

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Overview of Neuropathic Pain Diagnosis and Assessment – An Approach Based on Mechanisms

Ioana Mindruta, Ana-Maria Cobzaru and Ovidiu Alexandru Bajenaru
*University Emergency Hospital of Bucharest
 Romania*

1. Introduction

Neuropathic pain syndromes are, in the majority of cases, chronic conditions related to injuries or diseases occurring at different levels in the nervous systems which are involved in signaling pain. (Treede et al., 2008)

Regarded as heterogeneous states, usually these conditions could not be explained by a single cause or a single specific lesion. Many of these syndromes are expressed by the same clinical symptoms in different etiologies (e.g touch-evoked pain exists in both post herpetic neuralgia and painful diabetic neuropathy) and could be based on the same mechanism. However in the same disease, one mechanism may produce painful symptoms that take different aspects. (Gilron et al., 2006)

As neuroplastic changes occur in different structures of the nervous system, the distribution of pain will no longer respect nerves, roots, segments, proximal or distal territories. (Finnerup et al., 2006)

Recent advances in the field of pain mechanisms produced increasing evidences that old classifications based on underlying disease or anatomic grounds (see table 1) provide insufficient, arguments for the therapeutic approach. (Dworkin et al., 2003; Baron, 2006; Baron et al., 2010).

Therefore, we discuss in this chapter whether a different strategy, in which pain is analyzed on the basis of underlying mechanism, could provide an alternative approach for diagnosis of patients suffering from neuropathic pain conditions with the aim of obtaining a better treatment outcome.

Quantitative sensory testing applied on 1236 patients suffering from different neuropathic pain conditions revealed that despite the heterogeneity in etiology and anatomical distribution, neuropathic pain is characterized by certain clinical features (Maier et al., 2010):

- widespread pain otherwise unexplainable;
- burning continuous spontaneous pain;
- sudden, unprovoked attacks of pain;
- evoked pain (stimulus dependent);
- pain located in a neuroanatomical area with partial or complete sensory deficit;
- aftersensations;

- abnormal summation of pain;
- sympathetic involvement.

Peripheral neuropathic pain syndromes	Focal and multifocal neuropathies	Phantom pain, nerve partial or complete transection pain, neuroma, entrapment syndromes, postherpetic neuralgia, diabetic mononeuropathy, ischemic neuropathy, plexopathies (radiation, diabetic, infiltrative, idiopathic, hereditary), trigeminal or glossopharyngeal neuralgia, vascular compression
	Generalized neuropathies (polyneuropathies)	<i>Metabolic or nutritional</i> Diabetes, amyloidosis, hypothyroidism, beri beri, pellagra <i>Drug-related</i> Antiretrovirals, cisplatin, oxaliplatin, thalidomide, vincristine, methylthiouracil, disulfiram, ethambutol, isoniazid, nitrofurantoin, chloramfenicol, metronidazol, taxoids, gold <i>Toxin-related</i> Thallium, arsenic, acrylamide, ethylene oxide, dinitrophenol, pentachlorophenol <i>Hereditary</i> Amyloid neuropathy, Fabry's disease, hereditary sensory and autonomic neuropathy type 1 <i>Paraneoplastic syndromes</i> Paraneoplastic peripheral neuropathy <i>Infective or post-infective, immune</i> Acute inflammatory polyradiculoneuropathy, HIV, borreliosis <i>Other</i> Idiopathic small-fibers neuropathy, erythromelalgia
Central neuropathic pain syndromes	Vascular lesion in the brain (frequently in the brainstem and thalamus) and spinal cord Inflammatory diseases: multiple sclerosis and other Traumatic spinal cord and brain injury Tumors Abscesses Syringomyelia and syringobulbia Parkinson disease	
Mixed pain syndromes	Chronic low back pain with radiculopathy Complex regional pain syndromes Cancer pain with malignant plexus invasion	

Table 1. Neuropathic pain classification based on anatomy and underlying disease (modified from Baron R. et al., 2010)

These symptoms may occur in various combinations, but do not necessarily have to be present all together. The association of symptoms and signs is compatible with the process of general sensitization of the second and third order neurons in the central nervous system. These relay structures have lost part of their normal input that has been substituted by an altered afferent influx. Commonly, the process of sensitization is considered to be an essential phenomenon that explains persistent neuropathic pains. (Baron, 2006; Baron et al., 2010).

New insights regarding the pathophysiological mechanisms behind spontaneous and evoked phenomena were substantiated by experimental studies in animal models and clinical trials. The most relevant for clinical practice are:

- lesion in a peripheral nerve induce **ectopic activity in the primary nociceptive afferent fibers** both in injured and intact terminals. Alteration of ion-channels and up-regulation of a certain receptor proteins in the peripheral nociceptive endings are responsible for spontaneous pain as well as for allodynia and hyperalgesia that might evolve in the area innervated by the nerves with ectopic activity. (Wu et al. 2002; Amir et al. 2005).
- the local inflammatory reaction following a certain injury and exposure of the nerve terminals to the so called “inflammatory soup” may also lead to molecular changes in nociceptive neurons that will become abnormally sensitive, developing spontaneous pathological activity that contribute to **peripheral sensitisation**. This process is correlated with spontaneous and evoked pain and could occur even without any underlying nerve damage. (Finnerup et al. 2006)
- hyperactivity in the nociceptors lead to secondary changes in neurons processing somatosensory information in the dorsal horn, spinal cord and brain. Hence the input from the mechanoreceptive A beta, A delta fibers might activate second order neurons and hence, non innocuous stimulation could become painful. This process is called **central sensitization** and could be responsible for the central pain syndromes as well. (Baron, 2006; Finnerup et al. 2006).
- **loss of inhibitory interneurons** in the dorsal horn and brain stem in the context of neuroplastic changes may lead to alteration in segmental and descending modulation. Synaptic activity changes in the dorsal horn of the spinal cord thereby results in hyperexcitability of the second order neurons due to alteration of inhibitory control. This mechanism may mediate mechanical and thermal hyperalgesia. (Moore et al. 2002; Scholz et al. 2005).
- hyperactivity at the level of sensitized nociceptors that favor pain persistence and allodynia are correlated with **increasing activity in the sympathetic nervous system**. Spontaneous pain and dynamic mechanical hyperalgesia might get enhanced by the secondary changes in the sympathetic activity. This process could be interfered by sympathetic blocks. (Zhuo et al. 2011)
- **activation of the glial cells in the dorsal horn**, in the context of neuropathic pain conditions, is demonstrated to be responsible for neuronal hyperexcitability. Thus microglial cells are activated during the initial stages as well as the astrocytes are more involved in the process of pain maintenance. (Boucsein et al. 2000; Ji et al. 2007; Gosselin et al. 2010)
- **cortical maps reorganization and the role of mirror neurons** in the brain have been proposed in the generation of phantom limb pain. (Subedi et al. 2011)

2. Diagnosis

The neuropathic pain represents a devastating condition that can be diagnosed by taking a relevant history of pain and by adequately performed neurological examination. Complementary studies, including blood and serologic tests, electrophysiological studies, imaging procedures will contribute with information about the etiology of the underlying disease and also to predict the outcome. (Gilron et al. 2006; Haanpaa et al 2011).

Although the neuropathic pain is seen as a chronic condition, there are situations, poorly recognized, of acute neuropathic pain. Despite the fact that acute pain is perceived as having a nociceptive nature, in a small percent of cases, the pain is mixed, including a neuropathic component as well (e.g. acute disc herniation, postsurgery pain). Even if the incidence of acute neuropathic pain in acute pain services is low (1-3%), its importance resides in the high risk to progress to a persistent and debilitating status. Time interval which defines acute neuropathic pain is 6-12 weeks. (Hayes et al., 2002; Gray, 2008)

The nociceptive, neuropathic and mixed pains are the three main types of pain. The first one is induced by injured tissue, the second one is caused by a disorder in the somatosensory system and the third one refers to coexistence of the first two. To diagnose neuropathic pain and to differentiate it from the nociceptive type, or to identify the nociceptive component of the mixed condition, it is mandatory to analyze in detail the type of somatosensory abnormalities in a given case. By contrast with other neurological symptoms and signs (e.g motor deficit) pain as a subjective sensory symptom is difficult to measure because it is not something visible and does not involve only physical aspects, but also psychological and emotional components. (Baron et al 2010)

2.1 Interview and questionnaires

The first step in pain diagnostic and evaluation is a very detailed history with:

- description of qualities of pain;
- duration of pain;
- time course pattern;
- rating intensity of pain;
- the context and type of onset;
- presence of relieving factors;
- existence of provocative or enhancer factors;
- topographic distribution of pain;
- coexistence of other positive symptoms such as paresthesia;
- impact on daily activities and sleep.

Standardized screening tools have been developed to distinguish neuropathic pain on the basis of patient reported verbal descriptors of pain during the interview and a limited bedside examination. The purpose of these questionnaires is to identify the patients with neuropathic pain and also to distinguish between different pathophysiological groups. Some of these screening tools include items that refer to rating scales, time course pattern and topographical distribution. This particular aspect may help the examiner to find out if pain distribution respects a nerve or root territory. Moreover, the rating scales are also useful to monitor the efficacy of different therapeutic interventions (Cruccu et al., 2004; Haanpaa et al, 2011).

LANSS (Leedes Assessment of Neuropathic Symptoms and Signs Scale) is the first tool developed more for the diagnosis of neuropathic pain than for its rating(9) and consists of five items for description of symptoms and two items for clinical examination. Although it was not designed for measurement, LANNS proved its sensitivity to treatment. This tool has been subsequently tested and validated in several settings with sensitivity and specificity ranging from 82% to 91% and 80% to 94% respectively, comparing with clinical diagnosis. There is also a version of a self-report questionnaire, S-LANNS (Bennett, 2001).

NPQ (Neuropathic Pain Questionnaire) consists of twelve items of which ten refer to sensations and sensory responses and two are related to affect. NPQ has showed a sensitivity of 66% and a specificity of 74% versus clinical diagnosis. There is, also, a short variant that has only 3 items for similar discriminative properties (tingling, numbness and increasing pain in response to touch) (Krause et al., 2003).

DN4 (Douleur Neuropathique en 4 questions) is a questionnaire initially developed and validated in French and consists of seven items related to symptoms, which can be used as a self-report, and three items related to clinical examination. This tool is easy to use and a total score of 4 out of 10 or more suggests neuropathic pain. The DN4 proved 83% sensitivity and 90% specificity when compared with clinical diagnosis (Bouhassira et al., 2005).

ID-Pain does not require a clinical examination and was designed rather to screen for the presence of a neuropathic component. It consists of five sensory descriptor items with one item asking whether the pain is located in the joints (to identify nociceptive pain). In the validation study, 22% of patients in the nociceptive group, 39% in the mixed group and 58% in the neuropathic pain group scored above 3 points, the recommended cut-off score. (Portenoy, 2006).

PainDetect was developed and validated in a multicenter study conducted in Germany and includes seven weighted sensory descriptor items (from never to very strongly), two items relating to spatial (radiating and topography) and temporal characteristics of individual pain pattern and does not require clinical examination. This questionnaire showed a sensitivity of 85% and a specificity of 80% (Freynhagen et al., 2006).

Neuropathic Pain Scale (NPS) was designed and only preliminary validated in 1997 for evaluation of neuropathic pain symptoms (18). Although NPS has proved some sensitivity to treatment, it is no clear whether is adapted to detect differential effects of treatment on neuropathic symptoms. It consists in twelve items, self-reported, about the intensity and quality of pain (Galer et al., 1997).

Neuropathic Pain Symptoms Inventory (NPSI) includes ten descriptors and two items about temporal pattern of pain, that allow to differentiate and quantify five distinct features, clinically relevant, and sensitive to treatment. The questionnaire could be used to identify subgroups of patients with neuropathic pain characterized by specific clusters of symptoms and to verify if they respond in a different way to various pharmacological agents. The most important feature of this tool is the sensitivity to treatment variables (Bouhassira et al., 2004).

Standardized Evaluation of Pain (StEP) combines sixteen questions in the interview and twenty-three standardized clinical tests to evaluate symptoms and signs related to pain and to differentiate between various pain phenotypes reflecting distinct mechanisms. Scholz and colleagues evaluated the diagnostic utility of StEP in patients with low back

Symptoms	Definition	Bedside exam	Expected pathological response	Mechanism(s)
Spontaneous sensations or pain				
Paresthesia	Non-painful abnormal sensation	Grade intensity(0-10)	-	Spontaneous activity in low threshold A-β afferent
Dysesthesia	Unpleasant but non-painful abnormal sensation	Grade intensity(0-10)	-	Spontaneous activity in C/ A-δ afferents
Paroxysmal pain	Attacks for seconds of shooting, stabbing or electric shock-like	Number, Grade(0-10)	-	Spontaneous activity in C-nociceptors
Superficial burning pain	Permanent pain located in the skin often of burning quality	Grade(0-10)	-	Spontaneous activity in C-nociceptors?
Deep pain	Permanent pain located in the muscles, bones, or internal organs	Grade(0-10)	-	Spontaneous activity in joint/ muscle nociceptors?
Sympathetic maintained pain	Sustained burning pain associated with vasomotor, sudomotor and trophic changes on skin	Grade(0-10)	-	Peripheral sensitization: sympathetic-afferent coupling
Evoked pain				
Dynamic allodynia provoked by mechanical stimulation	Pain provoked by normally non-painful light-pressure moving stimuli on skin	Stroking skin with painter’s brush, cotton swab or gauze Grade(0-10)	Sharp burning superficial pain in the primary affected zone, spreading into unaffected skin areas(secondary zone)	Central sensitization: A-β fibers input

Mechanical static hyperalgesia	Pain provoked by normally non-painful gentle static pressure stimuli on skin	Apply gentle mechanical pressure to skin Grade(0-10)	Dull pain presented in the area of affected primary afferent nerve endings (primary zone)	Peripheral sensitization
Mechanical punctuate or pin-prick hyperalgesia	Pain provoked by normally stinging but non-painful stimuli	Prick skin with a safety pin, sharp stick or stiff von Frey hair Grade(0-10)	Sharp superficial pain presented in the primary affected zone, but spreads beyond into unaffected skin areas (secondary zone)	Central sensitization: A-δ fibers input
Temporal summation	Increasing pain sensation (wind-up-like pain) from repetitive application of identical single noxious stimuli	Prick skin with safety pin at intervals of 3 s for 30 s Grade(0-10)	Sharp superficial pain of increasing intensity	Central sensitization: A-δ fibers input
After sensation	Pain occurred during the stimulation and persists more than seconds after stimulus cessation	Grade(0-10) Duration	Persistent evoked pain	Central sensitization
Cold hyperalgesia	Pain provoked by non-painful cold stimuli	Contact skin with objects of 20° C for 10 s Grade(0-10)	Painful burning temperature sensation presented in the area of affected primary afferent nerve endings (primary zone)	Peripheral sensitization with reduced activation threshold to cold
Heat hyperalgesia	Pain provoked by non-painful heat stimuli	Contact skin with objects of 40° C for 10 s Grade(0-10)	Painful burning temperature sensation presented in the area of affected primary afferent nerve endings (primary zone)	Peripheral sensitization with reduced activation threshold to heat

Table 2. Definitions and assessment of sensory symptoms in patients with neuropathic pain (modified from Baron et al., 2010)

pain. The StEP identified the radicular pain with 92 % sensitivity and a specificity of 97% (Scholz et al., 2009).

One of the most important aspects in the patient's interview is whether the pain is spontaneous or stimulus depended.

The spontaneous pain can be continuous or paroxysmal. In case of continuous neuropathic pain, the most common verbal descriptor used by patients to describe its quality is "burning". There are also other words the patients have used to describe their pain as a cold (frozen) sensation, stinging, electric shock, painful pins and needles, dull, squeezing, shooting, stabbing, cramping, throbbing, sharp, or pulling. Episodic or paroxysmal type of pain is usually lasting for seconds and is described as a shooting, electric, shock-like or stabbing sensation.

A thorough interview can reveal different types of evoked pain (hyperalgesia, allodynia). Thus painful symptoms could be provoked by light touch, mild pressure, heat or cold and also might be associated with the presence of an aftersensation phenomena. Hyperalgesia (an increased response to noxious stimuli by lowering the pain threshold) and allodynia (pain due to non-noxious stimulus) are typical elements of neuropathic pain.

The stimulus-evoked pain is further classified according to the stimulus type (mechanical, thermal, and chemical) and the dynamic or static nature of stimuli that provoke it. Usually the evoked pain stops after cessation of the stimulation, but sometimes it can persist for minutes, hours or even days, causing aftersensations. This aspect is mainly explained by involvement of a central sensitization process.

Paresthesia (an abnormal, non-painful sensation) and disesthesia (an abnormal, unpleasant and non-painful sensation) whether spontaneous or evoked, may coexist with pain. They can be described as crawling, numbness, itching and tingling sensations and reflect peripheral nociceptor hyperexcitability with spontaneous activity in low-threshold A- β afferents and respectively in C/A- δ afferents. (see table 2) (Baron et al., 2010).

Usually the screening tools provide immediate information and some of them can be fully applied to the patient without any prior physical examination, for example in the waiting room. Many of them are suitable to be used by the non-specialist physician in order to identify potential patients with neuropathic pain. However, these screening tools may miss 10-20% of patients with clinical diagnosed neuropathic pain. (Benett et al., 2007). There are many screening tools designed for the diagnosis and assessment of neuropathic pain and none of them cover the entire spectrum of symptoms and signs that might be encountered in this condition. It is possible, therefore, to use a combination of these questionnaires (see table 3) to get a good picture of neuropathic pain condition for an individual patient. (Cruccu et al., 2009)

2.2 Assessment of comorbidities

Comorbidities are recognized as a major factor that impact the outcome of neuropathic pain conditions. The most common spectrum of associated disorders includes poor quality of sleep, depression and anxiety.

Symptoms/Questionnaire	LANSS	NPQ	DN4	ID-Pain	painDetect	NPSI	StEP
Self reporting symptoms	•		•	•	•	•	•
Ongoing pain rating					•	•	•
Electric shocks or shooting	•	•	•	•	•	•	
Hot or burning	•	•	•	•	•	•	•
Painful cold or freezing pain		•	•				•
Pricking, tingling pins, needles(any dysesthesia)	•	•	•	•	•	•	•
Numbness		•	•	•	•	•	
Itching			•				•
Pain provoked by light touching	•	•		•	•	•	
Pain provoked by mild pressure					•		
Pain provoked by heat or cold					•		
Pain provoked by changes in weather		•					
Pain provoked by activity or body position							•
Temporal patterns					•		•
Pain limited to joints				•			
Location, superficial or deep							•
Topography				•	•		
Radiation of pain					•		
Autonomic changes				•			
Affect disturbances		•					
Physical examination							
Abnormal response to cold temperature (decrease or allodynia)							•
Hyperalgesia							•
Abnormal response to blunt pressure (decreased or evoked pain)							•
Decreased response to vibration							•
Brush allodynia	•		•				•
Raised soft touch threshold			•				•
Raised pinprick threshold	•		•				•
Straight-leg-raising test							•
Skin changes							•

Table 3. Screening tools-items inventory (modified from Bennett M.I. et al., 2007)

Patients who suffer from chronic pain experience difficulties in initiating and maintaining sleep. Sleep deprivation has been associated with a decreased pain threshold. The interrelationship of these factors is complex. Many chronic pain patients are depressed and anxious; sleep deprivation can lead to anxiety; and depression can be both the cause and the result of sleep disturbances. Therefore, sleep as well as mood should be evaluated in patients suffering from painful conditions. Several specific instruments are used in practice to elicit qualitative and quantitative information from chronic pain patients.

PHQ-9 and MOS sleep questionnaire were used to track co-morbidities in a study that assessed the PainDETECT questionnaire as a screening tool to predict the likelihood of a neuropathic pain component in chronic pain disorders (Lowe et al., 2004; Hays & Stewart, 1992).

The study revealed fundamental differences, in respect of perceived pain and of various co-morbidities, between low back pain patients with neuropathic and those with nociceptive components and provided important information on the association between neuropathic pain and the occurrence and severity of co-morbidities. Patients with neuropathic pain generally experience a more severe burden of co-morbid disorders than patients affected only by nociceptive type of pain (Freynhagen et al., 2006).

2.3 Neurological examination

An injury anywhere in the somatosensory system typically, leads to an area of sensory deficit distributed in the related innervations territory. These negative sensory signs may be expressed as a deficit in the mechanical or vibratory perception, which indicates damage of the large diameter afferent fibers or of the dorsal column tract. The picture could include also a deficit of noxious and thermal perception, which indicates damage of the small diameter afferent fibers or of the central pain processing pathways such as the spinothalamic tract.

A standardized bedside examination of patients with neuropathic pain must include the following components: touch, pressure, vibration, pinprick, cold, heat, temporal summation. The responses should be graded as normal, decreased or increased. When present, allodynia and hyperalgesia should be quantified by measuring the intensity and the area that is affected. It is generally agreed that assessment should be carried out in the area of maximum pain with the contralateral or neighboring reference area, free of pain, as a control if possible. Touch can be assessed by gently applying cotton swab or von Frey filaments of 2 g and 26 g strength to the skin, pin-prick sensation by the response to sharp pinprick stimuli, cold and heat sensation by measuring the response to thermal stimuli (e.g. metal objects kept at 20° C or 40° C), vibration sensation by the response to a tuning fork. (Arning & Baron, 2009)

Mechanical dynamic allodynia and mechanical static hyperalgesia can be evaluated using a painter's brush and respectively a blunt eraser end of a pencil. Abnormal temporal summation consists to increasing pain sensation (wind-up-like pain) from repetitive application of identical single noxious stimulus (mechanical or thermal) and is the clinical equivalent of increasing neuronal activity after repetitive noxious C-fiber stimulation of more than 3 Hz. The antagonists of NMDA receptors can block this process.

Inspection of the skin within the painful area is also an important gesture to note the presence of vasomotor, sweating and trophic changes which define sympathetic maintained pain and express a pathological adrenergic coupling between sympathetic postganglionic fibers and nociceptive afferent fibers.

In the chronic conditions, trophic changes of the skin and nails occur as do motor symptoms such as weakness, tremor and dystonia (Cruccu et al. 2004, Cruccu et al., 2009).

Nerve percussion at points of entrapment, compression or irritation can elicit electrical sensations, pins and needles in innervation's territory (Tinel's sign).

As in the case of spontaneous pain assessment, it is important to establish topographical distribution of evoked pains because as the neuroplastic changes develop, the pain distribution will no longer respect nerves, roots, segmental, cortical territory. Hence, primary hyperalgesia or allodynia represent pain provoked by stimuli applied within a nerve/root territory with ectopic activity. Secondary hyperalgesia or allodynia represents pain occurred by application of stimuli in the neighboring area of innervations territory of the injured nerve/root.

Neurological assessment of neuropathic pain also should include an examination of the autonomic nervous system and a detailed inventory of the somatomotor involvement to define the underlying disease and the extension of it. The distribution of the motor deficit could help us sometimes to differentiate between primary and secondary hyperalgesia/allodynia and to localize the injury.

As peripheral and central sensitization develop, in attempt to control pain, the harmful condition is most of the times no longer important because the neuropathic pain persists long after the cessation of the initial injury. However, the management of the ongoing underlying diseases (eg metabolic disorders) remains important rather to prevent appearance of new lesions of somatosensory nervous system than to control neuropathic pain (Baron et al., 2010).

However, the non-sensory neurologic symptoms and signs can independently contribute to pain and disability. In the case of associated weakness, patients are more prone to adopt vicious positions and therefore, mixed pain could develop by superimposing the nociceptive component related to joints or tendon structures (Dworkin et al. 2003).

2.4 Ancillary tests

When pain is the only manifestation of an injury in the somatosensory system, additional diagnostic information could come from the use of ancillary tests (see table 4).

Some aspects must be considered an attempt to use complementary tests to support the diagnosis and characterize the involvement of specific neuropathic pain mechanisms (Horowitz et al, 2007):

- using these laboratory tests, the presence, distribution and mechanisms of neuropathic pain only can be inferred because the available tests evaluate nervous system structures and functions presumed to be relevant to pain perception and transmission;
- since pain mediating fibers (small myelinated, A δ , and unmyelinated, C fibers) are also responsible for other measurable functions, (e.g. temperature perception and autonomic

- activity), many tests have focused on proving alterations in these modalities in order to verify A-δ or C-fiber damage;
- in the clinical expression of each particular disorder is a spectrum of symptoms and signs that reflect neural injury, with chronic pain occurring in only a small percentage of affected individuals.

Fibers	Sensation	Testing			
		Clinical		Laboratory	
		Bedside assessment	Expected pathological response	QST	Other
A-β	Touch	Piece of painter’s brush or cotton swab	Reduced perception (hypoesthesia)	Von Frey filaments	NCS, SEPs
	Vibration	Tuning fork (128 Hz)	Reduced perception of threshold (pall-hypoesthesia)	Vibrameter	NCS, SEPs
A-δ	Pinprick, sharp pain	Prick skin with a pin single stimulus	Reduced perception (hypoalgesia)	Weighted needles	LEPs, IENF
	Cold	Thermoroller (20° C)	Reduced perception (thermal hypoesthesia)	Thermode	None
C	Warmth	Thermoroller (40° C)	Reduced perception (thermal hypoesthesia)	Thermode	LEPs, IENF
	Burning	none	-	Thermode	LEPs, IENF

IE NF intra-epidermal nerve fibre, LEP laser-evoked potential, NCS nerve conduction study, QST quantitative sensory testing; SEP, somatosensory-evoked potential

Table 4. Summary of assessment methods of nerve sensory functions (modified from Cruccu et al., 2004).

2.4.1 Clinical neurophysiology

The usual neurophysiologic tests (with surface electrodes for nerve stimulation and evoked potential recording) asses activity of the largest and fastest conducting sensory and motor myelinated nerve fibers (Aαβ). In order to assess the involvement of the central nervous system or the proximal part of the peripheral nerves, somatosensory and magnetic evoked potential studies can be helpful.

Although, unfortunately A-and C-fiber activities cannot be tested with these techniques, the abnormalities from these tests can be used to corroborate the clinical impression of damage to a specific peripheral nerve or to peripheral nerves in general as in a polyneuropathy (level A recommendation in the EFNS guidelines for neuropathic pain assessment, Cruccu et al., 2004).

2.4.2 Quantitative sensory testing

Quantitative sensory testing (QST) measures sensory thresholds for pain, touch, vibration and hot and cold temperature sensations. With this technology, specific fibers functions can be assessed: A δ -fibers with cold and cold-pain detection thresholds, C-fibers with heat and heat-pain detection thresholds and large fiber (A $\alpha\beta$) functions with vibration detection thresholds. The abnormal findings exist in both peripheral and central nervous disorder, without any distinction (Rolke et al., 2006).

It must be stressed that QST is a psychophysical test and therefore is highly dependent on the patient's alertness, concentration and motivation (level B recommendation EFNS guidelines for neuropathic pain assessment, Cruccu et al., 2004). QST is helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal a different effect of treatments on different pain components (level A recommendation in the EFNS guidelines for neuropathic pain assessment, Cruccu et al., 2010).

2.4.3 Autonomic function testing

Autonomic evaluation is an important step in refining the neuropathic pain diagnosis based on the frequent association between neuropathic pain disorders and signs of autonomic dysfunction (dry eyes or mouth, changes in the color of the skin, temperature, sweating abnormalities, edema, orthostatic hypotension, etc) as well as the anatomic similarities between fibers processing pain and autonomic functions. The most useful tests are quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test, heart rate responses to deep breathing, Valsalva ratio, and surface skin temperature (Novak et al., 2001). The value of autonomic testing in patients with general neuropathic pain disorder, painful small-fiber neuropathy with burning feet has been shown in several studies. Autonomic abnormalities were seen in more than 90% of patients (Low et al, 2006).

2.4.4 Skin biopsy

In the recent years the histological study of unmyelinated nerve fibers in the skin had proved its utility by providing reliable diagnostic information when there is little or no clinical evidence of neuropathy, such as in a patient complaining of burning feet and to distinguish conditions mimicking a neuropathy. Epidermal nerve fiber density and morphology, complex ramifications, clustering, and axon swelling can be quantified (Devigli et al, 2003; Kennedy, 2004)

Reduced epidermal innervations density has been used as mandatory criteria for the diagnosis of a small fiber neuropathy (level B recommendation in the EFNS guideline of neuropathic pain assessment, Cruccu et al., 2004, 2009).

2.4.5 Laser evoked potential

Laser evoked potential (LEP) based on radiant-heat pulse stimuli delivered by laser stimulators, provide a selective activation of the afferent fibers and the free nerve endings (A- δ and C) (Bromm et al. 1984). The cortical networks that generate LEPs are able to detect abrupt changes in the sensory input, but are much less qualified to reflect a slow-changing state. Thus, LEPs are inappropriate to reflect the slowly emerging, ill-defined and long

lasting phenomena that underlie over-reaction symptoms (hyperalgesia and allodynia), which are thought to depend on spino-reticulo-thalamic projection system. Late LEPs reflect activity of the A-fibers and ultralate LEPs of the unmyelinated nociceptive pathways (Garcia-Larrea & Godinho, 2007).

For the purpose of studying peripheral and central neuropathic pain, LEP are the most sensitive tool compared with any other neurophysiologic test. The finding of a LEP suppression helps to diagnose neuropathic pain (level A recommendation in the EFNS guideline neuropathic pain assessment, Cruccu et al., 2009).

2.5 Pathophysiology – From symptoms and signs to mechanism and vice versa

Our ability to translate pain complaints and sensory signs into specific physiopathologic mechanisms which will have implications for appropriate therapy is only in the beginnings (Baron et al. 2010). However, all this process of translation is difficult because:

- one single mechanism can give rise to several different symptoms; the same mechanism can be found in various diseases;
- in one individual patient different mechanisms might be involved;
- many of these mechanisms are independent on the etiology of a particular disorder;
- different mechanisms could lead to the same symptom or sign.

Different treatment regimens are needed for different pain mechanisms, thereby a mechanism based treatment approach would result in efficient analgesia. Hence, to progress at this point we have to assume that pain mechanisms can be identified by analyzing patient's individual symptoms and signs (see table 5).

At present, there are some data that could help us to understand the associations between at least some symptoms and suggested underlying mechanisms (Jensen & Baron, 2003).

It is worth to mention that the pain system is not static and the changes occur in a dynamic, step-up, from periphery to central and somewhat unpredictable manner whenever the system is activated (Baron, 2006).

A useful, oversimplified approach is to differentiate processes that involve the following (Finnerup & Jensen, 2006):

- increased firing in primary afferent nociceptors (e.g. ectopic discharges as a result of abnormal redistribution of sodium channels in damaged peripheral nerve fibers)
- changes in the central processing of sensory signals (central sensitization) and, consequently, normal sensory perception is amplified and sustained;
- decreased inhibition of neuronal activity in the central structures (e.g. due to loss of inhibitory neurons)

2.5.1 Ectopic nerve activity

Ectopic nerve activity has been involved in many *positive phenomena* (spontaneous, ongoing or paroxysmal pain, primary hyperalgesia/allodynia), characteristic of neuropathic pain:

- *ongoing spontaneous pain* and *paroxysmal stimulus-independent pain* has been correlated with ectopic impulse generation within the nociceptive pathways, either within

nociceptive afferent fibers (C- and A δ -fibers), either in the dorsal root ganglion or at the level of the second-order nociceptive neuron by increasing expression of voltage-gated sodium channels and secondary lowering action potential threshold until ectopic activity takes place (Amir et al. 2005; Wu et al., 2002)

Mechanism	Symptoms	Targets
Peripheral nociceptor hyperexcitability		
Ectopic impulses generation, oscillations in dorsal root ganglion	Paroxysmal shooting spontaneous pain	Sodium channels
Peripheral nociceptor sensitization		
Inflammation within nerves: cytokine release	Ongoing spontaneous pain	Cytokines
Reduced activation threshold to:		
Heat	Heat allodynia	TRPV1 receptor
Cold	Cold allodynia	TRPM8 receptor
Mechanical stimuli	Static mechanical allodynia	ASCI receptor(?)
Noradrenaline	Sympathetic maintained pain	α receptor
Central dorsal horn hyperexcitability		
Central sensitization on spinal level Ongoing C-input induces increased synaptic transmission		
Amplification of C fibers input	Ongoing spontaneous pain	Presynaptic: - μ -receptors -calcium channels(α 2- δ) Postsynaptic: -NMDA receptors -sodium channels -NK1 receptors
Gating of A β - fibers input	Mechanical dynamic allodynia	
Gating of A δ - fibers input	Mechanical static hyperalgesia	
Reduction intraspinal inhibitory interneurons		
GABA-ergic	Ongoing spontaneous pain Evoked pain	GABA-B receptors
Opiodergic	Ongoing spontaneous pain Evoked pain	μ -receptors
Changes in supraspinal descending modulation		
Decreased inhibitory control (NA, 5-HT)	Ongoing spontaneous pain Evoked pain	α 2 receptor 5-HT receptors
Increased faciliatory control	Ongoing spontaneous pain Evoked pain	

Table 5. Mechanisms-symptoms correlations (modified from Baron R. et al., 2006)

- *heat hyperalgesia* in addition to ongoing burning pain can have as underlying mechanism spontaneous nerve activity induced by changing expression of vanilloid receptor (TRPV1, physiologically activated by noxious heat at about 41°C, and additional sensitization to heat by intracellular signal transduction (Fischer & Reeh, 2007). After a nerve lesion TRPV1 is downregulated on injured nerve fibers and upregulated on uninjured C-fibers (Caterina & Julius, 2001).
- abnormal function and expression of TRPM8, a cold sensitive receptor of TRP family, triggered by nerve lesion, with secondary ongoing ectopic discharges have been recently identified in a patient with painful neuropathy in combination with *cold allodynia* (Serra et al., 2009).

2.5.2 Central sensitisation

Central sensitization can manifest in three ways ((Woolf, 1992; Jensen & Baron, 2003):

- enlargement of the peripheral area where a stimulus will determine neuronal activation (secondary hyperalgesia/ allodynia);
- increased response to suprathreshold input (hyperalgesia, hyperpatia)
- previously subthreshold input reach threshold and initiate action potential discharge (allodynia, in particular dynamic mechanical allodynia).

Central sensitization might develop as a consequence of ectopic activity in the primary nociceptive afferent fibers without any structural damage within the central nervous system. Ongoing discharges of peripheral afferent fibers lead to postsynaptic changes of the second-order nociceptive neurons, such as phosphorylation of NMDA and AMPA receptors (Ulfenius et al., 2007) or expression of voltage-gated sodium channels (Lai et al., 2003). These changes determine neuronal hyperexcitability that allow the mechanosensitive A β and A δ afferent fibers with low-threshold to activate second-order nociceptive neurons. As a consequence, normally innocuous tactile stimuli such as light brushing or pricking the skin become painful. This phenomena are called dynamic and punctate mechanical allodynia (Hains et al, 2004).

2.5.3 Decreased inhibition of neuronal activity in the central nervous structures

After a peripheral nerve lesion there is a loss of inhibitory GABAergic interneurons in the spinal horn. Prevention of interneurons cell death attenuates mechanical and thermal hyperalgesia, indicating that disinhibition contributes to neuropathic pain (Moore et al., 2002). There are, also, other inhibitory neurons, such as descending pathways originating in the brainstem, which contribute to modulation of pain and any injury of these opioidergic and monoaminergic systems lead to pain exacerbation via a disinhibition process. Paroxysms are traditionally thought to be generated by ectopic ongoing discharges from sodium channels and, therefore, may respond to sodium-channel blockers (Black et al., 2008; Siqueira et al., 2009). However, paroxysms can, also, be seen in patients with small fiber neuropathy and deafferentation, pointing to a central mechanism and are reported to be relieved by tricyclic antidepressants and serotonin-noradrenaline reuptake inhibitors, suggesting changes in supraspinal descending modulation with decreasing monoaminergic inhibitory control (Jensen & Baron, 2003).

2.5.4 Attempts to group patients according to sensory profiles

The complexity of neuropathic pain pathophysiology and translating process from mechanisms to symptoms and signs, suggests that the individual pattern of sensory abnormalities most likely closely reflects the underlying pain-generating mechanism (Baron, 2010). To identify phenotypic subgroups of patients with distinct sensory pattern several approaches were used:

- a standardized psychophysical technique to test both the nociceptive and non-nociceptive afferent systems (QST- quantitative sensory testing) was recently proposed by the German Network on Neuropathic Pain (DFNS). The DFNS nationwide multicentre trial comprised complete sensory profiles of 1236 patients with different types of neuropathic pain. The study conclusion was that a certain association of symptoms and signs could suggest a particular underlying mechanisms. For example, a combination of heat hyperalgesia with mechanical allodynia and mechanical hyperalgesia could indicate peripheral ectopic activity at the level of heat sensitive nociceptors that triggers a process of central sensitization. On the other hand, in patients with complete sensory loss is very unlikely that peripheral mechanisms are responsible for maintaining neuropathic pain (Meier et al., 2010).
- in another study the tool used to identify relevant subgroups of patients with postherpetic neuralgia and painful diabetic neuropathy who were characterized by a specific symptom profile, was the pain symptom questionnaire. Using a hierarchical cluster analysis were determined five distinct subgroups of patients. The sensory profiles showed remarkable differences in the expression of the symptoms, all subgroups occurring in both diseases but with different frequencies (Baron et al., 2009).
- In one study the neuropathic symptoms and signs were assessed using a structured interview and standardized bedside examination in patients with painful diabetic neuropathy, postherpetic neuralgia and radicular back pain as well as in a group of patients with non-neuropathic pain. The physical examination was considered more important for the distinction of pain subtypes than were the assessment of symptoms during the interview (Woolf et al., 1998).

All these different techniques to identify subgroups of patients show that there are phenotypic differences based on certain combinations of sensory abnormalities across the different etiologies and neuropathic pain syndromes. These efforts to identify and understand the underlying mechanisms involved in neuropathic pain will lead us to a more effective and specific mechanism based treatment approach. However, the management of neuropathic pain is, also, a matter of timing. The distinction between peripheral and central sensitization could be critical in the evolution and appropriate treatment of neuropathic pain (Attal et al., 2008; Baron et al., 2010).

2.6 Neuropathic pain diagnosis in special populations

2.6.1 Neuropathic pain in children

Most of the common neuropathic pain syndromes seen in adults are rare in pediatric population and some others are not even encountered. For example neuropathic pain from diabetic polyneuropathy is never a significant concern in children. Pain as a consequence of stroke or radiculopathy or trigeminal neuralgia is tremendously rare in this period of life.

Children with plexus avulsion at birth or traumatic nerve injuries rarely develop neuropathic pain as most of the adult population does in a similar context. Also some conditions gain increasing recognition in this special group. The spectrum of etiologies that induce neuropathic pain in children are mostly related to trauma, postsurgery, infectious myelitides, neuropathies (autoimmune, genetic), complex regional pain syndrome or phantom limb. Some of the rare neuropathic pain syndromes are exclusively encountered at this age: mitochondrial disorders, eritromelalgia, Fabry disease, lead intoxication (Walco et al. 2010).

Favorable neuroplasticity in younger patients might be the cause of a better recovery with lower incidence for neuropathic pain comparing to adults. Tools used in evaluation of adults with neuropathic pain could be extrapolated in children but aspects related to the developmental process should always taken into account as potentially modifiers of clinical expression. The assessment of pain and somatosensory examination is a challenging step in children. Appropriate instruments adapted for pediatric population are only developed for other types of pain: musculoskeletal, abdominal or headache (Craig & Korol, 2008).

A controlled study conducted in a group of children aged 7 to 17 with unilateral CRPS using QST showed that patients displayed cold allodynia and a combination of dynamic mechanical allodynia and hyperalgesia to pinprick (Tan et al., 2008).

A study that compared from medical records adult patients and children with CRPS and concluded that the skin temperature at onset was cooler among children, the lower extremity was involved more frequently and presence of sympathetic symptoms and abnormal neurological signs and symptoms were milder (Sethna et al., 2007).

2.6.2 Neuropathic pain in the elderly

Prevalence of neuropathic pain in the elderly population over 65 years of age is estimated around 9% (Bouhassira et al., 2007).

Different etiologies may be responsible for neuropathic painful condition in older people but the most frequent are related to diabetes, shingles, radiculopathies and stroke. Most of the people in this group of age do not report pain adequately and usually think that pain is a normal part of the aging process (Pickering & Capriz, 2008).

The most challenging points regarding the diagnostic approach in this age group are related to cognitive impairment and high incidence of affective disorders that will impact the way people report their pain or collaborate in answering to sometimes difficult questionnaires. Also comorbidities are usually accumulated in this population and the chance of facing different types of pain (joints inflammation, visceral, neoplastic, related to treatments) is considerably high (Weiner et al., 2006).

Instruments of pain assessment should be appropriate with the patient cognitive status and medical personnel should observe the patient's behavior. Best instruments are the numeric and visual scale but also faces and behavioral scales (Pickering, 2005).

2.6.3 Lessons learnt from randomized clinical trials (RCT's) for neuropathic pain

Most of the clinical trials were addressed to neuropathic pain associated with herpes zoster infection or diabetic neuropathy.

Regarding the outcome of different therapies, realistic expectations are defined by at least 30 % of pain alleviation. Multiple dimensions of pain experience need to take into consideration sleep quality, depression and social impact. As a consequence, the efficacy of a certain therapy must be judged also from this perspective (Moulin et al., 2007).

Evidences showed that different mechanisms and sensory profiles might be encountered in painful conditions with a similar etiology and conversely, one mechanism or sensory profile could be associated with different etiologies. For example cold hyperalgesia could be present in traumatic nerve injury but also in central post-stroke pain. Sympathetically maintained pain might characterize CRPS but also the acute pain in herpes zoster infection. As the time passes after the initial injury, multiple mechanisms get involved and become responsible for painful symptoms (Baron, 2006)

Based on this observation, trials that used drugs combination as opioids and calcium channel ligands reported a better outcome with lower doses compared with single drug administration (Gilron et al., 2005, Hanna et al., 2008). Caution is recommended for combining tricyclic antidepressants and tramadol regarding the risk of “serotonine syndrome”.

The major classes of medication used for pharmacological treatment of neuropathic pain have different modes of action. Sometimes is difficult to understand how the specific mode of action of a certain drug interfere with the painful symptoms explained by a particular mechanism. On the other hand the success of a certain therapeutic intervention in alleviating pain is a clear opportunity to test a hypothesis regarding a certain association between mechanism and symptoms (Dworkin et al., 2003)

Tricyclic antidepressants act on monoamine reuptake, also block sodium channels and have anticholinergic effects as well. Apart from improving depression and sleep, this class of medication has unquestionable analgesic effect. Therefore is rated as level A indication for diabetic polyneuropathy and postherpetic neuralgia and level B for central pain and chronic radiculopathy.

Serotonine end norepinephrine selective reuptake inhibitors are only studied in diabetic polyneuropathies and rated level A for evidence of efficacy. No other relevant information is available regarding their action in other painful conditions.

Calcium channel ligands lead to decrease of neurotransmitter release by acting on central terminals of primary nociceptive neurons were widely tested in the traditional models (DPN and PHN) but also in central pain syndromes and cancer related painful conditions.

Similarly the agonists of opioid receptors demonstrated efficacy in several RCT's conducted for peripheral as well as central neuropathic pain syndromes, cancer related and phantom pain (Dworkin et al., 2007).

Topical application of lidocaine was demonstrated to be efficient in a patient population characterized by peripheral localized pain and allodynia as occurs in PHN. Its action is explained by a nonspecific blockage of sodium channels in the peripheral afferent fibers. Although patients displaying allodynia are considered the best candidates and represented the majority in clinical trials, patients without allodynia might have considerable benefit as well (Baron et al., 2009b).

Single dose capsaicin patch (8%) apart from excellent results in PHN trials (Backonja et al., 2008), also proved its efficacy in treating pain related to HIV infection where other drugs had negative results (pregabalin, amitriptyline and topical lidocaine). Capsaicin patch acts as an agonist of TRPV1 receptor expressed on nociceptive nerve fibers in the skin (Simpson et al., 2008).

The complex psychosocial aspects of neuropathic pain are sometimes addressed only by an integrated multidisciplinary approach including pharmacological and non-pharmacologic treatment strategies such as cognitive, behavioral, physical and occupational therapy (Oerlemans et al., 2000). For example an original concept such as graded motor imagery (mirror therapy) has been demonstrated to be efficient in reducing pain in patients suffering from CRPS or phantom pain (Moseley, 2006; Ramachandran & Altschuler, 2009).

Interventional therapy is indicated for patients who failed to obtain sufficient relief with standard medication. RCT's showed efficacy for invasive interventions in drug resistant patients with failed back surgery syndrome, postherpetic neuralgia or CRPS. Studies using functional magnetic resonance imaging (fMRI) in patients under spinal cord stimulation (SCS) found increased activation of the medial primary sensorimotor cortex, contralateral posterior insula, and the ipsilateral secondary somatosensory cortex (S2). Decreased activation was seen in the bilateral primary motor cortices and the ipsilateral primary somatosensory cortex (Stančák et al., 2009)

3. Case discussions

3.1 Case 1

Male of 65 years old, known with myasthenia gravis under prednisone as immunosuppressive treatment developed herpes zoster infection in the left C3, C4, and C5 roots territory. He reported pain starting after 10 days from the vesicular rash onset and respecting the same distribution. During the first interview (3 months distance after vesicular rash remission) he described pain as a superficial burning, hot wire or shooting. Also he felt his skin like as a "cardboard". His pain was coming and going in episodes that lasted seconds with complete pain free periods between these episodes. The intensity was rated 10 on the numeric rating scale and the daily activity and sleep were significantly disturbed. He had itching, pain attacks like electric shocks and very slight sensation of numbness in the painful area. The light touching, slight pressure and warm water elicited pain. The neurological exam showed an increased threshold to pinprick sensation, static and dynamic mechanical allodynia, heat allodynia and temporal summation in the painful area. On the skin, small areas of abnormal paleness have been noted as a consequence of rash healing (figure 1a, b). We used for assessment of pain, painDetect questionnaire and StEP. The total score obtained for painDetect was 21 and was considered positive for neuropathic pain.

The paroxysmal pain, dysesthesia, raised pinprick threshold and threshold decreased for noxious heat stimuli pointed to a partial deafferentation of C and some of A δ fibers and spontaneous activity in nociceptive afferents, probably related to abnormal expression of voltage-gated sodium channels and vanilloid receptor, TRPV1. The clinical picture also

suggests central sensitization process on spinal level by pre- and post-synaptic changes on second-order neuron induced by ongoing C input: temporal summation, mechanical dynamic and static allodynia. Analyzing the patient's pain in this manner, it is easier to choose the potential optimal pharmacological agents. For this patient a selective sodium channel blocker, like carbamazepine or tricyclic antidepressive and μ -receptors agonists, opioids, are not suitable because of myasthenia gravis. A calcium-channel blocker α_2 - δ ligand was recommended with a rating of 8 (VAS) for the mean pain intensity per month. Further local application of capsaicin patch (8%) lowered the pain up to a rating of 5, which the patient considered acceptable in the long run.



Fig. 1. a)

Fig. 1. b)

Fig. 1.

3.2 Case 2

Male of 47 years old was operated for lumbar disc herniation at L4-L5 manifested as acute severe low back pain associated with diffusely distributed and intermittent left leg pain in the groin and anterior thigh and a part of the lower leg. Postoperatively, a novel pain has occurred immediately after surgery. The patient was examined at 6 months interval from onset. This time the pain has been spontaneous, permanent, with a clear distribution in left

L5 root territory (left lateral lower leg and medial dorsum of foot toward the big toe). The pain's intensity was rated 8/10 on the numeric rating scale, and the words sharp, stabbing, squeezing were used as descriptors. Also, the light touch on the dorsum of the foot determines pain. The low back pain still persists but only related to movements. No negative signs were found at the neurological exam.

Compared to the pain before surgery, the actual pain has a specific topography for L5 root territory and it could be considered as a neuropathic one, even if the specific pain descriptors were missing. The pain is generated in the spinal root and not in the painful area. Mechanical dynamic allodynia described, is the expression of central sensitization. In this case, the central sensitization did not occur secondary to ongoing C fibers input, instead of that, gating of A β -fiber input, reduction of intraspinal inhibitory interneurons and changes in supraspinal descending modulation are the most probable mechanisms to explain the patient's pain. Based on this judgment, topical pharmacological agents are useless. NMDA-receptor antagonists, μ -receptor agonists, GABA-B agonists or spinal cord stimulation are the reasonable options.

3.3 Case 3

Male of 45 years old complained about painful legs and weakness since he had an acute motor-sensory axonal neuropathy (AMSAN). The intensity of pain has been 9 from ten points on the numeric rating scale. The patient has spontaneous pain attacks superimposed on a milder but permanent pain largely distributed over the distal part of the limbs, but predominantly in the lower limbs where pain usually rise up to the knees. The words used to describe pain are: burning, electric shocks and stabbing. Also, at the interview he complained that the pain could be provoked by light touch, slight pressure and heat and also reports an abnormal sensation such as prickling and numbness. The total score on painDetect questionnaire was 27, which is positive for neuropathic character of pain. Clinical examination revealed symmetrical weakness in all limbs, more in the legs, mechanical dynamic and static allodynia, heat allodynia, raised threshold to heat stimuli but the skin looked permanent cold and cyanotic skin and sometimes swollen and reddish when the pain was more intense. The clinical picture present many elements which suggest peripheral sensitization (dysesthesia, heat allodynia and raised threshold to heat) associated with abnormal recruiting of sympathetic nervous system. The central sensitization is pointed by mechanical dynamic and static allodynia. In this case because of the presence of sympathetic maintained pain, it seems logical to recommend tricyclic antidepressive drugs or sympathetic block, but it will not be sufficient and combination with other kind of drugs (calcium channel blocker, α 2- δ ligands, μ -receptor agonists, NMDA receptors antagonists) will be of very much help.

4. Conclusion

The effort of grouping patients according to sensory profiles will allow us to better understand the mechanisms involved in neuropathic pain development and persistence. Future trials will probably select specific sensory profiles across different etiologies and test treatment interventions from other perspectives.

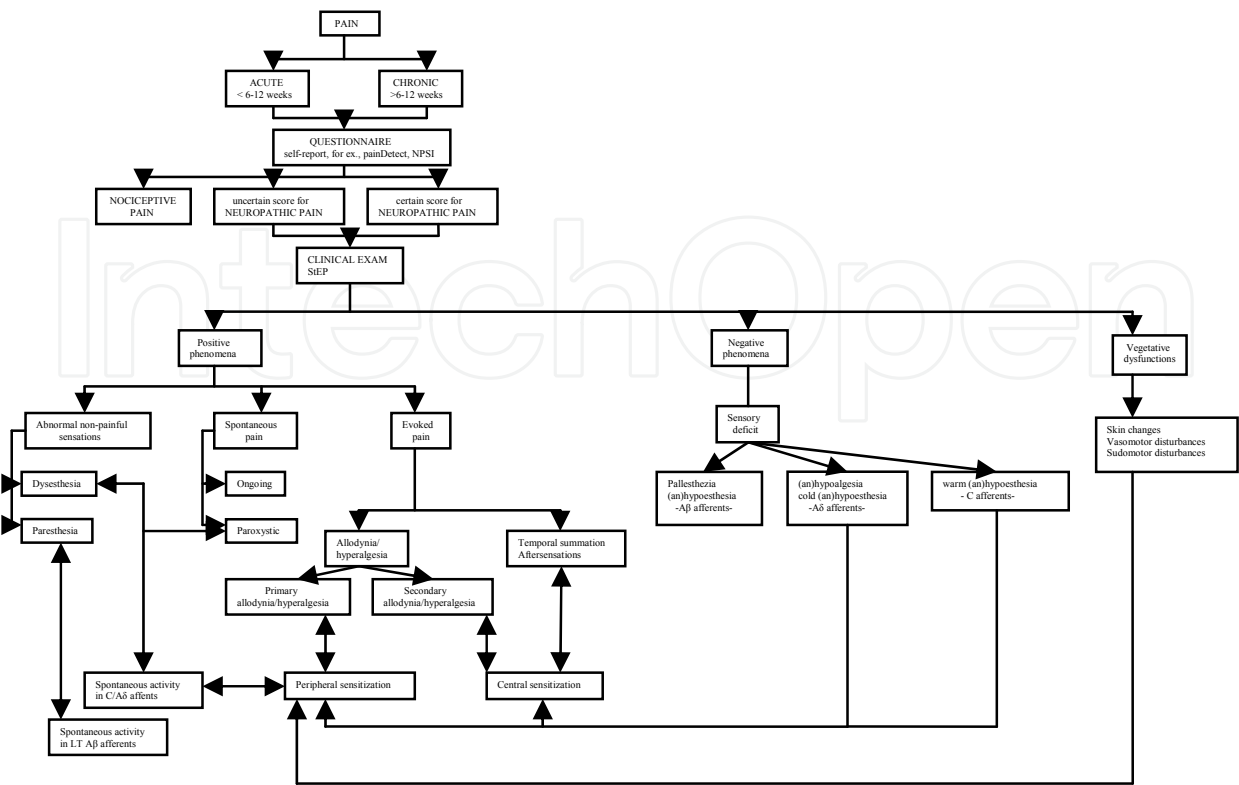


Fig. 2. Proposed algorithm for systematic approach for neuropathic pain assessment

5. References

- [1] Amir R, Kocsis JD, Devor M.(2005). Multiple interacting sites of ectopic spike electrogenesis in primary sensory neurons. *J Neurosci*; 25: 2576–85. ISSN:0270-6474
- [2] Arning K, Baron R. (2009). Evaluation of symptom heterogeneity in neuropathic pain using assessments of sensory functions. *Neurotherapeutics*; 6: 738–48. ISSN: 1933-7213
- [3] Attal N, Fermanian C, Fermanian J, Lanteri-Minet M, Alchaar H, Bouhassira D. (2008). Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion? *Pain.*;138(2):343-353. ISSN: 0304-3959
- [4] Backonja M, Wallace MS, Blonsky ER. (2008). NGX-4010, a high concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol*; 7: 1106–12. ISSN: 1474-4422
- [5] Baron R. (2006). Mechanism of Disease: neuropathic pain-a clinical perspective. *Nat. Clin. Pract. Neurol*; 2: 95–106. ISSN: 1745-834X
- [6] Baron R, Tolle TR, Gockel U, Brosz M, Freynhagen R.(2009). A crosssectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: differences in demographic data and sensory symptoms, *Pain*; 146: 34–40. ISSN: 0304-3959
- [7] Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. (2009) 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic

- polyneuropathy: an open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin*; 25: 1663–76. ISSN: 0300-7995
- [8] Baron R., Binder A., Wasner G. (2010). Neuropathic pain: diagnosis, pathophysiological mechanism and treatment. *Lancet Neurology*. 9:807-19. ISSN: 1474-4422
- [9] Bennett MI, Attal N, Backonja MM. (2007). Using screening tools to identify neuropathic pain. *Pain*. 127: 199–203. ISSN: 0304-3959
- [10] Bennett MI (2001) The LANSS Pain Scale: The Leeds Assessment of Neuropathic Symptoms and Signs. *Pain* 92: 147–157. ISSN: 0304-3959
- [11] Black JA, Nikolajsen L, Kroner K, Jensen TS, Waxman SG. (2008). Multiple sodium channel isoforms and mitogen-activated protein kinases are present in painful human neuromas, *Ann Neurol*; 64: 644–53. ISSN: 0364-5134
- [12] Boucsein C, Kettenmann H, Nolte C. (2000). Electrophysiological properties of microglial cells in normal and pathologic rat brain slices. *Eur J Neurosci*, 12:2049-2058. ISSN: 1460-9568
- [13] Bouhassira D., Attal N., Fermanian J., Alchaar H., Gautron M., Masquelier E., Rostaing S., Lanteri-Minet M., Collin E., Grisare J., Boureau F. (2004). Development and validation of the Neuropathic Pain Symptom Inventory. *Pain* 108 248–257; ISSN: 0304-3959
- [14] Bouhassira D, Attal N, Alchaar H, Boureau F, Bruxelles J, Cunin G, et al. (2005). Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*;114:29–36. ISSN: 0304-3959
- [15] Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. (2008) Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 136(3):380-7. ISSN: 0304-3959
- [16] Bromm B, Treede RD. (1984). Nerve fibre discharges, cerebral potentials and sensations induced by CO₂ laser stimulation, *Hum Neurobiol*, 3:33–40; ISSN: 0721-9075
- [17] Caterina MJ, Julius D., (2001) The vanilloid receptor: a molecular gateway to the pain pathway, *Annu Rev Neurosci*; 24: 487–517. ISSN: 0147-006X
- [18] Cruccu G., Anand P, Attal N., Garcia-Larrea L., Haanpää M., Jørum E., Serra J, and Jensen T. S. (2004) EFNS guidelines on neuropathic pain assessment, *European Journal of Neurology*, 11: 153–162; ISSN: 1351-5101
- [19] Cruccu G., Truini A. (2009). Tools for Assessing Neuropathic Pain. *PLoS Med.*, doi: 10.1371/journal.pmed.1000045;
- [20] Cruccu G., Sommera C., Anand P., N. Attal, Baron R., Garcia-Larrea L., Haanpa M., Jensen T. S, Serra J. and. Treede R.D., (2010) EFNS guidelines on neuropathic pain assessment: revised 2009. *European Journal of Neurology*; 17(8):1010-18. ISSN: 1351-5101
- [21] Craig KD, Korol CT. (2008). Developmental issues in understanding, assessing, and managing pediatric pain. In: *Pain in Children: A Practical Guide for Primary Care*. Walco GA, Goldschneider KR, eds. Totowa, NJ 07512: Humana Press; 9-20. USA, ISBN:978-1-934115-31-2
- [22] Devigili G., Tugnoli V., Penza P., Camozzi F., Lombardi R., Melli G., Broglio L., Granieri E., Lauria G., (2003). The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology, *Brain*; 131:1912-1925. ISSN: 0006-8950

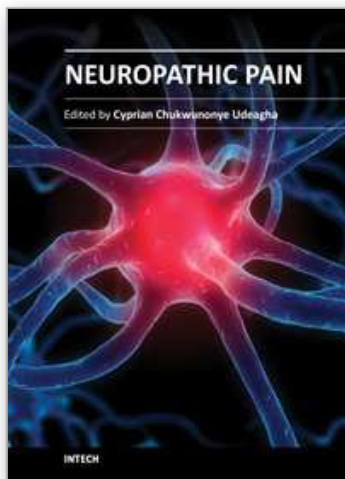
- [23] Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. (2003). Advances in Neuropathic Pain: diagnosis, mechanism and treatment recommendations. *Arch Neurol.*;60(11):1524-1534. ISSN: 1013-3119
- [24] Finnerup N., Troels J.S. , (2006). Mechanisms of Disease: mechanism-based classification of neuropathic pain—a critical analysis, *Nature Clinical Practice*;2(2)107-15. ISSN: 1745-834X
- [25] Fischer MJ, Reeh PW.(2007). Sensitization to heat through G-proteincoupled receptor pathways in the isolated sciatic mouse nerve, *Eur J Neurosci*; 25: 3570–75. ISSN: 1351-5101
- [26] Freynhagen R, Baron R, Gockel U, Tolle T., (2006). PainDetect: a new screening questionnaire to detect neuropathic components in patients with back pain, *Curr Med Res Opin*;22: 1911–20. ISSN: 0300-7995
- [27] Galer BS, Jensen MP. (1997). Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale., *Neurology*;48:332–8. ISSN:0028-3878
- [28] Garcia-Larrea L., Godinho F., (2007). Diagnostic Role of Laser-evoked Potentials in Central Neuropathic Pain, *European neurological disease.II*
- [29] Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. (2005). *N Engl J Med*; 352: 1324–34.
- [30] Gilron I., Peter C., Watson N., Cahill M., Moulin E. (2006). Neuropathic Pain: a practical guide for the clinician, CMAJ. ISSN: 0820-3946.
- [31] Gosselin RD, Suter MR, Ji RR, Decosterd I (2010): Glial Cells and Chronic Pain. *Neuroscientist*. 16(5):519-31. ISSN:1073-8584.
- [32] Gray P. (2008). Acute neuropathic pain: diagnosis and treatment, *Current Opinion in Anaesthesiology*.21(5):590-595. ISSN: 0952 – 7907.
- [33] Haanpaa M., Attal N., Backonja M., Baron R., Bouhassira D., Crrucu G., Hansson P., Haithomthwaite JA, Iannetti GD, Jensen TS,, Kaupila T., Nurmikko TJ, Rice AS, RowbothamM., Serra J., Sommer C., Smith BH, Treede RD.(2011). NeuPSIG guidelines on neuropathic pain assessment. *Pain*. 152(1):14-27.ISSN: 0304-3959
- [34] Hains BC, Saab CY, Klein JP, Craner MJ, Waxman SG. (2004). Altered sodium channel expression in second-order spinal sensory neurons contributes to pain after peripheral nerve injury., *J Neurosci*; 24: 4832–39. ISSN: 0270-6474
- [35] Hanna M, O'Brien C, Wilson MC. (2008). Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *Eur J Pain*; 12: 804–13. ISSN: 1090-3801
- [36] Hayes C, Browne S., Burstal R., (2002). Neuropathic pain in the acute pain service: a prospective survey, *Acute Pain*; 4;2; 45-8. ISSN: 1366-0071
- [37] Jensen T. S., Towards a mechanism-based approach to the treatment of neuropathic pain. In: *Neuropathic Pain: Bench to Bedside - International Congress and Symposium Series 259-2005*;
- [38] Jensen T. S., Baron R., (2003). Translation of symptoms and signs into mechanism in neuropathic pain,; *Pain*;102(1-2):1-8. ISSN: 0304-3959

- [39] Ji RR, Suter MR. (2007). p38 MAPK, microglial signaling, and neuropathic pain. *Mol Pain*, 3:33. ISSN: 1744-8069.
- [40] Kaki AM, El-Yaski AZ, Youseif E., (2005). Identifying neuropathic pain among patients with chronic low-back pain: use of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale, *Reg Anesth Pain Med*; 30:422–8. ISSN: 1098-7339
- [41] Karanikolas M., Aretha D., Tsolakis, I. et al., Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence, and frequency: a prospective, randomized, clinical trial, *Anesthesiology*, vol. 114, no. 5, pp. 1144–1154. ISSN: 003-3022
- [42] Krause SJ, Backonja MM. (2003). Development of a Neuropathic Pain Questionnaire, *Clin J Pain*; 19:306–14. ISSN: 0749-8047.
- [43] Kennedy WR., Opportunities afforded by the study of unmyelinated nerves in skin and other organs.(2004). *Muscle Nerve*; 29:756–67. ISSN: 0148-639X
- [44] Kennedy WR, Wendelschafer-Crabb G, Polydefkis M, et al., Pathology and quantitation of cutaneous innervation. (2005) In: *Peripheral neuropathy*. Dyck PJ, Thomas PK, editors. 4th edition. Philadelphia (PA): Elsevier Saunders;. p. 869–95; USA
- [45] Lai J, Hunter JC, Porreca F., (2003). The role of voltage-gated sodium channels in neuropathic pain, *Curr Opin Neurobiol*; 13: 291–97. ISSN: 0959-4388.
- [46] Low VA, Sandroni P, Fealey RD, et al. (2006). Detection of small-fiber neuropathy by sudomotor testing, *Muscle Nerve*; 34:57–61. ISSN: 0148-639X.
- [47] Ma W, Zhang Y, Bantel C, Eisenach JC. (2005). Medium and large injured dorsal root ganglion cells increase TRPV-1, accompanied by increased $\alpha 2C$ -adrenoceptor co-expression and functional inhibition by clonidine. *Pain*; 113: 386–94. ISSN: 0304-3959.
- [48] Maier C, Baron R, Toelle T, et al. (2010). Quantitative Sensory Testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain*; 150(3):439-450. ISSN: 0304-3959.
- [49] McGrath PJ, Walco GA, Turk DC, et al. PedIMMPACT. (2008). Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J Pain*. 9(9):771-783.
- [50] Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ. (2002). Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. *J Neurosci*; 22: 6724–31. ISSN: 0270-6474.
- [51] Moseley GL. (2006). Graded motor imagery for pathologic pain: a randomized controlled trial. *Neurology*; 67: 2129–34. ISSN: 0028-3878
- [52] Moulin DE, Clark AJ, Gilron I, et al. (2007). Pharmacological management of chronic neuropathic pain-consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag*; 12: 13–21. ISSN: 1203-6765.
- [53] Novak V, Freimer ML, Kissel JT, et al., (2001). Autonomic impairment in painful neuropathy, *Neurology*; 56:861–8. ISSN: 0028-3878
- [54] Oerlemans HM, Oostendorp RA, de Boo T, van der Laan L, Severens JL, Goris JA. (2000). Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/ complex regional pain syndrome type I. *Arch Phys Med Rehabil*; 81: 49–56. ISSN

- [55] Potter J, Higginson IJ, Scadding JW, Quigley CW. (2003). Identifying neuropathic pain in patients with head and neck cancer: use of the Leeds Assessment of Neuropathic Symptoms and Signs Scale, *J R Soc Med.*;96:379–83. ISSN: 0141-0768.
- [56] Portenoy R.(2006). Development and testing of a neuropathic pain screening questionnaire: ID Pain. *Curr Med Res Opin*;22:1555–65. ISSN: 0300-7995.
- [57] Pickering G, Capriz F. (2008). Neuropathic pain in the elderly. *Psychol NeuroPsychiatr Vieil.* 6 (2) : 107-14. ISSN: 2212-4926.
- [58] Pickering G. (2005). Age differences in clinical pain states. In *:.Pain in older persons.* Gibson SJ, Weiner DK, eds: IASP Press, : 67-85.8. Seattle, USA
- [59] Ramachandran VS, Altschuler EL.(2009). The use of visual feedback, in particular mirror visual feedback, in restoring brain function. *Brain*; 132: 1693–710. ISSN: 0006-8950
- [60] Rolke R, Baron R, Maier C, et al.,(2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values, *Pain*; 123: 231–43. ISSN: 0304-3959
- [61] Scholz J, Mannion RJ, Hord DE, Griffin RS, Rawal B, et al., (2009) A novel tool for the assessment of pain: Validation in low back pain. *PLoS Med* 6(4):e1000047, doi:10.1371/journal.pmed.1000047;
- [62] Scholz J, Broom DC, Youn DH, et al. (2005). Blocking caspase activity prevents transsynaptic neuronal apoptosis and the loss of inhibition in lamina II of the dorsal horn after peripheral nerve injury. *J Neurosci*; 25: 7317–23
- [63] Sethna NF, Meier PM, Zurakowski D, Berde CB. (2007). Cutaneous sensory abnormalities in children and adolescents with complex regional pain syndromes. *Pain.*;131(1-2):153-161. ISSN: 0304-3959
- [64] Serra J, Sola R, Quiles C, et al.(2009). C- nociceptors sensitized to cold in a patient with small-fiber neuropathy and cold allodynia. *Pain*; 147: 46–53. ISSN: 0304-3959
- [65] Simpson DM, Brown S, Tobias J. (2008). Controlled trial of high concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology*; 70: 2305–13.ISSN: 0028-3878
- [66] Siqueira SR, Alves B, Malpartida HM, Teixeira MJ, Siqueira JT. (2009). Abnormal expression of voltage-gated sodium channels Nav1.7, Nav1.3 and Nav1.8 in trigeminal neuralgia, *Neuroscience*; 164: 573–77.
- [67] Steven H. Horowitz, (2007). The Diagnostic Workup of Patients with Neuropathic Pain, *Anesthesiology Clin.* 25 699–708
- [68] Subedi B., Grossberg G.T. (2011). Phantom Limb Pain: Mechanisms and Treatment Approaches. *Pain Research and Treatment*,
- [69] Stančák A., Kozák J, Vrba I, Tintěra J, Vrána J , Poláček H, Stančák M. (2008). Functional magnetic resonance imaging of cerebral activation during spinal cord stimulation in failed back surgery syndrome patients. *European Journal of Pain*; 12:137-48
- [70] Tan EC, Zijlstra B, Essink ML, Goris RJ, Severijnen RS. (2008).Complex regional pain syndrome type I in children. *Acta Paediatr.*;97(7):875-879.
- [71] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, et al. (2008) Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Neurology* 70: 1630–1635. ISSN: 0028-3878

- [72] Walco G.A, Dworkin R, Elliot J. Krane, LeBel, A.A. and Treede RD. (2010). Neuropathic Pain in Children: Special Considerations. *Mayo Clin Proc.*;85(3)(suppl):S33-S41. ISSN: 0025-6196
- [73] Weiner DK, Rudy TE, Morrow L, Slaboda J, Lieber S. (2006). The relationship between pain, neuropsychological performance, and physical function in community-dwelling older adults with chronic low back pain. *Pain Med* ; 7 : 60-70.24. ISSN: 1526-2375
- [74] Woolf CJ. In: *Hyperalgesia and Allodynia*. (1992). Willis W, ed. New York, NY: Raven Press;221-243.
- [75] Woolf CJ, Bennett GJ, Doherty M, et al. (1998). Towards a mechanism-based classification of pain? *Pain*; 77: 227-29.147: 46-53. ISSN: 0304-3959
- [76] Wu G, Ringkamp M, Murinson BB, et al. (2002). Degeneration of myelinated afferent fibers induces spontaneous activity in uninjured C-fiber afferents. *J Neurosci*; 22: 7746-53. 42. ISSN: 0270-6474
- [77] Ultenius C, Linderöth B, Meyerson BA, Wallin J. (2006). Spinal, NMDA receptor phosphorylation correlates with the presence of neuropathic signs following peripheral nerve injury in the rat. *Neurosci Lett*; 399: 85-90. ISSN: 0304-3940
- [78] Zhuo M., Gongxiong W., Long-Jun W. (2011). Neuronal and glial mechanisms of neuropathic pain. *Molecular Brain*;4:31. ISSN: 1756-6606

IntechOpen



Neuropathic Pain

Edited by Dr. Cyprian Chukwunonye Udeagha

ISBN 978-953-51-0452-0

Hard cover, 140 pages

Publisher InTech

Published online 28, March, 2012

Published in print edition March, 2012

Neuropathic pain is known to be pain with nerve involvement. The intensity of which depends on the severity, pain threshold and the ability of suffers to cope. Neuropathic pain may need mono-therapy or combination of therapies to be resolved. Neuropathic pain may not resolve completely, therefore patient's compliance and understanding is essential in its management. Awareness and patient's education on targets may be of help during therapies for neuropathic pain. All chapters treated introduction, characteristics, diagnosis and randomized interventions to certain management of neuropathic pain. We acknowledge all those involve in the making of this book.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ioana Mindruta, Ana-Maria Cobzaru and Ovidiu Alexandru Bajenaru (2012). Overview of Neuropathic Pain Diagnosis and Assessment – An Approach Based on Mechanisms, Neuropathic Pain, Dr. Cyprian Chukwunonye Udeagha (Ed.), ISBN: 978-953-51-0452-0, InTech, Available from: <http://www.intechopen.com/books/neuropathic-pain/overview-of-neuropathic-pain-diagnosis-and-assessment-an-approach-based-on-mechanisms>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen