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Review

The clinical picture of neuropathic pain

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Abstract

Neuropathic pains refer to a heterogenous group of pain conditions characterised by lesion or dysfunction of the normal sensory pathways. Clinical characteristics include: delayed onset of pain after nervous system lesion, pain in area of sensory loss, spontaneous and different evoked types of pains. It has so far only been possible to classify these pains on basis of underlying cause or on anatomical location. The mechanisms underlying neuropathic pain are not yet clear, but neuronal hyperexcitability in those neurons that have lost their normal patterned input seems to be a common denominator for many, if not all types, of neuropathic pains. Along these lines, a mechanism-based classification has recently been proposed, which is an attractive approach because it provides a frame for a rationally based therapy of neuropathic pains. The clinical manifestations of neuronal hyperexcitability due to nervous system lesions is described.

Keywords: Neuropathic pain; Hyperexcitability; Manifestations; Pain, spontaneous; Pains, evoked

1. Introduction

Pain associated with disease or injury of the peripheral or central nervous system is neuropathic pain, a challenging pain category which is considered to be particularly difficult to treat.

Neuropathic pain is not a single entity; it is a heterogeneous group of conditions that differs not only in aetiology but also in location (Sindrup and Jensen, 1999; Woolf and Mannion, 1999) and symptoms do neither respect cause nor anatomical site (Bennett, 1994a,b; Koltzenburg, 1995; Jensen, 1996). Diabetes, immune deficiencies, malignant diseases, traumatic and ischemic disorders may all give rise to neuropathic pain. The anatomical site of lesions causing neuropathic pain are multiple: they can be located from the peripheral receptor to the highest cortical centers. The most common locations are the peripheral nerves, the plexus, dorsal nerve roots, the spinal cord and the brain. In spite of the diverse aetiology and topography, the clinical picture is in many cases surprisingly similar suggesting that pain in these many disorders share common mechanisms.

Recent studies have shown that a cascade of temporally related biological changes follow damage to the nervous system, which eventually results in a sensitisation of neural elements involved in the processing of noxious information (for review, see Besson, 1999; Costigan and Woolf, 2000; Woolf and Salter, 2000). Although the significance of these molecular changes following nerve damage still are under exploration, they may represent a link that ties different neuropathic conditions together. Hence, an understanding of the dynamic events after nerve damage may be a key to understand hyperexcitability and how to treat it.

A major recent contribution is the discovery that sustained noxious input induces changes in the nervous system which lead to altered processing of noxious information. This plasticity of the nervous system is displayed at many levels of the neuraxis from the peripheral nociceptor to the spinal cord and even to the cortex of the brain (Besson, 1999; Dubner, 1991; Casey, 2000). This paper reviews the clinical picture of neuropathic pain, its aetiology, and how the different conditions can be diagnosed both at the bedside and in the laboratory. Evaluation of neuropathic pain is often difficult; it is time consuming, requires expert skill and combined use of laboratory techniques (Jensen and Gottrup, in press).

2. Classification of neuropathic pain

Classification of neuropathic pain is an important but still an unsettled issue. The traditional approach for classi-

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fication of neuropathic pain is a division of pain on basis of the underlying aetiology or location of nerve injury (Ashbury and Fields, 1984; Fields, 1990). Another—and more recent introduced classification—seeks to divide the pain on basis of presumed mechanisms underlying the neuropathic pain as will be discussed in more detail below. Finally, it is possible to classify the pain on basis of drugs, i.e. the response to an agent with a pharmacological action on one or several molecular mechanisms (Sindrup and Jensen, 1999, 2000).

Table 1 presents a common used scheme for classifying neuropathic pains based on aetiology and anatomy. The aetiologies giving rise to neuropathic pain range from benign to malignant from traumatic to metabolic and from vascular to immunological. The listed causes are an incomplete list of disorders. More recently, a mechanism-based classification has been suggested by Woolf et al. (1998). This classification identify the mechanisms that may be involved in a particular pain patient and based on this suggests a rational drug therapy. It is beyond the scope of this chapter to present a detailed description of current mechanisms, some of which are still hypothetical (for review, see Woolf and Mannion, 1999; Woolf and Salter, 2000). However, briefly these mechanisms include the following.

(1) Pathological activity or sensitized nociceptors with recruitment of silent nociceptors and ectopic activity in spinal ganglion cells (Wall and Gutnick, 1974; Wall and Devor, 1983; Amir and Devor, 1993; Chapman et al., 1998). The increased afferent neuronal barrage causes sensitisation of dorsal horn neurons.

(2) A severe loss of small fibre input may also give rise to central sensitisation due to a spinal reorganisation from sprouting of large myelinated fibres into superficial "nociceptive" laminae in the dorsal horn (Woolf and Salter, 2000).

(3) Inflammation of nerve trunks with corresponding ectopic nerve activity represents a source for central sensitisation.

(4) Sympathetic activity may sensitise nociceptors.

(5) Altered brain processing due to plastic changes with recruitment of new brain areas usually not involved in pain (Casey et al., 1995; Casey, 2000).

Table 1
Classification of neuropathic pain according to disease and anatomical site

Peripheral	Spinal	Brain
Neuropathies	Multiple sclerosis	Stroke
Herpes zoster	Spinal cord injury	Multiple sclerosis
Nerve injuries	Arachnoiditis	Neoplasms
Amputations	Neoplasms	Syringomyelia
Plexopathies	Syringomyelia	Parkinson's disease?
Radiculopathies	Spinal stroke	Epilepsia?
Avulsions		
Neoplasms		
Trigeminal neuralgia		

Because of the intimate connection between the periphery and the central parts and because of the considerable plasticity in the nociceptive system, different mechanisms may be involved in each patient and one mechanism may account for several etiological different conditions and account for the various symptoms (Woolf and Mannion, 1999). For example, a diabetic patient may have: steady pain, touch evoked pain, paroxysms and non-painful paraesthesias. In these cases, several mechanisms can be involved such as tissue injury due to ischemia, sensitisation of peripheral receptors, ectopic activity in sprouting regenerating fibers, phenotypic changes in dorsal root ganglia cells, spinal reorganisation, etc. An additional approach for classifying pain involves the use of specific pharmacological agents. Based on their mode of action and their different molecular targets, drugs may be used to determine if a particular symptom can be modulated by a drug with a specific action. While a mechanism-based classification is an attractive approach, it is at present not known if this provides a better way for classifying neuropathic pain. However, it will be of interest to determine the possible additional yield provided by a hierarchical structured system that classifies pain on basis of:

1. symptoms,
2. symptoms + signs,
3. symptoms + signs + mechanisms and
4. symptoms + signs + mechanisms + pharmacological analysis.

Such studies are currently under way.

3. Symptoms in neuropathic pain

Clinically neuropathic pain is characterised by the presence of spontaneous ongoing types of pain termed stimulus-independent pains and various types of evoked pains called stimulus-dependent pains, reflecting the hyperexcitability in the nervous system (Bennett, 1994a; Bonica, 1992; Coderre and Katz, 1997; Dubner, 1991).

3.1. Stimulus-independent pain

These pains are spontaneous and may be continuous or paroxysmal. The character differs, but can be shooting, shock-like, aching, cramping, crushing, smarting, burning, etc. Episodic, paroxysmal types of pain are second-lasting shooting, electric, shock-like or stabbing in their character. In its most typical form, paroxysmal pain is seen in tic douloureux, in entrapment neuropathies, in amputees and in luetic diseases (Bennett, 1994a; Nikolajsen and Jensen, 2000; Jensen and Nikolajsen, 2000). In tabes dorsalis, shooting pains are described often in the form of transverse lightning pains in the legs and provoked by emo-

tional stress (Boivie, 1992, 1999). Shooting types of pain can occur in cases with nerve compression (e.g. slipped disc, vertebral compression, neoplastic nerve compression, and entrapment syndromes).

The mechanism underlying stimulus-independent pain is assumed to reflect an increased discharge in sensitised C-nociceptors, alternatively they may be due to increased activity in sensitised receptors associated with large myelinated A fibres and giving a sensation of burning or dysesthesia.

3.2. Stimulus-dependent pains

The stimulus-evoked pain is classified according to the stimulus type that provokes them. Several types of evoked pains can be present. However, the most prominent are: mechanical, thermal or chemical (Devor, 1994).

In some patients, several of these phenomena may be present, in others only one type of stimulus evoked pain is present. For example, patients with nerve injury pain or amputation may have trigger points to mechanical stimuli, but with entirely normal thermal sensation. In some patients with neuropathy, cold allodynia may be the only abnormality present. Therefore, a series of stimuli have to be used to document or exclude abnormality. The evoked pains are usually brief, lasting only for the period of stimulation but sometimes they can persist even after cessation of stimulation causing aftersensations (see below), which can last for minutes, hours, or perhaps days. In such cases, distinction between evoked and spontaneous types of pain can be difficult.

4. Findings in neuropathic pain

4.1. Sensory deficit and pain

An essential part of neuropathic pain is a loss (partial or complete) of afferent sensory function and the paradoxical presence of certain hyperphenomena (see below) in the painful area. In some patients, the sensory deficit may be gross in others subtle and difficult to detect with bed-side methods, but quantitative measures can usually disclose minor changes (Lindblom, 1994; Jensen and Brennum, 1994). The sensory loss may involve all sensory modalities, but a loss of spinothalamic functions (cold, warmth, pinprick) appears to be crucial and the possibility that such spinothalamic loss is a requirement has been raised (Jensen and Lenz, 1995). For example, in post-stroke pain, large-scale studies suggest that sensory deficit is a necessary, albeit not a sufficient criteria for the occurrence of pain (Andersen et al., 1995; Vestergaard et al., 1995). Recent studies indicate that sensory loss and areas with hypersensitivity also can be characteristic features in central pain caused by spinal cord injury. It remains to be seen whether similar patterns also occurs in other neuropathic pain states.

4.2. Allodynia and hyperalgesia

Hyperalgesia (= the lowering of pain threshold and an increased response to noxious stimuli), allodynia (= the evocation of pain by non-noxious stimuli) are typical elements of neuropathic pain. Several types of mechanical hyperalgesia can be distinguished (Bennett, 1994a; Gracely et al., 1992; Ochoa and Yarnitsky, 1993; Kilo et al., 1994):

- static hyperalgesia: gentle pressure on skin evokes pain;
- punctate hyperalgesia: punctate stimuli such as pinprick evokes pain;
- dynamic hyperalgesia: light brush evokes a sensation of pain.

Allodynia is also seen with thermal stimuli:

- cold hyperalgesia: cold stimuli evoke a sensation of pain (the underlying mechanism is unclear but cortical reorganisation due to loss of cold Aδ-fibres is one possibility);
- heat hyperalgesia: warm and heat stimuli evoke pain (sensitisation of C-nociceptors and a corresponding sensitisation of second order neurons).

The dynamic mechanical allodynia is mediated by A-β fibres, while the static high threshold type is evoked by blunt pressure appears to be mediated by sensitised C nociceptors (Torebjörk et al., 1992; Koltzenburg et al., 1992, 1994; Kilo et al., 1994; Ochoa and Yarnitsky, 1993; Baron, 2000). The static type of hyperalgesia would be expected also to be associated with a thermal hyperalgesia, which however is not always the case (Lindblom and Verillo, 1979). Punctate hyperalgesia evoked by pinprick usually a stiff von Frey hair is mediated by sensitised Aδ-nociceptors (Ziegler et al., 1999). While certain types of hyperalgesia reflect sensitization of receptors, allodynia is always a central phenomenon mediated by large myelinated fibers (Hansson and Lindblom, 1992).

Allodynia has been considered to be only a cutaneous disorder but recent findings point to the presence also of a deep type of allodynia. For example, in post-stroke pain, which is a central neuropathic disorder, deep pain may be associated with a lowering of pain threshold to mechanical pressure and with an exaggerated response to a challenge of i.m. 0.5 ml 9% hypertonic saline into the painful deep tissue (unpublished observations). In patients with sciatica or the Guillain–Barré syndrome, proximal limb pain is often accompanied by soreness on palpation. Allodynia can usually be separated from the tenderness seen in musculoskeletal pain conditions. In patients with allodynia,

a firm pressure in the allodynic area can sometimes relieve their pains. These findings indicate that at the receptor level, separate mechanisms are involved, e.g. touch allodynia is elicited by rapidly adapting mechanoreceptors, while the pressure-induced pain relief may recruit slowly adapting mechanoreceptors in addition to other deeply located receptors.

When present, allodynia or hyperalgesia can be quantitated by measuring intensity, threshold for elicitation, duration and area of distribution (Eide et al., 1994; Felsby et al., 1996; Max et al., 1995; Nikolajsen et al., 1996; Gottrup et al., 1998a,b, 2000). The evocation of pain by a stimulus implies that a complete abolition of afferent information does not give rise to allodynia. Nevertheless, on occasions, in spite of a complete injury abnormal sensations may at a later point develop, and present itself as an anaesthesia dolorosa in the deafferented body part. These phenomena can probably be ascribed to spontaneous firing in nerve sprouts which leave altered the innervation area of pheripheral nerves, an expansion of receptive fields of sensitised central neurons that have lost their normal innervation or to a combination of such mechanisms. Hyperalgesia can be provoked in normals following blockade of large diameter afferent fibers. Pinprick or cold is now perceived as burning or squeezing pain suggesting that afferent fibers under normal conditions exert an inhibitory input on dorsal horn neuronal activity. In neuropathic pain, this inhibition may be disrupted. The chemical mediators of this inhibition are unknown, but GABA (gamma amino butyric acid) and glycine are likely candidates.

4.3. Hyperpathia

A variant of hyperalgesia and allodynia is the prototypic disorder in neuropathic pain, whenever there is a fiber loss. In these cases, an explosive pain response is suddenly evoked from cutaneous areas with increased sensory detection threshold when the stimulus intensity exceeds sensory threshold. Hyperpathia is a reflection of the peripheral or central deafferentation leading to an elevation of threshold on one hand and a central hyperexcitability on the other hand due to lost or abnormal input from afferents.

4.4. Paroxysms

Distinct from the above type of evoked pains some patients complain of shooting, electric, shock like or stabbing pain that occur spontaneously, or more often following stimulation. These types of pain are termed paroxysms and can be elicited by an innocuous tactile stimulus or by a blunt pressure. In its most typical form, the paroxysms are seen in tic douloureux, where they dominate the clinical picture; it is characteristic that non-noxious tactile input elicit these paroxysms, while noxious stimuli usually fail to do so (Terrence and Jensen, 1999).

4.5. Paraesthesia

Paraesthesia is abnormal but non-painful sensations, which can be spontaneous or evoked. They are often described as pins and needles and are assumed to reflect spontaneous bursts of activity in A-β fibres.

4.6. Dysesthesia

Dysesthesia is an abnormal unpleasant but not necessarily painful sensation, which can be spontaneous or provoked by external stimuli. These sensations are probably due to sensitisation of C-nociceptors and it is unlikely that there is any qualitative difference between evoked dystesthesia and evoked hyperalgesia.

4.7. Referred pain and abnormal pain radiation

In neuropathic pain, abnormal spread of pain can be seen both following peripheral and central lesions. In painful myelopathic disorders, patients may experience a circular spreading sensation following single punctate stimulation with a relationship between spreading of pain and intensity of perceived pain. Similarly, there is a relationship between the magnitude of deep muscle pain and the area of referred cutaneous pain from such deep structures (Kellgren, 1938; Torebjörk, 1984; Graven-Nielsen et al., 1997). While referral generally is described from deep to cutaneous structures, the reverse is far less common. Referral can be seen following skin sensitization, e.g. in capsaicin-induced hyperalgesia (Gottrup et al., 1998a,b; Witting et al., 2000; Jensen et. al., unpublished observations). There is a link between pain intensity, pain radiation and pain referral. The magnitude of pain from, e.g. deep tissue is proportional to the extent of referral in cutaneous tissue both experimentally and clinically (Torebjörk et al., 1984; Graven-Nielsen, in preparation; Bonica, 1992). Similarly, in experimental pain induced by intradermal capsaicin the spread increases with increasing pain intensity (La Motte et al., 1991).

Experimental studies in humans and animals (for review, see Dubner, 1991) have shown that such abnormal radiation can be related to changes in spinal wide dynamic range (WDR) neurons encoding noxious information. Wide dynamic range cells are in part characterised by small receptive zones that can be excited by non-noxious stimuli (touch, gentle pressure) surrounded by a much larger zone from which noxious stimuli (pinch, firm pressure, temperature > 45 °C) can evoke neuronal discharges. These large receptive field zones are overlapping, extend over several dermatomes and their receptive fields are a reflection of synaptic propriospinal interconnections in the spinal dorsal horn that extends over several segments. Therefore, a noxious stimulus will, in contrast to a non-noxious stimulus, activate several wide dynamic range neurons and

increasing the stimulus intensity will result in activation of further wide dynamic range neurons in a rostro-caudal distribution manner. Since increasing stimulus intensities recruit more dorsal horn neurons, the degree of radiation and referral is likely to be a reflection of a progressive recruitment of wide dynamic range neurons spreading along the spinal cord. A similar mechanism may be involved in the sensory abnormalities seen in patients with nerve injury and extensive spread of sensory dysfunction to the contralateral side as well as proximally and distally to the lesion.

4.8. Wind-up like pain and aftersensations

Wind-up like pain or abnormal temporal summation is the clinical equivalent to increasing neuronal activity following repetitive C-fiber stimulation > 0.3 Hz (Mendel and Wall, 1965; Dickenson, 1990; McMahon et al., 1993). In humans, such pains may either be evoked by repetitive noxious or non-noxious stimulation from normal or hyperalgesic cutaneous areas, respectively. When repetitive low threshold stimuli, which exclusively activate A-beta fibers, are applied at intervals < 3 s give rise to pain, this means that these stimuli have gained access to central wind-up mechanisms that normally is reserved nociceptors and C-fiber input (Price, 1991; Price et al., 1977, 1989). The wind-up like pain can be produced by a variety of stimuli including mechanical, thermal and electrical types. Aftersensations—the persistence of pain long after termination of a painful stimulus—is another characteristic features of neuropathic pain (Lindblom, 1994), which is closely related to a coexistent dynamic or static hyperalgesia (Gottrup et al., 2000). Consistent with this notion, windup-like pain and aftersensations may both reflect neuronal discharges in wide dynamic range neurons.

5. Assessment of neuropathic pain

5.1. History

The examination of the patient with suspected neuropathic pain starts with the history. Patients may describe their pains in a variety of ways: they may complain of unpleasant pricking or sticking sensations in parts of the body. They may have a burning, scalding, aching or deep sore pain. A characteristic in many neuropathic pain conditions is the presence of allodynia following exposure to nonpainful cold. In such cases, patients may describe their pain in a paradoxical manner like burning-hot or ice-burning as if holding a snow-ball in the hand. Some patients with central pain complain of pain by movement in which the movement itself elicits a tightening squeezing or burning sensation in the skin. At other times, the pain is one of paroxysms with stabbing, shooting, lancinating types of pain. Paroxysms last seconds, but can be repeated with ultra short intervals giving a false impression of continuous types of pains.

An important point concerns the possible classification of pain just on basis symptoms. There are at present no data documenting such classification. However, Galer and Jensen (1997) has presented a neuropathic pain scale in which presumed common symptoms encountered in neuropathic pain are recorded and scored: intensity, sharp, heat, dull, cold, itchy skin sensitivity are recorded supplied by a few other phenomena. While this test has shown validity in normal volunteers and in response to treatment, it remains to be seen, if it can distinguish neuropathic pain patients form other chronic pain patients.

5.2. Distribution of sensory abnormalities on a map

The distribution of different pain types on a phantom map represents an important initial step for pain assessment. The area can be quantitated and the size over time spontaneous as well as evoked and following treatment can be measured. Automatic drawing systems have been proposed, which may be of value for more accurate measurements.

5.3. Clinical examination

Sensory examination at bedside includes: pinprick, touch, cold, heat and vibration. Pinprick sensation is assessed by the response to pinprick stimuli; touch is examined by gently stroking the involved skin area with a cotton swab, cold and warm sensation is recorded by measuring the response to a specific cold or warm thermal stimulus, e.g. thermorollers kept at 20 and 40 °C, respectively (Lindblom, 1994; Jensen and Brennum, 1994). Cold sensation can also be assessed by the response to an acetone drop on the skin. Vibration is assessed by a tuning fork placed at strategic points (malleol, interphaleangel joints, etc.). At present there is no consensus about the site, where such activity should be measured, but it is generally agreed that this is best done in the area with maximal abnormality using the contralateral area as control. However, it needs to be said that some animal studies have pointed to contralateral segmental changes following a unilateral nerve or root lesion (Coderre and Melzack, 1985, 1987). An examination at the mirror area of a nerve injury may therefore not necessarily represent a true control, but without a normal material for the various psychophysical modalities, this appears at the moment to be the best alternative. For all types of stimuli, the response can simply be graded as: normal, decreased or increased (Andersen et al., 1995).

If the response is increased, it is classified as dysesthetic, hyperalgesic or allodynic. A correlation of spontaneous pain and sensory response in the painful area suggest that the two phenomena are reflections of the same phenomenon: a central sensitisation of dorsal horn neurons

Table 2
Stimulus and response measures in neuropathic pain patients

Stimulus modality	Threshold	Summation	Stimulus Response	Area of abnormality
Touch	Detection	Touch evoked allodynia	+	+
Von Frey hair	Detection Pain	Repetitive stimulation > 2Hz	+	+
Thermal	Detection Pain	Repetitive stimulation	+	+
Mechanical pressure	Pain	Repetitive stimulation	+	+
Capsaicin	Pain	Repetitive stimulation	+	+
Electrical stimuli	Detection Pain	Repetitive stimulation	+	+ (Referred pain)

(Felsby et al., 1996; Gottrup et al., 1998a,b; Rowbotham and Fields, 1996; Koltzenburg et al., 1994).

An essential point concerns a detailed description of the sensory abnormalities whether they reflect a distribution corresponding to a innervation territory of a sensory nerve, fascicles, roots, cord segment or a cerebral structure. This is not always an easy task and may require detailed neurological knowledge. The issue is however important because a distinction has to be made between the sensory abnormalities seen in, e.g. somatisation disorders and those due to disease of nerves or CNS (central nervous system). However, with the above-described changes in receptive fields, etc., sensory abnormalities which do not correspond to well known innervation areas may not preclude a somatic neuropathic pain condition.

5.4. Experimental examination

A more detailed and accurate testing can be done with various other methods which may also be useful in the assessment of the individual patient and as outcome measures in clinical trials (Tables 2 and 3).

5.4.1. Mechanical stimuli

Standard tools for mechanical testing in the experimental laboratory are von Frey hairs. von Frey hairs bend at different forces permitting both a stimulus-dependent (threshold to detection and threshold to pain perception) and a response-dependent (evoked sensation to a particular stimulus) pain assessment. This can be done for single and for repetitive pinprick stimuli and for dynamic brush using, for example, camel hairbrush. Determination of area of abnormality in the painful area may also be a useful outcome measure because such area of cutaneous abnormality probably reflect expansions of receptive fields of sensitised dorsal horn neurons (Gracely et al., 1992; Bennett, 1994a,b).

Table 3
Recording of phenomena in neuropathic pain

Stimulus independent	Stimulus dependent
pain character	stimulus type(s)
pain duration	pain character
pain intensity of	pain intensity evoked
different pain types	by different stimuli
pain unpleasantness	pain radiation
pain radiation	pain aftersensation
pain distribution	pain summation
pain area	pain area

(Chapman et al., 1985; Jensen and Brennum, 1994).

5.4.2. Thermal stimuli

Thermal testing can be done with commercially available thermodes or argon or CO_2 laser stimuli can be used (Verdugo and Ochoa, 1992; Jensen and Brennum, 1994). The size and duration of the thermal stimulus seem to be important because temporal and spatial summation is pronounced for C-fiber, but only weakly so for Aδ-fibers. So while short lasting heat stimuli on small areas normally evoke a pinprick sensation (indicating Aδ-fiber activation) heat stimuli of long duration on larger areas give rise to a burning sensation (indicating C-fiber activation). To what extent this observation also is present in neuropathic skin is unclear.

5.4.3. Chemical stimuli

Chemical stimuli can be used to determine the threshold or the evoked response. Capsaicin either applied topically or intradermally has been widely used in normal volunteers where an area of primary and secondary hyperalgesia develops due to an explosive discharge from activated C nociceptors (Carpenter and Lynn, 1981; Simone et al., 1989; Culp et al., 1989). A similar approach has been used in patients with postherpetic neuralgia to test C-fiber activity and assess the degree of surviving sensitised C nociceptors as opposed to the degree of deafferentation (Petersen et al., 2000). It remains to be seen if this technique can differentiate between peripheral and central sensitisation.

5.5. Paradoxical presentation of hyposensitivity and signs of hyperexcitability

A characteristic and a central feature in many patients with neuropathic pain are a paradox sensibility with an increased detection threshold to cold/heat and a reduced pain threshold to the same stimuli. Such response pattern

reflects both a loss of afferent fibers/disturbance of central pathways and a sensitisation of peripheral receptors/central neurons along the somatosensory pathway.

Change of the spatial and temporal characteristics of these stimuli may add another dimension to the pain experience, e.g. the presence of spatial and temporal summation. In addition to the above measures, various physiological correlates are used in the analysis of neuropathic pain. These include: microneurographic recordings, EMG (electromyography) activity, brain-imaging techniques, evoked potentials, measurement of "pain substances" in body fluids, etc. There is at present not sufficient information to indicate, which pain correlate is best, but it is expected that addition of these measures may permit a further dissection of the underlying mechanisms in neuropathic pain.

5.6. Assessment of sympathetic activity

Sympathetic hyperactivity may be present in some peripheral neuropathic pain states as part of either CRPS (complex regional pain syndrome) type I or type II (former causalgia). The clinical aspects of sympathetic hyperactivity includes a burning type of pain immediately (hours or days) after injury together with the demonstration of swelling, smooth, glossy skin and vasomotor instability. Later characteristic bone atrophy occurs in hands and fingers (Sudek's atrophy). These features may exist alone or in combination. Sweating may be affected in each direction with either wet or dry skin. Similarly, the skin may be cooler or warmer dependent on the degree of cutaneous vasoconstriction. In patients suspected of sympathetic dysfunction, tests can be useful to document the degree of sympathetic involvement. These include: sweat testing, Galvanic skin resistance, pletysmography, skin blood flow measurement (Laser Doppler test, thermography), cutaneous histamine response. Diagnostic sympathetic blocks may also be used to determine the possible involvement of the sympathetic nervous system in a particular pain condition (Löfström and Cousins, 1988). It should be noted that there is at present no single test that can be used to exclude sympathetically maintained pain (SMP) and there are no clear symptom that predict sympathetically mediated pain (Baron, 2000).

6. Outcome measures of pain

In the evaluation of a pharmacological or non-pharmacological intervention, therapeutic success is often equated with pain reduction. As a result, many clinicians limit themselves to the measurement of pain and pain relief, thereby overlooking other important aspects of the therapeutic outcome, such as functional improvement or improvement in quality of life. Further, pain is usually not differentiated into its subtypes, i.e. pain paroxysms versus steady burning pain versus stimulus-evoked pains.

6.1. Clinical pain measures

These can be divided into recordings of spontaneous ongoing pain and evoked pain and both unidimensional category and VAS (visual analogue scale) scaling as well as multidimensional descriptor (e.g. McGill Pain Questionnaire) and cross-modality matching scales have been used. In neuropathic pain, it may be important also to assess specific measures, e.g. aftersensations, "wind-up like" pain, radiation, area of allodynia to specific stimuli, etc. Recording of pain intensity is still the most frequently assessed dimension of therapeutic outcome. The VAS, verbal category scales and numerical rating scales are the most commonly used scales. An example of a numerical rating scale is the 11-point Lickert rating scale, whereby the subject is asked to rate his pain by giving a number between "0" (no pain) and "10" (most intense pain). A widely used category scale is the four-point intensity scale (none, mild, moderate and severe pain). However, this scale usually does not have enough levels to describe accurately treatment effects. Improved category scales with more descriptors are available. In many clinical pain conditions, pain intensity fluctuates over time. In these cases, it may be necessary to rate the percentage of time his/her pain falls within certain intensity categories. A slightly different approach has been taken in the Brief Pain Inventory of Wisconsin (BPI), which involves measurement of the pain intensity when it is worst, when it is least and the average pain intensity.

In neuropathic pain, it is not sufficient to record one single type of pain category, the various specific pain phenomena such as paroxysms, spontaneous ongoing pain, touch evoked pain, cold allodynia are equally important. Each pain component in a particular neuropathic pain condition may have its own magnitude and each may be influenced separately by a particular drug.

Whereas, pain intensity scales focus on the present pain experience, pain relief scores rely on the patient's memory for pain. Since patients tend to overestimate their past pain, the use of pain relief scores may lead to an overestimation of the effects of the treatment, certainly in cases of prolonged follow-up. On the other hand, there is some evidence that pain relief category scales are more sensitive to small reductions in pain. A neuropathic pain scale has recently been introduced and validated (Galer and Jensen, 1997). It remains to be seen if this scale offers an additional value in neuropathic pain assessment and in measuring outcome.

6.2. Assessment of quality of life and health status

An increasing number of clinical trials on treatment of chronic pain include measures of quality of life. These measures have become an important indicator of treatment "success". Among the measures of quality of life, the Sickness Impact Profile (SIP), the SIP Roland, the West

Haven–Yale Multidimensional pain inventory, the Nottingham Health Profile and the SF-36 have been validated.

7. Treatment as a tool to assess neuropathic pain

Pharmacological trials have previously attempted to determine in a rather simple fashion whether a treatment is of any beneficial effect by using measures such as pain intensity, pain relief, patient satisfaction, drug preference, etc., for calculating efficacy. Now clinicians are challenged with a series of possible pathophysiological mechanisms that each may contribute to neuropathic pain. If these mechanisms can be identified, it is likely that an optimal treatment for the particular patient also can be found. Following a systematic assessment of the single neuropathic pain patient with respect to pain phenomena, clinical examination and specific sensory testing, it should—at least in the future—be possible to tailor the pharmacological treatment to the individual patient (Sindrup and Jensen, 1999). Table 4 is a proposal for combining symptoms, mechanisms and pharmacology in neuropathic pain. It should be noted that this scheme is tentative and does not necessarily account for all possible mechanisms in a particular neuropathic pain patient.

Specific treatments have been designed and tried for different pain conditions including neuropathic pain. They will be described in detail in other chapters. These treatments, which currently includes tricyclic antidepressants, sodium channel blockers (such as carbamazepin and lamotrigine), gabapentin, opioids, NMDA receptor blockers among others all have specific targets for their mode of action. It has been suggested that this may help unravel mechanisms of neuropathic pain based on the specific action of these drugs. Previous studies have shown that such drugs may have an action not only on pain intensity, but also on specific aspects of pain. Studies have shown that in patients with neuropathic pain due to nerve injury and amputation, NMDA receptor antagonists (Max et al., 1995; Felsby et al., 1996; Nikolajsen et al., 1996) can block spontaneous pain and evoked pain produced by touch stimuli indicating that these phenomena probably are produced by the same mechanism, i.e. a central sensitisation mediated by excess activity at NMDA receptor channels (Dickenson and Sullivan, 1987; Dickenson, 1990; Woolf and Thompson, 1991). A similar modulation of central hyperexcitability has been suggested for tramadol where pain reduction and touch-evoked pain also has correlated (Sindrup et al., 1999). Another additional example could be the additional effect by using sodium channel blocking agents and NMDA receptor blocking drugs together suggesting that at least two different mechanisms may operate in concert.

A useful way to select drugs for neuropathic pain is the consultation of systematic reviews to determine the best available drugs. In this respect the measure: "NNT" (numbers needed to treat) has been a useful measure (McQuay and Moore, 1998). NNT is: the number of patients needed to treat with a certain drug to obtain one patient with a defined degree of pain relief. This method permit a comparison between different drugs and diseases and it allows generation of large numbers in order to judge efficacy for a particular agent more precisely. Usually, the NNT for more that 50% pain relief is used because it is easily understood and seems in many cases to be a relevant clinical effect. It is to be noted that NNT can also be

Table 4
Symptoms and findings in neuropathic pain

Symptom/finding	stimulus	Clinical presentation	Mechanism	Pharmacol. modulation
Static hyperalgesia	Gentle mechanical pressure	In area of injury (primary hyperalgesic zone)	Sensitised C-nociceptors	Systemic and topical lidocaine, opioids
Punctate hyperalgesia	Pinprick stimuli	In area of injury and outside (primary and secondary zone)	Sensitised Aδ nociceptors and central sensitisation	Systemic and topical lidocaine Opioids?
Dynamic hyperalgesia	Light brush stimuli	In area of injury and outside (primary and secondary zone)	Central sensitisation due to increased input; due to loss of input	Systemic NMDA antagonists and lidocaine systemically Opioids?
Cold hyperalgesia	Cool stimuli (acetone, alcohol)	Nerve injuries, neuropathies and central pain	Central disinhibition because of loss of input	None?
Heat hyperalgesia	Radiating heat	In area of injury (primary hyperalgesia)	Sensitised C-nociceptors	Systemic and topical lidocaine, opioids
Wind-up like pain	Light brush or pin prick > 3Hz	Evoked pain by reptive stimulation in and surrounding injury	Central sensitisation due to increased input	Systemic NMDA antagonists and lidocaine systemically
Chemical hyperalgesia	Capsaicin topical Histamine topical	Evoked pain/itch or vasodilatation	Sensitised mechanoinsensitive VR1/histamine receptors	Topical lidocine
Aftersensations	Any stimulus	In and outside injury zone	Central sensitisation	?
Sympathetic maintained	Sympathetic stimulation or blockade	Present in nerve injuries	Sympathetic hyperactivity	Stimulation: Noradrenaline Blockade: stellate block

Table 5
Drug action and numbers-needed-to-treat (NNT) for > 50% pain relief calculated from placebo-controlled trials for seleceted drugs in some neuropathic pain conditions

		Drugs							
		TCA	DEXT	CBZ	LAMO	GABA	BACLO	OXY	CAPSA
Drug action	Monoaminergic	+							
	NMDA-blockade	+	+						
	Na^+-channel-blockade	+		+	+	+			
	Ca^{2+}-channel-blockade					+			
	GABA-agonist						+		
	Opioid							+	
	Substance P depleter								+
Pain condition	Painful polyneuropathy	2.6	1.9	3.3	3.2	4.1			5.9
	Trigeminal neuralgia			1.7	2.1		1.4		
	Postherpetic neuralgia	2.3	NA			3.2		2.5	5.3
	Central pain	1.7	NA	3.4					

TCA = Tricyclic antidepressants; DEXT = Dextromethorphan; CBZ = Carbamazepine; LAMO = Lamotrigine; GABA = Gabapentin; BACLO = Baclofen; OXY = Oxycodone; CAPSA = Capsaicin.

determined for a 25% or a 75% pain relief. Since calculations always are compared with the corresponding control value the chosen cut off point for efficacy is less important.

The introduction of NNT values has made it possible to compare a particular drug on different conditions in order to determine if mechanisms are similar. The same principle can also be applied using separate drugs on the same pathological condition to determine whether distinct mechanisms may be in operation (Sindrup and Jensen, 1999, 2000).

Table 5 details suggested mechanism of action of different drugs and corresponding NNT as calculated from placebo-controlled clinical trials in different neuropathic pain conditions. In the interpretation of these NNT values, it is important to be aware of some potential problems with this method, which reduces the results from several or single drug trials to a single number. Firstly, insufficient dosing may cause underestimation of drug efficacy. This situation typically emerges when side effects from the drug are prominent as, e.g. with tricyclic antidepressants. With these drugs, it has in fact been indicated that strict dosing according to drug levels improves efficacy (Sindrup and Jensen, 1999). Secondly, with low numbers of patients exposed to the drug and placebo the estimates become less certain. Finally, the NNTs that have been calculated so far cannot really be related to either effect on specific pain phenomena or mechanisms, since the outcome measure in the trials from which they are calculated does not include such information.

Tricyclic antidepressants which probably acts by multiple pharmacologic actions appear to be superior in painful polyneuropathy and postherpetic neuralgia in accordance with the suggested multiple pain mechanism at play in these conditions. The very weak effect of the substance P depleter capsaicin and somehow weaker effect of other more selectively acting drugs in these conditions supports this view. The effect of the sodium channel blockers carbamazepine and lamotrigine as well as the GABA receptor agonist baclofen in trigeminal neuralgia points at hyperactive nociceptors and reduced segmental inhibitory controls as pain mechanisms.

With improved trial methodology, including registration of specific pain phenomena, neurological signs and sophisticated testing of pain processing, it will hopefully become possibly to elucidate pain mechanisms by use of the available pharmacologic tools and tailor the pharmacologic treatment to the single patient.

8. Conclusion

Assessment of neuropathic pain involves a systematic approach which includes a series of steps; which includes past and present history, detailed description of pain distribution, quality, pain intensity and a neurological examination with emphasis on sensory testing. The sensory examination needs often to be supplied by neurophysiological testing and quantitative sensory analysis. It has now become clear that neuroplastic changes in the nervous system play a significant role in development and maintenance of chronic neuropathic pain with interaction between peripheral and central mechanisms. There is still a wide gap between our preclinical knowledge about pain mechanisms and the clinical translation of such mechanisms into daily clinical practice.

Lack of standardised criteria for pain assessment and lack of systematically examination of patients has hampered us in closing this gap. A better understanding of neuropathic pain mechanisms and their clinical manifestations is a prerequisite for designing a rational founded treatment.

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