

Tailor treatment to the patient with neuropathic pain

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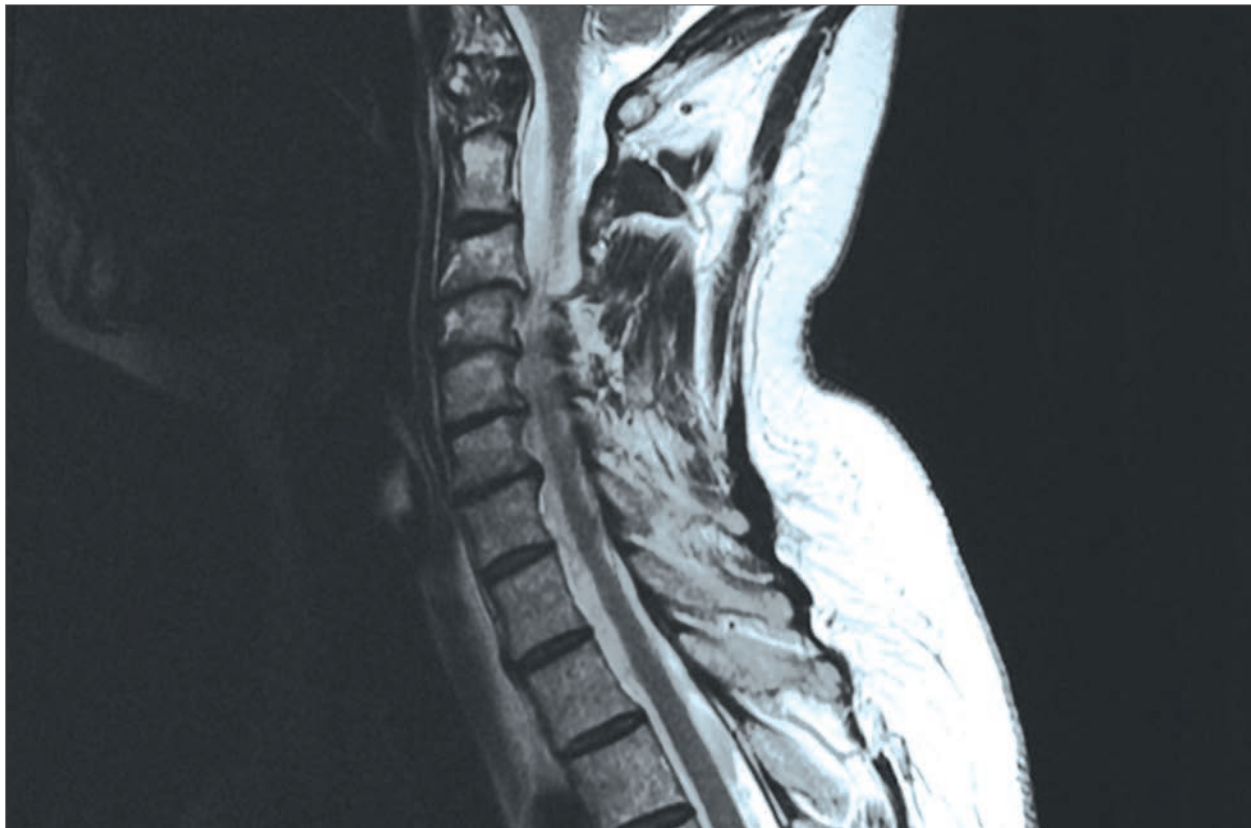
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Cervical spine MRI showing cervical nerve root compression from cervical spondylosis

How should patients be assessed?

How should examination be carried out?

What are the treatment options?



NEUROPATHIC PAIN IS ESTIMATED TO AFFECT 6-8% OF THE GENERAL POPULATION.¹² IT LEADS

to significant distress and disability for many patients making it a significant healthcare burden. Neuropathic pain was redefined in 2008 by the International Association for the Study of Pain as 'pain that is caused by a lesion or disease of the somatosensory nervous system'.¹³

Neuropathic pain is distinct from nociceptive pain in terms of aetiology, symptoms, signs and therapeutic options for management and thus a different approach is required.⁴ Neuropathic pain can be viewed as a clinical syndrome with multiple causes ranging from damage to peripheral

nerve pathways at the level of peripheral nociceptors to abnormalities in the cortical neurones in the brain. Central neuropathic pain is pain caused by a lesion or disease of the central somatosensory nervous system, and peripheral neuropathic pain is caused by a lesion or disease of the peripheral somatosensory nervous system. While

'Neuropathic pain is distinct from nociceptive pain in terms of aetiology, symptoms, signs and therapeutic options'

these terms can be useful in defining the cause, central neuropathic pain should not be confused with the central sensitisation that can occur in the chronification of acute pain.

COMMON CAUSES

The causes of neuropathic pain are diverse and numerous. They include cervical or lumbar radiculopathy, diabetic neuropathy, postherpetic neuralgia, malignancy-related neuropathy (including chemotherapy-related neuropathy, neuropathy secondary to tumour antigens, or direct compression or invasion of nerves), multiple sclerosis, spinal cord injury, central post-stroke pain, trigeminal neuralgia, pain after trauma or surgery, and complex regional pain syndrome.⁵ »

This heterogeneity in terms of aetiology, symptoms and underlying mechanisms adds to the challenges faced when managing neuropathic pain.⁶

DIAGNOSIS

Having a low threshold of suspicion in conditions associated with neuropathic pain can aid diagnosis. Data from the past decade suggest that neuropathic pain is present in 16-26% of patients with diabetes,^{7,8} 8% of all patients who have suffered from shingles in the previous three months⁹ (increasing to 40% and 75% in patients aged over 50 and over 75 respectively¹⁰), and 10-50% of

patients following surgery.¹¹ It is also estimated to occur in 10% of patients undergoing common procedures such as hernia repair or caesarean section,¹² although this may be an overestimate as not all chronic postsurgical pain is neuropathic in nature.

HISTORY

Using a biopsychosocial model, the goals in assessing the patient who presents with pain suspected to be neuropathic include determining whether there is a neuropathic element to the pain and whether this is alone or in combination with a nociceptive

component. Typical descriptors of neuropathic pain include burning, shooting, electric shock pain with numbness, pins and needles or itching.

Specifics to be addressed in the history of the pain itself include the nature, location, temporal profile, and any exacerbating factors. Further assessment should then aim to elucidate the disease process or event that triggered the pain. Finally, the effect of any functional limitation as a result of the pain should be assessed, taking into account any comorbidities and psychological impact.

'Typical descriptors of neuropathic pain include burning, shooting, electric shock pain with numbness, pins and needles or itching'

History taking can be facilitated by the use of validated tools such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale, see table 1, left.¹³ This gives a dimensionless score for the pain out of 24, with a score > 12 suggesting a neuropathic component is likely. Other tools available for assessing the impact of the pain include the Brief Pain Inventory or the Short-Form 36.

EXAMINATION

Examination begins when the patient enters the room and continues during the history taking. Any discrepancy between what is observed then and during subsequent formal examination should alert the clinician to the possibility of a functional element or conversion syndrome.¹⁴

After a general and neurological examination the focus should turn to the affected pain area using an unaffected body part as a control. Sensory response to cotton wool, pinprick, temperature and vibration should all be assessed. This will identify the positive and negative signs found in neuropathic pain, see table 2, left.¹⁵

In the context of certain conditions, specific tests such as straight leg raising (for lumbar/sacral radiculopathy) or Tinel's test (for carpal tunnel syndrome) can be used.¹⁴

Further in-depth guidance on particular conditions such as low back pain, peripheral neuropathy and facial

Table 1

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale¹³

Five questions about the nature of the pain	Score
A In the area where you have pain, do you also have pins and needles, tingling or prickling sensations?	0 or 5
B Does the painful area change colour (perhaps looks mottled or more red) when the pain is particularly bad?	0 or 5
C Does your pain make the affected skin abnormally sensitive to touch?	0 or 3
D Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Electric shocks, jumping and bursting might describe this.	0 or 2
E In the area where you have pain, does your skin feel unusually hot like a burning pain?	0 or 1
Two signs	
● Cotton wool allodynia	0 or 5
● Pinprick threshold altered	0 or 3
Total score > 12/24 implies neuropathic pain	

Table 2

Positive and negative signs in the diagnosis of neuropathic pain

Positive signs	Description
Allodynia	Painful response to a non-painful stimulus e.g. cotton wool, cold metal etc
Hyperalgesia	Exaggerated painful response to painful stimuli e.g. pinprick compared with opposite side
Hyperpathia	Repeated innocuous stimuli produce pain
Autonomic signs	Local changes in skin colour, temperature, sweating or swelling
Negative signs	Description
Hypoaesthesia	Loss of normal sensation to non-painful stimulus
Hypoalgesia	Reduced sensation to painful stimuli. Often seen in peripheral neuropathies accompanied by a spontaneous burning sensation
Motor deficit	Weakness, paralysis, reduced reflexes e.g. post-stroke pain or in demyelination disorders

pain is outside the scope of this article but can be found in the literature.¹⁶⁻²⁰

INVESTIGATION

Unfortunately there are no conclusive investigations which can prove the diagnosis which is frequently heavily reliant on the history and clinical examination. That said, any investigation which proves an underlying disorder associated with neuropathic pain supports the diagnosis. Of the laboratory investigations available (nerve biopsy, evoked potentials, quantitative sensory testing, confocal corneal microscopy) none are used routinely in clinical practice and these serve more as research tools at present.¹⁴

MANAGEMENT

The pervasive nature and chronicity of neuropathic pain make it difficult to treat. Often it is poorly responsive to conventional analgesia with the mainstay of pharmacological treatment being anticonvulsant and antidepressant medication. In order for significant rehabilitation to take place, multidisciplinary assessment and management in the specialist setting of the pain clinic is often required. This allows management tailored to the individual with input from specialist pain

physiotherapists and pain psychologists if required, and the use of specialist treatments such as neuromodulation where indicated.

‘After a general and neurological examination the focus should turn to the affected pain area using an unaffected body part as a control’

NICE recommends referral to a pain management specialist in the following:²¹

- Severe pain
- Pain with a significant impact on function or sleep
- Patients whose underlying health condition has deteriorated

We appreciate that the provision of specialist pain services in some areas of the UK is such that GPs are often required to undertake the initial months of treatment. This issue has recently been highlighted in an article detailing the challenges facing chronic pain

management services which outlined a strategy for constructively tackling this increasing healthcare burden.²²

Pharmacological treatment

The principles of pharmacological treatment include regular clinical review to assess the effect of any new medication on the patient’s pain, function, and psychological state, and the presence of side effects and the need for continuation of therapy.

First-line medications for neuropathic pain that can be tried include amitriptyline, gabapentin, pregabalin and duloxetine, except in trigeminal neuralgia, see below. If treatment fails with first-line therapy, NICE advises careful discontinuation and a trial of one of the other three drugs.²¹

Combination therapy of an antidepressant with an anticonvulsant is also advocated. This requires gradual titration of the second drug once the first drug dose is optimised. Analgesic efficacy is increased with combination therapy, but side effects are also increased, so it is only an option with patients who tolerate drugs well. Further information about these antidepressant and anticonvulsant medications and suggested doses employed are shown in table 3, below.



Table 3

Antidepressant and anticonvulsant treatments for neuropathic pain

Medication	Initial dose	NNT for 50% pain reduction ²⁸	Titration	Comments	Duration of trial
Amitriptyline	10 mg nocte	3.6	Increase every 3-7 days as tolerated to maximum 100 mg	Morning sedation/hangover effect can be negated by taking earlier in the evening e.g. 7 pm	6-8 weeks with at least 2 weeks at maximum tolerated dose
Nortriptyline	10 mg nocte	3.6	Increase every 3-7 days as tolerated to 75 mg maximum (50 mg in the elderly)	Potentially better tolerated in the elderly	6-8 weeks with at least 2 weeks at maximum tolerated dose
Duloxetine	30 mg od	6.4	Increase weekly to 60 mg bd maximum	GI upset common	4 weeks
Gabapentin	100 mg tds or 300 mg nocte	7.2	Increase weekly by 300 mg/day to maximum 3,600 mg daily	Lower doses required in the elderly and in renal impairment	3-8 weeks for titration followed by 2 weeks at maximum tolerated dose
Pregabalin	75 mg bd	7.7	Increase weekly by 150 mg/day to 600 mg/day maximum	More linear absorption profile compared with gabapentin. Similar side effects of sedation and weight gain	4 weeks
Carbamazepine	100 mg daily	-	Increase weekly by 200 mg/day. 1,600 mg/day total	Leukopaenia (10%), with neutropaenia in 1-10%	6-8 weeks

key points

SELECTED BY

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Neuropathic pain can be considered to be a clinical syndrome with multiple causes ranging from damage to peripheral nerve pathways at the level of peripheral nociceptors to abnormalities in the cortical neurones in the brain. It is defined as pain that is caused by a lesion or disease of the somatosensory nervous system and is estimated to affect 6-8% of the general population. Neuropathic pain leads to significant distress and disability for many patients making it a significant healthcare burden.

A low threshold of suspicion in conditions associated with neuropathic pain can aid diagnosis. Data from the past decade suggest that it is found in 16-26% of patients with diabetes, 8% of patients suffering from shingles in the past three months (increasing to 40% and 75% in patients aged over 50 and 75 respectively), and 10-50% of patients following surgery. Typical neuropathic descriptors include burning, shooting, electric shock pain with numbness, pins and needles or itching.

After a general and neurological examination the focus should turn to the affected pain area using an unaffected body part as a control. Sensory response to cotton wool, pinprick, temperature and vibration should all be assessed. This will identify the positive and negative signs found in neuropathic pain. Tinel's sign and Phalen's sign, although classically taught, have such poor sensitivity and specificity that GPs are no longer encouraged to rely on them, and they should not be advocated.

Neuropathic pain is often poorly responsive to conventional analgesia with the mainstay of treatment being anticonvulsant and antidepressant medication. Multidisciplinary assessment and management in the specialist setting of the pain clinic is often required.

First-line medications for neuropathic pain include amitriptyline, gabapentin, pregabalin and duloxetine (except in the case of trigeminal neuralgia). If treatment fails with first-line therapy, NICE advises careful discontinuation and a trial of one of the other three drugs. Combination therapy with an antidepressant and anticonvulsant is also advocated. In the case of trigeminal neuralgia, carbamazepine is used first line with specialist referral if this fails.

The use of opioids for non-malignant pain remains controversial as neuroendocrine and immune modulatory side effects are increasingly being recognised alongside the characteristic side effects of tolerance, addiction and dependence. Guidance for their safe prescription is available from the British Pain Society. In the context of neuropathic pain, NICE advocates reserving tramadol for short-term rescue therapy only. Capsaicin cream can be considered for those with localised neuropathic pain as an additional therapy, starting with the 0.025% formulation.

In the case of trigeminal neuralgia, carbamazepine is used first line with specialist referral if this fails.²³

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'Analgesic efficacy is increased with combined therapy but side effects are also increased'

Topical treatment

Capsaicin cream can be considered for those with localised neuropathic pain as an additional therapy, starting with the 0.025% formulation. Patients should be warned of the attendant side effects of burning and an itching discomfort that subsides with ongoing use.

Lignocaine 5% plasters are licensed for the treatment of postherpetic neuralgia but are occasionally used as an off-licence prescription for neuropathic pain in other contexts. It is our practice to advise a trial period of four weeks for topical lignocaine patches to establish if this relatively costly treatment is effective for the individual patient's symptoms. Using the patch continuously for 36 hours of the initial 48 hours of treatment can reduce the pain from repeated application and removal.

Refractory pain

When the above measures fail (and if the aforementioned criteria have not already been met) then referral to a pain specialist is warranted.

NICE does not support the use of further pharmacological treatment such as step 3 opioids, cannabinoids, lamotrigine, or lacosamide in a non-specialist setting.²¹

A full biopsychosocial assessment will be performed in the pain clinic and a management plan tailored to the individual patient will be agreed upon. Further therapies available include treatment with an 8% capsaicin patch, titration of antidepressants with analgesic benefit, or cautious

prescription of an opioid trial with close assessment of any resultant improvement in function and defined goal setting. The need for specialist pain physiotherapy or psychology will be evaluated and offered if appropriate. In certain clinical conditions such as failed back surgery syndrome and complex regional pain syndrome, neuromodulation with a spinal cord stimulator or intrathecal drug delivery system will be considered.

In those patients with significant distress and disability and in whom management options have been exhausted, the role of the pain management programme will be explored. This is a course of sessions run on an outpatient or inpatient basis, with input from the psychology and physiotherapy services that addresses coping strategies for living with persistent pain.

FUTURE DEVELOPMENTS

New therapeutic options are continuously being researched for the treatment of neuropathic pain. Novel treatments recently investigated include acetyl-L-carnitine (ALC), alpha-lipoic acid, cannabinoids, botulinum toxin, and angiotensin receptor antagonists.²⁵ In a randomised controlled trial of 1,257 patients, ALC was shown to reduce pain and promote nerve fibre regeneration in patients with diabetic neuropathy.²⁶ In another randomised controlled trial of 179 patients, topical clonidine was shown to reduce painful diabetic neuropathy compared with placebo.²⁷

Despite these promising advances, neuropathic pain remains a difficult clinical entity to treat. With greater understanding of the pathophysiology and the development of novel therapies, it is hoped that some of the encouraging results seen will translate into improved treatment for patients and a reduction in the number of people suffering from refractory pain.

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Useful information

British Pain Society
www.britishpainsociety.org

Pain management

Advice and information for patients and healthcare professionals from patient information leaflets to drug conversion tables
www.paindata.org

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