseases causing neuropathic pain [71]. Laser evoked potentials (LEPs) are the easiest and most reliable neurophysiological technique for assessing nociceptive pathway function [68, 72]). Laser-generated radiant heat pulses selectively excite Aδ and C nociceptors in the superficial skin layers [73]. LEPs related to Aδ-fibers activation have been standardized for clinical application. They consist of a lateralized component (N1), generated in the SII area and in the insular cortex bilaterally, and a vertex potential consisting of a N2–P2 complex [74]. In diseases associated with nociceptive-pathway damage, LEPs can be absent, reduced in amplitude or delayed in latency[75, 76,77].

- *Skin biopsy*

Skin punch biopsies assesses epidermal innervation consisting mainly of unmyelinated C-fiber terminals, with relatively few small myelinated Aδ-fibers that lose their myelin sheath and reach the epidermis as unmyelinated free nerve endings [78, 79]. The technique is regarded as the most sensitive tool for diagnosing small-fiber neuropathies [80], the relationship between skin biopsy data and neuropathic pain is, however, still unclear. One study in 139 patients with peripheral neuropathy suggested that a partial sparing of intraepidermal nerve fibers, as assessed with skin biopsy is associated with provoked pain [81].

- *Corneal confocal microscopy*

The corneal innervation consists of small-myelinated Aδ and C-fibers. Corneal confocal microscopy is a non-invasive, in vivo, technique, useful for assessing corneal innervation and quantifying corneal nerve fiber damage in patients with peripheral neuropathies[82, 83].
Although corneal confocal microscopy represents a novel and promising tool for investigating small nerve fiber damage in patients with peripheral neuropathy, this technique has several limitations, such as the high cost and the reduced availability in most clinical centers. It is still unclear the influence of some conditions such as sicca syndrome, eye diseases or previous eye surgery on the corneal confocal variables. No study has reliably investigated the association between corneal confocal microscopy variables and neuropathic pain.

PREVENTION

Existing treatments have meaningful but modest benefits, and interventions that prevent neuropathic pain can therefore have a substantial impact on public health. The identification of risk factors is essential to preventing neuropathic pain. Primary prevention of neuropathic pain involves interventions administered to generally healthy individuals who are at risk for developing neuropathic pain. An important example is provided by the live attenuated [84] and subunit adjuvanted [85] herpes zoster vaccines, which reduce the likelihood of developing herpes zoster in older individuals and thereby prevent postherpetic neuralgia. Secondary prevention involves administering preventive interventions to individuals who are experiencing an illness, injury, or treatment that can cause chronic neuropathic pain. Examples of this approach include the peri-operative treatment of surgical patients to prevent chronic post-surgical pain [86] and antiviral or analgesic treatment in patients with herpes zoster to prevent postherpetic neuralgia [87]. Proper management of health conditions, such as diabetes, that cause neuropathic pain, may prevent neuropathic pain before it even presents [88]. Increased attention to prevention has great potential to reduce the suffering and disability experienced by many patients with chronic neuropathic pain. Leading a healthy lifestyle and education regarding pain-causing health conditions are important components of prevention, especially in those who are at greater risk of developing neuropathic pain [89]. Prevention programs that would combine mutually reinforcing medical and behavioral interventions may lead to greater preventive benefits.

MANAGEMENT

Pharmacological approach

Different drug classes for the treatment of peripheral or central neuropathic pain have been evaluated in randomized controlled trials [4, 90]. In this section we will only present drugs given in single or repeated dose administration and with long-term efficacy (Figure 6; Table 2).

- *Drugs effective in neuropathic pain*

Antidepressants and antiepileptics have been the most studied drugs in neuropathic pain. Among antidepressants, tricyclic antidepressants (TCAs), particularly amitriptyline, and serotonin–norepinephrine reuptake inhibitors (SNRIs), particularly duloxetine, have confirmed efficacy in

various neuropathic pain conditions. Their analgesic efficacy seems largely mediated by their action on descending modulatory inhibitory controls, but other mechanisms have been proposed, particularly an action on beta-2 adrenoceptors [91]. Among antiepileptics, the efficacy of pregabalin and gabapentin, including extended release formulations, is best established for the treatment of peripheral neuropathic pain, and to a lesser extent spinal cord injury pain. However the number of negative trials has increased over the last 5 years. Their analgesic effects are mainly related to a decrease in central sensitization through binding to the alpha2-delta subunit of calcium channels [92].

Opioids have also been found effective, mainly in peripheral NP. Tramadol, a weak opioid with serotonin and norepinephrine reuptake inhibition, seems to have less potential for misuse and abuse than stronger opioids but should be used with caution in the elderly. Opioid agonists, particularly oxycodone and morphine, are moderately effective, but there is concern about prescription opioid-associated overdose diversion, misuse and morbidity [93].

An additional effect of pregabalin or gabapentin combined with TCAs or opioids as compared to monotherapy has been reported in peripheral neuropathic pain [94, 95, 96]. However, in a large study with a trial design reflecting clinical practice the efficacy and side effect profile of monotherapy at high dosages (600 mg pregabalin or 120 mg duloxetine) were similar to those of combination therapy at moderate dosages (300 mg pregabalin and 60 mg duloxetine daily) in patients with diabetic neuropathic pain not responding to monotherapy at moderate dosages [97].

Topical agents (lidocaine and capsaicin patches) are also prescribed. Lidocaine is believed to act on ectopic neuronal discharges through its sodium channel–blocking properties. The efficacy of lidocaine 5% patches has been assessed in focal peripheral NP, particularly post-herpetic neuralgia, but their therapeutic gain is modest compared with placebo [98, 99]. Capsaicin initially activates transient receptor potential vanilloid 1 (TRPV1) ligand-gated channels on nociceptive fibers leading to TRPV1 desensitization and defunctionalization. The sustained efficacy (up to 3 months) of a single application of high-concentration capsaicin patch (8%) has been reported in PHN and diabetic and non-diabetic painful neuropathies. The long-term safety of repeated applications seems favorable based on open studies, but there are no long-term data on the effects on epidermal nerve fibers in patients.

Botulinum toxin type A (BTX-A), a potent neurotoxin commonly used for the treatment of focal muscle hyperactivity, has shown efficacy in neuropathic pain for up to 3 months after a single set of injections, possibly through a central or mechanotransduction effect. A recent larger-scale trial has confirmed the efficacy of repeated administrations over 6 months, with enhanced effects of the second injection [90].

- *Drugs with inconsistent results or lack of efficacy*

Studies of antiepileptics other than alpha2delta ligands (for example, topiramate, oxcarbazepine, carbamazepine, valproate, zonisamide, lacosamide, levetiracetam) have reported negative, weak or inconsistent results in neuropathic pain, although some are probably effective in subgroups of patients. Oromucosal cannabinoids (2.7 mg delta-9-tetrahydrocannabinol/2.5 mg cannabidiol) have been found variably effective, particularly in multiple sclerosis–associated pain, but several unpublished trials were negative on the primary outcome. Results for selective serotonin reuptake inhibitors (SSRIs), *N-methyl-D-aspartate* (NMDA) antagonists, mexiletine and topical clonidine have generally been inconsistent or negative except in patient subgroups.

- *Emerging drug treatments*

A few drugs targeting novel mechanisms of action are under clinical development for the treatment of peripheral neuropathic pain. These include in particular subtype selective sodium blocking agents particularly Nav1.7 antagonists [100] and EMA 401, a novel angiotensin type II antagonist that has been found effective in a phase II clinical trial in postherpetic neuralgia [101].

- *Therapeutic recommendations*

Numerous therapeutic recommendations for neuropathic pain have been proposed in recent years [102-107]. Based on a new systematic review and meta-analysis of all drug studies published since 1966, including unpublished trials [108], pregabalin, gabapentin and SNRIs, particularly duloxetine and TCAs, have strong recommendations for use and are recommended as first-line drugs for the treatment of peripheral and central neuropathic pain. High-concentration capsaicin patches, lidocaine patches and tramadol have weak quality of evidence and are recommended as second-line treatment for peripheral neuropathic pain only. Strong opioids and BTX-A (for specialists only) also have weak recommendations for use. There are weak, against or inconclusive recommendations for the use of all other drug treatments for neuropathic pain in general.

- *Recommendations for future therapeutic trials in neuropathic pain*

The outcome of clinical trials in neuropathic pain is modest, with numbers needed to treat (NNT) for 50% pain relief (the number of patients necessary to treat to obtain one responder as compared with placebo) ranging from 6 to 8 for positive studies in the latest meta-analysis [108]. Several reasons may account for these results [90], including high placebo responses (which may underestimate drug effects), the paucity of use of validated diagnostic criteria for neuropathic pain in clinical trials, and trial failures. Thus, it has been proposed over the past decade that a preferable therapeutic approach to neuropathic pain should focus mainly on stratifying patients according to clinical phenotypes (symptoms and signs) [67, 109, 110] [10, 67, 77, 111, 112], which are suggestive of specific mechanisms, whereas most trials have essentially been conducted in patients classified according to their etiology. A number of recently well-conducted prospective trials tend to support the relevance of phenotypic subgrouping of patients, which should lead to a more personalized pain therapy in the future [90, 99, 113] [114]. In particular, two often combined phenotypes, the presence of mechanical allodynia and preserved nociceptive function, seem to predict the response to systemic or topical sodium channel blockers, BTX-A and clonidine gel in distinct clinical trials [90, 99, 113].

Interventional therapies for neuropathic pain

Pharmacological treatments for chronic neuropathic pain are effective in <50% of patients and may be associated with adverse effects that limit their clinical utility [115]. Interventional treatments, such as invasive procedures to deliver drugs to targeted areas or ablation/modulation of specific neural structures or pathways provide alternative treatment strategies in selected patients with refractory neuropathic pain [116, 117] (Figure 7).

- *Neural Blockade and Steroid Injections*

Local anesthetic nerve blocks have been used as a diagnostic tool to determine if a particular nerve or nerve root is involved in pain signaling or is the source of ectopic activity that leads to neuropathic pain. The results of these procedures, however, need to be interpreted with caution, as their predictive value in defining treatment is uncertain. Perineural injection of steroids provides transient relief (1-3 months) for trauma- and compression-related peripheral neuropathic pain[118]. Epidural and paravertebral local anesthetic and steroid nerve blocks were

given a weak recommendation by NeuPSIG (Neuropathic Pain Special Interest Group, International Association for the Study of Pain) for the treatment of acute zoster-associated neuropathic pain[117]. Epidural steroid injections are commonly used in the treatment of cervical and lumbar radiculopathies, but their efficacy and safety remain controversial. An evidence-based review of randomized trials on epidural steroid injection suggested a modest effect size with pain relief lasting <3 months, [119] consistent with NeuPSIG's weak recommendation for its use in radiculopathy secondary to a lumbar herniated disc. Transforaminal epidural steroid injections were more likely to yield positive results than caudal and interlaminar techniques. Recent controlled trials provide moderate evidence that subcutaneous injection of botulinum toxin A has a beneficial role in the treatment of peripheral neuropathic pain (e.g., diabetic neuropathic pain, postherpetic and trigeminal neuralgia) [90, 120, 121]. Although sympathetic ganglion blocks have been used to treat pain some patients with complex regional pain syndromes (CRPS; causalgia, reflex sympathetic dystrophy), the evidence for long-term benefit is weak.

- *Neurostimulation Therapies*

Spinal Cord Stimulation (SCS)

The relative safety and reversibility of SCS, as well as its cost-effectiveness over the long term, has made it an attractive strategy for managing patients with refractory, chronic NP [122-124]. Systematic reviews, randomized controlled trials, and several case series provide evidence for long-term efficacy of SCS relative to conventional medical management in patients with CRPS type I and treatment-refractory failed back surgery syndrome (FBSS) with radicular symptoms [125-127] SCS offered better pain relief, health-related quality of life, and functional capacity that were sustained at 24 months of treatment [128, 129]. Both NeuPSIG and the European Academy of Neurology gave a weak recommendation to SCS use in CRPS type I and FBSS with radiculopathy on the basis of the moderate evidence from controlled trials [116, 117, 130]. The NICE guidance also recommended SCS as a possible treatment for adults with chronic pain of neuropathic origin[17]. The NeuPSIG report considered the evidence for the efficacy of SCS in diabetic neuropathic pain to be low and made an "inconclusive" recommendation. Two subsequent randomized trials of SCS in subjects with painful diabetic neuropathy provide additional evidence for its efficacy, with greater reduction in pain and improvements in quality

of life measures compared to a control group [131, 132]. Although SCS is used to treat several other neuropathic pain states, (e.g., post-amputation stump and phantom pains, post-herpetic neuralgia, spinal cord injury, and traumatic peripheral neuralgias), the evidence for its effectiveness is based primarily on small observational studies. The success of SCS for neuropathic pain may depend on appropriate selection of patients, based on psychological traits, sensory phenotype, and pain mechanism [133, 134].

Traditional SCS parameters use a monophasic, square-wave pulse at a frequency in the 30–100-Hz range that results in paresthesia in the painful region[135]. Newer stimulation parameters, such as burst (40-Hz burst with 5 spikes at 500 Hz per burst) and high-frequency (10 kHz with sinusoidal wave forms) SCS, provide paresthesia-free stimulation and equivalent or better pain relief compared to traditional SCS [136, 137].

Dorsal Root Ganglion (DRG), Peripheral Nerve, and Peripheral Nerve Field Stimulation

Neurostimulation of afferent fibers outside the spinal cord (e.g., DRG and peripheral nerves) and subcutaneous peripheral nerve field stimulation have been reported to provide pain relief in a variety of chronic neuropathic pain states, such as postsurgical and post-traumatic neuralgia, CRPS, occipital neuralgia, and postherpetic neuralgia [138, 139]. A multicenter, prospective, cohort study in subjects with chronic neuropathic pain reported that DRG stimulation provided 56% pain reduction with a 60% responder rate (>50% reduction in pain) [140]. These preliminary observations require further validation with controlled trials.

SCS and peripheral nerve stimulation are generally safe and reversible therapies. However, hardware-related, biological complications such as infections and programming- or treatment-related adverse effects (e.g., painful paresthesias) have been reported in 30-40% of patients [141, 142]. Systematic reviews have reported the most common hardware-related complication, lead migration, to have rates of 20-27% [143]. Other hardware-related complications include lead fracture and malfunction (6-10%), and battery failure. Pain over the device components has a reported incidence of 1-12% across studies. Wound infection (2.5-10%) and wound breakdown are major complications associated with DRG stimulation that sometimes require removal of the device.

Epidural and Transcranial Cortical Neurostimulation

Stimulation of the pre-central motor cortex (M1) below motor threshold using invasive (epidural, [EMCS]) or transcranial noninvasive techniques (e.g., repetitive transcranial magnetic stimulation [rTMS], transcranial direct current stimulation [tDCS]), has been proposed for drug-resistant peripheral and central neuropathic pain [144-146]. M1 rTMS and EMCS may reduce pain-related thalamic hyperactivity or activate descending inhibitory pathways. Meta-analysis reports suggest that 60-65% of patients respond (>40% pain reduction) to EMCS [146]. Repetitive sessions (5-10 over 1-2 weeks) with high-frequency rTMS (5-20 Hz) of contralateral M1 have shown benefits in a mixture of central, peripheral, and facial neuropathic pain states, with effects lasting >2 weeks after the stimulation. Anodal tDCS over M1 has been reported to be beneficial in reducing several neuropathic conditions (phantom pain, trigeminal neuralgia, diabetic neuropathy, post-stroke pain, and pain associated with multiple sclerosis). The primary advantage of noninvasive neurostimulation techniques is their excellent safety profile; hence they have been suggested as complementary therapies in patients with chronic refractory neuropathic pain. Relative contraindications of TMS include a history of epilepsy and the presence of aneurysm clips, deep brain electrodes, or cochlear implants.

Deep Brain Stimulation (DBS)

The use of chronic intracranial stimulation for neuropathic pain remains controversial. Multiple DBS sites, including the internal capsule, various nuclei in the sensory thalamus, periaqueductal and periventricular gray, motor cortex, septum, nucleus accumbens, posterior hypothalamus, and anterior cingulate cortex, have been examined as potential brain targets for pain control [147]. The NICE guidelines recognize that the procedure may be efficacious in some patients refractory to other forms of pain control, but current evidence on the safety of DBS shows serious potential risks [148]. Contrary to NICE, the EAN guidelines give inconclusive recommendations to DBS [130].

- Intrathecal Therapies

Intrathecal therapies have been suggested as a targeted drug delivery option in patients with severe and chronic pain refractory to conservative treatments, including psychological, physical, pharmacological and neuromodulation therapies [149, 150]. The Polyanalgesic Consensus Conference report highlighted that this therapy is associated with risks for serious morbidity and mortality and made recommendations to reduce the incidence of these serious adverse effects [151].

The only two FDA approved drugs are morphine and ziconitide, an N-type calcium channel antagonist [152]. The most frequently reported adverse reactions associated with intrathecal ziconitide are dizziness, nausea, confusional state, memory impairment, nystagmus, and elevation of serum creatine kinase. Ziconitide is contraindicated in patients with a history of psychosis and patients should be monitored for evidence of cognitive impairment, hallucinations, or changes in mood and consciousness.

Psychological therapies

Psychological therapies are likely to play an increasingly important role in our attempts to help people adapt to neuropathic pain. People with chronic pain are not passive; they actively attempt to change the causes of pain and change their own behavior in response to pain. But, for many patients change without therapeutic help is unachievable, and repeated misdirected attempts to solve the problem of pain drive them further into a cycle of pain, depression, and disability [153] Psychological interventions are designed to promote the management of pain and to reduce its adverse consequences. Cognitive Behavioral Therapy (CBT) has received most research attention; however CBT is not a single treatment, and can usefully be thought of as a family of techniques woven together by a clinical narrative of 'individual change' delivered by therapists actively managing treatment. The targets of treatment go beyond the analgesic to domains of affect, function, and social engagement. Secondary outcomes are sometimes reported because they are deemed important to treatment delivery (e.g., therapeutic alliance; self-efficacy), or because they are valued by one or more stakeholder (e.g., return to work; analgesic use).
Trials of CBT reflect clinical practice: they are largely undertaken with samples heterogeneous by medical diagnosis, but homogenous in the extent of depression, anxiety, disability, social withdrawal, and difficulty self-managing pain. The most recent Cochrane systematic review of psychological interventions for chronic pain identified sixty-five trials, of which analyzable data were available from thirty-five. There are studies of both specific Behavioral Therapies (BT) and programs of CBT across multiple comparisons in different domains of outcome (pain, disability, mood), which taken together give a clear picture—there are small to moderate effects of CBT over comparisons [154]. In a companion review of fifteen trials delivering treatment using the internet, a similar broadly positive conclusion emerged, although the confidence in the estimates

of effects was low [155]. Psychological treatments other than BT and CBT were included in this review, but there were no trials of sufficient quality to include. More recently a specific Cochrane review of trials specifically undertaken with neuropathic pain patients found no evidence, reporting only two small trials [156]. There is no evidence base for or against the efficacy and safety of psychological interventions for chronic neuropathic pain. That the evidence for the efficacy of psychological interventions for chronic neuropathic pain is either missing or underwhelming is not surprising, and is in line with the evidence for non-psychological interventions [157]. There is an urgent need for studies of treatments designed specifically for patients with neuropathic pain, in particular those with painful diabetic neuropathy [158]. It is likely that these studies will be different to those that went before in both content and design. First, needed are studies of CBT with content specifically designed to meet the psychosocial needs of patients with neuropathy, in particular with regard to the multiple sensory challenge, co-morbidity, and polypharmacy [159]. A recognition that neuropathic pain increases with age will also mean that an understanding of later life accommodation to illness will be important [160]. Second, a methodological focus on individual experience and trajectories of change is needed, either through single case experiments or through ecological momentary assessment [161]. Third, communication technology, in particular the use of mobile health innovation, is likely to play an important role in future solutions. The computing technology already exists to deliver behavior change interventions to patients distant from therapists. What is missing is the basic behavioral science of how to manage effective therapeutic relationships at a distance, and how technology can augment and improve face-to-face CBT [162]. Technical psychological variables—such as catastrophic thinking, acceptance, or readiness to change—should be relegated to process variables. Conversely, essential will be a pragmatic focus on patient reported outcomes with the scope of reducing pain, improving mood, and reducing disability which ultimately results in improving quality of life. CBT remains an excellent candidate treatment for development.

QUALITY OF LIFE

Neuropathic pain can significantly impair quality of life as it often associates with other problems such as loss of function, anxiety, depression, disturbed sleep, and impaired cognition. Health Related Quality of Life (HRQoL) is a measure that captures broad dimensions of health

including physical, mental, emotional and social functioning. HRQoL is increasingly used when assessing the efficacy of different interventions to manage chronic neuropathic and non-neuropathic pain. It is particularly useful when calculating quality-adjusted life years (QALYs) necessary for cost-utility analyses.

The most commonly used HRQoL instruments are presented below. Some of them are general whereas others have been designed to assess HRQoL in neuropathic pain. Meyer-Rosberg and colleagues validated both the SF-36 and Nottingham Health Profile (NHP) in the assessment of HRQoL in neuropathic pain related to peripheral nerve or root lesion in patients attending multidisciplinary pain clinics [163]. The scores of all eight dimensions in the Short Form 36 Health Survey (SF-36) were significantly lower in the neuropathic pain patients compared with the general population in line with another study [164].

The onset of neuropathy in diabetic patients has been shown to significantly decrease all aspects of quality of life [165]. If diabetic polyneuropathy is accompanied by pain, both physical and mental components of quality of life are further affected [166]. A recent study also showed that both EuroQol five dimensions (EQ-5D) and Short Form-6 dimension (SF-6D) questionnaires can discriminate between chronic pain patients with or without neuropathic pain [167]. The role of psychological factors in impairing quality of life in neuropathic pain has been analyzed in two recent studies [168, 169]. One of them showed that pain catastrophizing associated with decreased HRQoL in neuropathic pain [168].

The SF-36 and the EQ-5D have been the most commonly used instrument in clinical trials e.g. to assess the efficacy of gabapentin in post-herpetic neuralgia[170], diabetic polyneuropathy [171], or neuropathic pain due to peripheral nerve injury [164], the efficacy of duloxetine in diabetic peripheral neuropathy [172], and the efficacy of spinal cord stimulation in diabetic polyneuropathy[173],[172 174]. Improvement in pain scores was positively correlated with improvement in quality of life. The largest improvements were in patients achieving ≥50% pain relief. General HRGoL instruments enable comparison of neuropathic pain with other conditions and the general population. A sensitive HRQoL instrument specifically developed for neuropathic pain would help to analyze factors that are affected by neuropathic pain and help to focus management to all domains that are affected.

OUTLOOK

Limitations of existing neuropathic pain treatments provide a compelling impetus for the development of novel interventions with improved efficacy and tolerability, but there have been few major advances. The explanations for this slow progress that are receiving the greatest attention are inadequate clinical trial assay sensitivity and the need to target treatment to patients who are most likely to respond. Assay sensitivity refers to the ability of a clinical trial to distinguish an efficacious treatment from placebo (or another comparator). The possibility that recent neuropathic pain clinical trials may suffer from limited assay sensitivity is consistent with the observation that a considerable number of recent negative trials investigated medications with well-established efficacy[5, 175]. Research designs, methodological features, patient characteristics, outcome measures, statistical analysis methods, and statistical power may all play a role in accounting for difficulties in demonstrating the benefits of efficacious treatments vs. placebo [176, 177]. The essence of an evidence-based approach to the design of clinical trials is to first examine associations between clinical trial characteristics and study outcomes to identify modifiable factors associated with assay sensitivity, and to then apply that knowledge prospectively in the design of new trials. An example is provided by a recent analysis of neuropathic pain trials that showed that assay sensitivity was compromised by patients with highly variable baseline pain ratings [178] which suggests that trials might have greater assay sensitivity if highly variable baseline pain ratings were an exclusion criterion [101].

Another critically important approach to increasing clinical trial assay sensitivity and to accelerating the development of personalized pain treatments involves selecting patients who have an increased likelihood of treatment response [179]. The strongest evidence showing that profiles of symptoms and signs can identify treatment responders is a trial in which patients who were defined as having an "irritable nociceptor" phenotype had a larger decrease in pain with oxcarbazepine vs. placebo than those without this phenotype [32]. This is the only trial in which a pre-specified primary analysis demonstrated a difference in treatment vs. placebo response in patient subgroups identified by phenotyping. These results are very promising, but require replication as well as use of phenotyping measures that would be suitable for larger confirmatory trials and use in clinical practice [180, 181]. Phenotyping could also be used to test whether certain patients have a more robust response to non-pharmacologic treatments, for example, invasive, psychological, and complementary interventions [180], as well as to identify which patients are

most likely to respond to combinations of treatments. Indeed, given the importance of expectations and psychological and social factors — including adaptive coping and catastrophizing — in the development and maintenance of chronic pain, it would not be surprising if phenotyping has as great a role to play in demonstrating the efficacy of psychological interventions as it does for medications (Figure 8).

To advance the design, execution, analysis, and interpretation of clinical trials of pain treatments, several public-private partnerships have undertaken systematic efforts to increase assay sensitivity and provide validated approaches for phenotyping patients and identifying those most likely to respond to treatment. These efforts—which include ACTTION (www.acttion.org), EuroPain (www.imieuropain.org), and the German Research Network on Neuropathic Pain (www.neuro.med.tu-muenchen.de/dfns/e_index.html)—are providing an evidence-based foundation for the design of future neuropathic pain clinical trials and for the development of mechanism-based approaches to personalized neuropathic pain treatment.

The emergence of personalized pain medicine

Personalized medical care refers to the principle that patients can be stratified such that each patient receives the most effective and tolerable treatment for their individual needs. Patients can be stratified on a number of levels: clinical phenotype, detailed sensory profiling, genetics and potentially (in the future) using cellular models. Close consultation with the patient is required and this involves complex discussions around the uncertainties of genetic risk and the balance between efficacy and tolerability of potential treatments. Human genetics has demonstrated that $Na_v1.7$ is a critical pain target [182] and therapeutics aimed at targeting $Na_v1.7$ provide an example of a situation in which testing for specific genetic mutations can inform patient care. Loss of function mutations lead to congenital insensitivity to pain and gain of function mutations cause rare inherited pain disorders including: inherited erythromelalgia (IEM, pain and erythema of the extremities, exacerbated by warmth) [183], paroxysmal extreme pain disorder (PEPD, pain and erythema affecting the sacrum and mandible) [184] and idiopathic small fiber neuropathy (SFN, pain and small-fiber degeneration in the extremities) [185].

Genetic information can therefore inform diagnostics however the interpretation of genetic results is complex and aided by functional analysis of ion channels [186] for instance in the context of SFN in which mutations may not be fully penetrant. Finding a mutation in $Na_v1.7$ may have

immediate implications for treatment in choosing a drug with activity against VGSCs (not normally first line agents in the treatment of neuropathic pain). For example, mexiletine is not recommended in the treatment of neuropathic pain but exception is made in IEM in which mexiletine has proven efficacy in normalizing abnormal channel properties *in vitro* [187] and clinical efficacy in individual cases. A further step has been taken in using structural modelling of $Na_v1.7$ to predict what treatment a specific mutation will respond to [188] and this was recently used to predict efficacy of carbamazepine in IEM associated with the S241T mutation [189]. By taking a blood sample or skin biopsy from a patient it is now possible to generate nociceptors *in vitro*. In rare Mendelian pain disorders (such as IEM) these nociceptors have been shown to be hyper-excitable [190]. Treatments such as selective inhibitors of $Na_v1.7$ can be screened in such cellular models and related to clinical efficacy in Mendelian pain disorders as proof of concept prior to their use in acquired neuropathic pain conditions. Genetic stratification is more challenging in common acquired neuropathic pain states such as painful diabetic neuropathy which are polygenic with a significant environmental interaction. Despite these limitations the prospect of personalized medicine is a step forward towards promising pain management strategies.

Conclusions

Neuropathic pain is a notable health concern since it impairs quality of life and functioning. Nervous system mechanisms underlying chronic neuropathic pain have been uncovered through animal and human research. Major progressive strides have been made, particularly with the utilization of genetics which can guide diagnostics and treatment choices. Technological advances have helped improve the efficacy of invasive and non-invasive neurostimulation techniques for the treatment of select neuropathic pain states. Moreover, increased understanding of pain modulatory mechanisms (e.g. CPM, placebo effects) and psychological therapies, such as CBT, is the key for improving patient-oriented outcomes. New and more effective therapeutic targets, specifically those that have been individualized based on genotypic and phenotypic profiles, are promising and have opened many doors for progressing neuropathic pain basic and translational research.

Acknowledgements

This manuscript was supported in part by the UMB and National Institutes of Health, NIDCR (R01, LC); Wellcome Trust Pain Consortium (AD and DLB); EU Project No 633491: DOLOR-isk, IMI Europain, Pfizer, Genzyme GmbH, Grünenthal GmbH, Mundipharma (RB); Israel Science Foundation, European Horizons 2020; US Department of Defense (DY) and National Institutes of Health (NS26363, SR).

Author contributions

Introduction (LC and TD); Epidemiology (DB); Mechanisms/pathophysiology (AD, LC, DY and RF); Diagnosis, screening and prevention (RB, AT and RD); Management (NA, NF, SR and CE); Quality of life (EK); Outlook (RD and DLB). Critical revision of the manuscript (All authors).

Competing interests

LC received research funding, lecture honoraria and acted as speaker or consultant for Grünenthal and Emmi Solution.
TL declared no competing interests.
RB is an industry member of Astra Zeneca, Pfizer, Esteve, UCB-Pharma, Sanofi Aventis, Grünenthal GmbH, Eli Lilly, and Boehringer Ingelheim Pharma GmbH&Co.KG; German Federal Ministry of Education and Research member (ERA_NET NEU-RON / IM-PAIN Project) and German Research Net-work on Neuropathic Pain, NoPain system biology German Research Foundation (DFG); RB received lecture honoraria from Pfizer, Genzyme GmbH, Grünenthal GmbH, Mundipharma, Sanofi Pasteur, Medtronic Inc. Neuromodulation, Eisai Co.Ltd., Lilly GmbH, Boehringer Ingelheim Pharma GmbH&Co.KG, Astellas, Desitin, Teva Pharma, Bayer-Schering, MSD GmbH, Seqirus and served as a consultant for Pfizer, Genzyme GmbH, Grünenthal GmbH, Mundipharma, Allergan, Sanofi Pasteur, Medtronic Inc. Neuromodulation, Eisai Co.Ltd., Lilly GmbH, Boehringer Ingelheim Pharma GmbH&Co.KG, Astellas, Novartis, Bristol-Myers-Squibb, Biogenidec, AstraZeneca, Merck, Abbvie, Daiichi Sankyo, Glenmark Pharmaceuticals, Seqirus, Teva Pharma, Genentech and Galapagos NV.
AD has acted as speaker or consultant for Seqirus, Grünenthal, Allergan and Mundipharma.

DB acted as a consultant for Grünenthal, Pfizer, and Indivior.
DLB has acted as a consultant for Abide, Eli-Lilly, Mundi-pharma, Pfizer and TEVA.
DY received a lecture honorarium from Pfizer and holds equity in the BrainsGate and Theranica companies.
RF acted as advisory board member for Abide, Astellas, Biogen, Glenmark, Hydra, Novartis and Pfizer.
AT declared no competing interests.
NA received honoraria for participation in advisory boards or speaker bureau by Astellas, Teva, Mundipharma, Johnson and Johnson, Novartis and Sanofi Pasteur MSD.
NBF has received honoraria for participation in advisory board from Teva Pharmaceuticals, Novartis, and Grünenthal and research support from EUROPAIN Investigational Medicines Initiative (IMI).
CE declared no competing interests.
EK has served in the advisory boards of Orion Pharma and Grunenthal and received lecture honoraria from Orion Pharma and Astra Zeneca.
RHD received research grants and contracts from the US Food and Drug Administration and US National Institutes of Health, and compensation for activities involving clinical trial research methods from Abide, Aptinyx, Astellas, Boston Scientific, Centrexion, Dong-A, Eli Lilly, Glenmark, Hope, Hydra, Immune, Novartis, NsGene, Olatec, Phosphagenics, Quark, Reckitt Benckiser, Relmada, Semnur, Syntrix, Teva, Trevena, and Vertex.
SR received a research grant from Medtronic Inc. and honoraria for participation in advisory boards of Allergan, Daiichi-Sankyo, and Grünenthal USA Inc.

References

1. Jensen, T.S. et al. A new definition of neuropathic pain. *Pain* **152**, 2204-5 (2011).
2. 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* **152**, 2836-43 (2011).
3. Torrance, N., Smith, B.H., Bennett, M.I. & Lee, A.J. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain* **7**, 281-9 (2006).
4. **Finnerup, N.B. et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain* 157, 1599-606 (2016).**

This paper presents a grading system helping health care providers and researhcers to improve the classification and grading of neuropathic pain in the daily clinical practice

5. Tuttle, A.H. et al. Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. *Pain* **156**, 2616-26 (2015).
6. Dolgin, E. Fluctuating baseline pain implicated in failure of clinical trials. *Nat Med* **16**, 1053 (2010).
7. Bartfai, T. & Lees, G.V. Pharma TARP: a troubled asset relief program for novel, abandoned projects in the pharmaceutical industry. *ScientificWorldJournal* **11**, 454-7 (2011).
8. Katz, J., Finnerup, N.B. & Dworkin, R.H. Clinical trial outcome in neuropathic pain: relationship to study characteristics. *Neurology* **70**, 263-72 (2008).
9. van Hecke, O., Austin, S.K., Khan, R.A., Smith, B.H. & Torrance, N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain* **155**, 654-62 (2014).
10. Bouhassira, D. et al. Patient perspective on herpes zoster and its complications: an observational prospective study in patients aged over 50 years in general practice. *Pain* **153**, 342-9 (2012).
11. Helgason, S., Petursson, G., Gudmundsson, S. & Sigurdsson, J.A. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. *BMJ* **321**, 794-6 (2000).
12. Daousi, C. et al. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med* **21**, 976-82 (2004).
13. Davies, M., Brophy, S., Williams, R. & Taylor, A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care* **29**, 1518-22 (2006).
14. Bouhassira, D., Letanoux, M. & Hartemann, A. Chronic pain with neuropathic characteristics in diabetic patients: a French cross-sectional study. *PLoS One* **8**, e74195 (2013).
15. Abbott, C.A., Malik, R.A., van Ross, E.R., Kulkarni, J. & Boulton, A.J. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* **34**, 2220-4 (2011).
16. Jensen, M.P., Chodroff, M.J. & Dworkin, R.H. The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology* **68**, 1178-82 (2007).
17. Solaro, C. et al. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. *Neurology* **63**, 919-21 (2004).
18. Osterberg, A., Boivie, J. & Thuomas, K.A. Central pain in multiple sclerosis--prevalence and clinical characteristics. *Eur J Pain* **9**, 531-42 (2005).
19. Siddall, P.J., McClelland, J.M., Rutkowski, S.B. & Cousins, M.J. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain* **103**, 249-57 (2003).
20. Klit, H., Finnerup, N.B., Andersen, G. & Jensen, T.S. Central poststroke pain: a population-based study. *Pain* **152**, 818-24 (2011).

21. Rayment, C. et al. Neuropathic cancer pain: prevalence, severity, analgesics and impact from the European Palliative Care Research Collaborative-Computerised Symptom Assessment study. *Palliat Med* **27**, 714-21 (2013).
22. Bennett, M.I. et al. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain* **153**, 359-65 (2012).
23. Bouhassira, D. & Attal, N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. *Pain* **152**, S74-83 (2011).
24. Bennett, M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* **92**, 147-57 (2001).
25. Bouhassira, D. et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* **114**, 29-36 (2005).
26. Yawn, B.P. et al. The prevalence of neuropathic pain: clinical evaluation compared with screening tools in a community population. *Pain Med* **10**, 586-93 (2009).
27. Bouhassira, D., Lanteri-Minet, M., Attal, N., Laurent, B. & Touboul, C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* **136**, 380-7 (2008).
28. de Moraes Vieira, E.B., Garcia, J.B., da Silva, A.A., Mualem Araujo, R.L. & Jansen, R.C. Prevalence, characteristics, and factors associated with chronic pain with and without neuropathic characteristics in Sao Luis, Brazil. *J Pain Symptom Manage* **44**, 239-51 (2012).
29. Freynhagen, R. et al. Screening of neuropathic pain components in patients with chronic back pain associated with nerve root compression: a prospective observational pilot study (MIPORT). *Curr Med Res Opin* **22**, 529-37 (2006).
30. Tesfaye, S., Boulton, A.J. & Dickenson, A.H. Mechanisms and management of diabetic painful distal symmetrical polyneuropathy. *Diabetes Care* **36**, 2456-65 (2013).
31. Fields, H.L., Rowbotham, M. & Baron, R. Postherpetic neuralgia: irritable nociceptors and deafferentation. *Neurobiol Dis* **5**, 209-27 (1998).
32. Demant, D.T. et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain* **155**, 2263-73 (2014).
33. Patel, R. & Dickenson, A.H. Mechanisms of the gabapentinoids and alpha 2 delta-1 calcium channel subunit in neuropathic pain. *Pharmacol Res Perspect* **4**, e00205 (2016).
34. Woolf, C.J. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* **152**, S2-15 (2011).
35. Baron, R., Hans, G. & Dickenson, A.H. Peripheral input and its importance for central sensitization. *Ann Neurol* **74**, 630-6 (2013).
36. Patel, R. & Dickenson, A.H. Neuronal hyperexcitability in the ventral posterior thalamus of neuropathic rats: modality selective effects of pregabalin. *J Neurophysiol* **116**, 159-70 (2016).
37. Gagnon, M. et al. Chloride extrusion enhancers as novel therapeutics for neurological diseases. *Nat Med* **19**, 1524-8 (2013).
38. Tsuda, M., Beggs, S., Salter, M.W. & Inoue, K. Microglia and intractable chronic pain. *Glia* **61**, 55-61 (2013).
39. Navratilova, E., Atcherley, C.W. & Porreca, F. Brain Circuits Encoding Reward from Pain Relief. *Trends Neurosci* **38**, 741-50 (2015).
40. Bannister, K. & Dickenson, A.H. What the brain tells the spinal cord. *Pain* (2016).
41. Burma, N.E., Leduc-Pessah, H., Fan, C.Y. & Trang, T. Animal models of chronic pain: Advances and challenges for clinical translation. *J Neurosci Res* (2016).
42. Haroutounian, S. et al. Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy. *Pain* **155**, 1272-9 (2014).

43. Vaso, A. et al. Peripheral nervous system origin of phantom limb pain. *Pain* **155**, 1384-91 (2014).
44. Serra, J. et al. Microneurographic identification of spontaneous activity in C-nociceptors in neuropathic pain states in humans and rats. *Pain* **153**, 42-55 (2012).
45. Kleggetveit, I.P. et al. High spontaneous activity of C-nociceptors in painful polyneuropathy. *Pain* **153**, 2040-7 (2012).
46. Yarnitsky, D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain* **156 Suppl 1**, S24-31 (2015).
47. Lewis, G.N., Rice, D.A. & McNair, P.J. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain* **13**, 936-44 (2012).
48. Yarnitsky, D., Granot, M., Nahman-Averbuch, H., Khamaisi, M. & Granovsky, Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain* **153**, 1193-8 (2012).
49. Wilder-Smith, O.H., Schreyer, T., Scheffer, G.J. & Arendt-Nielsen, L. Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: a pilot study. *J Pain Palliat Care Pharmacother* **24**, 119-28 (2010).
50. Petersen, K.K., Graven-Nielsen, T., Simonsen, O., Laursen, M.B. & Arendt-Nielsen, L. Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. *Pain* **157**, 1400-6 (2016).
51. Kosek, E. & Ordeberg, G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. *Pain* **88**, 69-78 (2000).
52. Graven-Nielsen, T., Wodehouse, T., Langford, R.M., Arendt-Nielsen, L. & Kidd, B.L. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis Rheum* **64**, 2907-16 (2012).
53. Colloca, L. & Miller, F.G. Role of expectations in health. *Curr Opin Psychiatry* **24**, 149-55 (2011).
54. Colloca, L. Placebo, nocebo, and learning mechanisms. *Handb Exp Pharmacol* **225**, 17-35 (2014).
55. Hall, K.T. et al. Conscientiousness is modified by genetic variation in catechol-O-methyltransferase to reduce symptom complaints in IBS patients. *Brain Behav* **5**, 39-44 (2015).
56. Kaptchuk, T.J. et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* **336**, 999-1003 (2008).
57. Vase, L., Robinson, M.E., Verne, G.N. & Price, D.D. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation. *Pain* **105**, 17-25 (2003).
58. Vase, L., Skyt, I. & Hall, K.T. Placebo, nocebo, and neuropathic pain. *Pain* **157 Suppl 1**, S98-105 (2016).
59. Petersen, G.L. et al. Placebo manipulations reduce hyperalgesia in neuropathic pain. *Pain* **153**, 1292-300 (2012).
60. Petersen, G.L. et al. Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. *Pain* **155**, 2687-98 (2014).
61. Colloca, L., Lopiano, L., Lanotte, M. & Benedetti, F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol* **3**, 679-84 (2004).
62. Freeman, R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. *Curr Diab Rep* **9**, 423-31 (2009).
63. Borsook, D. Neurological diseases and pain. *Brain* **135**, 320-44 (2012).
64. Watson, J.C. & Sandroni, P. Central Neuropathic Pain Syndromes. *Mayo Clin Proc* **91**, 372-85 (2016).
65. Bennett, M.I. et al. Using screening tools to identify neuropathic pain. *Pain* **127**, 199-203 (2007).

66. Freynhagen, R., Baron, R., Gockel, U. & Tolle, T.R. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* **22**, 1911-20 (2006).

67. 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* 11, 999-1005 (2012).

This paper describes the importance of sensory phenotyping to a stratified treatment approach and ultimately to personalised treatment.68. Cruccu, G. et al. EFNS guidelines on neuropathic pain assessment: revised 2009. *Eur J Neurol* **17**, 1010-8 (2010).

69. Backonja, M.M. et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain* **154**, 1807-19 (2013).

70. Rolke, R. et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* **123**, 231-43 (2006).

71. Garcia-Larrea, L. Objective pain diagnostics: clinical neurophysiology. *Neurophysiol Clin* **42**, 187-97 (2012).

72. Haanpaa, M. et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* **152**, 14-27 (2011).

73. Truini, A. et al. Pathophysiology of pain in postherpetic neuralgia: a clinical and neurophysiological study. *Pain* **140**, 405-10 (2008).

74. Valeriani, M., Pazzaglia, C., Cruccu, G. & Truini, A. Clinical usefulness of laser evoked potentials. *Neurophysiol Clin* **42**, 345-53 (2012).

75. Truini, A. et al. Differential involvement of A-delta and A-beta fibres in neuropathic pain related to carpal tunnel syndrome. *Pain* **145**, 105-9 (2009).

76. Truini, A. et al. Mechanisms of pain in distal symmetric polyneuropathy: a combined clinical and neurophysiological study. *Pain* **150**, 516-21 (2010).

77. Truini, A., Garcia-Larrea, L. & Cruccu, G. Reappraising neuropathic pain in humans--how symptoms help disclose mechanisms. *Nat Rev Neurol* **9**, 572-82 (2013).

78. Lauria, G. et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol* **17**, 903-12, e44-9 (2010).

79. Nolano, M. et al. Cutaneous innervation of the human face as assessed by skin biopsy. *J Anat* **222**, 161-9 (2013).

80. Tesfaye, S. et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* **33**, 2285-93 (2010).

81. Truini, A. et al. Does the epidermal nerve fibre density measured by skin biopsy in patients with peripheral neuropathies correlate with neuropathic pain? *Pain* **155**, 828-32 (2014).

82. Papanas, N. & Ziegler, D. Corneal confocal microscopy: Recent progress in the evaluation of diabetic neuropathy. *J Diabetes Investig* **6**, 381-9 (2015).

83. Ziegler, D. et al. Early detection of nerve fiber loss by corneal confocal microscopy and skin biopsy in recently diagnosed type 2 diabetes. *Diabetes* **63**, 2454-63 (2014).

84. Oxman, M.N. et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* **352**, 2271-84 (2005).

85. Lal, H. et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 372, 2087-96 (2015).

This research outlines the role of an adjuvanted herpes zoster subunit vaccine in preventing development of neuropathic pain in elderly.

86. Gewandter, J.S. et al. Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations. *Pain* **156**, 1184-97 (2015).

87. Dworkin, R.H. et al. Recommendations for the management of herpes zoster. *Clin Infect Dis* **44 Suppl 1**, S1-26 (2007).
88. Smith, A.G. et al. Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care* **29**, 1294-9 (2006).
89. Smith, B.H. & Torrance, N. Epidemiology of neuropathic pain and its impact on quality of life. *Curr Pain Headache Rep* **16**, 191-8 (2012).
90. Attal, N. et al. Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* **15**, 555-65 (2016).
91. Yalcin, I. et al. beta(2)-adrenoceptors are critical for antidepressant treatment of neuropathic pain. *Ann Neurol* **65**, 218-25 (2009).
92. Luo, Z.D. et al. Upregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. *J Neurosci* **21**, 1868-75 (2001).
93. 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* **33**, 19-26 (2014).
94. Gilron, I., Jensen, T.S. & Dickenson, A.H. Combination pharmacotherapy for management of chronic pain: from bench to bedside. *Lancet Neurol* **12**, 1084-95 (2013).
95. Gilron, I., Tu, D., Holden, R.R., Jackson, A.C. & DuMerton-Shore, D. Combination of morphine with nortriptyline for neuropathic pain. *Pain* **156**, 1440-8 (2015).
96. Holbech, J.V. et al. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. *Pain* **156**, 958-66 (2015).
97. Tesfaye, S. et al. 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* **154**, 2616-25 (2013).
98. Binder, A. et al. 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* **29**, 393-408 (2009).
99. Demant, D.T. et al. Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype: a randomised, double-blind, and placebo-controlled, phenotype panel study. *Pain* **156**, 2234-44 (2015).
100. Emery, E.C., Luiz, A.P. & Wood, J.N. Nav1.7 and other voltage-gated sodium channels as drug targets for pain relief. *Expert Opin Ther Targets* **20**, 975-83 (2016).
101. Rice, A.S. et al. 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* **383**, 1637-47 (2014).
102. Attal, N. et al. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* **13**, 1153-69 (2006).
103. Dworkin, R.H. et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* **132**, 237-51 (2007).
104. Moulin, D. et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag* **19**, 328-35 (2014).
105. Tan, T., Barry, P., Reken, S., Baker, M. & Guideline Development, G. Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance. *BMJ* **340**, c1079 (2010).
106. Attal, N. et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* **17**, 1113-e88 (2010).
107. (June 24, 2013).

108. Finnerup, N.B. & Attal, N. Pharmacotherapy of neuropathic pain: time to rewrite the rulebook? *Pain Manag* **6**, 1-3 (2016).
109. Attal, N. et al. Assessing symptom profiles in neuropathic pain clinical trials: can it improve outcome? *Eur J Pain* **15**, 441-3 (2011).
110. Bouhassira, D. & Attal, N. Translational neuropathic pain research: A clinical perspective. *Neuroscience* (2016).
111. Finnerup, N.B. & Jensen, T.S. Mechanisms of disease: mechanism-based classification of neuropathic pain-a critical analysis. *Nat Clin Pract Neurol* **2**, 107-15 (2006).
112. von Hehn, C.A., Baron, R. & Woolf, C.J. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron* **73**, 638-52 (2012).
113. Campbell, C.M. et al. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. *Pain* **153**, 1815-23 (2012).
114. Attal, N. & Bouhassira, D. Pharmacotherapy of neuropathic pain: which drugs, which treatment algorithms? *Pain* **156 Suppl 1**, S104-14 (2015).
115. Finnerup, N.B. et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* **14**, 162-73 (2015).
116. Cruccu, G. et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* **14**, 952-70 (2007).
117. Dworkin, R.H. et al. Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain* **154**, 2249-61 (2013).
118. Bhatia, A., Flamer, D. & Shah, P.S. Perineural steroids for trauma and compression-related peripheral neuropathic pain: a systematic review and meta-analysis. *Can J Anaesth* **62**, 650-62 (2015).
119. Cohen, S.P., Bicket, M.C., Jamison, D., Wilkinson, I. & Rathmell, J.P. Epidural steroids: a comprehensive, evidence-based review. *Reg Anesth Pain Med* **38**, 175-200 (2013).
120. Shackleton, T. et al. The efficacy of botulinum toxin for the treatment of trigeminal and postherpetic neuralgia: a systematic review with meta-analyses. *Oral Surg Oral Med Oral Pathol Oral Radiol* **122**, 61-71 (2016).
121. Lakhan, S.E., Velasco, D.N. & Tepper, D. Botulinum Toxin-A for Painful Diabetic Neuropathy: A Meta-Analysis. *Pain Med* **16**, 1773-80 (2015).
122. Manca, A. et al. Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). *Eur J Pain* **12**, 1047-58 (2008).
123. Kumar, K. & Rizvi, S. Cost-effectiveness of spinal cord stimulation therapy in management of chronic pain. *Pain Med* **14**, 1631-49 (2013).
124. Deer, T.R. et al. The appropriate use of neurostimulation: new and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* **17**, 599-615; discussion 615 (2014).
125. North, R.B. et al. Spinal cord stimulation versus re-operation in patients with failed back surgery syndrome: an international multicenter randomized controlled trial (EVIDENCE study). *Neuromodulation* **14**, 330-5; discussion 335-6 (2011).
126. Kumar, K. et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* **132**, 179-88 (2007).
127. Simpson, E.L., Duenas, A., Holmes, M.W., Papaioannou, D. & Chilcott, J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess* **13**, iii, ix-x, 1-154 (2009).

128. Kumar, K. et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery* **63**, 762-70; discussion 770 (2008).
129. Kemler, M.A., De Vet, H.C., Barendse, G.A., Van Den Wildenberg, F.A. & Van Kleef, M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* **55**, 13-8 (2004).
130. Cruccu, G. et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur J Neurol* (2016).
131. de Vos, C.C. et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. *Pain* **155**, 2426-31 (2014).
132. Slangen, R. et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. *Diabetes Care* **37**, 3016-24 (2014).
133. Campbell, C.M., Jamison, R.N. & Edwards, R.R. Psychological screening/phenotyping as predictors for spinal cord stimulation. *Curr Pain Headache Rep* **17**, 307 (2013).
134. Campbell, C.M. et al. Dynamic Pain Phenotypes are Associated with Spinal Cord Stimulation-Induced Reduction in Pain: A Repeated Measures Observational Pilot Study. *Pain Med* **16**, 1349-60 (2015).
135. Yearwood, T.L., Hershey, B., Bradley, K. & Lee, D. Pulse width programming in spinal cord stimulation: a clinical study. *Pain Physician* **13**, 321-35 (2010).
136. De Ridder, D., Plazier, M., Kamerling, N., Menovsky, T. & Vanneste, S. Burst spinal cord stimulation for limb and back pain. *World Neurosurg* **80**, 642-649 e1 (2013).
137. Russo, M. & Van Buyten, J.P. 10-kHz High-Frequency SCS Therapy: A Clinical Summary. *Pain Med* **16**, 934-42 (2015).
138. Krames, E.S. The role of the dorsal root ganglion in the development of neuropathic pain. *Pain Med* **15**, 1669-85 (2014).
139. Petersen, E.A. & Slavin, K.V. Peripheral nerve/field stimulation for chronic pain. *Neurosurg Clin N Am* **25**, 789-97 (2014).
140. Liem, L. et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation* **18**, 41-8; discussion 48-9 (2015).
141. Mekhail, N.A. et al. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. *Pain Pract* **11**, 148-53 (2011).
142. Eldabe, S., Buchser, E. & Duarte, R.V. Complications of Spinal Cord Stimulation and Peripheral Nerve Stimulation Techniques: A Review of the Literature. *Pain Med* (2015).
143. Taylor, R.S., Van Buyten, J.P. & Buchser, E. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. *Spine (Phila Pa 1976)* **30**, 152-60 (2005).
144. Sukul, V.V. & Slavin, K.V. Deep brain and motor cortex stimulation. *Curr Pain Headache Rep* **18**, 427 (2014).
145. Moore, N.Z., Lempka, S.F. & Machado, A. Central neuromodulation for refractory pain. *Neurosurg Clin N Am* **25**, 77-83 (2014).
146. Lefaucheur, J.P. Cortical neurostimulation for neuropathic pain: state of the art and perspectives. *Pain* **157 Suppl 1**, S81-9 (2016).
147. Keifer, O.P., Jr., Riley, J.P. & Boulis, N.M. Deep brain stimulation for chronic pain: intracranial targets, clinical outcomes, and trial design considerations. *Neurosurg Clin N Am* **25**, 671-92 (2014).
148. in Interventional procedure guidance. (London, 2011).

149. Prager, J. et al. Best practices for intrathecal drug delivery for pain. *Neuromodulation* **17**, 354-72; discussion 372 (2014).
150. Bolash, R. & Mekhail, N. Intrathecal pain pumps: indications, patient selection, techniques, and outcomes. *Neurosurg Clin N Am* **25**, 735-42 (2014).
151. Deer, T.R. et al. Polyanalgesic Consensus Conference--2012: recommendations to reduce morbidity and mortality in intrathecal drug delivery in the treatment of chronic pain. *Neuromodulation* **15**, 467-82; discussion 482 (2012).
152. Pope, J.E., Deer, T.R., Bruel, B.M. & Falowski, S. Clinical Uses of Intrathecal Therapy and Its Placement in the Pain Care Algorithm. *Pain Pract* (2016).
153. Eccleston, C. & Crombez, G. Worry and chronic pain: a misdirected problem solving model. *Pain* **132**, 233-6 (2007).
154. Williams, A.C., Eccleston, C. & Morley, S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* **11**, CD007407 (2012).
155. Eccleston, C. et al. Psychological therapies (Internet-delivered) for the management of chronic pain in adults. *Cochrane Database Syst Rev*, CD010152 (2014).
156. Eccleston, C., Hearn, L. & Williams, A.C. Psychological therapies for the management of chronic neuropathic pain in adults. *Cochrane Database Syst Rev*, CD011259 (2015).
157. Moore, A., Derry, S., Eccleston, C. & Kalso, E. Expect analgesic failure; pursue analgesic success. *BMJ* **346**, f2690 (2013).
158. Otis, J.D. et al. A randomized controlled pilot study of a cognitive-behavioral therapy approach for painful diabetic peripheral neuropathy. *J Pain* **14**, 475-82 (2013).
159. Eccleston, C. Embodied: the psychology of physical sensation (ed. Press, O.U.) (Oxford, 2016).
160. Eccleston C, T.A., Edwards RT, Keogh EM. Psychological approaches to coping with pain in later life. *Clinics in Geriatric Pain Management* (In press).
161. Morley, S., Williams, A. & Eccleston, C. Examining the evidence about psychological treatments for chronic pain: time for a paradigm shift? *Pain* **154**, 1929-31 (2013).
162. Duggan, G.B. et al. Qualitative evaluation of the SMART2 self-management system for people in chronic pain. *Disabil Rehabil Assist Technol* **10**, 53-60 (2015).
163. Meyer-Rosberg, K. et al. Peripheral neuropathic pain--a multidimensional burden for patients. *Eur J Pain* **5**, 379-89 (2001).
164. Gordh, T.E. et al. Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross-over, multi-center study. *Pain* **138**, 255-66 (2008).
165. Ahroni, J.H. & Boyko, E.J. Responsiveness of the SF-36 among veterans with diabetes mellitus. *J Diabetes Complications* **14**, 31-9 (2000).
166. Van Acker, K. et al. Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. *Diabetes Metab* **35**, 206-13 (2009).
167. Torrance, N. et al. Estimating the burden of disease in chronic pain with and without neuropathic characteristics: does the choice between the EQ-5D and SF-6D matter? *Pain* **155**, 1996-2004 (2014).
168. Geelen, C.C., Kindermans, H.P., van den Bergh, J.P. & Verbunt, J.A. Perceived Physical Activity Decline as a Mediator in the Relationship Between Pain Catastrophizing, Disability, and Quality of Life in Patients with Painful Diabetic Neuropathy. *Pain Pract* (2016).
169. Poulin, P.A. et al. The relationship between mindfulness, pain intensity, pain catastrophizing, depression, and quality of life among cancer survivors living with chronic neuropathic pain. *Support Care Cancer* (2016).
170. Backonja, M. et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* **280**, 1831-6 (1998).

171. Rowbotham, M., Harden, N., Stacey, B., Bernstein, P. & Magnus-Miller, L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* **280**, 1837-42 (1998).
172. Ogawa, K., Fujikoshi, S., Montgomery, W. & Alev, L. Correlation between pain response and improvements in patient-reported outcomes and health-related quality of life in duloxetine-treated patients with diabetic peripheral neuropathic pain. *Neuropsychiatr Dis Treat* **11**, 2101-7 (2015).
173. Duarte, R.V., Andronis, L., Lenders, M.W. & de Vos, C.C. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. *Qual Life Res* **25**, 1771-7 (2016).
174. Moore, R.A. et al. Fibromyalgia: Moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. *Pain* **149**, 360-4 (2010).
175. Dworkin, R.H. et al. Assay sensitivity and study features in neuropathic pain trials: an ACTTION meta-analysis. *Neurology* **81**, 67-75 (2013).
176. Dworkin, R.H. et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain* **153**, 1148-58 (2012).
177. Gewandter, J.S. et al. Research designs for proof-of-concept chronic pain clinical trials: IMMPACT recommendations. *Pain* **155**, 1683-95 (2014).
178. Farrar, J.T. et al. Effect of variability in the 7-day baseline pain diary on the assay sensitivity of neuropathic pain randomized clinical trials: an ACTTION study. *Pain* **155**, 1622-31 (2014).
179. Dworkin, R.H., McDermott, M.P., Farrar, J.T., O'Connor, A.B. & Senn, S. Interpreting patient treatment response in analgesic clinical trials: implications for genotyping, phenotyping, and personalized pain treatment. *Pain* **155**, 457-60 (2014).
180. Edwards, R.R. et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. *Pain* (2016).
181. Themistocleous, A.C. et al. The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. *Pain* **157**, 1132-45 (2016).
182. Bennett, D.L. & Woods, C.G. Painful and painless channelopathies. *Lancet Neurol* **13**, 587-99 (2014).
183. Yang, Y. et al. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *J Med Genet* **41**, 171-4 (2004).
184. Fertleman, C.R. et al. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron* **52**, 767-74 (2006).
185. Faber, C.G. et al. Gain of function Nanu1.7 mutations in idiopathic small fiber neuropathy. *Ann Neurol* **71**, 26-39 (2012).
186. Waxman, S.G. et al. Sodium channel genes in pain-related disorders: phenotype-genotype associations and recommendations for clinical use. *Lancet Neurol* **13**, 1152-60 (2014).
187. Cregg, R., Cox, J.J., Bennett, D.L., Wood, J.N. & Werdehausen, R. Mexiletine as a treatment for primary erythromelalgia: normalization of biophysical properties of mutant L858F NaV 1.7 sodium channels. *Br J Pharmacol* **171**, 4455-63 (2014).
188. Carvas, J.M. et al. Period2 gene mutant mice show compromised insulin-mediated endothelial nitric oxide release and altered glucose homeostasis. *Front Physiol* **3**, 337 (2012).
189. Geha, P. et al. Pharmacotherapy for Pain in a Family With Inherited Erythromelalgia Guided by Genomic Analysis and Functional Profiling. *JAMA Neurol* **73**, 659-67 (2016).
190. Cao, L. et al. Pharmacological reversal of a pain phenotype in iPSC-derived sensory neurons and patients with inherited erythromelalgia. *Sci Transl Med* **8**, 335ra56 (2016).