Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms

Troels S Jensen, Nanna B Finnerup

Lancet Neurol 2014; 13: 924–35

Department of Neurology, Aarhus University Hospital, Aarhus, Denmark (Prof TS Jensen DMSc)**; and Danish Pain Research Center, Aarhus University, Aarhus, Denmark** (NB Finnerup DMSc, Prof TS Jensen)

Correspondence to: Prof Troels S Jensen, Danish Pain Research Center, Aarhus University Hospital, 8000 Aarhus C, Denmark
tsjensen@clin.au.dk

Allodynia (pain due to a stimulus that does not usually provoke pain) and hyperalgesia (increased pain from a stimulus that usually provokes pain) are prominent symptoms in patients with neuropathic pain. Both are seen in various peripheral neuropathies and central pain disorders, and affect 15–50% of patients with neuropathic pain. Allodynia and hyperalgesia are classified according to the sensory modality (touch, pressure, pinprick, cold, and heat) that is used to elicit the sensation. Peripheral sensitisation and maladaptive central changes contribute to the generation and maintenance of these reactions, with separate mechanisms in different subtypes of allodynia and hyperalgesia. Pain intensity and relief are important measures in clinical pain studies, but might be insufficient to capture the complexity of the pain experience. Better understanding of allodynia and hyperalgesia might provide clues to the underlying pathophysiology of neuropathic pain and, as such, they represent new or additional endpoints in pain trials.

Introduction

Neuropathic pain is an umbrella term for a series of different conditions caused by a lesion or disease of the parts of the nervous system that usually signal somatosensory information.[1] A range of disorders of the peripheral nervous system—such as postherpetic neuralgia, painful nerve lesions, trigeminal neuralgia, postamputation pain—and a series of neuropathies are included under the term. Additionally, CNS disorders such as stroke, spinal cord injury, and multiple sclerosis can have pain as an important symptom. Diseases causing neuropathic pain therefore vary substantially both in terms of anatomical location and cause. Despite this diversity, neuropathic pain disorders have common clinical characteristics, including some, but not necessarily all, of the following: pain in an area with partial or complete sensory loss; different types of evoked pain; specific descriptors such as burning pain; increased pain after repetitive stimulation; and pain persisting after stimulation.[1–4] Two particularly bothersome and prominent symptoms in different types of neuropathic pain are allodynia (ie, pain elicited by a stimulus that normally does not cause pain) and hyperalgesia (ie, an increased pain response produced by a stimulus that normally causes pain; figure 1).[5]

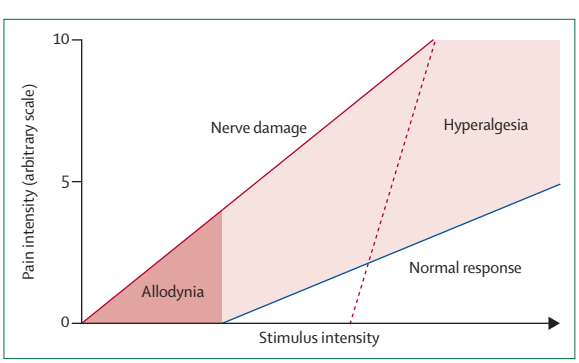

Figure 1: **Stimulus–response function illustrating allodynia and hyperalgesia following nerve damage**
The blue line illustrates the stimulus–pain relationship in normal skin, whereas the red lines represent the relationship in skin following nerve damage. Patterns of sensory abnormalities can differ with varying degrees of allodynia and hyperalgesia present at different test sites within the affected region in a patient with neuropathic pain. The stimulus–response function depends on the degree of nerve damage and location of the stimulation. In some sites, the stimulus response is shifted to the left, resulting in a lower stimulus intensity needed to evoke a painful response and with a steep slope, resulting in a high gain in the system (red solid line). In other areas dominated by loss of sensitivity, the stimulus–response function can be shifted to the right (red dashed line). Because of a steep slope, the result at suprathreshold stimuli might still be hyperalgesic responses. There is an overlap between allodynia and hyperalgesia, which are both part of a general hypersensitivity to a particular sensory stimulus, but the evoked sensory experience might shift so that one sensory modality is perceived differently—eg, touch as burning pain, heat as cold pain.[6,7]

In clinical pain trials, the intensity and degree of pain relief represent important outcome measures. However, these two measures might not capture all aspects of pain, particularly not with the development of new compounds targeting specific occurrences of pain. Current pain treatment is not satisfactory. An elaborate and detailed assessment of neuropathic pain might help to identify subsets of patients who respond to a particular pain treatment.[4,8–10] Allodynia and hyperalgesia are symptoms and signs that might serve as readouts for pain and thus contribute to improved delineation of neuropathic pain.[4,8–10]

This Review presents an overview of allodynia and hyperalgesia in neuropathic pain conditions, including their clinical manifestations, underlying mechanisms, and potential value as novel outcome measures.

Epidemiology of allodynia and hyperalgesia in neuropathic pain

Allodynia is Greek for other (allo) pain (odynia) according to the International Association for the Study of Pain.[5] The authors of a systematic review[11] showed that the prevalence of pain associated with predominantly neuropathic pain descriptors in questionnaire studies ranged from 7% to 18%, whereas studies based on diagnostic codes reported lower rates of neuropathic pain of 1% to 2%. The authors additionally stressed the variability in the prevalence of neuropathic pain associated with specific conditions; the estimated

prevalence of, for example, painful diabetic polyneuropathy ranged from 15 to 72 per 100 000 person-years. The main difficulty in epidemiological studies of pain is the subjective nature of the symptoms, preventing proper validation studies from being done.[11] The prevalence of allodynia in neuropathic pain is likewise difficult to assess. In a questionnaire study of more than 1600 patients with painful diabetic neuropathy,[12] 18% reported that light touching was painful, and 14% reported that cold or heat was occasionally painful. Only 47% with postherpetic neuralgia had touch-evoked allodynia, although this is usually reported to be present in at least 70% of cases.[13] On the basis of quantitative sensory testing in 1236 patients with different neuropathic pain syndromes, brush-evoked allodynia was present in 20% of all patients, 12% of patients with painful polyneuropathy, and 49% of patients with postherpetic neuralgia.[14] In another study of 482 patients with different causes of neuropathic pain,[15] 55% had brush-evoked allodynia, whereas pain evoked by contact with cold objects was reported in 31% of patients, with pressure-evoked pain reported in 52% of patients. Any pain evoked by brush, pressure, or cold stimuli was present in 52% of patients with painful diabetic polyneuropathy and 92% of patients with postherpetic neuralgia. The presence of evoked phenomena is therefore not only dependent on the patients examined, but also on the criteria and methods used to assess these evoked responses.

Clinical assessment and manifestations of allodynia and hyperalgesia

Theoretically, allodynia can be defined as a painful response to a non-nociceptive stimulus—ie, one not encoded by nociceptors[16]—but this definition cannot be used in the clinical setting because it would be impossible to establish whether a stimulus is capable of activating nociceptors in the individual patient. Therefore, the clinical terms allodynia and hyperalgesia need to be defined according to the sensation experienced after a stimulus that would normally produce either no pain or pain that can be tested in a non-affected body part, usually the contralateral part.[5] The clinical assessment of allodynia and hyperalgesia includes examination of trigger points, mapping of the area of abnormality, and determination of the intensity of hypersensitivity. Simple bedside tests include responses to cotton swab, finger pressure, pinprick, cold, and warm stimuli—eg, thermorollers kept at 20°C and 40°C, respectively (table).[17,18]

More detailed but time-consuming testing includes laser stimuli and quantitative sensory testing,[17,18] with the use of monofilaments, pressure or pinch algometers, and thermotest equipment. Sensory profiles including different aspects of allodynia and hyperalgesia have been described.[14] The clinical significance of these profiles is still unclear, mainly because of an absence of specific and selective compounds that can address the potential underlying mechanisms.[19,20] The paradoxical presentation of areas of hyperalgesia and sites with sensory loss can pose difficulty regarding where the assessment should be done. Examination at hyperalgesic sites might mask the presence of a potential sensory loss area (figure 2), whereas examination within a hypoalgesic area might preclude the identification of hypersensitivity. In these situations, mapping of sensory abnormalities is a way to obtain additional information.

The distribution of different pain types on a phantom map represents an important initial step for pain assessment (figure 2). The area can be quantitated and the evoked intensities and qualities measured both before and after an intervention. Such procedures are useful—eg, when recording the effect of drugs. Automatic drawing systems have been proposed, which might likewise be of value for more accurate measurements. An essential element of neuropathic pain is a lesion of the afferent

	Bedside assessment	Experimental assessment	Experimental readout	Clinical examples
Mechanical				
Dynamic mechanical	Cotton bud, painter's brush, or cotton ball	Brush (SENSElab 05; Somedic, Hörby, Sweden), speed 1–2 cm/s	Evoked pain intensity; area of abnormality	PHN; neuropathies; trigeminal neuralgia; central pain
Punctate	Prick with stick or pin; monofilament	Monofilament stimulus	Evoked pain intensity; pain threshold; area of abnormality	Traumatic nerve injury; trigeminal neuralgia
Static (superficial)	Gentle finger pressure applied to skin	Pressure algometer, fixed rate	Evoked pain intensity; pain threshold; area of abnormality	PHN; neuropathies: traumatic nerve injury
Static (deep)	Finger pressure applied to skin and underlying tissue	Pressure algometer, fixed rate	Evoked pain intensity; pain threshold; area of abnormality	CRPS; traumatic nerve injury
Thermal				
Cold	Thermoroller kept at 20°C, cold metal or glass object	Thermotest	Evoked pain intensity; pain threshold; area of abnormality	Chemotherapy neuropathy; post-stroke pain
Heat	Thermoroller kept at 40°C, warm metal or glass object	Thermotest; laser stimulus	Evoked pain intensity; pain threshold; area of abnormality	Erytromelalgia; burning mouth syndrome

PHN=postherpetic neuralgia. CRPS=complex regional pain syndrome.

Table: **Assessment of allodynia and hyperalgesia**

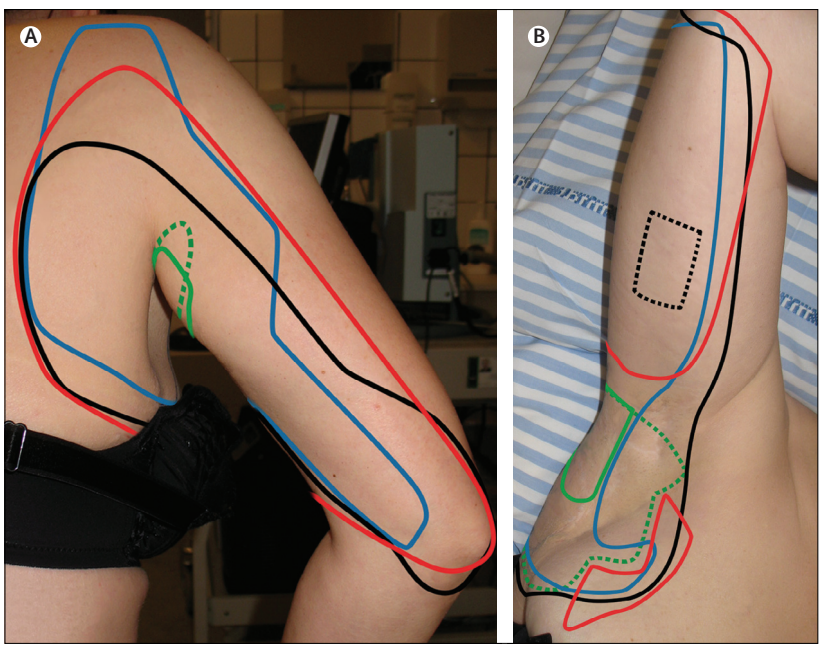

Figure 2: **Mapping of allodynia and hyperalgesia**
An example of areas of allodynia and hyperalgesia after a lesion of the intercostobrachial nerve during complete axillary lymph node excision in a patient treated for malignant melanoma. (A, B) Black line: spontaneous pain. Green line: decreased sensation to touch (solid) or pinprick (dotted). Blue line: dynamic mechanical allodynia. Red line: pinprick hyperalgesia. (B) Black dotted line: quantitative sensory examination.

transmission system. Depending on the particular type of afferent fibres implicated, a corresponding loss of the respective sensory function is seen. As a result of the nerve injury, maladaptive changes occur in cell structure, function, biochemical properties, and connections. These neuroplastic changes take place peripherally at the injury site and in the CNS (figure 3). The clinical manifestation of these maladaptive changes includes the development of pain in the innervation territory of the damaged nerve and allodynia or hyperalgesia extending beyond the innervation territory of the damaged nerve. On the basis of the symptom description, a distinction is often made between spontaneous (stimulus-independent) and evoked (stimulus-dependent) pain.[2,4,21–23] This concept has been challenged by Bennett,[24] who argues that the two types of pain are hard to separate and that spontaneous neuropathic pain might represent unrecognised allodynia or hyperalgesia due to subliminal internal or external stimuli that occur during daily life. He postulates that repeated episodes of such stimuli might summate and generate sensitisation. This hypothesis is difficult to either prove or refute. Nevertheless, the separation into stimulus-dependent and stimulus-independent pain is clinically useful because it is easy to identify on the basis of the patients' descriptions and, as shown below, is probably important in clarification of potential mechanisms of pain. Importantly, although hyperexcitability in the pain pathways can give rise to allodynia and hyperalgesia, these symptoms and signs do not always show a peripherally driven neuronal hyperexcitability, but might be manifestations of a psychological disturbance too.[25] Moreover, allodynia and hyperalgesia are not limited to neuropathic pain, but can be part of almost any type of chronic pain condition, ranging from simple local soreness in patients with osteoarthritis, sensitivity of facial skin in a patient with a migraine attack, and sensitivity of the abdominal wall in a patient with peritonitis, to generalised hypersensitivity in patients with fibromyalgia. Allodynia and hyperalgesia can in some, but not all, instances represent hyperexcitability in the nervous system, and it is important to note that allodynia and hyperalgesia are clinical terms that do not imply a mechanism.[5] Allodynia and hyperalgesia are classified according to the sensory modality used to elicit pain—ie, mechanical (dynamic, punctate, and static) and thermal (cold and heat) stimuli, which are seen in various peripheral nerve disorders, such as trigeminal neuralgia,[26] peripheral nerve injuries,[27] and postherpetic neuralgia,[28] as well as in central neuropathic pain conditions, such as central post-stroke pain,[6] multiple sclerosis,[29] spinal cord injury,[30] and syringomyelia.[31] The clinical presentation can be quite different in these conditions (figure 4). There has been interest in the predictive value of sensory changes for the development of pain. Studies have found that sensory hypersensitivity precedes the development of some neuropathic pain conditions. For example, after spinal cord injury[30,32] and central post-stroke pain (Klit and colleagues, unpublished), early sensory hypersensitivity predicted the development of central pain, suggesting that central neuronal hyperexcitability develops gradually and precedes the development of spontaneous central pain. In peripheral neuropathic pain, early hyperaesthesia has been found to increase the likelihood of persistent pain—eg, after surgery.[8]

Mechanical allodynia and hyperalgesia

Three types of mechanical allodynia and hyperalgesia are usually described: dynamic mechanical allodynia evoked by light touch; punctate allodynia and hyperalgesia evoked by punctate skin stimulation with a pin or monofilament (400 mN); and static allodynia and hyperalgesia provoked by pressure to skin or deep tissue.[33,34] On the basis of experimental studies using capsaicin and freezing lesions, Kilo and colleagues[34] described a fourth type, termed impact hyperalgesia, elicited in the primary hyperalgesic area by shooting small bullets against the freezing zone. To what extent this type of hyperalgesia is implicated in clinical neuropathic pain remains to be seen. Most investigators have focused their attention on dynamic mechanical allodynia and punctate hyperalgesia, probably because they are most obvious to the patient and clinician.

Dynamic mechanical allodynia

Dynamic mechanical allodynia in neuropathic pain is suggested to be perceptually similar to the same disorder

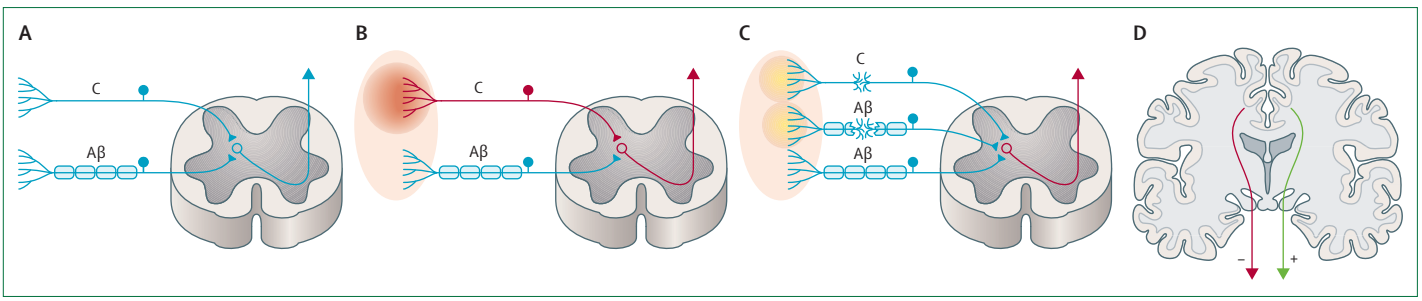

Figure 3: **Mechanism for development of central sensitisation**
(A) Diagram of noxious (C fibres) and non-noxious (Aβ fibres) input to second-order projection neurons in the spinal cord. (B) Following stimulation of C fibres (red area)—eg, by capsaicin amplification of spinal cord signalling systems—central sensitisation develops and non-noxious stimulation outside the injured area is sufficient to elicit a painful sensation. (C) After injury to nerves, second-order neurons are excited by abnormal and increased input form the periphery, causing central sensitisation and non-noxious input from damaged or undamaged Aβ fibres, which may now elicit activity sufficient to cause pain. Because of injury, there are also areas with a loss of sensitivity (yellow areas). (D) Additionally, a change in the balance of descending inhibitory (–) and facilitating (+) pathways from the brain to the spinal cord can affect dorsal horn neuronal activity and can therefore cause central sensitisation. Red represents sensitisation of fibres and blue represents normal fibres in A–C.

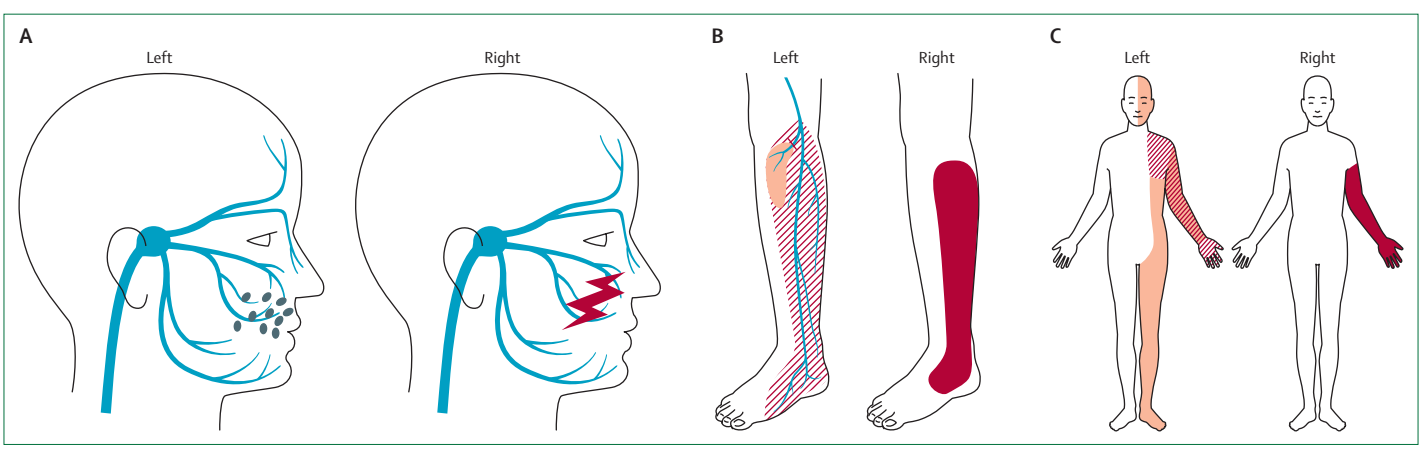

Figure 4: **Three different neuropathic pain conditions with separate and distinguishable types of allodynia and hyperalgesia**
Orange areas: sensory loss to tactile stimuli. Red-hatched areas: dysaesthesia to tactile stimuli. Red areas: pain. Dots: tactile trigger zones for neuralgic attacks. (A) Trigeminal neuralgia is characterised by flashes of pain in the face evoked from trigger points (dots) in the trigeminal innervation area (left). Non-noxious stimuli, such as a wind blowing, touching stiff hairs on the face, chewing, and tooth brushing, and more rare noxious mechanical stimuli, can elicit episodes of pain (right). Trigger zones are concentrated around the mouth, lips, and nose, and diminish in frequency more laterally. Their distribution corresponds to the onion peel-like distribution of the facial somatotopic representation in the sensory nucleus of the trigeminal nerve. Damage to myelinated fibres, as seen, for example, by compression of the trigeminal root by vessels or a plaque from multiple sclerosis, has been suggested to be related to the presence of paroxysmal pain. By contrast with other neuropathic pain conditions, there is no clinically demonstrable sensory loss present in trigeminal neuralgia. Another distinguishing feature of trigeminal neuralgia is the refractory period after a period of paroxysm, which can last up to several minutes, where either no or only a weak paroxysm can be elicited. This could, in part, explain the pain-free episodes seen in trigeminal neuralgia by contrast with other types of compression neuropathies, in which longer-lasting or even persistent areas of allodynia or hyperalgesia are present. (B) Nerve injury pain is a common cause of neuropathic pain associated with allodynia. A series of conditions qualify, such as post-traumatic nerve injury following surgery, traumatic injuries (eg, amputations), nerve compressions (eg, carpal tunnel syndrome), and degeneration after inflammation (eg, postherpetic neuralgia). In these cases, the clinical picture is characterised by negative symptoms, with simultaneous sensory loss (left) surrounded by areas of allodynia in the painful area (right). The allodynic area can be mapped and specified for each sensory modality. The illustrated case shows an iatrogenic lesion of the infrapatellar branch of the saphenous nerve that is damaged following arthroscopy of the knee joint. (C) Central neuropathic pain is pain due to a lesion or disease of the classic pain signalling systems in the CNS—ie, the spinothalamic system. As for nerve injury pain, there are negative symptoms, but in this case, temperature and pinprick sensitivity are specifically affected, which are sensory modalities conveyed via the spinothalamic tract (left). In the same area, there are positive symptoms and signs with spontaneous pain and allodynia (right), which might be deep or cutaneous, and include one or several sensory qualities. The classic examples are spinal cord injury pain, multiple sclerosis, and post-stroke pain. Here, the overlap of attenuation of spinothalamic functions (temperature and pinprick) is associated with dynamic allodynia. In the illustrated case, the development of pain occurred after a middle cerebral artery occlusion with an infarct in the right hemisphere, giving rise to a right-sided hemiparesis, dysaesthesia in the left hemibody, and spontaneous pain in the left arm.

seen in the secondary hyperalgesic area after capsaicin application, with similar temporospatial stimulus parameters and pain descriptors.[35–37] This similarity suggests, but does not prove, that the mechanisms underlying dynamic mechanical allodynia in some neuropathic pain states are similar to those seen after experimental capsaicin application, which produces a zone of primary hyperalgesia at the site of injury and secondary hyperalgesia extending beyond the injury site.[35,38] Stimulus-dependent pain is, by nature, only present in areas with preserved ascending sensory pathways and, consequently, patients with allodynia and hyperalgesia often have fewer sensory deficits compared with patients with spontaneous pain only.[28,39–41] In patients with partial nerve injury, a deficit to one or several modalities can be masked by an associated hypersensitivity in intact or regenerating nerve fibres in the same or adjacent territories.[42]

Dynamic mechanical allodynia is generally accepted to be mediated by low-threshold Aβ fibres in most

instances. In a classic investigation by Gracely and colleagues,[43] a local anaesthetic block of nerve injury trigger points attenuated both continuing pain and brush-evoked allodynia, with a return of both pain and allodynia as the anaesthetic effect disappeared. Moreover, by selectively blocking A fibre input in patients with nerve injury, dynamic mechanical allodynia disappeared, whereas burning pain mediated by continuing C fibre activity remained.[35] Studies of reaction times in dynamic mechanical allodynia confirm that large myelinated fibres mediate the disorder.[44] The Aβ input might be necessary not only for the presence of allodynia, but also for the quality of the pain felt. A gradually increasing compression block of Aβ input in patients with nerve injury pain showed that the modality of the evoked sensation changed from dynamic mechanical allodynia to dynamic mechanical dysaesthesia, which suggests that dysaesthesia and allodynia are part of the same spectrum, and that both are orchestrated by the degree of input from non-noxious mechanosensitive fibres.[45]

Small-fibre input seems to be an important driver of allodynia. In experimental studies using capsaicin or mustard oil to elicit pain and hyperalgesia in human volunteers and patients with nerve injury pain,[35] elicited burning pain and dynamic mechanical allodynia increased after warming of the skin. The authors of another study[46] found that preservation of thermal pain pathways (estimated using laser-evoked potentials) rather than large fibre pathways (estimated using nerve conduction recordings) were more common in patients with peripheral neuropathy and dynamic mechanical allodynia. Whether or not the testing was done in the area of dynamic mechanical allodynia was not certain, but the authors do suggest a role for at least partly preserved and sensitised thin fibres. Dynamic mechanical allodynia might, in some cases, be mediated through unmyelinated, low-threshold mechanosensitive afferents that signal the pleasantness of gentle skin stroking,[47,48] although the role of these fibres in patients with neuropathic pain is still unsettled. In central pain conditions such as central post-stroke pain, tactile allodynia has been shown to occur in patients with disturbances of thermal pathways but spared tactile signalling pathways,[49] which suggests that disruption of the thermal input is necessary for the development of pain.

Punctate allodynia and hyperalgesia

Punctate allodynia and hyperalgesia present in the innervation territory of the affected nerve usually involve a larger area compared with dynamic mechanical allodynia[34,50,51] and depend on central changes in addition to peripheral input.[52] Based on differential nerve fibre blocks by compression, punctate hyperalgesia is driven by activity in Aδ fibres[53] and a minor input from C fibres, by contrast with the Aβ-mediated dynamic mechanical allodynia.[34] Various animal models of nerve injury pain use a monofilament stimulation method to evoke motor responses,[54] which is similar to that used in human studies to examine for punctate hyperalgesia.

Static evoked allodynia or hyperalgesia

Static (ie, pressure) evoked allodynia or hyperalgesia is another important, but less recognised, form of allodynia and hyperalgesia. Static hyperalgesia is phenomenologically different from dynamic and punctate allodynia and hyperalgesia produced by chemical irritants such as capsaicin or mustard oil. Static allodynia is generally short lasting and confined to the primary hyperalgesic area (primary hyperalgesia), whereas dynamic and punctate hyperalgesia extends beyond this area (secondary hyperalgesia). Based on nerve compression blocks, static allodynia[55]—by contrast with dynamic mechanical allodynia and similar to heat hyperalgesia[56]—is mediated by sensitised peripheral nociceptors.[33–35,43–45,55] Importantly, the authors of a clinical study[32] showed the simultaneous presence of static and dynamic allodynia in 28 patients with nerve injury, and found that these two signs represented distinct and separable types of sensory hypersensitivity. The clinical significance of static hyperalgesia has been mentioned only briefly in the literature.[17] However, deep (static) mechanical hyperalgesia has subsequently been noted in other peripheral neuropathic pain conditions, such as traumatic nerve injuries[39,57] and diabetic neuropathies.[12,58]

Molecular mechanisms of mechanical allodynia and hyperalgesia

Several molecular mechanisms underlie neuronal hyperexcitability and allodynia, with much knowledge gained from preclinical studies, but a detailed description is beyond the scope of this Review. After injury, cytokines, nerve growth factors, and other algogenic substances invade the injured tissue area, which contributes to a change in the expression and trafficking of non-specific ion channels and specific sodium and potassium channels.[59–61]

Spontaneous ectopic activity in nerve endings or along the axon is important for spontaneous pain, but might also be a driving factor of allodynic responses. After nerve injury, the expression of sodium channels is changed, particularly the isoforms $Na_v1{\cdot}3$, $Na_v1{\cdot}7$, $Na_v1{\cdot}8$, and $Na_v1{\cdot}9$.[4,60,62] Other channels in the development of ectopia are the neuronal hyperpolarisation-activated cation channels,[63,64] which, together with calcium channels, are important to neurons to display repetitive firing patterns. This peripherally increased input—whether caused by sensitised nociceptors or ectopia—is an important driving force for central sensitisation and its clinical expression with spread of pain outside the damaged nerve innervation territory, the increase of pain despite the same stimulus intensity, and the persistence of pain after stimulation has stopped.

Many signalling molecules are implicated in the sensitisation and include several glutamate receptor

types, substance P, proinflammatory cytokines, tyrosine kinase B receptors, and different protein kinases.[4,9,59]

Another potential mechanism underlying mechanical allodynia is a phenotypic switch in which Aβ fibres start to express neuropeptides such as calcitonin-gene-related peptide, substance P, and the neurotrophin BDNF, which are usually only expressed by small fibres.[65,66] Postsynaptic changes probably contribute to allodynia too. These include increased activity at NMDA, AMPA, and metabotropic glutamate receptors, different kinases, and other signalling systems that increase synaptic strength.[4]

Reduction of normal GABA and glycine inhibition of second-order neurons will probably be involved too. Downregulation of potassium-chloride exporters leads to a shift in the transmembrane anion gradient and a net excitation rather than an inhibition of second-order neurons.[67,68] A range of molecular mechanisms is probably involved in these sensitisation phenomena and the activation of nociceptive spinothalamic pathways by normally non-painful stimuli. Understanding the contribution of each of these mechanisms to the different symptoms and signs seen in individual neuropathic pain conditions and individual patients remains a future challenge.

***Panel:* The thermal grill illusion as a model for cold allodynia**

After studies by Thunberg[80] in the 19th century on what was termed the thermal grill illusion, there has been an interest in mechanisms giving rise to thermal allodynia. The thermal grill illusion showed how simultaneous application of innocuous cold and warm stimuli to skin elicited a warm sensation or a noxious sensation, described as a "cold burning pain sensation" or the thermal grill illusion. Different theories have been proposed to explain the thermal grill illusion.

Cold neurons, which are exclusively activated by cool stimuli, have a lower activity during the illusion stimuli compared with when a real cold stimulus is present.[81] In the polymodal neurons termed heat-pinch-cold cells, the neuronal firing pattern was similar for pure cold or illusion conditions. On the basis of these findings, investigators postulated that the thermal grill illusion represents an unmasking phenomenon in which the simultaneous presentation of cool and warm stimuli disinhibits activity in cold-sensitive polymodal lamina 1 spinothalamic neurons (figure 5).[7,82] Functional imaging has shown that the thermal grill activates the anterior cingulate cortex, which is frequently excited by noxious stimuli, whereas separate presentation of warm and cold stimulation alone does not activate the anterior cingulate cortex.[82] This could show an imbalance between the activity of cold-specific and cold-nociceptive cells, resulting in differential excitation of the insular cortex and medial and lateral aspects of the thalamus.

Few investigators have tried to alter the illusion phenomena pharmacologically. However, studies by Bouhassira and his group[83] have shown that the paradoxical pain produced by the grill can be reduced by the NMDA ion channel antagonist ketamine, suggesting that NMDA receptor-mediated systems play a part in this thermal hyperalgesia.

Thermal allodynia and hyperalgesia

Cold perception and allodynia

The authors of early psychophysical studies in human beings showed that the perception of cold can usually be separated into three categories: perception of innocuous cool temperatures when the skin is cooled by between 0·5°C and 1·0°C in the most sensitive areas; cold pain sensation that is perceived in the range of 30–15°C; and a freezing or stinging cold pain sensation at very cold temperatures, usually less than 0°C (separable from cold pain).[69–71] The perception of innocuous and noxious cold is mediated by unmyelinated (C) and thinly myelinated (Aδ) fibres. Differential blocks of A fibres in human volunteers have shown that the sensitivity to innocuous cold is mediated by Aδ fibres,[72] although C fibres have also been shown to respond to innocuous cold.[73,74] The existence of two types of neurons has been suggested: a low-threshold cool type, responding to activating temperatures close to 30°C, and a high-threshold cold nociceptor neuron population, activated at temperatures less than 20°C.[75]

Cold allodynia is a frequent finding in neuropathic pain, but it is also seen in patients with permanent sequelae after cold injuries[76] and in ciguatera, a neurological disease caused by consumption of ciguatoxins, which are a group of compounds that accumulate in some tropical and subtropical fish.[77] The character of cold allodynia differs between patients. For example, it might be perceived as a deep aching and burning sensation in a patient with small-fibre neuropathy,[78] a pricking sensation in a patient with acute oxaliplatin neuropathy, or an intense cold or burning sensation in a patient with central pain. Patients with cold injury have normal detection thresholds, but report pain at non-painful cold temperatures. By contrast with patients with neuropathic pain, those with cold injury tolerate further cooling from the pain threshold.[76] Cold allodynia is often the sole finding in patients with cold injury, by contrast with those with neuropathic pain, who might have additional signs of sensitisation.[79] These differences in the clinical expression of cold hypersensitivity indicate differences in the underlying neurophysiological mechanisms and suggest that phenotyping of patients based on quantitative sensory testing should be coupled with a more detailed description and analysis to achieve a more distinct classification (panel).

Molecular mechanisms of cold sensation

The exact cellular and molecular mechanisms of cold sensation are not wholly understood. However, both voltage-gated ion channels and members of the transient receptor potential (TRP) ion channel family are associated with the transduction of cold sensation and cold-related pain.[84–86]

TRPM8 and TRPA1 are two cation channels expressed in trigeminal and dorsal root ganglion cells that both respond to cooling temperatures.[87] Essentially, TRPM8 is exclusively expressed in neurons that participate in cold signalling. Low-threshold cold cells expressing TRPM8 have been suggested to activate a postsynaptic channel resulting in a cool sensation, and high-threshold cells[88]

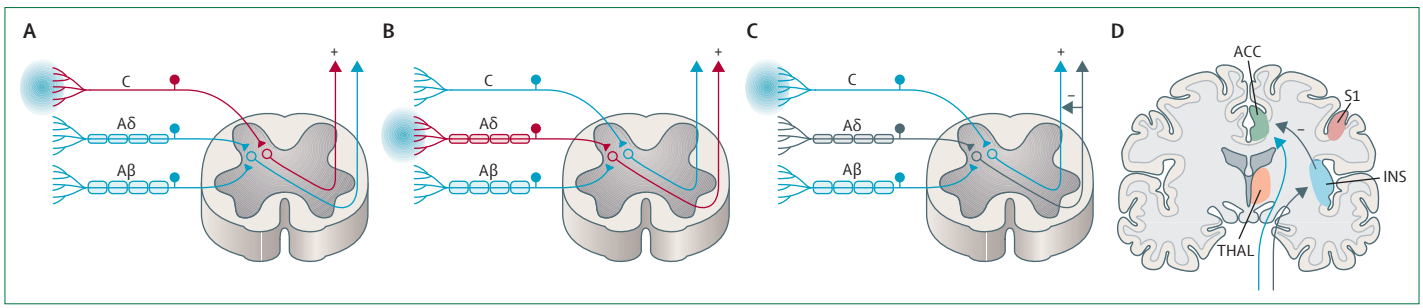

Figure 5: **Potential mechanisms for cold allodynia and hyperalgesia**
(A) Peripheral sensitisation of cold-sensitive C fibres through abnormal expression or function of, for example, TRPM8 and TRPV1 receptors, or sodium, potassium, or calcium channels, can cause decreased thresholds and exaggerated responses to cold. (B) Peripheral sensitisation of Aδ fibres might likewise cause cold allodynia and hyperalgesia. (C) Loss of peripheral Aδ fibres or (D) of central innocuous cold pathways (eg, by disruption of a thermosensory area in the insular cortex) might disinhibit cold-sensitive polymodal nociceptive heat-pinch-cold-sensitive pathways, causing cold to be experienced as burning pain. Red represents sensitisation of fibres, grey represents loss of fibres, and blue represents normal fibres in A–D. Blue areas show where a cold stimulus is applied. ACC=anterior cingulate cortex. INS=insular cortex. S1=primary somatosensory area. THAL=thalamus.

also expressing TRPM8, but at lower level, have been suggested to lead to cold pain. $Na_v1·8$, which is also expressed in high-threshold cells, might elicit a response in the cold pain channel.[87,89] Under normal conditions, the participation of TRPA1 is not clear, but in experimental nerve injury, TRPA1 might act as a facilitator on TRPM8-expressing neurons, resulting in pain. Alternatively, TRPM8 and TRPA1 might be expressed in a so far unidentified nociceptor type, causing pain.

Molecular mechanisms of cold allodynia and hyperalgesia

Several hypotheses exist for the mechanisms of cold allodynia and hyperalgesia. These include peripheral and central sensitisation, or central disinhibition, such as sensitisation of C nociceptors or Aδ fibres (figure 5). Microneurographic recordings in a patient with small-fibre neuropathy and cold allodynia showed sensitisation to cold and menthol responsiveness of subtypes of C nociceptors,[78] which provides a potential explanation for cold allodynia. TRPM8 upregulation might explain this sensitisation. Although supported by animal studies,[90] the role of TRPM8 upregulation in human neuropathic pain is less clear,[78] and patients with neuropathic pain with cold allodynia might have both increased[91] and decreased[92] sensitivity to menthol. Sodium channel dysfunction is another mechanism that could explain peripheral sensitisation. Changes in axonal excitability, indicating sodium channel dysfunction, have been documented in sensory neurons immediately after oxaliplatin infusion.[93] In these patients, cold allodynia might therefore be due to increased excitability of cold-sensitive neurons through changes in transient Na^+ conductances. Additionally, ciguatoxins elicit cold allodynia via complex mechanisms, including activated sodium channels.[77] Authors of experimental studies suggest that different sodium channels are important. Whereas $Na_v1·7$ expression within the peripheral nervous system has been proved necessary for mechanical or cold-evoked responses in some models,[94] this is not true for oxaliplatin-induced cold behaviour, in which $Na_v1·6$ expression plays an essential part,[94] as likewise found in an earlier study.[95] The authors of studies in rodents have also implicated TRPA1 receptors,[96,97] potassium hyperpolarisation-activated cation channels,[75,98] and calcium channels[99] in cold allodynia and hyperalgesia. Additionally, central sensitisation of spinothalamic or cortical neurons caused by the same molecular mechanisms implicated in mechanical allodynia and hyperalgesia might underlie cold allodynia and hyperalgesia in both central and peripheral neuropathic pain.[21,79,100]

Blockade of Aδ fibres during nerve compression[101,102] or disease[103] causes an increase in cold detection thresholds, a decrease in cold pain thresholds, and a change in the quality of cold sensation to icy, stinging, hot, and burning sensations. This is thought to result from disinhibition of C-polymodal nociceptive fibres (heat-pinch-cold fibres) by loss of Aδ fibres[104] and could provide an explanation for cold allodynia in neuropathic pain patients (figure 5). A similar mechanism has been proposed to explain cold allodynia in patients with central pain, in whom loss of central innocuous cold pathways or disruption of a thermosensory area in the insular cortex is proposed to disinhibit polymodal nociceptive activation of the anterior cingulate cortex (figure 5).[81,105]

The authors of a preclinical investigation found that peptidergic calcitonin gene-related peptide α-expressing sensory neurons sensitive to heat and itch tonically suppress cold sensitivity.[106] These neurons were TRP ion channel V1 (TRPV1) positive, and the results are therefore consistent with the fact that activation of TRPV1 afferents by capsaicin reduces sensitivity to cold and cold pain in human beings.[107] Disruption of this crosstalk could unmask cold hypersensitivity and result in cold allodynia and increased TRPM8 activation activity, and therefore provides another possible central mechanism for cold allodynia and hyperalgesia in neuropathic pain.[106]

Heat allodynia and hyperalgesia

Heat stimuli are conducted via C fibres and Aδ fibres. The corresponding transduction receptors are the C fibre

and A fibre mechanoheat nociceptors, which respond to mechanical and heat stimuli. There seem to be two types of thermosensitive C nociceptors: one quickly adapting type that discharges during an increment of temperature and a more slowly adapting type that responds throughout a gradually maintained temperature increase.[108] The key transducer in warm and heat pain-responding neurons is TRPV1, the activity of which increases gradually with temperature.[109] Other channels of the TRP family—ie, TRP ion channels V2–4—and purinergic receptors might also participate in the transduction of heat. Hyperalgesia to heat, which is prominent in inflammatory disorders, can likewise be seen in neuropathic pain disorders. Such heat hyperalgesia can be either peripherally or centrally mediated. Resiniferatoxin—a potent capsaicin analogue—produces long-lasting desensitisation of TRPV1 receptors[110] and blocks heat but not tactile hypersensitivity in experimental nerve injury, suggesting that peripheral sensitisation of the nerve fibres that express TRP channels plays a part in heat hyperalgesia.[111]

Heat hyperalgesia is probably likewise a result of central mechanisms and is present in 10% of patients with central pain.[14] Hyperalgesia to laser stimuli in both peripheral and central neuropathic pain has been found to coexist with decreased, delayed, and desynchronised laser-evoked potentials.[40,112] In some of these patients, the ultra-late components of heat-evoked potentials, which are described in healthy controls after C fibre sensitisation and Aδ fibre blockade,[113] have been seen. Such responses have been hypothesised to show activation of a slowly conducting multisynaptic medial pain system because of either sensitisation or disinhibition.[40]

A classic example of heat hyperalgesia is inherited erythromelalgia—a condition characterised by bilateral severe burning pain in distal extremities, particularly the feet—associated with vasodilatation and reddening of the feet or hands.[114] This condition, which is an autosomal dominant disorder, is caused by a missense mutation in the $Na_v1{\cdot}7$ channel, resulting in a reduction of the activation threshold.[115] With microneurography, ectopic activity has been noticed in C fibres from these patients, which represents one example of increased membrane excitability.[116]

In nerve injury, expression of the key heat transducer TRPV1 changes. TRPV1 is downregulated in injured nerve fibres, but upregulated in uninjured fibres,[117,118] and has a de-novo expression in cells belonging to the Aδ and Aβ type.[119] Taken together, these findings suggest that both peripheral—via TRPV1-sensitised nociceptors—and central mechanisms might have a role in the development and maintenance of heat hyperalgesia after damage to the nervous system. It can also be envisioned that the general lowering of thresholds to stimuli such as warm stimuli could lead to spontaneous activity, which could provide a mechanism for other sensory perceptions, such as sticking or burning sensations.

Modulation of allodynia and hyperalgesia

Pharmacological treatment

Pharmacological treatment is the mainstay of neuropathic pain treatment. A series of compounds has been used to modulate neuropathic allodynia and other manifestations of neuropathic pain. These include drugs acting at voltage-gated and ligand-gated ion channels, metabotropic glutamate receptor ligands, opioids, cannabinoid receptor modulators, and glycine transporter inhibitors.[120,121]

Few trials have specifically addressed the treatment of evoked pain. Several randomised, double-blind, placebo-controlled studies with the primary aim to study the effect of pharmacological treatment in neuropathic pain conditions have reported on the effect of the drug on allodynia or hyperalgesia, assessed by history, at the bedside, or by quantitative sensory testing. Dynamic mechanical allodynia to a brush or cotton swab is the outcome most often assessed, followed by hyperalgesia to pinprick and allodynia to cold. Allodynia or hyperalgesia was made an inclusion criterion in only a few studies, and most had too few patients with a specific type of evoked pain or the intensity was too low to be able to show an effect. Tricyclic antidepressants,[122] serotonin-norepinephrine reuptake inhibitors,[123,124] gabapentinoids,[125–127] opioids,[128–132] cannabinoids,[131] lamotrigine,[132] mexiletine,[133] lidocaine gel,[134] and botulinum toxin-A[135] have been found to relieve dynamic mechanical allodynia, cold allodynia, or pinprick hyperalgesia in different peripheral and central neuropathic pain conditions. The authors of studies with intravenous treatment additionally investigated the effect on different types of evoked pain, and sodium channel blockers, opioids, NMDA antagonists, and propofol have shown effect on mechanical and cold allodynia.[52,79,136–145]

Studies have also been done to examine whether allodynia or hyperalgesia are predictors of overall treatment effect. Pinprick hyperalgesia predicted an overall effect of pregabalin in HIV polyneuropathy[146] and dynamic mechanical allodynia or temporal summation to repetitive pinprick predicted the response to lamotrigine in spinal cord injury,[147] whereas dynamic mechanical allodynia was a negative predictor of the overall effect of pregabalin in postherpetic neuralgia[126] and levetiracetam in multiple sclerosis.[148] These results were all based on posthoc analyses. Six intravenous treatment trials[52,138–141,143] were done to examine allodynia or hyperalgesia as predictors of overall pain-relieving effect, but only as a predefined outcome in one of them.[139] In one study, static or dynamic mechanical allodynia predicted the response to intravenous lidocaine,[141] whereas authors of the other studies failed to find evoked pain to predict the response to lidocaine,[52,138,139,143] morphine,[140] or ketamine.[52]

Recently, a study was done to try to establish whether a reduction of spontaneous pain is matched by a similar reduction of evoked pain. In a group of patients with peripheral nerve injury pain and evoked pain who underwent a complete block of afferent input to the CNS,

Search strategy and selection criteria

We identified papers for this Review through searches of PubMed with the search terms "allodynia", "hyperalgesia", "neuropathic", "neuralgia", and "pain" from 1966 until January, 2014. For treatment, papers from previous systematic reviews were included. Only papers published in English were reviewed. Studies of humans and animals were included. Both original research and review articles were included. The reference lists of the papers, articles from our own files, and relevant book chapters were also searched. The final reference list was generated on the basis of relevance to the topic covered in this Review and randomised controlled trials and clinical studies were given precedence over case reports.

blockade of spontaneous continuing pain additionally blocked aspects of evoked pain, which suggests that the afferent drive from the periphery is necessary for the centrally mediated evoked pain.[149]

Non-pharmacological modulation

For the **Innovative Medicines Initiative** see http://www.imi.europa.eu

Allodynia and hyperalgesia produced by nerve injury can be modified from the brain. Psychological and physical modulations have been shown to alter allodynic phenomena in patients with peripheral nerve injury. The authors of systematic reviews covering different electrical or magnetic stimulation techniques for neuropathic pain after spinal cord injury showed that these techniques might have a beneficial effect in neuropathic pain and the associated dysaesthesia and allodynia.[150,151] The authors of these neuromodulation studies took advantage of the powerful control exerted by the brain on dorsal horn pain processing—eg, Witting and colleagues[152] showed that a paradigm with diffuse noxious inhibitory control, in which a painful stimulus was applied at a distance from a neuropathic pain area, could reduce the perceived intensity of allodynia in patients with nerve injury when exposed to a cold pressor test. Results of another study in patients with post-thoracotomy pain[153] showed that placebo responses could modify the area of allodynia. In general, larger studies are needed to establish the value of stimulation on allodynia and hyperalgesia.

Conclusions and future directions

Allodynia and hyperalgesia in neuropathic conditions, together with sensory loss, represent an important imprint of the activity in the nociceptive system. On the one hand, the extent and degree of sensory loss will show the magnitude of peripheral deafferentation or the CNS structures that have lost their normal patterned input. The areas of allodynia and hyperalgesia in neuropathic pain, on the other hand, provide a measure of those structures within the nervous system where signs of neuronal hyperexcitability are present. By further classification of allodynia or hyperalgesia according to different types of stimuli, additional insight might be gained into the underlying pain mechanisms, which can then be targeted by different types of management. Existing drugs are rather non-specific in their mode of action.[154] This non-specificity limits the possibility of dissection of the underlying pathophysiologies. However, with novel and more specific drugs, these subtypes of allodynia and hyperalgesia could be used as additional endpoint measures in clinical trials.

Contributors

TSJ wrote the first draft. TSJ and NBF both searched for studies and edited the Review.

Declaration of interests

TSJ and NBF have received funding from the EuroPain project, supported by the Innovative Medicines Initiative Joint Undertaking, under grant agreement 115007, resources for which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/20072013) and the European Federation of Pharmaceutical Industries and Associations companies' in-kind contributions. TSJ has received grant support or honoraria from Pfizer, Grünenthal, and Astellas, and NBF has received honoraria from Pfizer and Grünenthal.

Acknowledgments

The work for this Review is part of the EuroPain Collaboration, which has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement 115007, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and the European Federation of Pharmaceutical Industries and Association companies' in-kind contributions.

References

1 Jensen TS, Baron R, Haanpää M, et al. A new definition of neuropathic pain. *Pain* 2011; **152:** 2204–05.
2 Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. *Pain* 2003; **102:** 1–8.
3 Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. *Life Sci* 2004; **74:** 2605–10.
4 von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron* 2012; **73:** 638–52.
5 International Association for the Study of Pain Taxonomy. 2011. http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576 2011 (accessed Jan 15, 2014).
6 Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol* 2009; **8:** 857–68.
7 Craig AD. Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci* 2003; **26:** 1–30.
8 Kaasa T, Romundstad L, Roald H, Skolleborg K, Stubhaug A. Hyperesthesia one year after breast augmentation surgery increases the odds for persisting pain at four years: a prospective four-year follow-up study *Scand J Pain* 2010; **1:** 75–81.
9 Truini A, Garcia-Larrea L, Cruccu G. Reappraising neuropathic pain in humans—how symptoms help disclose mechanisms. *Nat Rev Neurol* 2013; **9:** 572–82.
10 Max MB. Towards physiologically based treatment of patients with neuropathic pain. *Pain* 1990; **42:** 131–37.
11 van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain* 2014; **155:** 654–62.
12 Baron R, Tölle TR, Gockel U, Brosz M, Freynhagen R. A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: differences in demographic data and sensory symptoms. *Pain* 2009; **146:** 34–40.
13 Johnson RW, Wasner G, Saddier P, Baron R. Herpes zoster and postherpetic neuralgia: optimizing management in the elderly patient. *Drugs Aging* 2008; **25:** 991–1006.
14 Maier C, Baron R, Tölle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010; **150:** 439–50.

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

16 Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. *Pain* 2008; **137:** 473–77.

17 Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011; **152:** 14–27.

18 Backonja MM, Attal N, Baron R, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain* 2013; **154:** 1807–19.

19 Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010; **150:** 573–81.

20 Attal N, Bouhassira D, Baron R, et al. Assessing symptom profiles in neuropathic pain clinical trials: can it improve outcome? *Eur J Pain* 2011; **15:** 441–43.

21 Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* 1999; **353:** 1959–64.

22 Koltzenburg M, Scadding J. Neuropathic pain. *Curr Opin Neurol* 2001; **14:** 641–47.

23 Jensen TS, Hansson PT. Chapter 34 Classification of neuropathic pain syndromes based on symptoms and signs. *Handb Clin Neurol* 2006; **81:** 517–26.

24 Bennett GJ. What is spontaneous pain and who has it? *J Pain* 2012; **13:** 921–29.

25 Vase L, Nikolajsen L, Christensen B, et al. Cognitive-emotional sensitization contributes to wind-up-like pain in phantom limb pain patients. *Pain* 2011; **152:** 157–62.

26 Kugelberg E, Lindblom U. The mechanism of the pain in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1959; **22:** 36–43.

27 Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367:** 1618–25.

28 Rowbotham MC, Fields HL. The relationship of pain, allodynia and thermal sensation in post-herpetic neuralgia. *Brain* 1996; **119:** 347–54.

29 Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. *Pain* 2005; **114:** 473–81.

30 Finnerup NB, Norrbrink C, Trok K, et al. Phenotypes and predictors of pain following traumatic spinal cord injury: a prospective study. *J Pain* 2014; **15:** 40–48.

31 Hatem SM, Attal N, Ducreux D, et al. Clinical, functional and structural determinants of central pain in syringomyelia. *Brain* 2010; **133:** 3409–22.

32 Zeilig G, Enosh S, Rubin-Asher D, Lehr B, Defrin R. The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. *Brain* 2012; **135:** 418–30.

33 Ochoa JL, Yarnitsky D. Mechanical hyperalgesias in neuropathic pain patients: dynamic and static subtypes. *Ann Neurol* 1993; **33:** 465–72.

34 Kilo S, Schmelz M, Koltzenburg M, Handwerker HO. Different patterns of hyperalgesia induced by experimental inflammation in human skin. *Brain* 1994; **117:** 385–96.

35 Koltzenburg M, Torebjörk HE, Wahren LK. Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. *Brain* 1994; **117:** 579–91.

36 Gottrup H, Kristensen AD, Bach FW, Jensen TS. Aftersensations in experimental and clinical hypersensitivity. *Pain* 2003; **103:** 57–64.

37 Samuelsson M, Leffler A-S, Hansson P. Dynamic mechanical allodynia in the secondary hyperalgesic area in the capsaicin model—perceptually similar phenomena as in painful neuropathy? *Scand J Pain* 2011; **2:** 85–92.

38 Warncke T, Jørum E, Stubhaug A. Local treatment with the N-methyl-D-aspartate receptor antagonist ketamine, inhibit development of secondary hyperalgesia in man by a peripheral action. *Neurosci Lett* 1997; **227:** 1–4.

39 Gottrup H, Nielsen J, Arendt-Nielsen L, Jensen TS. The relationship between sensory thresholds and mechanical hyperalgesia in nerve injury. *Pain* 1998; **75:** 321–29.

40 Garcia-Larrea L, Convers P, Magnin M, et al. Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain. *Brain* 2002; **125:** 2766–81.

41 Ducreux D, Attal N, Parker F, Bouhassira D. Mechanisms of central neuropathic pain: a combined psychophysical and fMRI study in syringomyelia. *Brain* 2006; **129:** 963–76.

42 Torvin Møller A, Winther Bach F, Feldt-Rasmussen U, et al. Functional and structural nerve fiber findings in heterozygote patients with Fabry disease. *Pain* 2009; **145:** 237–45.

43 Gracely RH, Lynch SA, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. *Pain* 1992; **51:** 175–94.

44 Campbell JN, Raja SN, Meyer RA, Mackinnon SE. Myelinated afferents signal the hyperalgesia associated with nerve injury. *Pain* 1988; **32:** 89–94.

45 Landerholm AH, Hansson PT. Mechanisms of dynamic mechanical allodynia and dysesthesia in patients with peripheral and central neuropathic pain. *Eur J Pain* 2011; **15:** 498–503.

46 Truini A, Biasiotta A, Di Stefano G, et al. Peripheral nociceptor sensitization mediates allodynia in patients with distal symmetric polyneuropathy. *J Neurol* 2013; **260:** 761–66.

47 Liljencrantz J, Björnsdotter M, Morrison I, et al. Altered C-tactile processing in human dynamic tactile allodynia. *Pain* 2013; **154:** 227–34.

48 Seal RP, Wang X, Guan Y, et al. Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. *Nature* 2009; **462:** 651–55.

49 Greenspan JD, Ohara S, Sarlani E, Lenz FA. Allodynia in patients with post-stroke central pain (CPSP) studied by statistical quantitative sensory testing within individuals. *Pain* 2004; **109:** 357–66.

50 Park KM, Max MB, Robinovitz E, Gracely RH, Bennett GJ. Effects of intravenous ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin in human subjects. *Pain* 1995; **63:** 163–72.

51 Gottrup H, Bach FW, Juhl G, Jensen TS. Differential effect of ketamine and lidocaine on spontaneous and mechanical evoked pain in patients with nerve injury pain. *Anesthesiology* 2006; **104:** 527–36.

52 LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *J Neurophysiol* 1991; **66:** 190–211.

53 Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli: central sensitization to A-fibre nociceptor input. *Brain* 1999; **122:** 2245–57.

54 Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL. Quantitative assessment of tactile allodynia in the rat paw. *J Neurosci Methods* 1994; **53:** 55–63.

55 Koltzenburg M, Lundberg LE, Torebjörk HE. Dynamic and static components of mechanical hyperalgesia in human hairy skin. *Pain* 1992; **51:** 207–19.

56 Raja SN, Campbell JN, Meyer RA. Evidence for different mechanisms of primary and secondary hyperalgesia following heat injury to the glabrous skin. *Brain* 1984; **107:** 1179–88.

57 Mahn F, Hüllemann P, Gockel U, et al. Sensory symptom profiles and co-morbidities in painful radiculopathy. *PLoS One* 2011; **6:** e18018.

58 Otto M, Bak S, Bach FW, Jensen TS, Sindrup SH. Pain phenomena and possible mechanisms in patients with painful polyneuropathy. *Pain* 2003; **101:** 187–92.

59 Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell* 2009; **139:** 267–84.

60 Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. *Annu Rev Neurosci* 2010; **33:** 325–47.

61 Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009; **10:** 895–926.

62 Devor M. Sodium channels and mechanisms of neuropathic pain. *J Pain* 2006; **7** (suppl 1)**:** S3–12.

63 Chaplan SR, Guo HQ, Lee DH, et al. Neuronal hyperpolarization-activated pacemaker channels drive neuropathic pain. *J Neurosci* 2003; **23:** 1169–78.

64 Biel M, Wahl-Schott C, Michalakis S, Zong X. Hyperpolarization-activated cation channels: from genes to function. *Physiol Rev* 2009; **89:** 847–85.

65 Berger JV, Knaepen L, Janssen SP, et al. Cellular and molecular insights into neuropathy-induced pain hypersensitivity for mechanism-based treatment approaches. *Brain Res Brain Res Rev* 2011; **67:** 282–310.

66 Nitzan-Luques A, Minert A, Devor M, Tal M. Dynamic genotype-selective "phenotypic switching" of CGRP expression contributes to differential neuropathic pain phenotype. *Exp Neurol* 2013; **250:** 194–204.

67 Coull JA, Boudreau D, Bachand K, et al. Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. *Nature* 2003; **424:** 938–42.

68 Coull JA, Beggs S, Boudreau D, et al. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature* 2005; **438:** 1017–21.

69 Davis KD, Kwan CL, Crawley AP, Mikulis DJ. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J Neurophysiol* 1998; **80:** 1533–46.

70 Harrison JL, Davis KD. Cold-evoked pain varies with skin type and cooling rate: a psychophysical study in humans. *Pain* 1999; **83:** 123–35.

71 Simone DA, Kajander KC. Responses of cutaneous A-fiber nociceptors to noxious cold. *J Neurophysiol* 1997; **77:** 2049–60.

72 Torebjörk HE, Hallin RG. Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. *Exp Brain Res* 1973; **16:** 321–32.

73 Campero M, Serra J, Bostock H, Ochoa JL. Slowly conducting afferents activated by innocuous low temperature in human skin. *J Physiol* 2001; **535:** 855–65.

74 Campero M, Bostock H. Unmyelinated afferents in human skin and their responsiveness to low temperature. *Neurosci Lett* 2010; **470:** 188–92.

75 Madrid R, de la Peña E, Donovan-Rodriguez T, Belmonte C, Viana F. Variable threshold of trigeminal cold-thermosensitive neurons is determined by a balance between TRPM8 and Kv1 potassium channels. *J Neurosci* 2009; **29:** 3120–31.

76 Namer B, Kleggetveit IP, Handwerker H, Schmelz M, Jorum E. Role of TRPM8 and TRPA1 for cold allodynia in patients with cold injury. *Pain* 2008; **139:** 63–72.

77 Zimmermann K, Deuis JR, Inserra MC, et al. Analgesic treatment of ciguatoxin-induced cold allodynia. *Pain* 2013; **154:** 1999–2006.

78 Serra J, Solà R, Quiles C, et al. C-nociceptors sensitized to cold in a patient with small-fiber neuropathy and cold allodynia. *Pain* 2009; **147:** 46–53.

79 Jørum E, Warncke T, Stubhaug A. Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist ketamine—a double-blind, cross-over comparison with alfentanil and placebo. *Pain* 2003; **101:** 229–35.

80 Thunberg T. Förnimmelserne vid till samma ställe lokaliserad, samtidigt pägående köld-och värmeretning. *Uppsala Läkfören Förh* 1896; **1:** 489–95.

81 Craig AD, Bushnell MC. The thermal grill illusion: unmasking the burn of cold pain. *Science* 1994; **265:** 252–55.

82 Craig AD, Reiman EM, Evans A, Bushnell MC. Functional imaging of an illusion of pain. *Nature* 1996; **384:** 258–60.

83 Kern D, Pelle-Lancien E, Luce V, Bouhassira D. Pharmacological dissection of the paradoxical pain induced by a thermal grill. *Pain* 2008; **135:** 291–99.

84 Tominaga M, Caterina MJ. Thermosensation and pain. *J Neurobiol* 2004; **61:** 3–12.

85 Clapham DE. TRP channels as cellular sensors. *Nature* 2003; **426:** 517–24.

86 Patapoutian A, Peier AM, Story GM, Viswanath V. ThermoTRP channels and beyond: mechanisms of temperature sensation. *Nat Rev Neurosci* 2003; **4:** 529–39.

87 Belmonte C, Brock JA, Viana F. Converting cold into pain. *Exp Brain Res* 2009; **196:** 13–30.

88 Madrid R, Donovan-Rodríguez T, Meseguer V, Acosta MC, Belmonte C, Viana F. Contribution of TRPM8 channels to cold transduction in primary sensory neurons and peripheral nerve terminals. *J Neurosci* 2006; **26:** 12512–25.

89 McKemy DD. The molecular and cellular basis of cold sensation. *ACS Chem Neurosci* 2013; **4:** 238–47.

90 Gauchan P, Andoh T, Kato A, Kuraishi Y. Involvement of increased expression of transient receptor potential melastatin 8 in oxaliplatin-induced cold allodynia in mice. *Neurosci Lett* 2009; **458:** 93–95.

91 Kono T, Satomi M, Suno M, et al. Oxaliplatin-induced neurotoxicity involves TRPM8 in the mechanism of acute hypersensitivity to cold sensation. *Brain Behav* 2012; **2:** 68–73.

92 Wasner G, Naleschinski D, Binder A, Schattschneider J, McLachlan EM, Baron R. The effect of menthol on cold allodynia in patients with neuropathic pain. *Pain Med* 2008; **9:** 354–58.

93 Park SB, Lin CS, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC. Dose effects of oxaliplatin on persistent and transient Na+ conductances and the development of neurotoxicity. *PLoS One* 2011; **6:** e18469.

94 Minett MS, Falk S, Santana-Varela S, et al. Pain without nociceptors? Nav1.7-independent pain mechanisms. *Cell Reports* 2014; **6:** 301–12.

95 Sittl R, Lampert A, Huth T, et al. Anticancer drug oxaliplatin induces acute cooling-aggravated neuropathy via sodium channel subtype Na(V)1.6-resurgent and persistent current. *Proc Natl Acad Sci USA* 2012; **109:** 6704–09.

96 Zhao M, Isami K, Nakamura S, Shirakawa H, Nakagawa T, Kaneko S. Acute cold hypersensitivity characteristically induced by oxaliplatin is caused by the enhanced responsiveness of TRPA1 in mice. *Mol Pain* 2012; **8:** 55.

97 Nassini R, Gees M, Harrison S, et al. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. *Pain* 2011; **152:** 1621–31.

98 Descoeur J, Pereira V, Pizzoccaro A, et al. Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. *EMBO Mol Med* 2011; **3:** 266–78.

99 Shirahama M, Ushio S, Egashira N, et al. Inhibition of Ca2+/calmodulin-dependent protein kinase II reverses oxaliplatin-induced mechanical allodynia in rats. *Mol Pain* 2012; **8:** 26.

100 Vestergaard K, Nielsen J, Andersen G, Ingeman-Nielsen M, Arendt-Nielsen L, Jensen TS. Sensory abnormalities in consecutive, unselected patients with central post-stroke pain. *Pain* 1995; **61:** 177–86.

101 Fruhstorfer H. Thermal sensibility changes during ischemic nerve block. *Pain* 1984; **20:** 355–61.

102 Yarnitsky D, Ochoa JL. Release of cold-induced burning pain by block of cold-specific afferent input. *Brain* 1990; **113:** 893–902.

103 Ochoa JL, Yarnitsky D. The triple cold syndrome. Cold hyperalgesia, cold hypoaesthesia and cold skin in peripheral nerve disease. *Brain* 1994; **117:** 185–97.

104 Campero M, Baumann TK, Bostock H, Ochoa JL. Human cutaneous C fibres activated by cooling, heating and menthol. *J Physiol* 2009; **587:** 5633–52.

105 Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. *Nat Neurosci* 2000; **3:** 184–90.

106 McCoy ES, Taylor-Blake B, Street SE, Pribisko AL, Zheng J, Zylka MJ. Peptidergic CGRPα primary sensory neurons encode heat and itch and tonically suppress sensitivity to cold. *Neuron* 2013; **78:** 138–51.

107 Callsen MG, Moller AT, Sorensen K, Jensen TS, Finnerup NB. Cold hyposensitivity after topical application of capsaicin in humans. *Exp Brain Res* 2008; **191:** 447–52.

108 Johanek LM, Meyer RA, Friedman RM, et al. A role for polymodal C-fiber afferents in nonhistaminergic itch. *J Neurosci* 2008; **28:** 7659–69.

109 Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997; **389:** 816–24.

110 Brederson JD, Kym PR, Szallasi A. Targeting TRP channels for pain relief. *Eur J Pharmacol* 2013; **716:** 61–76.

111 Treede RD, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol* 1992; **38:** 397–421.

112 Wu Q, García-Larrea L, Mertens P, Beschet A, Sindou M, Mauguière F. Hyperalgesia with reduced laser evoked potentials in neuropathic pain. *Pain* 1999; **80:** 209–14.

113 Madsen CS, Johnsen B, Fuglsang-Frederiksen A, Jensen TS, Finnerup NB. The effect of nerve compression and capsaicin on contact heat-evoked potentials related to Aδ- and C-fibers. *Neuroscience* 2012; **223:** 92–101.

114 Dib-Hajj SD, Black JA, Waxman SG. Voltage-gated sodium channels: therapeutic targets for pain. *Pain Med* 2009; **10:** 1260–69.

115 Dib-Hajj SD, Rush AM, Cummins TR, et al. Gain-of-function mutation in Nav1.7 in familial erythromelalgia induces bursting of sensory neurons. *Brain* 2005; **128:** 1847–54.

116 Ørstavik K, Weidner C, Schmidt R, et al. Pathological C-fibres in patients with a chronic painful condition. *Brain* 2003; **126:** 567–78.

117 Ma W, Zhang Y, Bantel C, Eisenach JC. Medium and large injured dorsal root ganglion cells increase TRPV-1, accompanied by increased alpha2C-adrenoceptor co-expression and functional inhibition by clonidine. *Pain* 2005; **113:** 386–94.

118 Kim HY, Park CK, Cho IH, Jung SJ, Kim JS, Oh SB. Differential changes in TRPV1 expression after trigeminal sensory nerve injury. *J Pain* 2008; **9:** 280–88.

119 Urano H, Ara T, Fujinami Y, Hiraoka BY. Aberrant TRPV1 expression in heat hyperalgesia associated with trigeminal neuropathic pain. *Int J Med Sci* 2012; **9:** 690–97.

120 Dray A. Neuropathic pain: emerging treatments. *Br J Anaesth* 2008; **101:** 48–58.

121 Colombo E, Francisconi S, Faravelli L, Izzo E, Pevarello P. Ion channel blockers for the treatment of neuropathic pain. *Future Med Chem* 2010; **2:** 803–42.

122 Kishore-Kumar R, Max MB, Schafer SC, et al. Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990; **47:** 305–12.

123 Vranken JH, Hollmann MW, van der Vegt MH, et al. Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: a randomized, double-blind, placebo-controlled trial. *Pain* 2011; **152:** 267–73.

124 Yucel A, Ozyalcin S, Koknel Talu G, et al. The effect of venlafaxine on ongoing and experimentally induced pain in neuropathic pain patients: a double blind, placebo controlled study. *Eur J Pain* 2005; **9:** 407–16.

125 Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. *Pain* 2011; **152:** 1018–23.

126 Stacey BR, Barrett JA, Whalen E, Phillips KF, Rowbotham MC. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. *J Pain* 2008; **9:** 1006–17.

127 Serpell MG, and the Neuropathic pain study group. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. *Pain* 2002; **99:** 557–66.

128 Sindrup SH, Andersen G, Madsen C, Smith T, Brøsen K, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. *Pain* 1999; **83:** 85–90.

129 Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology* 1998; **50:** 1837–41.

130 Teixeira MJ, Okada M, Moscoso AS, et al. Methadone in post-herpetic neuralgia: a pilot proof-of-concept study. *Clinics (Sao Paulo)* 2013; **68:** 1057–60.

131 Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007; **133:** 210–20.

132 Vestergaard K, Andersen G, Gottrup H, Kristensen BT, Jensen TS. Lamotrigine for central poststroke pain: a randomized controlled trial. *Neurology* 2001; **56:** 184–90.

133 Wallace MS, Magnuson S, Ridgeway B. Efficacy of oral mexiletine for neuropathic pain with allodynia: a double-blind, placebo-controlled, crossover study. *Reg Anesth Pain Med* 2000; **25:** 459–67.

134 Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. *Ann Neurol* 1995; **37:** 246–53.

135 Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. *Ann Neurol* 2008; **64:** 274–83.

136 Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain* 2001; **91:** 177–87.

137 Baranowski AP, De Courcey J, Bonello E. A trial of intravenous lidocaine on the pain and allodynia of postherpetic neuralgia. *J Pain Symptom Manage* 1999; **17:** 429–33.

138 Attal N, Gaudé V, Brasseur L, et al. Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* 2000; **54:** 564–74.

139 Finnerup NB, Biering-Sørensen F, Johannesen IL, et al. Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. *Anesthesiology* 2005; **102:** 1023–30.

140 Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D. Effects of IV morphine in central pain: a randomized placebo-controlled study. *Neurology* 2002; **58:** 554–63.

141 Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. *Neurology* 2004; **62:** 218–25.

142 Eide PK, Jørum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994; **58:** 347–54.

143 Gormsen L, Finnerup NB, Almqvist PM, Jensen TS. The efficacy of the AMPA receptor antagonist NS1209 and lidocaine in nerve injury pain: a randomized, double-blind, placebo-controlled, three-way crossover study. *Anesth Analg* 2009; **108:** 1311–19.

144 Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. *Clin Neuropharmacol* 1995; **18:** 360–68.

145 Canavero S, Bonicalzi V. Intravenous subhypnotic propofol in central pain: a double-blind, placebo-controlled, crossover study. *Clin Neuropharmacol* 2004; **27:** 182–86.

146 Simpson DM, Schifitto G, Clifford DB, et al, and the 1066 HIV Neuropathy Study Group. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. *Neurology* 2010; **74:** 413–20.

147 Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain* 2002; **96:** 375–83.

148 Falah M, Madsen C, Holbech JV, Sindrup SH. A randomized, placebo-controlled trial of levetiracetam in central pain in multiple sclerosis. *Eur J Pain* 2012; **16:** 860–69.

149 Haroutiunian S, Nikolajsen L, Bendtsen TF, et al. Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy. *Pain* 2014; published online April 2. http://dx.doi.org/10.1016/j.pain.2014.03.022.

150 Moreno-Duarte I, Morse LR, Alam M, Bikson M, Zafonte R, Fregni F. Targeted therapies using electrical and magnetic neural stimulation for the treatment of chronic pain in spinal cord injury. *Neuroimage* 2014; **85:** 1003–13.

151 Nardone R, Höller Y, Leis S, et al. Invasive and non-invasive brain stimulation for treatment of neuropathic pain in patients with spinal cord injury: a review. *J Spinal Cord Med* 2014; **37:** 19–31.

152 Witting N, Svensson P, Jensen TS. Differential recruitment of endogenous pain inhibitory systems in neuropathic pain patients. *Pain* 2003; **103:** 75–81.

153 Petersen GL, Finnerup NB, Nørskov KN, et al. Placebo manipulations reduce hyperalgesia in neuropathic pain. *Pain* 2012; **153:** 1292–300.

154 Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. *Lancet Neurol* 2013; **12:** 1084–95.