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Optimising the management of neuropathic pain

Lewis G, Serpell M, Paisley P. Optimising the management of neuropathic pain.
Practitioner Sept 2019;263(1829):11-15

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Medical Publishing Ltd

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

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 ● Pinprick threshold altered	0 or 5 0 or 3
Total score > 12/24 implies neuropathic pain	

TABLE 1
The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale[15]

What are the common underlying causes?

What are the positive and negative signs?

What are the management approaches?

NEUROPATHIC PAIN HAS BEEN DEFINED BY THE INTERNATIONAL ASSOCIATION FOR THE Study of Pain (IASP) as 'pain that is caused by a lesion or disease of the somatosensory nervous system.'[1]

Neuropathic pain is not one disease entity but rather a number of diseases or lesions with a cluster of symptoms and signs, where understanding of the pathophysiology is evolving.[2] It differs from nociceptive pain with respect to aetiology, symptoms and signs, and treatment options.[3] The causes of neuropathic pain range 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 caused by a lesion or disease of the central somatosensory nervous system (secondary and tertiary afferents in the spinal cord and supraspinal structures). Peripheral neuropathic pain is caused by a lesion or disease of the peripheral somatosensory nervous system (primary afferents, from nociceptor to dorsal horn of the spinal cord).

Central neuropathic pain should not be confused with the central sensitisation that can occur in the transition of acute to chronic pain.

Peripheral neuropathic pain can be caused by a wide variety of conditions, for example, diabetic neuropathy, trigeminal neuralgia, postherpetic neuralgia, radicular pain, chemotherapy-induced neuropathy, neuropathy secondary to tumour infiltration, and injury to nerves from trauma, surgery or electric shock. Conditions affecting the CNS such as stroke, spinal cord injury and multiple sclerosis may cause central neuropathic pain.[4] The prevalence of specifically diagnosed neuropathic pain as described is 1-2% of the general population. However, a much larger proportion of the population (8%) have chronic pain with neuropathic pain type symptoms that do not fulfill the criteria to be diagnosed as neuropathic pain. This group has been labelled as POPNO (pain of predominantly neuropathic origin). It is thought appropriate that this group is managed in the same way as formally diagnosed neuropathic pain.[5] The diversity of symptoms and underlying mechanisms make the management of neuropathic pain challenging.[6]

DIAGNOSIS

Diagnosis is often very reliant on the history and clinical examination. It is important to have a low threshold of suspicion in patients with conditions associated with neuropathic pain. Neuropathic pain has been reported in 16-26% of patients with diabetes,[7,8] 8% of all patients who have suffered from shingles in the previous three months[9] (40% in patients aged over 50 and 75% in those over 75 respectively[10]), and 10-50% of patients following surgery.[11] It is also estimated to occur in 12% of patients undergoing common procedures such as caesarean section and as many as 35% of hernia repairs,[12,13] although this may be an overestimate as not all chronic postsurgical pain is neuropathic in nature. »

ASSESSMENT

When assessing patients it is important to determine not only whether there is a neuropathic element to the pain but also whether this is alone or in combination with a nociceptive component. Neuropathic pain may be constant or intermittent, spontaneous or provoked and is typically described as shooting, stabbing, like an electric shock, burning, tingling, tight, numb, prickling or itching.[14]

The nature of the pain, location, temporal profile, and any exacerbating factors should be ascertained. It is also important to try to elucidate the disease process or event that triggered the pain. Functional limitation due to pain should be assessed, as well as the psychological impact, and also any comorbidities.

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale,[15] (see table 1, p11) gives a dimensionless score for the pain out of 24, with a score > 12 suggesting a neuropathic component is likely (80% sensitivity and > 90% specificity). The Brief Pain Inventory or the Short-Form 36 can also be used.

'Neuropathic pain may be constant or intermittent, spontaneous or provoked'

Within the confines and time pressures of primary care, many of the neuropathic pain scoring tools can be cumbersome for the clinician not accustomed to their routine use. It may be more beneficial, and simpler, to use the IASP criteria of 'possible', 'probable' and 'definite' neuropathic pain. This classifies the pain depending on whether the patient has a history of a relevant neurological lesion or disease and describes pain in an anatomically plausible distribution of a nerve, has corresponding findings on examination in that same distribution, and then a confirmatory diagnostic test to satisfy those three definitions in sequence respectively. Using carpal tunnel syndrome as an example, a patient describing pain in the distribution of the median nerve (possible neuropathic pain) having examination findings such as Phalen's or Tinel's sign in that distribution (probable neuropathic pain), and then having confirmation by formal nerve conduction studies (definite neuropathic pain).

'The sensory response to cotton wool, pinprick, temperature and vibration should be assessed ...

EXAMINATION

Examination should start as soon as the patient enters the consulting room and should continue during the history taking. If any discrepancy is noticed between what the clinician observes initially and during the ensuing formal examination this should alert them to the possibility of a functional element or conversion syndrome, although this is uncommon.[16]

Following general and neurological examination the area affected by the pain should be investigated using an unaffected body part as the control. The sensory response to cotton wool, pinprick, temperature and vibration should be assessed to help identify the positive and negative signs found in neuropathic pain, see table 2, below.[17]

Specific tests such as straight leg raising (for lumbar/sacral radiculopathy) or Tinel's test (for carpel tunnel syndrome) can also be used.[16]

... to help identify the positive and negative signs found in neuropathic pain'

Detailed management of specific conditions such as low back pain, peripheral neuropathy and facial pain is outside the scope of this article but can be found in the literature.[18-22]

There are no conclusive investigations that can prove the diagnosis, any investigation which demonstrates an underlying disorder associated with neuropathic pain supports the diagnosis. Laboratory investigations such as nerve biopsy, evoked potentials, quantitative sensory testing, and confocal corneal microscopy, are primarily research tools and not routinely used in clinical practice.[16]

MANAGEMENT

Neuropathic pain is persistent in many cases. As it is not always possible to cure the underlying disease or lesion causing the neuropathic pain completely, the aim of treatment is management rather than cure.[14,23] It often fails to respond to conventional analgesia such as paracetamol and NSAIDs. Furthermore, the mainstays of pharmacological treatments, e.g. anticonvulsants and antidepressants, are associated with potential adverse effects. No single drug works for all patients and treatment needs to be individualised.[23]

Multidisciplinary team (MDT) assessment and management in a specialist pain clinic may be required in order to achieve optimal analgesic response and rehabilitation. This will enable access to specialist pain physiotherapists, pain psychologists and education classes and pain management programmes. Patients with chronic neuropathic pain have higher anxiety and depression scores, and a greater likelihood of sleep disturbances, when compared with those with

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

non-neuropathic chronic pain.[24]

Pain management programmes generally comprise a course of 10-12 sessions run on an outpatient basis, with input from the psychology, medical, nursing and physiotherapy services focusing on non-pharmacological coping strategies for dealing with persistent pain and improving sleep, mood and quality of life as a result. There are also specific programmes for certain conditions and programmes for inpatients with significant disability.

Over recent years the categorisation of some commonly used pain drugs has been changed with both tramadol (2014) and gabapentinoids (2019) now listed as Schedule 3 controlled drugs. It is worth noting that the NICE guidelines only recommend the use of tramadol as a short-term rescue medication in neuropathic pain.[25] NICE does not define the duration of short-term use for tramadol. However, the authors consider it would usually entail 2-4 weeks of treatment. Advice can be sought by phone from the pain clinic if the patient is still waiting to be seen. If GPs choose to prescribe opioids, they should follow guidelines from the British Pain Society (rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware).

NICE recommends referral to a pain management specialist in the following cases: severe pain; pain with a significant impact on function or sleep; patients whose underlying health condition has deteriorated.[25] 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.

PHARMACOLOGICAL TREATMENT

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 is essential. It is important to advise the patient on dosage titration and the titration process and that regular review possibly including a trial cessation of therapy is mandatory.[25] It is also paramount to explain that treatment does not work immediately; it commonly takes weeks to titrate up to an effective dose, with an effective treatment being considered as a 30% reduction in pain score and/or improved function.[23]

First-line medications include amitriptyline, gabapentin, pregabalin and duloxetine, except in trigeminal neuralgia, see table 3, below. (In trigeminal neuralgia, carbamazepine is used first line with specialist referral if this fails.[27])

If there is no improvement in pain or function it is important not to continue treatment. Compliance should always be checked before making changes to treatment.[23] If treatment fails with first-line therapy, NICE advises careful discontinuation and a trial of one of the other three drugs.[25]

NICE does not currently recommend any combination treatments for neuropathic pain owing to the lack of trial evidence comparing the clinical and cost effectiveness and tolerability of different drug combinations.[25] However, combination therapy of an antidepressant with an anticonvulsant may be advocated. This requires gradual titration of the second drug once the first drug dose is optimised. Analgesic efficacy is increased with combination therapy but so are side effects. Hence, it is only an option for patients who tolerate the drugs well.[28] Further details and suggested doses for these medications are listed in table 3, below.

Guidance for the prescription of opioids is available from the British Pain Society.[29] Their use for patients with non-malignant pain remains controversial as neuroendocrine and »

Table 3

Antidepressant and anticonvulsant treatments for neuropathic pain

Medication	Initial dose	NNT for 50% pain reduction[26]	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 is defined as 'pain that is caused by a lesion or disease of the somatosensory nervous system.' Common peripheral causes of neuropathic pain are diabetic neuropathy, trigeminal neuralgia, postherpetic neuralgia, radicular pain, chemotherapy-induced neuropathy, neuropathy secondary to tumour infiltration, and injury to nerves from trauma, surgery or electric shock. Conditions affecting the CNS such as stroke, spinal cord injury and multiple sclerosis may cause central neuropathic pain. It is important to have a low threshold of suspicion in patients with conditions associated with neuropathic pain such as diabetes and shingles.

When assessing patients it is important to determine not only whether there is a neuropathic element to the pain but also whether this is alone or in combination with a nociceptive component. Neuropathic pain may be constant or intermittent, spontaneous or provoked and is typically described as shooting, stabbing, like an electric shock, burning, tingling, tight, numb, prickling or itching. The International Association for the Study of Pain (IASP) pain grading system is a simple way of determining the likelihood of a neuropathic component. If the history suggests a relevant neurological lesion or disease and the patient describes pain in an anatomically plausible distribution of a nerve, neuropathic pain is 'possible'; it is 'probable' if there are corresponding examination findings in that same distribution and 'definite' if there is a confirmatory diagnostic test.

Neuropathic pain is persistent in many cases. As it is not always possible to cure the underlying disease or lesion causing the neuropathic pain completely, the aim of treatment is management rather than cure. Multidisciplinary team assessment and management in a specialist pain clinic may be required in order to achieve optimal analgesic response and rehabilitation. NICE recommends referral to a pain management specialist if the pain is severe, if it has a significant impact on function or sleep, or if the underlying health condition has deteriorated.

First-line medications include amitriptyline, gabapentin, pregabalin and duloxetine. If there is no improvement in pain or function it is important not to continue treatment. However, compliance should always be checked before making changes to treatment. If treatment fails with first-line therapy, NICE advises careful discontinuation and a trial of one of the other three drugs. In trigeminal neuralgia, carbamazepine is the first-line treatment with specialist referral if this fails. Tramadol should only be used as a short-term rescue medication. Capsaicin cream can be used for patients with localised neuropathic pain as an additional therapy, starting with the 0.075% formulation.

immune modulatory side effects are being increasingly recognised alongside the characteristic side effects of tolerance, addiction and dependence.

The authors are not aware of any significant trial evidence greater than six months duration, that would advocate initiating step 3 opioids for non-malignant chronic neuropathic pain. There are some patients who following specialist assessment may benefit, but this would need to be after a formal opioid trial with predetermined endpoints that are assessed at regular review.

TOPICAL TREATMENT

Capsaicin cream can be used for patients with localised neuropathic pain as an additional therapy, starting with the 0.075% formulation. It is important to warn patients that they may experience a sensation of burning and itching that frequently subsides with ongoing use.[25]

Lignocaine 5% plasters are only licensed for postherpetic neuralgia but are occasionally used as an off-licence prescription for neuropathic pain. These plasters are also listed on PrescQIPP DROP-List, as there are cheaper and safer alternatives[30] and because of this NICE recommends that they should not be used in primary care.[29] It is our practice to advise patients to cut the plaster if needed and apply it to the painful sites for a trial period of four weeks to establish whether it is effective for that individual. Using the patch continuously for 36 of the initial 48 hours of treatment can reduce the pain from repeated application and removal.

REFRACTORY PAIN

NICE does not advocate the use of further pharmacological treatment such as step 3 opioids, cannabinoids, lamotrigine, lacosamide, imipramine or nortriptyline in a non-specialist setting.[25] When initial treatments have failed, and if the criteria previously mentioned have not already been met, then referral to a pain specialist is warranted. In the pain clinic the patient will undergo a full biopsychosocial assessment and an individualised management plan will be drawn up.

Treatment with an 8% capsaicin patch, a single patch applied for an hour by a healthcare professional, can provide pain relief for more than three months. Titration of antidepressants to analgesic benefit, or cautious prescription of an opioid trial with close assessment of any resultant improvement in function and defined goal setting as outlined above, may be considered. The patient's requirement for specialist pain physiotherapy or psychology will also be evaluated. Neuromodulation with a spinal cord stimulator or intrathecal drug delivery system may be considered for certain clinical conditions such as failed back surgery syndrome and complex regional pain syndrome.

CONCLUSION

Neuropathic pain is a complex condition that affects the quality of life of many patients and can be difficult to treat effectively. Currently, the recommended first-line treatments are amitriptyline, duloxetine, pregabalin and gabapentin. Patients who receive pharmacotherapy for neuropathic pain may not experience pain relief but the aim is to improve overall function and quality of life with an MDT approach.

Novel treatments currently being investigated for the management of neuropathic pain include acetyl-L-carnitine (ALC), alpha-lipoic acid, cannabinoids, botulinum toxin, and angiotensin receptor antagonists.[31] In a randomised controlled trial (RCT) involving 1,257 patients, ALC was shown to reduce pain and promote nerve fibre regeneration in those with diabetic neuropathy.[32] Topical clonidine reduced painful diabetic neuropathy compared with placebo in an RCT of 179 patients.[33]

Additionally, there are new voltage-gated sodium channel blockers that are receptor specific and may have less risk of cardiac, motor and CNS adverse effects[34,35] and a new selective angiotensin type 2-receptor antagonist, EMA401, has been investigated in trials including one that focused on treating patients with postherpetic neuralgia.[36]

Personalised pain therapy is another approach that can provide patients with the most effective treatment for neuropathic pain. The phenotype-based classification system focuses on categorising patients by mechanisms responsible for neuropathic pain rather than aetiology.[34,37] By focusing on patients' profiles of signs and symptoms, researchers can identify treatment responders. Studies that focus on genetics and subgrouping patients based on their phenotypes may play an important role in the future of personalised pain management for neuropathic pain.[34]

With improved understanding of the pathophysiology and the development of novel therapies, it is hoped that some of the encouraging results from trials will translate into improved treatment for patients and a reduction in the number of those suffering from refractory pain.

Competing interests

Dr Mick Serpell has received honoraria from Astellas, Grünenthal, NAPP and Pfizer for speaking at meetings. Dr Grant Lewis and Dr Peter Paisley have no competing interests.

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British Pain Society
www.britishpainsociety.org

Pain management
Advice and information for patients and healthcare professionals from patient information leaflets to drug conversion tables
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