Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment

Ralf Baron, Andreas Binder, Gunnar Wasner

Neuropathic pain develops as a result of lesions or disease affecting the somatosensory nervous system either in the periphery or centrally. Examples of neuropathic pain include painful polyneuropathy, postherpetic neuralgia, trigeminal neuralgia, and post-stroke pain. Clinically, neuropathic pain is characterised by spontaneous ongoing or shooting pain and evoked amplified pain responses after noxious or non-noxious stimuli. Methods such as questionnaires for screening and assessment focus on the presence and quality of neuropathic pain. Basic research is enabling the identification of different pathophysiological mechanisms, and clinical assessment of symptoms and signs can help to determine which mechanisms are involved in specific neuropathic pain disorders. Management of neuropathic pain requires an interdisciplinary approach, centred around pharmacological treatment. A better understanding of neuropathic pain and, in particular, of the translation of pathophysiological mechanisms into sensory signs will lead to a more effective and specific mechanism-based treatment approach.

Introduction

Management of patients who present with chronic pain is a common problem in medical care. The classification of chronic pain falls into three broad categories: pain owing to tissue disease or damage (nociceptive pain, such as osteoarthritis), pain caused by somatosensory system disease or damage (neuropathic pain), and coexistence of nociceptive and neuropathic pain (mixed pain).[1] Various nerve damaging stimuli in the peripheral or central nervous system can lead to neuropathic pain, yet the clinical manifestation of the pain is similar across the different neuropathic syndromes and causes (panel). Patients typically have paradoxical sensory perceptions with pain as a dominating positive symptom combined with lesion-induced reduced sensations. These perceptions are usually unique and have not been experienced before by patients. This coexistence of signs of hypersensitivity and hyposensitivity is quite common in neurological disorders; for example, when parkinsonian tremor develops after degeneration of the substantia nigra or when spasticity develops after spinal cord injury. However, by contrast with these motor disturbances, pain as a subjective sensory symptom is not visible, is difficult to measure, and involves not only physical aspects, but also psychological and emotional components.

The characteristic sensory abnormalities are crucial findings to correctly diagnose neuropathic pain and to distinguish this from other pain types. The key challenges in development of a targeted holistic approach to neuropathic pain management include appropriate diagnosis of the cause of pain, identification of the type of pain and assessment of the importance of its various components, and determination of appropriate treatment.

Recent research into pathophysiological mechanisms has revealed new treatment targets, new classification schemes have opened up novel options for individualised treatment strategies, and implementation of several international guidelines should help to improve care of patients. In this Review, we provide an update on the recent developments in assessment, diagnostic tools, and treatment and we give a short overview of the current pathophysiological concepts underlying pain symptoms and signs of neuropathic pain.

Diagnosis

Abnormal sensory perception as a diagnostic clue

Recent research into the mechanisms of neuropathic pain has indicated that a nerve lesion leads to dramatic changes in the nervous system, which makes it distinct from other chronic pain types that have an intact nociceptive system (nociceptive pain). Furthermore, distinct therapies are needed for treatment of neuropathic pain that are not effective for nociceptive pain. Therefore, it is important to know the specific medical history of neuropathic pain in the patient and to have valid diagnostic tools that differentiate neuropathic pain from nociceptive pain.[3]

A lesion to a sensory or mixed peripheral nerve with a cutaneous branch, or damage to a central somatosensory pathway, characteristically leads to an area of sensory deficit in the related innervation territory. These negative sensory signs can include a deficit in the perception of mechanical or vibratory stimuli, which indicates damage to large diameter afferent fibres or to the dorsal column tract, and a loss of noxious and thermal percerption, which indicates damage to small diameter afferent fibres or to central pain processing pathways such as the spinothalamic tract. Electrophysiological techniques and nerve biopsy samples can be useful to help assess the attenuation of neuronal function and to document the extent of neuropathy. The important question in the management of patients with chronic pain is, however, whether their pain is caused by the neuronal lesion or whether other pain disorders dominate the clinical picture and coexist with a neuropathy.

To diagnose neuropathic pain and distinguish it from nociceptive pain it is helpful to analyse the exact quality of somatosensory abnormalities. Patients with neuropathic pain almost always have areas of abnormal sensation or hypersensitivity in the affected area, which

Painful peripheral neuropathies

Focal, multifocal

Phantom pain, stump pain, nerve transection pain (partial or complete), neuroma (post-traumatic or postoperative), post-traumatic neuralgia, entrapment syndromes, mastectomy, post-thoracotomy, Morton's neuralgia, painful scars, herpes zoster and postherpetic neuralgia, diabetic mononeuropathy, diabetic amyotrophy, ischaemic neuropathy, borreliosis, connective tissue disease (vasculitis), neuralgic amyotrophy, peripheral nerve tumours, radiation plexopathy, plexus neuritis (idiopathic or hereditary), trigeminal or glossopharyngeal neuralgia, vascular compression syndromes

Generalised (polyneuropathies)

Metabolic or nutritional

Diabetes (often "burning feet syndrome"), alcoholism, amyloidosis, hypothyroidism, beri beri, pellagra

Drug-related

Antiretrovirals, cisplatin, oxaliplatin, disulfiram, ethambutol, isoniazid, nitrofurantoin, thalidomide, methylthiouracil, vincristine, chloramphenicol, metronidazole, taxoids, gold

Toxin-related

Acrylamide, arsenic, clioquinol, dinitrophenol, ethylene oxide, pentachlorophenol, thallium

Hereditary

Amyloid neuropathy, Fabry's disease, Charcot-Marie-Tooth disease type 5, type 2B, hereditary sensory and autonomic neuropathy type 1, type 1B

Malignant

Carcinoma-associated paraneoplastic peripheral neuropathy, myeloma

Infective or post-infective, immune

Acute or inflammatory polyradiculoneuropathy (Guillain-Barré syndrome), borreliosis, HIV

Other polyneuropathies

Erythromelalgia, idiopathic small-fibre neuropathy, trench foot (cold injury)

Central pain syndromes

- Vascular lesions in the brain (particularly the brainstem and thalamus) and spinal cord, including infarct, haemorrhage, vascular malformation
- Multiple sclerosis
- Traumatic spinal cord injury including iatrogenic cordotomy
- Traumatic brain injury
- Syringomyelia and syringobulbia
- Tumours
- Abscesses
- Inflammatory diseases other than multiple sclerosis; myelitis caused by viruses, syphilis
- Epilepsy*
- Parkinson's disease†

Complex painful neuropathic disorders

Complex regional pain syndromes type I and II (reflex sympathetic dystrophy, causalgia)

Mixed pain syndromes

Chronic low back pain with radiculopathy, cancer pain with malignant plexus invasion, complex regional pain syndromes

*In some epilepsies, these features can be the clinical symptom of a seizure when the epileptic focus is located within a pain processing cortical area. †About 5–10% of patients with Parkinson's disease report chronic pain that can be clinically related to abnormalities in pain processing brain areas. Reproduced from Baron,[2] with permission from Elsevier.

can be adjacent to or combined with skin areas of sensory deficit (table 1). These positive symptoms are paraesthesias (ie, skin crawling sensation or tingling), spontaneous (not stimulus-induced) ongoing pain, and shooting, electric shock-like sensations. Many patients with neuropathic pain also have evoked pain (ie, stimulus-induced pain and hypersensitivity). Patients usually report mechanical and thermal hypersensitivity. Two types of hypersensitivity can be distinguished. First, allodynia is defined as pain in response to a non-nociceptive stimulus. In cases of mechanical allodynia, even gentle mechanical stimuli such as a slight bending of hairs can evoke severe pain. Second, hyperalgesia is defined as an increased pain sensitivity to a nociceptive stimulus. Another evoked feature is summation, which is the progressive worsening of pain evoked by slow repetitive stimulation with mildly noxious stimuli, for example, pin pricks. In terms of clinical practice and research, the term allodynia is mainly reserved for pain induced by light moving stimuli (mechanical dynamic allodynia), whereas the term hyperalgesia is used for other forms of mechanically induced pain (table 1). For thermally evoked pain, the terms cold hyperalgesia and heat hyperalgesia have been widely accepted instead of allodynia. Investigation of evoked pain in a group of 1236 patients with neuropathic pain indicated that 49% of patients with postherpetic neuralgia and 20% of all patients had mechanical dynamic allodynia.[4] Cold hyperalgesia was detected in 21% of patients with postherpetic neuralgia and heat hyperalgesia was found in about 25% of patients with a post-traumatic nerve lesion. Pin-prick hyperalgesia was found in 29% of all patients.[4] Cold hyperalgesia was reported in about 20% of patients with central pain after a thalamic lesion.[5] By contrast, for painful polyneuropathy, mechanical hyper-algesia was reported in only 8·5% of patients, mechanical allodynia in 12%, and thermal hyperalgesia in 1·5–7%.[4]

The quality of the reported sensation might also be informative; neuropathic pain commonly has a burning and/or shooting quality with unusual tingling, crawling, or electrical sensations (dysaesthesias). Although all these characteristics are neither universally present in, nor absolutely diagnostic of, neuropathic pain, when they are present the diagnosis of neuropathic pain is likely. Thus, taking the patient's history and undertaking a clinical examination are necessary steps to confirm the presence of neuropathic pain.[3]

Screening tools

Pain is essentially a subjective experience described with patient-specific symptoms. Consequently, standardised screening tools, such as the neuropathic pain question-naire, PainDetect, ID-Pain, and DN4, have been developed to classify neuropathic pain on the basis of patient-reported verbal descriptors of pain qualities. Most of these questionnaires comprise questions about burning

	Definition	Bedside assessment	Expected pathological response
Negative symptoms and signs			
Hypoaesthesia	Reduced sensation to non-painful stimuli	Touch skin with painter's brush, cotton swab, or gauze	Reduced perception, numbness
Pall-hypoaesthesia	Reduced sensation to vibration	Apply tuning fork on bone or joint	Reduced perception threshold
Hypoalgesia	Reduced sensation to painful stimuli	Prick skin with single pin stimulus	Reduced perception, numbness
Thermal hypoaesthesia	Reduced sensation to cold or warm stimuli	Contact skin with objects of 10°C (metal roller, glass with water, coolants such as acetone); contact skin with objects of 45°C (metal roller, glass with water)	Reduced perception
Spontaneous sensations or pain			
Paraesthesia	Non-painful ongoing sensation (skin crawling sensation)	Grade intensity (0–10); area in cm²	..
Paroxysmal pain	Shooting electrical attacks for seconds	Number per time; grade intensity (0–10); threshold for evocation	..
Superficial pain	Painful ongoing sensation, often a burning sensation	Grade intensity (0–10); area in cm²	..
Evoked pain			
Mechanical dynamic allodynia	Pain from normally non-painful light moving stimuli on skin	Stroke skin with painter's brush, cotton swab, or gauze	Sharp burning superficial pain; present in the primary affected zone but spreads beyond into unaffected skin areas (secondary zone)
Mechanical static hyperalgesia	Pain from normally non-painful gentle static pressure stimuli on skin	Apply manual gentle mechanical pressure to skin	Dull pain; present in the area of affected (damaged or sensitised) primary afferent nerve endings (primary zone)
Mechanical punctate, pin-prick hyperalgesia	Pain from normally stinging but non-painful stimuli	Prick skin with a safety pin, sharp stick, or stiff von Frey hair	Sharp superficial pain; present in the primary affected zone but spreads beyond into unaffected skin areas (secondary zone)
Temporal summation	Increasing pain sensation (wind-up-like pain) from repetitive application of identical single noxious stimuli	Prick skin with safety pin at intervals of <3 s for 30 s	Sharp superficial pain of increasing intensity
Cold hyperalgesia	Pain from normally non-painful cold stimuli	Contact skin with objects of 20°C (metal roller, glass with water, coolants such as acetone); control: contact skin with objects of skin temperature	Painful, often burning, temperature sensation; present in the area of affected (damaged or sensitised) primary afferent nerve endings (primary zone)
Heat hyperalgesia	Pain from normally non-painful heat stimuli	Contact skin with objects of 40°C (metal roller, glass with water); control: contact skin with objects of skin temperature	Painful burning temperature sensation; present in the area of affected (damaged or sensitised) primary afferent nerve endings (primary zone)
Mechanical deep somatic hyperalgesia	Pain from normally non-painful pressure on deep somatic tissues	Apply manual light pressure at joints or muscles	Deep pain at joints or muscles

..=not applicable. Reproduced from Baron,[1] with permission from Nature Publishing Group.

Table 1: Definition and assessment of negative and positive sensory symptoms and signs in patients with neuropathic pain

pain, paraesthesias, pain attacks, mechanical and thermal hypersensitivity, and numbness.[3,6] The clinical strength of the screening tools is that they can be used to identify potential patients with neuropathic pain, particularly by non-specialists. Their ease of use for both clinicians and patients makes these screening tools attractive because they provide immediate information. If patients with neuropathic pain are identified, clinicians should then be alerted to undertake further assessment, which might subsequently affect treatment decisions. However, these screening tools do not identify about 10–20% of patients with clinician-diagnosed neuropathic pain.[3] In summary, there is good evidence that screening tools can offer guidance for further diagnostic evaluation, although they should not replace clinical judgment.[3]

Bedside assessment and assessment of sensory signs

A standardised bedside examination of patients with neuropathic pain should include the following components: touch, pin prick, pressure, cold, heat, vibration, and temporal summation.[3,7,8] The responses should be graded as normal, decreased, or increased. The stimulus-evoked (positive) pain types are classified as hyperalgesic or allodynic and categorised in accordance with the dynamic or static character of the stimulus.[9] Touch can be assessed by gently applying cotton wool to the skin, pin-prick sensation by the response to sharp pin-prick stimuli, deep pain by gentle pressure on muscle and joints, and cold and heat sensation by measuring the response to a thermal stimulus (eg, metal objects kept at 20°C or 40°C). Vibration can be assessed by determining

response to a tuning fork. Abnormal temporal summation is the clinical equivalent of increasing neuronal activity after repetitive noxious C-fibre stimulation of more than 0·3 Hz. This wind-up-like pain can be produced by mechanical and thermal stimuli. When present, allodynia or hyperalgesia can be quantified by measuring the intensity and area affected. It is generally agreed that assessment should be carried out in the area of maximum pain with the contralateral area as a control if possible. In neuropathic disorders, the distinction between primary and secondary areas corresponds to the tissue supplied by damaged nerves and the area outside this innervation territory, respectively. Mechanical hypersensitivity often expands into the secondary area. A summary of clinical symptoms and signs is given in table 1.

Additionally, assessment tools such as the McGill pain questionnaire are useful to discriminate different pain dimensions that might be associated with different underlying mechanisms, although further studies are needed to confirm their relation.[3] Moreover, there is strong evidence to suggest that the neuropathic pain scale and the neuropathic pain symptom inventory can be recommended to assess efficacy of treatment for symptoms and might be used in the future to predict treatment response.[3]

Pathophysiology

Most of our understanding of pain mechanisms derives from basic research, including in-vivo and in-vitro cellular and molecular studies. Although this research has led to an enormous increase in our knowledge, these data need to be interpreted with care because of the limitations associated with preclinical studies. For example, there are difficulties in translation from animal behaviour to human pain sensation and there are few long-term data that correlate with the chronic time scale of human pain to distinguish between acute injury-related adaptive changes and pathological dysfunction leading to chronic pain states. Nevertheless, pain research in human beings has progressed immensely over the past decade, and results from quantitative sensory testing, questionnaires, skin punch biopsies, functional imaging, and experimental human pain models have provided us with further insights into human pain pathology. Exchange of information between basic and clinical research is essential to determine the clinically important pain pathology.[10]

So far, both basic and human research indicates that a lesion of afferent pathways is necessary for development of neuropathic pain.[1] Furthermore, data clearly indicate that not one but several mechanisms can lead to neuropathic pain. Importantly, many of these mechanisms do not depend on the cause of the disease: the same mechanism can be found in different diseases (eg, in postherpetic neuralgia and in painful poly-neuropathy). In one individual patient, different mechanisms might be involved and different mech-anisms could lead to the same symptom. This not only

indicates the complexity of neuropathic pain, but also highlights the clinical importance of identifying underlying pain mechanisms in individual patients. Because different treatment regimens are needed for different pain mechanisms, a mechanism-based treat-ment approach can lead to efficient analgesia. One way to progress at this point in research and in the clinic is to hypothesise that pain mechanisms can be identified by analysing patients' individual symptoms and signs with the above-mentioned methods. By analysing the effect of treatment that targets these suggested pain mechanisms, the concept of mechanism-based treat-ment can be verified (see section below on specific sensory profiles).[11–15] Such an approach will enable design of large controlled trials that are more focused on treating mechanism-related symptoms and signs instead of aetiology-based studies.[16,17] At present, the available data can help to understand the associations between at least some clinical symptoms and suggested underlying mechanisms.

Ectopic nerve activity

Sensing ongoing spontaneous pain and paroxysmal shooting pain in the absence of any external stimulus is caused by ectopic impulse generation within the nociceptive pathways. Such spontaneous ectopic activity has been recorded by miconeurography in afferent fibres from a neuroma in patients with stump and phantom pain, as well as in patients with painful diabetic neuropathy.[18–20] Under physiological conditions, activation of unmyelinated (C-fibre) and thinly myelinated (Aδ-fibre) nociceptive afferent fibres indicates potential tissue damage, which is reflected in the high thresholds of nociceptors for mechanical, thermal, and chemical stimuli. These conditions change dramatically in neuropathic pain states. After a peripheral nerve lesion, spontaneous activity is evident in both injured and neighbouring uninjured nociceptive afferents.[21–23] Increasing levels of mRNA for voltage-gated sodium channels seem to correlate with ectopic activity, and increased expression of sodium channels in lesioned and intact fibres might lower action potential threshold until ectopic activity takes place.[24–26] Similar changes within second-order nociceptive neurons are thought to occur after central lesions, leading to central neuropathic pain.[27]

Further evidence for the crucial role of voltage-gated sodium channels in chronic pain states comes from patients with erythromelalgia and paroxysmal extreme pain disorder who have severe ongoing pain at different sites of the body. These hereditary disorders are caused by gain-of-function mutations in the *SCN9A* gene that encodes the Nav1.7 voltage-gated sodium channel.[28] Microneurographic recordings have indicated ongoing ectopic activity of nociceptive afferents in these patients after increased membrane excitability: this activity is not associated with any direct nerve lesion but is caused by underlying pain channelopathies.[20,29]

In addition to voltage-gated sodium channels, several other ion channels probably undergo alterations after a nerve lesion, such as voltage-gated potassium channels,[30] which might also contribute to changes in membrane excitability of nociceptive nerves.

Nerve injury also induces upregulation of various receptor proteins such as the transient receptor potential V1 (TRPV1). TRPV1 is located on subtypes of peripheral nocicevipe endings and is physiologically activated by noxious heat at about 41°C.[31] After a nerve lesion, TRPV1 is downregulated on injured nerve fibres but upregulated on uninjured C-fibres.[32] This novel expression of TRPV1 and additional sensitisation to heat by intracellular signal transduction[33] might lead to spontaneous nerve activity induced by normal body temperature, if the threshold of TRPV1 is reduced to below 38°C.[34] Clinically, patients with such underlying pain mechanisms can also be characterised by the presence of heat hyperalgesia in addition to ongoing burning pain. Similarly, ongoing ectopic discharges of nociceptive afferent fibres have been recently identified in a patient with painful neuropathy in combination with cold allodynia.[35] Abnormal responses to cold and topical application of menthol indicated that a nerve lesion triggered abnormal function or expression of TRPM8, a cold-sensitive receptor of the TRP family.[35,36]

According to data from basic research, from human experimental pain models, and from patients, it can be concluded that the mechanisms listed above not only contribute to ectopic activity, but also to primary allodynia and primary hyperalgesia (ie, mechanically or thermally evoked pain within the innervation areas of the ectopic nerves[8,35,36]).

Central sensitisation

Secondary allodynia and hyperalgesia (ie, evoked pain, in particular dynamic mechanical allodynia) in the area adjacent to the innervation territory of the lesioned nerves requires involvement of the CNS. Central sensitisation might develop as a consequence of ectopic activity in primary nociceptive afferent fibres and structural damage within the CNS itself might not be necessarily involved. Ongoing discharges of peripheral afferent fibres that release excitatory aminoacids and neuropeptides within the dorsal horn of the spinal cord lead to postsynaptic changes of second-order nociceptive neurons, such as phosphorylation of NMDA and AMPA receptors[37] or expression of voltage-gated sodium channels.[38] These changes induce neuronal hyper-excitability that enables low-threshold mechanosensitive Aβ and Aδ afferent fibres to activate second-order nociceptive neurons. This means that normally innocuous tactile stimuli such as light brushing or pricking the skin become painful. Similar mechanisms might take place not only within the spinal cord, but also at supraspinal levels, as has been reported in patients with central pain.[39–41]

Mechanisms contributing to ectopic nerve activity and central sensitisation

Further pathophysiological mechanisms involved in neuropathic pain contribute to ectopic activity and central sensitisation. Inflammation after a nerve lesion induces activation and migration of macrophages into the nerve and dorsal root ganglion, which contribute to pain hypersensitivity by releasing proinflammatory cytokines, including tumour necrosis factor α.[42] After peripheral and central nerve lesions, activated microglia within the CNS release several immune modulators that also maintain neuropathic pain.[43,44] These inflammatory processes, as well as other changes within the milieu of the peripheral nerve endings, contribute to peripheral sensitisation (ie, decreased activation thresholds and increased membrane excitability).[8] Similar to central sensitisation, peripheral sensitisation can also occur in intact nociceptors without any underlying nerve damage; however, in combination with lesion-related pathological receptor expression, ectopic activation can be facilitated and maintained.

After a peripheral nerve lesion, there is a loss of inhibitory GABAergic interneurons in the spinal horn.[45] Prevention of cell death of interneurons attenuates mechanical and thermal hyperalgesia, indicating that disinhibition contributes to neuropathic pain.[46] Further potent inhibitory neurons, such as descending pathways originating in the brainstem, contribute to modulation of pain processing. Lesions that affect these opiodergic and monoaminergic systems also lead to pain exacerbation via disinhibition. Another suggested form of disinhibition is the underlying mechanism of cold hyperalgesia, which is present in 23% of patients with central post-stroke pain after lesions of innocuous cold conducting fibre afferents. According to the thermosensory disinhibition theory of Craig,[5,47] these afferents normally inhibit cold-activated pain pathways.

In some cases of amputations, postherpetic neuralgia, complex regional pain syndromes, and post-traumatic neuralgias, topical administration of norepinephrine and enhancement of physiological sympathetic activity increased spontaneous pain and dynamic mechanical hyperalgesia.[48–51] This finding indicates a pathological adrenergic coupling between sympathetic postganglionic fibres and nociceptive afferent fibres, which might result from expression of α-receptors on cutaneous afferent fibres or from sprouting of sympathetic fibres within the dorsal root ganglion.[52] Consequently, this symptom of sympathetically maintained pain can be treated by use of sympathetic blocks.[53] Pathophysiological mechanisms of neuropathic pain are summarised in figure 1.

Specific sensory profiles

Although all neuropathic pain disorders involve neuronal damage, the pattern of sensory abnormalities in the affected skin can vary between the different disorders or even within individual patients. Some

patients have spontaneous pain, paraesthesias, and electric shocks, whereas in other patients, the affected body area is hypersensitive to temperature or touch.[1] The individual pattern of sensory symptoms most likely closely reflects the underlying pain-generating mechanisms and might also determine the reason for differential and individual treatment responses (see above). Therefore, a new classification strategy was proposed by which pain is analysed on the basis of the sensory phenotype rather than the underlying cause. Several approaches were used to identify phenotypic subgroups of patients with distinct sensory profiles.[54] A standardised psychophysical technique to test both the nociceptive and non-nociceptive afferent systems (quantitative sensory testing) was recently proposed by the German Network on Neuropathic Pain (DFNS).[55] This protocol uses 13 different mechanical and thermal stimuli (graded von Frey hairs, several pin-prick stimuli, pressure algometers, and quantitative thermotesting). The DFNS nationwide multicentre trial comprised complete sensory profiles of more than 1200 patients with different types of neuropathic pain.[4] The combination of different signs was suggested to indicate different underlying pathophysiological mechanisms. For example, heat hyperalgesia in combination with mechanical allodynia and mechanical hyperalgesia could indicate peripheral ectopic activity within heat-sensitive nociceptors, triggering central sensitisation; by contrast, peripheral mechanisms maintaining neuropathic pain in patients with complete sensory deficits is unlikely.

In another study of patient-reported outcomes, health-related data were collected directly from the patients to determine whether subtle differences in individual sensory characteristics could be identified. Patients with postherpetic neuralgia and painful diabetic neuropathy completed a neuropathic pain symptom questionnaire.[56] To identify relevant subgroups of patients who were characterised by a specific symptom profile, a hierarchical cluster analysis was done in this cohort. The clusters were determined by the patterns of questionnaire scores, showing the typical pathological structure of the respective group. By using this approach,
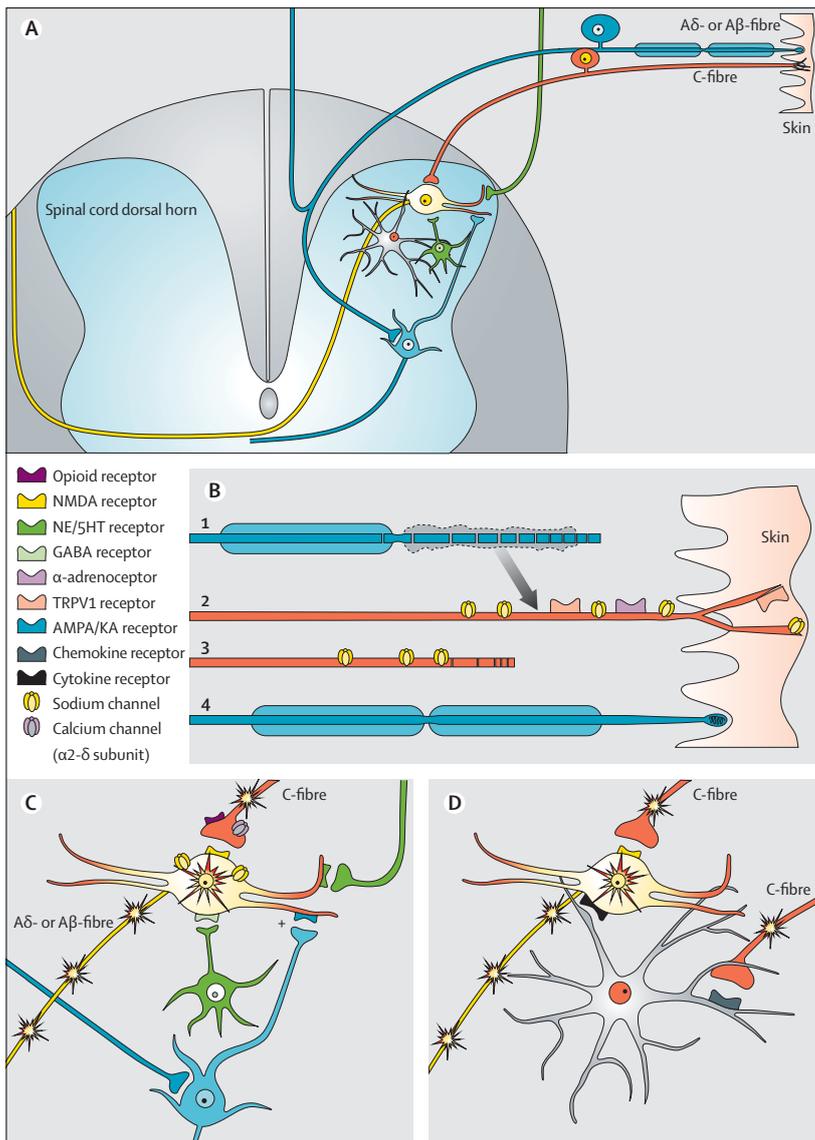
Figure 1: **Pathophysiological mechanisms of neuropathic pain**
(A) Primary afferent pathways and their connections in the spinal cord dorsal horn. Note that nociceptive C-fibres (red) terminate at spinothalamic projection neurons in upper laminae (yellow neuron). Non-nociceptive myelinated A-fibres project to deeper laminae. The second-order projection neuron is a WDR type—it receives direct synaptic input from nociceptive terminals and also multisynaptic input from myelinated A-fibres (non-noxions information, blue neuron system). Interaction with microglia (grey cell) facilitates synaptic transmission. GABAergic interneurons (green neuron) normally exert inhibitory synaptic input on the WDR neuron. Furthermore, descending modulatory systems synapse at the WDR neuron (only the inhibitory projection, green descending terminal). (B) Peripheral changes at primary afferent neurons after a partial nerve lesion, leading to peripheral sensitisation. Note that some axons are damaged and degenerate (axons 1 and 3) and some are still intact and connected to the peripheral end organ (skin; axons 2 and 4). Expression of sodium channels is increased on damaged neurons (axon 3), triggered as a consequence of the lesion. Furthermore, products such as nerve growth factor, associated with Wallerian degeneration and released in the vicinity of spared fibres (arrow), trigger expression of channels and receptors (eg, sodium channels, TRPV1 receptors, adrenoreceptors) on uninjured fibres. (C) Spontaneous activity in C-nociceptors induces secondary changes in central sensory processing, leading to spinal cord hyperexcitability (central sensitisation of second-order nociceptive neurons, star in yellow neuron) that causes input from mechanoreceptive A-fibres (blue neuron system, light touching and punctate stimuli) to be perceived as pain (dynamic and punctate mechanical allodynia, + indicates gating at synapse). Several presynaptic (opioid receptors, calcium channels) and postsynaptic molecular structures (glutamate receptors, AMPA/kainate receptors, sodium/5HT receptors, GABA receptors, sodium channels) are involved in central sensitisation. Inhibitory interneurons and descending modulatory control systems (green neurons) are dysfunctional after nerve lesions, leading to disinhibition or facilitation of spinal cord dorsal horn neurons and to further central sensitisation. (D) Peripheral nerve injury activates spinal cord glial cells (grey cell) via chemokines, such as CCL2 acting on chemokine receptors. Activated microglia further enhance excitability in WDR neurons by releasing cytokines and growth factors (eg, tumour necrosis fator α, bone-derived nerve factor) and increasing glutamate concentrations. Adapted from Baron,[1] with permission from Nature Publishing Group. WDR=wide dynamic range. TRPV1=transient receptor potential V1. CCL2=chemokine (C-C motif) ligand 2. NE=norepinephrine. KA=kainate.

five distinct clusters (subgroups) of patients were identified that show a characteristic sensory profile (ie, a typical constellation and combination of neuropathic symptoms; figure 2). The sensory profiles show remarkable differences in the expression of the symptoms. All subgroups occur in both disease types but with different frequencies.

In one study, a combination of neuropathic symptoms and signs was assessed by use of a structured interview and a standardised bedside examination in patients with painful diabetic neuropathy, postherpetic neuralgia, and radicular back pain, as well as in a group of patients with non-neuropathic pain.[11] Six subgroups of patients with neuropathic pain and two subgroups of patients with non-neuropathic pain were distinguished with this approach. The physical examination was more important for the distinction of pain subtypes than were the symptoms assessed during the interview.

All these different techniques to identify subgroups of patients show that there are phenotypic differences based on certain constellations of sensory abnormalities across the different aetiologies and neuropathic pain syndromes
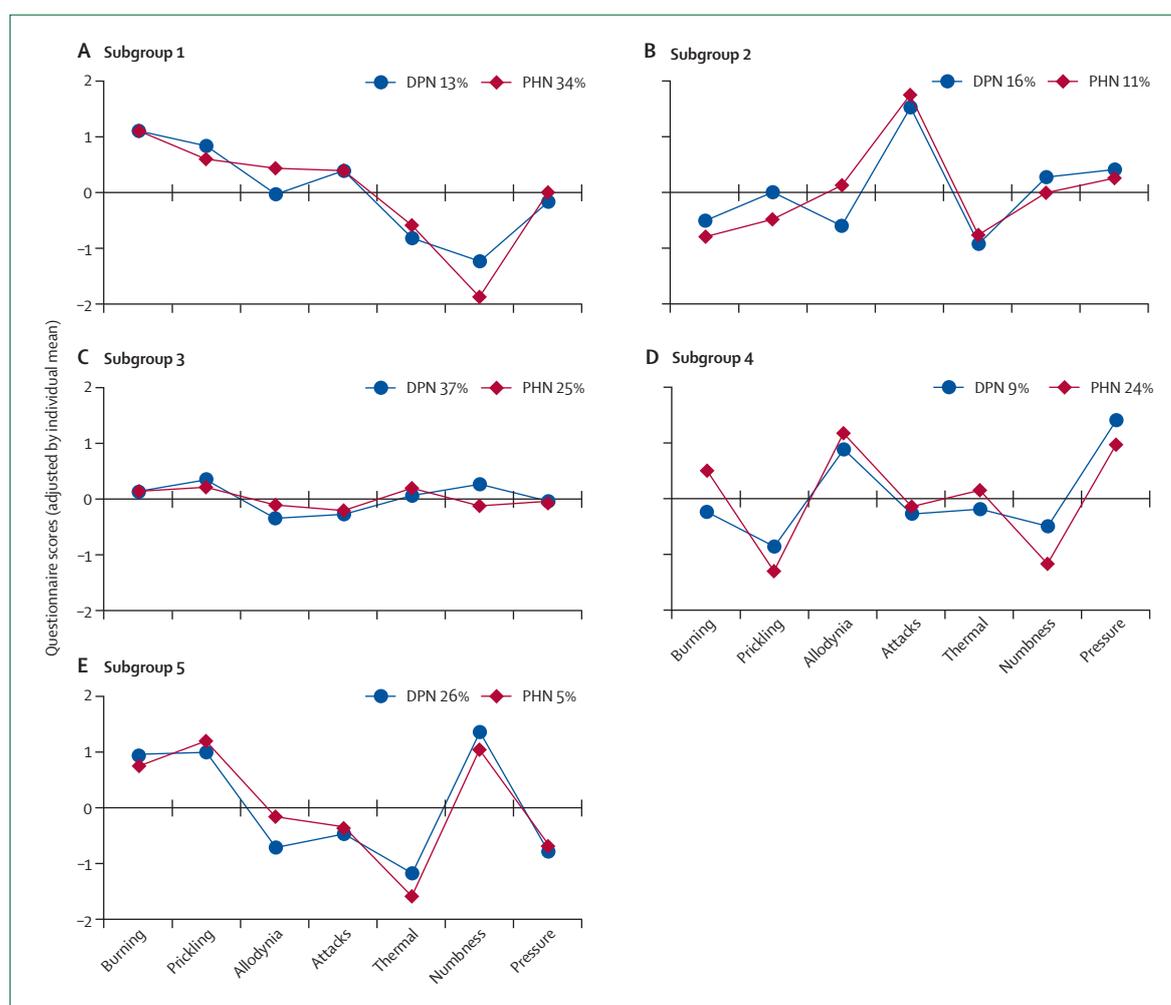
Figure 2: **Subgrouping of patients with neuropathic pain according to sensory profiles from patient-reported outcomes**
Responses to seven questions (from the PainDetect questionnaire) about the severity and quality of patients' pain were analysed in a cohort of 2100 patients with DPN and PHN. The patients could rate the perceived severity of each of these symptoms from 0–5 (never, hardly noticed, slightly, moderately, strongly, very strongly). The questions incorporated the following sensations: spontaneous burning pain, spontaneous prickling sensations, pain evoked by light touch (allodynia), spontaneous pain attacks, pain evoked by thermal stimuli, numbness, and pressure-induced pain. To identify relevant subgroups of patients who were characterised by a particular symptom constellation, a hierarchical cluster analysis was done. The clusters are shown by the patterns of questionnaire scores (adjusted individual mean, see below), thus showing the typical pathological structure of the group. By using this approach, five clusters (subgroups) with distinct symptom profiles were identified. Sensory profiles show remarkable differences in the expression of the symptoms.[56] The adjusted individual mean was determined as follows: to eliminate inter-individual differences of the general perception of sensory stimuli (differences in individual pain perception thresholds), a score was calculated whereby the given 0–5 score for each question was subtracted by the mean of all values marked in the seven questions. In this individual score, values above 0 indicate a sensation that is more intense than the individual mean pain perception, and values below 0 indicate a sensation that is less intense than the individual mean pain perception. %=frequency of occurrence. DPN=diabetic painful neuropathy. PHN=postherpetic neuralgia. Reproduced from Baron et al,[56] with permission from the International Association for the Study of Pain.

	Possible diagnosis
Cold hyperalgesia	Traumatic nerve injury Trench foot syndrome Complex regional pain syndrome Oxaliplatin-induced polyneuropathy Central post-stroke pain
Deep somatic hyperalgesia	Complex regional pain syndrome
Sympathetically maintained pain	Complex regional pain syndrome, acute herpes zoster
Isolated small fibre neuropathy	Diabetic polyneuropathy Amyloid polyneuropathy Fabry's disease Hereditary polyneuropathy Idiopathic small fibre polyneuropathy
Painful polyneuropathy in several family members	Amyloid polyneuropathy Fabry's disease Charcot-Marie-Tooth disease type 5, type 2B Hereditary sensory, autonomic polyneuropathy type 1, type 1B

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Table 2: Clinical features that are relevant for specific diagnoses of neuropathic pain

(table 2). This knowledge is important for the design of future clinical trials and the optimum selection of the patients to be studied.

Treatment

Treatment of neuropathic pain is still a challenge because many patients do not experience sufficient pain relief, as determined from clinical experience and from clinical trial outcomes. This difficulty in treatment might be a result of the heterogeneity of neuropathic pain mechanisms and the frequently coexisting psychological and emotional aspects of chronic pain. As a first step, a thorough diagnosis might unravel the cause of pain; for example, in patients with diabetes or local nerve compression that needs to be treated accordingly to prevent further nerve damage, treatment of the underlying cause might result in partial or full pain relief. When starting symptomatic treatment, education of patients, including information on neuropathic pain, the treatment plan, and possible side-effects of drugs, is important to increase patient compliance. To avoid unrealistic expectations from patients on efficacy and tolerability, realistic treatment goals should be determined. Pain reduction of at least 30% is generally accepted to be a clinically meaningful result.[57] In addition to pain, both sleep disturbance and health-related quality of life, including social and emotional functioning, should be assessed when analysing analgesic efficacy. Additionally, coexisting depression and anxiety might hinder pain treatment and should be identified and targeted for specific treatment. In clinical practice, this complexity is taken into account by an interdisciplinary therapeutic approach, including pharmacological and non-pharmacological treatment regimens, such as cognitive behavioural, physical, and occupational therapy. Although the efficacy of such a multidisciplinary biopsychosocial concept has been typically reported in chronic pain states other than neuropathic pain, its benefit

in this group of patients is well accepted. In patients who have complex regional pain syndromes and phantom limb pain, cognitive behavioural therapy and occupational therapy, as well as new methods such as graded motor imagery (including mirror therapy), have been shown to reduce pain.[58–60]

In this section, we focus on pharmacological treatment of peripheral neuropathic pain except for trigeminal neuralgia, for which there are different treatment recommendations.[61–63] Interventional and invasive treatment will be discussed briefly because these approaches are often used only in selected cases. Several meta-analyses have summarised the available evidence for treatment of neuropathic pain and guidelines for a structured treatment approach have been published.[61,64–69] The optimum individual regimen should balance analgesia with harm in terms of side-effects, comorbidities, and drug interactions (tables 3 and 4). Apart from the vaccination against varicella zoster virus, which has been efficacious in preventing postherpetic neuralgia, there are no other proven medical strategies for the prevention of neuropathic pain.[70]

Pharmacological treatment of peripheral neuropathic pain

So far, no clear predictors of treatment response have been identified in patients with neuropathic pain. Furthermore, the suggested underlying pain mechanisms do not necessarily correspond to the suggested drug actions, probably because we are yet to fully understand these mechanisms and actions. Thus, the general therapeutic approach is still a stepwise process to identify which drugs or drug combinations provide the greatest pain relief with fewest side-effects, particularly as neuropathic pain typically affects elderly patients with several morbidities (see below).[65]

Various types of drugs, including antidepressants with norepinephrine and serotonin reuptake inhibition, calcium channel α2-δ ligands, opioid analgesics, and topical lidocaine, have been shown to have consistent efficacy in randomised controlled clinical trials and meta-analyses.[61,64–69] The modes of action and information on dosing, precautions, side-effects of the different drug classes, and evidence levels are summarised in table 3. Table 4 gives an overview of the disorders for which the different drugs have been investigated. Long-acting compounds should be used when possible.

Antidepressants with both norepinephrine and serotonin reuptake inhibition

Tricyclic antidepressants have several modes of action other than the monoamine reuptake inhibition in descending inhibitory systems. Although their analgesic effect is independent of an antidepressant effect, this effect could be beneficial because depression is a frequent comorbidity in chronic neuropathic pain. Tricyclic antidepressants have several side-effects and

reasons for precautions, which are mostly due to their anticholinergic properties. Thus, an electrocardiogram (ECG) before the start of treatment is mandatory and careful dose titration is needed. The selective norepinephrine and serotonin reuptake inhibitors duloxetine and venlafaxine are efficacious in painful polyneuropathies.[67–69] Neither drug has been studied in other neuropathic pain syndromes.

Calcium channel α2-δ ligands

Gabapentin and pregabalin bind to calcium channels on central terminals of primary afferent nociceptors, leading to decreased release of neurotransmitters. Both drugs have been widely studied in peripheral pain syndromes, although pregabalin has been the focus of most studies in central neuropathic pain syndromes.[67–69] Only a few drug interactions have been reported for

	Mode of action	Major side-effects	Precautions	Other benefits	Efficacy: level A/B rating	Starting dose/ maximum dose	Titration	Duration of adequate trial
Tricyclic antidepressants*								
Nortriptyline Desipramine	Inhibition of reuptake of serotonin and/or norepinephrine, block of sodium channels, anticholinergic	Sedation, anticholinergic effects (eg, dry mouth or urinary retention, weight gain	Cardiac disease (ECG), glaucoma, seizure disorder, use of tramadol	Improvement of depression and sleep disturbance	A: diabetic neuropathy, PHN B: SCI/CPSP, chronic radiculopathy	25 mg at bedtime/150 mg daily	Increase by 25 mg every 3–7 days as tolerated	6–8 weeks (at least 2 weeks maximum tolerated dose)
SSNRIs								
Duloxetine	Inhibition of both serotonin and norepinephrine reuptake	Nausea	Hepatic dysfunction, renal insufficiency, alcohol abuse, use of tramadol	Improvement of depression	A: diabetic neuropathy	30 mg once daily/ 60 mg twice daily	Increase by 60 mg once daily after 1 week as tolerated	4 weeks
Venlafaxine	Inhibition of both serotonin and norepinephrine reuptake	Nausea	Cardiac disease, use of tramadol, withdrawal syndrome with abrupt discontinuation	Improvement of depression	A: diabetic neuropathy	37·5 mg once or twice daily/225 mg daily	Increase by 37·5–75 mg each week as tolerated	4–6 weeks
Calcium channel α2-δ ligands								
Gabapentin	Decreases release of glutamate, norepinephrine, and substance P, with ligands on α2-δ subunit of voltage-gated calcium channel	Sedation, dizziness, peripheral oedema	Renal insufficiency	No clinically significant drug interactions	A: diabetic neuropathy, PHN, cancer-associated neuropathic pain	100–300 mg once to three times daily/1200 mg three times daily, reduce if impaired renal function	Increase by 100–300 mg three times daily every 1–7 days as tolerated	4 weeks
Pregabalin	Decreases release of glutamate, norepinephrine, and substance P, with ligands on α2-δ subunit of voltage-gated calcium channel	Sedation, dizziness, peripheral oedema	Renal insufficiency	No clinically significant drug interactions, improvement of sleep disturbance and anxiety	A: diabetic neuropathy, PHN, SCI	50 mg three times daily or 75 mg twice daily/200 mg three times or 300 mg twice daily, reduce if impaired renal function	Increase to 300 mg daily after 3–7 days, then by 150 mg daily every 3–7 days as tolerated	4 weeks
Topical lidocaine								
5% lidocaine patch	Block of sodium channels	Local erythema, rash	None	No systemic side-effects	A: PHN	1–3 patches/3 patches	None	2 weeks
Opioid agonists*								
Morphine, oxycodone, methadone, levorphanol	μ-receptor agonism (oxycodone also causes κ-receptor antagonism)	Nausea/ vomiting, constipation, dizziness	History of substance abuse, suicide risk, driving impairment	Rapid onset of analgesic effect	A: diabetic neuropathy, PHN, phantom pain, pain from several causes B: chronic radiculopathy	10–15 mg morphine every 4 h or as needed (equianalgesic doses should be used for other opioids)/no maximum doses	After 1–2 weeks convert to long-acting opioids/ transdermal applications, use short-acting drug as needed and as tolerated	4–6 weeks
Tramadol	μ-receptor agonism, inhibition of norepinephrine and serotonin reuptake	Nausea/ vomiting, constipation, dizziness	History of substance abuse, suicide risk, driving impairment, concomitant use of SSNRI, tricyclic antidepressant (serotonin syndrome)	Rapid onset of analgesic effect	A: Diabetic neuropathy, phantom pain B: SCI, cancer-associated neuropathic pain	50 mg once or twice daily/400 mg daily as long-acting drug	Increase by 50–100 mg every 3–7 days	4 weeks

Recommendations summarised and adapted from Dworkin and colleagues[68] and Attal and colleagues.[69] CPSP=central post-stroke pain. ECG=electrocardiogram. PHN=postherpetic neuralgia. SCI=central pain after spinal cord injury. SSNRI=selective serotonin and norepinephrine reuptake inhibitors. Recommendation grading level A=good scientific evidence suggests that the benefits of the treatment substantially outweigh the potential risks. Clinicians should discuss the treatment with eligible patients. Recommendation grading level B=some scientific evidence suggests that the benefits of the treatment outweigh the potential risks. Clinicians should discuss the treatment with eligible patients. *Other drugs in this class have also been assessed for the treatment of neuropathic pain and are also recommended first-line treatments.

Table 3: **Recommended first-line treatments for patients with neuropathic pain**

	Evidence
Antidepressants	
Tricyclic antidepressants	PNP*, PHN*, STR†, MIX†
Duloxetine	PNP*
Venlafaxine	PNP*
Anticonvulsants (sodium channel)	
Carbamazepine	TGN*
Lacosamide	PNP‡
Lamotrigine	HIV†, PNP‡, SCI‡
Oxcarbazepine	PNP‡
Topiramate	PNP‡
Valproate	PNP‡, PHN‡
Anticonvulsants (calcium channel)	
Gabapentin	PHN*, PNP*, CRPS†, PHAN‡, SCI‡, MIX†, CANC†
Pregabalin	PHN*, PNP*, SCI†, STR†, PTN†
Opioid agonists	
Morphine	PHN†, PHAN†
Oxycodone	PHN†, PNP*
Tramadol	PNP*, PHAN†
Cannabinoids§	
Tetrahydrocannabinol	MS*, PA†, MIX†
Topical therapy	
High-dose capsaicin patch	HIV‡, PHN*
Capsaicin cream	PHN†, PNP‡, PTN†, MIX†
Lidocaine patch	PHN*, MIX†

Negative efficacy data are not shown. Only class I randomised controlled clinical trials were considered. In cases in which there are negative and positive trial results, and in which positive trial results did not clearly outweigh negative trial results, the evidence was rated as "unclear". Evidence levels are summarised from Finnerup and colleagues,[64] Dworkin and colleagues,[68] and Attal and colleagues.[69] This table does not show all medications assessed in randomised controlled clinical trials in neuropathic pain (for complete data readers are referred to Finnerup and colleagues,[64] Dworkin and colleagues,[68] and Attal and colleagues[69]). PHN=postherpetic neuralgia. PNP=polyneuropathy (mainly diabetic). PTN=post-traumatic neuralgia. CRPS=complex regional pain syndrome. SCI=spinal cord injury. STR=post-stroke pain. HIV=HIV neuropathy. PHAN=phantom pain. MIX=mixed neuropathic pain cohort. CANC=neuropathic cancer pain. MS=central neuropathic pain associated with MS. PA=central neuropathic pain after plexus avulsion. TGN=trigeminal neuralgia. *Evidence from several randomised controlled clinical trials or meta-analyses. †Evidence from at least one randomised controlled clinical trial. ‡Evidence is unclear. §Other drugs in this class have also been assessed for the treatment of neuropathic pain and are also recommended first-line treatments.

Table 4: **Pharmacological therapy for patients with neuropathic pain syndromes**

both drugs but doses need to be adjusted according to kidney function.

Opioids
Opioid analgesics are agonists at presynaptic and postsynaptic opioid receptors. Efficacy has been reported in several randomised controlled trials in different peripheral and central neuropathic pain disorders.[67–69,71] Tramadol also inhibits serotonin and norepinephrine reuptake and can therefore interact with serotoninergic drugs (selective norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors), causing a serotonin syndrome, although this risk seems to be low in clinical practice. Opioids have a comparable analgesic efficacy to tricyclic antidepressants.[72] Concerns about long-term side-effects, such as immunological changes, physical dependency, and misuse or abuse, can limit the use of

strong opioids in patients with neuropathic non-cancer-related pain.

Topical lidocaine
Lidocaine relieves pain through non-specific block of sodium channels on ectopic peripheral afferent fibres without causing numbness of the treated skin. The topical application without a relevant systemic absorption offers a good benefit to risk ratio with only local side-effects, such as erythema or rash. Topical lidocaine is most appropriate in localised peripheral neuropathic pain. Although patients with allodynia and postherpetic neuralgia were included in most trials, topical lidocaine did relieve pain in patients without allodynia.[73,74]

Other drugs
Unlike trigeminal neuralgia, for which anticonvulsants with sodium channel action are clearly effective, drugs such as carbamazepine, oxcarbazepine, valproic acid, lamotrigine, topiramate, and lacosamide have had inconsistent results in patients with other neuropathic pain syndromes. No efficacy was reported for levetiracetam in patients with post-mastectomy pain or spinal cord injury pain.[75,76] Selective serotonin reuptake inhibitors are not included in treatment recommendations because of inconsistent efficacy results for this class of drugs.[77] Repetitive application of 0·05–0·075% capsaicin cream in patients with painful diabetic neuropathy, postherpetic neuralgia, and post-mastectomy pain has had inconsistent results. In two recent trials, efficacy of a single topical high-dose (8%) capsaicin patch in patients with postherpetic neuralgia and HIV neuropathy was reported.[78,79] After a single application, pain relief was documented from the second week for up to 3 months. Long-term data on efficacy and safety, particularly on the effect on nerve fibre structure within the skin, are still needed. In two placebo-controlled trials of peripheral nerve injury and painful diabetic neuropathy, multiple intracutaneous injections of botulinum toxin A had a significant analgesic effect that lasted for up to 12 weeks.[80,81] However, larger studies are needed to substantiate these preliminary results.

Because most of the randomised controlled clinical trials have been done in patients with postherpetic neuralgia and painful diabetic neuropathy, translation of the efficacy data to other neuropathic pain syndromes is still uncertain. Moreover, negative results of recent trials suggest that some neuropathic pain syndromes have lower treatment response than others. For example, pregabalin, amitriptyline, and topical lidocaine did not have efficacy in patients with HIV neuropathy.[69] In patients with chemotherapy-induced neuropathy, nortriptyline, amitriptyline, and gabapentin were not effective; nortriptyline, morphine, the combination of the two, and pregabalin were also not efficacious in patients with chronic lumbosacral radiculopathy.[69] Thus, in addition to

the possible design concerns that might lead to negative trial results, the pain syndromes themselves might vary in their response to treatment.

Combination therapy

In clinical practice, a combination of two or more drugs is often needed to achieve satisfactory pain relief, although there have been few trials done to support this clinical observation. However, combination therapy with gabapentin and extended-release morphine in patients with postherpetic neuralgia or painful diabetic neuropathy[82,83] and extended-release morphine and pregabalin in different neuropathic pain syndromes (neuropathic back pain, postherpetic neuralgia, radiculo-pathy, painful diabetic neuropathy) had higher pain relief with lower doses compared with administration of one drug alone. These results have also been confirmed for the combination of nortriptyline and gabapentin,[84] as well as for pregabalin and topical lidocaine,[74] in patients with painful diabetic neuropathy and postherpetic neuralgia. Taken together, these results substantiate the usefulness of combination therapy in patients with neuropathic pain.

Treatment in the elderly

There is a higher risk of developing neuropathic pain with increasing age.[85] Moreover, comorbidities and polypharmacotherapy are serious confounding factors. Both might limit the use of drugs and increase the risk of side-effects. Confusional states, falls, and injuries as a result of sedation and dizziness and drug accumulation from changes in pharmacokinetics and pharmaco-dynamics, resulting in reduced metabolism or clearance, have to be anticipated. Thus, drugs should be titrated with caution in older patients. Starting doses need to be low, up-titration slow, and the doses should be adjusted to liver and renal function. Topical drugs have a lower risk of side-effects than do systemically acting drugs and might provide a useful benefit to risk ratio. In general, close monitoring of side-effects is needed in elderly patients.

Interventional therapy

There are several shortcomings of trial data on the safety and efficacy of the different interventional therapies. Thus, the validity of recommendations is limited.[69] Usually, interventional management is considered in patients who do not respond or who only partially respond to treatment: this management should be part of a treatment plan involving pharmacological, non-pharmacological, and non-interventional treatments.[69] Guidelines propose treatment algorithms that are specific for the different neuropathic pain syndromes (for details readers are referred to Cruccu and colleagues[86]). Transcutaneous electrical stimulation is commonly used for non-invasive interventional therapy and, although the evidence level is low,[87] the benefit to risk ratio is favourable and, therefore, this stimulation is a therapeutic option in patients with neuropathic pain.[88]

For invasive interventions, spinal cord stimulation is efficacious in patients with complex regional pain syndrome and failed back surgery syndrome, and motor cortex stimulation is efficacious in patients with central post-stroke pain. Neural blockade with epidural blocks is recommended for patients with postherpetic neuralgia, radiculopathy, and failed back surgery syndrome, and sympathetic nerve blocks are recommended for patients with postherpetic neuralgia and complex regional pain syndrome. Opioids, ziconotide, and local anaesthetics can be delivered intrathecally in patients with postherpetic neuralgia, painful diabetic neuropathy, spinal cord injury, failed back surgery syndrome, and complex regional pain syndrome (for complete indications and evidence levels, readers are referred to Cruccu and colleagues[86]).

Conclusions and future perspectives

The reasons that only some patients with nerve lesions develop neuropathic pain is still unknown. Risk factors such as age, gender, pain intensity before and after the lesion, and emotional and cognitive features indicate that there are multiple factors other than the nerve lesion itself that contribute to manifestation of chronic pain.[8] Differences in the extent of the lesion of certain subgroups of nociceptive afferent pathways might also be a predictor for development of neuropathic pain,[41] as well as genetic determinants.[89]

The prospect for developing a mechanism-based classification and treatment approach seems promising. Although there are still important hurdles, several research groups across the world are systematically analysing sensory profiles that are likely to correspond to underlying mechanisms. Given the diverse mechanisms of action of the drugs, this research provides hope that we will soon be able to target specific drugs to individual patients and improve the outlook for patients with neuropathic pain.

Contributors
All authors contributed equally to the literature search, writing, and editing, and to the drawing of the figures and tables.

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