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Review Article

Neuropathic Pain and its Management

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Abstract

Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system is defined as neuropathic pain. It is common in clinical practice affecting 6-8% of the general population causing considerable suffering and substantial reduction in the patients' health-related quality of life. Quality of the pain is often difficult to characterize but burning, tingling, lancinating, pricking terms are often used by patients to describe their pain. The response to stimulus is also altered causing allodynia, hyperalgesia and hyperpathia. Treatment is difficult with current therapies resulting in 30 to 50% reduction. Treatment aims to reduce suffering and disability with the reassurance that is rarely a life threatening condition. The review describes the evidence-based pharmacologic treatment options available for the management of neuropathic pain.

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Definition

Pain usually results from activation of nociceptive afferents by actually or potentially tissue-damaging stimuli. Pain may also arise by activity generated within the nervous system without adequate stimulation of its peripheral sensory endings. For this type of pain, the International Association for the Study of Pain in 1994, introduced the term neuropathic pain, defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system."[1] While this definition was useful in distinguishing some characteristics of neuropathic and nociceptive types of pain, it lacked defined boundaries. Since the sensitivity of the nociceptive system is modulated by its adequate activation (e.g., by central sensitization), it has been difficult to distinguish neuropathic dysfunction from physiologic neuroplasticity. So a more precise definition was developed by the Neuropathic Pain Working Group, 2006 – "Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[2] This revised definition fits into the nosology of neurologic disorders. The reference to the somatosensory system was derived from a wide range of neuropathic pain conditions ranging from painful neuropathy to central poststroke pain. The term neuropathic pain is used to designate pain that arises from direct stimulation of nervous tissue itself, central or peripheral, exclusive of pain due to stimulation of sensitized C fibers by lesions of other bodily structures (i.e. nociceptive pain). In nociceptive pain the pain system only conveys or processes information from a pain source such as diseased tissue.

Neuropathic pain is further subdivided into:

Sympathetically mediated pain is pain arising from a peripheral nerve lesion and associated with

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autonomic changes (e.g., complex regional pain syndrome I and II [reflex sympathetic dystrophy and causalgia]). Table 1 shows the characteristics of the complex regional pain syndromes.

Nonsympathetically mediated pain is due to damage to a peripheral nerve without autonomic change (e.g., post-herpetic neuralgia, neuroma formation).

Central pain arises from abnormal central nervous system (CNS) activity (e.g., phantom limb pain, pain from spinal cord injuries, and post-stroke pain).

Examples of neuropathic pain syndromes are provided in table 2. The common causes of neuropathic pain are listed in table 3.

Epidemiology

Chronic neuropathic pain is common in clinical practice, causing considerable suffering and substantial reduction in the patients' health-related quality of life.[3,4] The true prevalence of neuropathic pain is largely unknown, as comprehensive epidemiological studies have not been performed. Neuropathic pain is also difficult to quantify, and exact data are lacking because of the large number of underlying causes and the lack of standardized measurement methods. Nevertheless, epidemiological surveys suggest that 6-8% of the general population report chronic pain with neuropathic characteristics.[5,6,7,8] There is evidence that more than 50% of chronic pain sufferers have pain predominantly neuropathic in nature.[9]

Estimates of neuropathic pain associated with specific aetiologies are well described. A 2008 study reported age standardized incidence rates of 27.3 per 100,000 person years for post-herpetic neuralgia, 26.7 for trigeminal neuralgia, 26.7 for painful diabetic neuropathy, and 0.8 for phantom limb pain.[10] In the United States, 1 and 3 million people suffer from post herpetic neuralgia and diabetic peripheral neuropathy, respectively.[11,12] Approximately 5% of patients with traumatic nerve injury suffer from neuropathic pain,[13] whereas this specific type of central pain has been reported with multiple sclerosis, syringomyelia, spinal cord injury, and stroke in 28%, 75%, 60-70%, and 8% patients, respectively.[14,15,16] The prevalence of neuropathic pain typically rises with age and severity of the underlying condition.[17,18]

Characteristics of Neuropathic Pain

Patients with neuropathic pain often find it difficult to characterize the qualities of their painful symptoms, because these fall outside their previous lifelong experience of nociceptive pain. The most commonly described ongoing symptoms are deep aching in the extremities and a superficial burning, stinging, or pricking pain. Burning, tingling, itching, or pricking, electric shock like lancinating pain are terms commonly used by patients to describe the quality of their NP. These are usually stimulus independent pains and maybe continuous, intermittent, or paroxysmal.

Stimulus dependent pains include allodynia, hyperalgesia, and hyperpathia, evoked by mechanical, thermal, or chemical stimulations. These terms are defined in Table 4.

NP and nociceptive pain frequently coexist. A common example is cervical and lumbar spine disease, in which pain is often of musculoskeletal, nociceptive, and neuropathic types. In painful diabetic peripheral neuropathy, distal pain in the lower legs is neuropathic, but pain may also arise from vascular insufficiency, foot and ankle arthropathies, or diabetic skin ulceration.

NP is often associated with other comorbidities which further contributes to loss of function and impair quality of life. Depression is very common, present in 100 per cent of patients in some series.[19] In patients presenting with various types of pain, anxiety is a significantly associated symptom.[20] Conversely, in panic disorder, pain is a presenting complaint in up to 81 per cent of patients.[21] Substance abuse is an important cause of co-morbidity in patients with chronic pain.[22]

Diagnosis

The diagnosis of neuropathic pain is based on a detailed medical history, analytical systems review, meticulous physical and neurological examination, appropriate laboratory studies,

including blood and serological tests, magnetic resonance imaging, and electrophysiological studies. In some instances, nerve or skin biopsy is necessary to directly visualize the nerve fibers.[23] The diagnosis of peripheral or central neuropathic pain should be made only when the history and signs are indicative of neuropathy, in conjunction with neuro-anatomically correlated pain distribution and sensory abnormalities within the area of pain. Cornerstones of the diagnostic work up in neuropathic pain, which also aim at disclosing the etiology of the pain, are listed in table 5.[24]

Treatment of neuropathic pain

Treatment of neuropathic pain begins with adequate counseling of the patient. NP is a complex disorder with minimum predictors of response. Treatment options are limited with many side-effects. It is difficult to expect a complete resolution of symptoms and patients should be warned beforehand about the limitations of treatment. At best current therapies result in a 30% to 50% reduction in pain.[25] Treatment rather aims to reduce suffering and disability with the reassurance that it is rarely a life threatening condition.

Evidence - based pharmacologic treatment options for neuropathic pain are:

First-line treatment	Tricyclic anti-depressants, gabapentin, pregabalin
Second-line treatments	Serotonin noradrenergic reuptake inhibitors (Venlafaxine), topical lignocaine
Third-line treatments	Tramadol, controlled-release opioids
Fourth-line treatments	cannabinoids, methadone, anticonvulsants with lesser efficacy (lamotrigine, topiramate, valproic acid)

The characteristics of the drugs used in the treatment of NP are provided in table 6. The effectiveness of the different drugs is given in table 7.[26,27] A useful calculated measure of effectiveness of treatments is the number needed to treat, NNT, defined as the number of patients who have to be treated to produce pain relief in one patient.[28,29] The degree of analgesia is usually defined as 50 or 30 percent, the latter figure equating to a value patients describe as at least 'moderate' pain relief. Similarly, the number needed to harm, NNH, provides a useful measure of safety and acceptability of a drug. This is defined as the number of patients who need to be treated for one patient to drop out due to adverse effects.

Stepwise pharmacologic management of neuropathic pain:

- **Step 1**

Assess pain and establish the diagnosis of NP; if uncertain about the diagnosis, refer to a pain specialist or neurologist

Establish and treat the cause of NP; if uncertain about availability of treatments addressing NP etiology, refer to appropriate specialist

Identify relevant co-morbidities (e.g. cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy

Explain the diagnosis and treatment plan to the patient, and establish realistic expectations

- **Step 2**

Initiate therapy of the disease causing NP, if applicable Initiate symptom treatment with one or more of the following:

* A secondary amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, Venlafaxine)
* A calcium channel α2-β ligand, either gabapentin or pregabalin
* For patients with localized peripheral NP; topical lidocaine used alone or in combination with one of the other first-line therapies
* For patients with acute neuropathic pain, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or Tramadol may be used alone or in combination with one of the first-line therapies

Evaluate patient for non-pharmacologic treatments, and initiate if appropriate

- **Step 3**

Reassess pain and health-related quality of life frequently

If substantial pain relief (e.g. average pain reduced to ≤3/10 and tolerable side effects, continue treatment

If partial pain relief (e.g., average pain remains ≥4/10) after an adequate trial, add one of the other first-line medications

If no or inadequate pain relief (e.g., <30% reduction) at target dosage after an adequate trial, switch to an alternative first-line medication

- **Step 4**

If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain center

Duration of trial:

If partial response occurs to 1st drug, consider adding in another drug from a different class. If no response is seen within the trial period or side effects are intolerable discontinue therapy and choose another agent from the treatment algorithm.

Apart from the pharmacological agents used in the treatment of NP some surgical procedures are also practiced for the relief of pain. The commonly used surgical procedures applied for the relief of neuropathic pain is listed in Table 8.

Conclusion

Neuropathic pain is a common condition causing widespread suffering and disability. It is a multifactorial disorder having different mechanisms and aetiologies. Response to treatment is difficult to predict and drugs often produces unpleasant side effects. Support and follow up over long periods are needed. Many patients are most appropriately managed in an integrated multidisciplinary setting that includes input from neurologists, anaesthetists, psychologists, physiotherapists, and occupational therapists. With the advent of new dimensions in the treatment of this condition, much can now be done to provide relief to patients suffering from this chronic disorder.

Table 1: IASP classification of the complex regional pain syndrome.[1]

Type I (reflex sympathetic dystrophy)	**Type II (causalgia)**
Definition: A syndrome that develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of oedema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia	*Definition*: Burning pain, allodynia, and hyperpathia usually in the hand or foot after partial injury of a nerve or one of its major branches
Diagnostic criteria (2–4 must be satisfied):	*Diagnostic criteria* (all three must be satisfied):
1. The presence of an initiating noxious event, or a cause of immobilisation	1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event	2. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
3. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain	3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction	

Table 2: Examples of neuropathic pain syndromes

Peripheral nervous system focal and multifocal lesions
Post-herpetic neuralgia
Cranial neuralgias (such as trigeminal neuralgia, glossopharyngeal neuralgia)
Diabetic mononeuropathy
Nerve entrapment syndromes
Plexopathy from malignancy or radiation
Phantom limb pain
Post-traumatic neuralgia (such as nerve root compression, post-thoracotomy) Ischaemic neuropathy
Peripheral nervous system generalised polyneuropathies
Metabolic/nutritional—Diabetes mellitus, amyloid, pellagra, beriberi, multiple nutritional deficiency, hypothyroidism
Toxic—Alcohol, platinum, or taxane based chemotherapy, isoniazid, antiretroviral drugs
Infective/autoimmune—HIV, acute inflammatory polyneuropathy (Guillain-Barré syndrome), neuroborreliosis (Bannwarth's syndrome)
Heriditary—Fabry's disease
Malignancy—Carcinomatosis
Others—Idiopathic small fibre neuropathy
Central nervous system lesions
Spinal cord injury
Prolapsed disc
Stroke (brain infarction, spinal infarction)
Multiple sclerosis
Parkinson's disease
Surgical lesions (such as rhizotomy, cordotomy)

Table 3: Common causes of Neuropathic pain.

Common causes of neuropathic pain
❖ Alcoholism
❖ Amputation
❖ Back, leg, and hip problems (sciatica)
❖ Cancer chemotherapy
❖ **Diabetes**
❖ Facial nerve problems (trigeminal neuralgia)
❖ HIV infection or AIDS
❖ Multiple sclerosis
❖ Shingles (herpes zoster virus infection)
❖ Spine surgery

Table 4: Definition of some common terms related to pain and sensation

Symptom	Definition
ALLODYNIA	Pain from stimulus that would not normally produce pain
HYPERALGESIA	An increased response to a stimulus which is normally painful
DYSAESTHESIA	Unpleasant abnormal sensations, not necessarily painful
PARAESTHESIA	An abnormal sensation, but not unpleasant or painful
HYPEREPATHIA	Abnormal pain response to stimuli applied to an area of decreased sensitivity
HYPOAESTHESIA	Decreased sensitivity to stimulation
HYPOALGESIA	Decreased sensitivity to painful stimuli
ANAESTHESIA	Lack of sensation

Table 5: Cornerstones of the neuropathic pain diagnostic workup[24]

Basic components of diagnostic workup	Detailed workup Neurophysiological testing
Careful medical history	Electroneurography
Patients coping skills	Electromyography
Specific characteristics of pain	Microneurography
Patients; functional condition –status	Somatosensory evoked potentials
Previous therapy	Quantitative sensory testing
Detailed clinical examination	Quantitative sudomat axon reflex test
Motor, sensory, autonomic system	Magnetic Resonance Imaging (MRI)
Pain drawing	Positron Emission tomography (PET)
Comprehensive neurologic examination	Functional MRI (fMRI)
Survey of somatosensory functions	Pharmacological fMRI
	Laser-evoked potentials (LEP)

Table 6: Characteristics of drugs used in treatment of Neuropathic Pain

Drug	Dose	Maximum daily dose	Dose titration & duration of trial	Side-effects / comments
Tricyclic antidepressants				
Amitriptyline (unlicensed) £1.62 x 28 of 25 mg	Initially 10-25 mg daily at night orally	Up to 75 mg daily (higher doses under specialist supervision of 150mg dependent on age & co-morbidity)	Increase dose by 10 to 25mg weekly. Duration of adequate trial 3 months at maximum tolerated dosage	Side-effects: Dry mouth, sedation, cardiotoxicity, postural hypotension, bladder problems, constipation. Give dose at night to minimise sedation. Unlicensed indication.
Nortriptyline (unlicensed) £24.02x100 of 25 mg	Initially 10-25 mg daily at night orally	Upto 75mg daily (higher doses under specialist supervision)	Increase dose by 10 to 25mg weekly. Duration of adequate trial 3 months at maximum tolerated dosage	Use in place of amitriptyline if sedation with amitriptyline is problematic. Unlicensed indication
Anti – epileptics				
Gabapentin £16.08x100 300mg caps	300mg orally OD on day 1, then 300mg BD on day 2, 300mg TDS thereafter, increased as needed	Maximum dose 1.8 gm daily in 3 divided doses.	Increase dose gradually each week to a max of 1.8 g total daily dose. Duration of adequate trial 3 months in total including titration period.	Side-effects: Dry mouth, dizziness and cognitive impairment. Licensed for treatment of neuropathic pain (age >18 years), unlicensed use in trigeminal neuralgia.
Pregabalin £64.40 x 56 75mg	Initially 75mg BD orally, increased if necessary after 7 days	Maximum dose 600 mg daily in 2 divided doses	Increase after 3-7 days to 150mg BD, increased further if necessary after 7 days to maximum dose of 300mg BD. 3 month trial to assess efficacy.	Licensed for treatment peripheral and central neuropathic pain (age>18 yrs) Consider if side effects develop with gabapentin, which aren't tolerated but has had a response to therapy (these could also be a problem with pregabalin)
Anti – epileptics (contd.)				
Carbama-zepine (Trigeminal neuralgia only) £4.50 x 84 of 200mg	Initially 100mg OD-BD orally & then titrate upwards to usual dose around 200mg TDS-QDS.	Maximum 1.6gm daily in some patients given in divided doses	Small doses should be used initially to minimise side-effects. Build up dose slowly with increments of 200mg every week. 3 month trial to assess efficacy	Licensed for treatment of paroxysmal pain of trigeminal neuralgia. Counsel patient to recognise signs of blood, hepatic or skin disorders – seek medical advice if fever, sore throat, rash or mouth ulcers, bruising/bleeding develop. Side effects: dizziness, nausea & vomiting, visual disturbances.
Lamotrigine (unlicensed) £4.92 x 56 of 25mg	Initially 25mg daily orally for 2 weeks, increased to 50mg daily for 2 weeks	Titrated upwards every 7 days by 50-100 mg until reach max of 100mg BD	Titrate slowly to minimise side effects. 3 month trial to assess efficacy including titration period.	Counsel patients to contact doctor if signs of rash, most occur within first 8 weeks of therapy. Be alert also for signs of bone marrow suppression e.g. anaemia, bruising or infection.

Serotonin & nor-adrenaline re-uptake inhibitor anti-depressants (SSNRI)				
Duloxetine £27.72 x 28 of 60mg	Initially 30mg for one week (to minimise side effects including nausea)	Maximum 60 mg daily	Titrate to 60mg OD after first week. Trial period to assess efficacy 2 months	Licensed for diabetic neuropathy in >18 yrs of age. Side effects: drowsiness, constipation, dry mouth, insomnia, nausea.
Additional therapy				
Lidocaine (post herpetic neuralgia only) £72.40 x 30 5%	5% w/w medicated plaster for topical application. One plaster to be applied to affected area at any one time for up to 12 hr duration. Plaster-free period of at least 12 hrs a day	A maximum of 3 plasters to be applied once daily for up to 12 hrs, at any one time to cover the affected area	Some pain relief may occur on 1st day of using the plaster. It may take up to 2-4 weeks until the full pain-relief effect is seen. Trial period to assess efficacy 1 month.	Lidocaine 5% medicated plaster is licensed for treatment of pain caused by post-herpetic neuralgia. Useful in the elderly population as topical application minimises side effect profile. Side effects: skin irritation at or around site of application
Drug	**Dose**	**Maximum daily dose**	**Dose titration & duration of trial**	**Side-effects / comments**
Additional therapy (contd.)				
Capsaicin cream £12.15 x 45g	Capsaicin 0.075% topical cream. Apply a small amount up to 3-4 times a day	Do not apply more than four times a day	Trial period to assess efficacy 2 months	Avoid contact with eyes, inflamed & broken skin. Only to be used for posterpetic neuralgia once open skin lesions have healed. Hands should be washed immediately after use. Side effects include transient burning sensation during initial treatment.
Baclofen (unlicensed) £3.17 x 84 10mg	Initially 10mg OD, orally with or after food. Increased after 7 days if necessary to 10mg BD for 7 days then 10mg TDS	Maximum dose 30mg TDS	Titrate slowly each week to minimise side effects. 3 month trial period to assess efficacy	Side effects include sedation, nausea, urinary disturbances, ataxia, insomnia, hallucinations

Table 7: Effectiveness of Drugs Used in Treatment of neuropathic pain.[26,27]

Drug	Peripheral neuro-pathic pain NNT	Central neuro-pathic pain NNT	Mixed neuro-pathic pain NNT	NNH
Antidepressants:				
TCAD	2.1 – 2.8	4.0		14.7
SSRI	6.8			
SNRI	5.5			
Combined	3.3.	4.0	1.6	16.7
Anticonvulsant drugs:				
Phenytoin	2.1			
Carbamazepin	2.3			
GBP & PGB	3.9 – 4.6			
Lamotrigine	4.0 – 5.4			
Valproate	2.1 – 2.4			
Topiramate	7.4			6.3
Combined	4.2		10.0	10.6
Opioids:				
Strong opioids	2.3 – 3.0		2.1	17.1
Tramadol	3.5 – 4.8			9.0
NMDA antagonists:				
Dextromethorphan	2.5 -3.4			8.8
Antiarrhythmics:				
Mexiletine	2.2 – 7.8			
Topical Lignocaine	4.4			
Cannabinoids		3.4	9.5	
Topical Capsaicin	3.2 – 11.			11.5

Abbreviations: GBP- Gabapentin, NNT – number needed to treat, NNH – number needed to harm, PGB – pregabalin, SNRI – selective noradrenaline and serotonic re-uptake inhibitors, SSRI – selective serotonin re-uptake inhibitor, TCAD – tricyclic antidepressant drugs.

The NNT is an estimate of the total number of patients who need to be treated to obtain one patient with at least 50% pain relief. Similarly NNH is defined as the number of patients who need to be treated for one patient to drop out due to adverse effects.

Table 8: Surgical techniques used in the treatment of Neuropathic Pain.

Peripheral surgical techniques	Central surgical techniques
Nerve Blocks	Precentral (Motor) Cortex Stimulation
Intraspinal : phenol or hypertonic saline.	Deep Brain Stimulation
Epidural : local anaesthetic produces temporary analgesia.	Hypophysectomy
Sympathetic Ganglion or Trunk	Percutaneous Anterolateral Cordotomy
Paravertebral or Peripheral Nerve	Mesencephalotomy
Acupuncture	Myelotomy midline
Dorsal Rhizotomy & ganglionectomy	Spinal cord stimulation
Facet Joint Injection	Dorsal root entry zone lesioning
Transcutaneous Electrical Nerve Stimulation (TENS)	

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