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Neuropathic Pain

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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 accepted¹. 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 studies⁹ conducted by specialized centers with a focus on specific conditions such as post-

herpetic neuralgia^{10, 11}, painful diabetic polyneuropathy¹²⁻¹⁵, post-surgery neuropathic pain¹⁶, multiple sclerosis^{17, 18}, spinal cord injury¹⁹, stroke²⁰ 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 questionnaires²³. 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 pain³. 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 Germany²⁹, 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 results³⁰. 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 assumed³². 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 pregabalin³³. 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 coding³⁶. Hyperexcitability is compounded by a loss of GABA mediated inhibitions at spinal levels³⁷ 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 hypersensitivity³⁸. 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 pain³⁹. 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 hand⁴⁰. 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 nerves⁴¹. 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 lidocaine⁴². 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 pain⁴³. 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 system⁴⁶. 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 increase⁴⁶. CPM has been shown to be less efficient in a variety of pain syndromes compared to healthy controls⁴⁷.

Studies have shown that the pain modulation profile predicts the development and extent of chronic post-operative pain⁴⁸⁻⁵⁰. 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 noradrenaline⁴⁸. 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 patients⁴⁰. 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 Syndrome⁵⁵⁻⁵⁷, idiopathic and neuropathic pain⁵⁸. 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 combinations⁶⁷. Diagnostic sensory bedside examinations should include the following modalities: touch, pinprick, pressure, cold, heat, vibration, temporal summation and after sensations⁶⁸. 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 classes⁶⁹. A standardized protocol for QST was proposed by the nationwide German Network on Neuropathic Pain⁷⁰ 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 A β -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 A δ and C nociceptors in the superficial skin layers ⁷³. LEPs related to A δ -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 A δ -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 A δ 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 attenuated⁸⁴ and subunit adjuvanted⁸⁵ 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 pain⁸⁶ and antiviral or analgesic treatment in patients with herpes zoster to prevent postherpetic neuralgia⁸⁷. Proper management of health conditions, such as diabetes, that cause neuropathic pain, may prevent neuropathic pain before it even presents⁸⁸. 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 pain⁸⁹. 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-analysis¹⁰⁸. Several reasons may account for these results⁹⁰, 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, 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 utility¹¹⁵. 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 pain¹¹⁸. 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 pain¹¹⁷. 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 NP¹²²⁻¹²⁴. 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 symptoms¹²⁵⁻¹²⁷ 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 origin¹⁷. 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 region¹³⁵. 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 pain¹⁴⁴⁻¹⁴⁶. 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 EMCS¹⁴⁶. 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 control¹⁴⁷. 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 risks¹⁴⁸. Contrary to NICE, the EAN guidelines give inconclusive recommendations to DBS¹³⁰.

- 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 effects¹⁵¹.

The only two FDA approved drugs are morphine and ziconitide, an N-type calcium channel antagonist¹⁵². 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 disability¹⁵³. 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 comparisons¹⁵⁴. 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 neuralgia¹⁷⁰, 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 $\geq 50\%$ 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 ratings¹⁷⁸ which suggests that trials might have greater assay sensitivity if highly variable baseline pain ratings were an exclusion criterion¹⁰¹.

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 response¹⁷⁹. 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 phenotype³². 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 interventions¹⁸⁰, 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 ACTION (www.action.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 $\text{Na}_v1.7$ is a critical pain target¹⁸² and therapeutics aimed at targeting $\text{Na}_v1.7$ 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 channels¹⁸⁶ for instance in the context of SFN in which mutations may not be fully penetrant. Finding a mutation in $\text{Na}_v1.7$ 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 Nav1.7 to predict what treatment a specific mutation will respond to¹⁸⁸ and this was recently used to predict efficacy of carbamazepine in IEM associated with the S241T mutation¹⁸⁹. 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-excitabile¹⁹⁰. Treatments such as selective inhibitors of Nav1.7 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.

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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.

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