Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms

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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.2–4 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).1

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.5–10 Allodynia and hyperalgesia are symptoms and signs that might serve as readouts for pain and thus contribute to improved delineation of neuropathic pain.5–10

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.1 The authors of a systematic review19 showed that the prevalence of pain associated with predominately 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

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 stimulus 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
The prevalence of alldynia 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 pressure-evoked pain reported in 52% of patients. Any pain evoked by brush, pressure, or cold stimuli was present 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 alldynia and hyperalgesia**

Theoretically, alldynia can be defined as a painful response to a non-nociceptive stimulus—ie, one not encoded by nociceptors—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 alldynia 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. The clinical assessment of alldynia 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).

More detailed but time-consuming testing includes laser stimuli and quantitative sensory testing, with the use of monofilaments, pressure or pinch algometers, and thermotest equipment. Sensory profiles including different aspects of alldynia and hyperalgesia have been described. 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. 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 affective

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**Table:** Assessment of alldynia and hyperalgesia

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

PHN=postherpetic neuralgia. CRPS=complex regional pain syndrome.
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. 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. 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,4 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 injury13,12 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.

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.10 On the basis of experimental studies using capsaicin and freezing lesions, Kilo and colleagues32 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
seen in the secondary hyperalgesic area after capsaicin application, with similar temporospatial stimulus parameters and pain descriptors.\textsuperscript{15,27} 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.\textsuperscript{18,19} Stimulus-dependent pain is, by nature, only present in areas with preserved ascending sensory pathways and, consequently, patients with alldynia and hyperalgesia often have fewer sensory deficits compared with patients with spontaneous pain only.\textsuperscript{19,29,41} 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.\textsuperscript{41}

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

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 from 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 oropharyngeal and palatal area, and the maxillary and mandibular areas of the somatosensory cortex. (B) Nerve injury pain is a common cause of neuropathic pain associated with dynamic 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 amputation (eg, postherpetic neuralgia). In these cases, the clinical picture is characterised by negative symptoms, with simultaneous sensory loss (left) surrounded by areas of alldynia in the painful area (right). The allodynic area can be mapped and specified for each sensory modality. The illustrated case shows an intrapartetar branch of the spinothalamic system 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—in 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 by the spinothalamic tract (left). In the same area, there are positive symptoms and signs with spontaneous pain and alldynia (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.
instances. In a classic investigation by Gracely and colleagues, a local anaesthetic block of nerve injury trigger points attenuated both ongoing 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. Studies of reaction times in dynamic mechanical allodynia confirm that large myelinated fibres mediate the disorder. 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 modulation 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.

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, elicited burning pain and dynamic mechanical allodynia increased after warming of the skin. The authors of another study 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 with peripheral neuropathy and 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, 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, 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 and depend on central changes in addition to peripheral input. Based on differential nerve fibre blocks by compression, punctate hyperalgesia is driven by activity in Aδ fibres and a minor input from C fibres, by contrast with the Aβ-mediated dynamic mechanical allodynia. Various animal models of nerve injury pain use a monofilament stimulation method to evoke motor responses, 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—by contrast with dynamic mechanical allodynia and similar to heat hyperalgesia—is mediated by sensitised peripheral nociceptors. Importantly, the authors of a clinical study 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. However, deep (static) mechanical hyperalgesia has subsequently been noted in other peripheral neuropathic pain conditions, such as traumatic nerve injuries and diabetic neuropathies.

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.

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,1·3, Na,1·7, Na,1·8, and Na,1·9. Other channels in the development of ectopia are the neuronal hyperpolarisation-activated cation channels, which, together with calcium channels, are important to neurons to display repetitive firing patterns. This peripheraly 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.43,39

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.40,46 Post synaptic
changes probably contribute to alldynia too. These
include increased activity at NMDA, AMPA, and metabotro pic
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.48,48 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 contribu-
tion of each of these mechanisms to the different
symptoms and signs seen in individual neuropathic pain
conditions and individual patients remains a future
challenge.

Thermal allodynia and hyperalgesia
Cold perception and alldynia

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).60,71 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,3 although C fibres have also been shown to respond to innocuous
cold.72,73 The existence of two types of neurons has been
suggested to explain 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.73

Cold allodynia is a frequent finding in neuropathic
pain, but it also is seen in patients with persistent
sequelae after cold injuries75 and in ciguatera, a
neurological disease caused by consumption of cigua-
toxins, which are a group of compounds that accumulate
in some tropical and subtropical fish.76 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,77 a
pricking sensation in a patient with acute oxaliplatin
neuropathy, or an intense cold or burning sensation in

Panel: The thermal grill illusion as a model for cold alldynia

After studies by Thunberg80 in the 19th century on what was termed the thermal grill
illusion, there has been an interest in mechanisms giving rise to thermal alldynia. 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-pincher-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).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.83 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 group84 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.

Molecular mechanisms of cold sensation

The exact cellular and molecular mechanisms of cold
sensation are not wholly understood. However, both
electrically 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.85,86

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 cells88

www.thelancet.com/neurology Vol 13 September 2014 929

929
also expressing TRPM8, but at a lower level, have been suggested to lead to cold pain. Na,1-8, which is also expressed in high-threshold cells, might elicit a response in the cold pain channel. 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). Micro-neurographic recordings in a patient with small-fibre neuropathy and cold allodynia showed sensitisation to cold and menthol responsiveness of subtypes of C nociceptors, which provides a potential explanation for cold allodynia. TRPM8 upregulation might explain this sensitisation. Although supported by animal studies, the role of TRPM8 upregulation in human neuropathic pain is less clear, and patients with neuropathic pain with cold allodynia might have both increased and decreased 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. 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. Authors of experimental studies suggest that different sodium channels are important. Whereas Na,1-7 expression within the peripheral nervous system has been proved necessary for mechanical or cold-evoked responses in some models, this is not true for oxaliplatin-induced cold behaviour, in which Na,1-6 expression plays an essential part, as likewise found in an earlier study. The authors of studies in rodents have also implicated TRPA1 receptors, potassium hyperpolarisation-activated cation channels, and calcium channels 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.

Blockade of Aδ fibres during nerve compression or disease 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 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 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.

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 mechanooheat 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.\(^{39}\) The key transducer in warm and heat pain–responding neurons is TRPV1, the activity of which increases gradually with temperature.\(^{40}\) 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. Resiniferoxin—a potent capsaicin analogue—produces long-lasting desensitisation of TRPV1 receptors\(^{40}\) 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.\(^{39}\)

Heat hyperalgesia is probably likewise a result of central mechanisms and is present in 10% of patients with central pain.\(^{44}\) Hyperalgesia to laser stimuli in both peripheral and central neuropathic pain has been found to coexist with decreased, delayed, and desynchronised laser-evoked potentials.\(^{41,42}\) 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,\(^{41}\) 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.\(^{44}\)

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.\(^{45}\) This condition, which is an autosomal dominant disorder, is caused by a missense mutation in the Na,1-7 channel, resulting in a reduction of the activation threshold.\(^{46}\) With microneurography, ectopic activity has been noticed in C fibres from these patients, which represents one example of increased membrane excitability.\(^{46}\)

In nerve injury, expression of the key heat transducer TRPV1 changes. TRPV1 is downregulated in injured nerve fibres, but upregulated in uninjured fibres,\(^{47,48}\) and has a de-novo expression in cells belonging to the Aδ and Aβ type.\(^{39}\) 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.\(^{49,50}\)

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,\(^{51,52}\) serotonin-norepinephrine reuptake inhibitors,\(^{53,54}\) gabapentinoids,\(^{55–57}\) opioids,\(^{52–54,58}\) cannabinoids,\(^{59}\) lamotrigine,\(^{60}\) mexiletine,\(^{61}\) lidocaine gel,\(^{62}\) and botulinum toxin-A\(^{63}\) 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.\(^{52,53,56–58}\)

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\(^{64}\) and dynamic mechanical allodynia or temporal summation to repetitive pinprick predicted the response to lamotrigine in spinal cord injury,\(^{65}\) whereas dynamic mechanical allodynia was a negative predictor of the overall effect of pregabalin in postherpetic neuralgia\(^{66}\) and levetiracetam in multiple sclerosis.\(^{67}\) These results were all based on posthoc analyses. Six intravenous treatment trials\(^{52,53,56–58,68–70}\) were done to examine alldynia or hyperalgesia as predictors of overall pain-relieving effect, but only as a predefined outcome in one of them.\(^{71}\) In one study, static or dynamic mechanical allodynia predicted the response to intravenous lidocaine,\(^{68}\) whereas authors of the other studies failed to find evoked pain to predict the response to lidocaine,\(^{52,53,56–58,71}\) morphine,\(^{69}\) or ketamine.\(^{68}\)

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,
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.180

Non-pharmacological modulation
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.178,179 The authors of these neuromodulation studies took advantage of the powerful control exerted by the brain on dorsal horn pain processing—e.g., Witting and colleagues182 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 pain183 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.181 This non-specificity limits the possibility of dissection of the underlying pathophysiologicals. However, with novel and more specific drugs, these subtypes of allodynia and hyperalgesia could be used as additional endpoint measures in clinical trials.

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.

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Review


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