

REVIEW

Neuropathic pain in leprosy

MAIJA HAANPÄÄ*, DIANA N. J. LOCKWOOD** &
AKI HIETAHARJU***

**Pain Clinic, Department of Anaesthesia and Intensive Care
Medicine and Department of Neurosurgery, Helsinki University
Central Hospital, Helsinki, Finland*

***Department of Infectious & Tropical Diseases,
London School of Hygiene & Tropical Medicine, London, UK*

****Pain Clinic, Department of Neurology and Rehabilitation,
Tampere University Hospital, Tampere, Finland*

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Summary Chronic neuropathic pain in treated leprosy has received scant attention. In this article the concept, clinical features and diagnosis of neuropathic pain are reviewed. The possible pathophysiological mechanisms, treatment challenges and research needs in this area are discussed.

Introduction

Leprosy, a chronic granulomatous disease caused by *Mycobacterium leprae*, primarily manifests with damage to peripheral nerves and skin.¹ Even though the prevalence rate of leprosy has dropped by 85% over the past 15 years, it is still considered as the most common treatable neuropathy in the world,² in spite of ongoing eradication programmes. It is increasingly being recognized that leprosy may be associated with neuropathic pain.^{3–6} This contradicts earlier assumptions that neuropathic pain could not occur in leprosy. In this article nerve involvement in leprosy and the concept and diagnosis of neurogenic and neuropathic pain are reviewed. We also discuss the possible mechanisms of neuropathic pain and outline some of the research that is needed to clarify this area.

Nerve involvement in leprosy

Different types of leprosy are associated with different patterns of nerve damage, both pathologically and clinically. In established tuberculoid disease, there is gross destruction

with a heavy lymphocytic infiltrate producing a fibrosed epineurium and replacement of the endoneurium with epithelioid granulomata. The neurological involvement is limited. Mononeuropathy is usually a consequence of entrapment of a nerve within a granuloma.² Painful nerve abscesses with caseation can also form.²

In lepromatous neuropathy there is quiet asymptomatic bacillation of Schwann cells with late foamy degeneration. Demyelination, damage and destruction of the axis cylinder are prominent features, and later Wallerian degeneration occurs.⁷ Despite heavy bacillation there is only a small inflammatory response, later the nerve fibres and is hyalinized.^{8,9} Those cutaneous nerve branches that are most superficial and hence coolest, are the predilection sites for the mycobacterial colonization and subsequent nerve damage, resulting first in patchy localization and later glove and stocking-like distribution of sensory loss.² This temperature-dependent nerve damage explains why palms and soles are usually spared in the early phase of the disease as well as the long-lasting preservation of long tendon reflexes and joint position sense.

The formation of small granulomata is characteristic of borderline leprosy, and granulomatous regions may abut strands of normal looking but heavily bacillated Schwann cells.¹⁰ The combination of lepromatous bacillation and a tuberculoid tissue damaging response produce widespread nerve damage in borderline leprosy. Acute neuritis occurs particularly during reversal reactions; oedema of the epithelioid cell granuloma compresses the remaining Schwann cells, causing rapid functional loss in an already compromised nerve. The damage may be compounded by new granuloma formation. Patients with borderline leprosy develop multiple peripheral nerve trunk mononeuropathies with motor and sensory involvement in addition to the involvement of dermal nerves.¹ The most devastating clinical consequence of the intracutaneous nerve damage is the total sensory loss of the extremities.¹¹

The concept of neuropathic pain

Chronic pain is pain that persists after resolution of an acute injury. Chronic pain is divided into nociceptive pain, neuropathic pain, and pain of unknown origin. Nociceptive pain is initiated or caused by activation of nerve receptors in skin, muscle, fascia, and organs.¹² These nociceptors respond to potential or true tissue damage, and serve as protective system against noxious stimuli. According to the definitions of the International Association for the Study of Pain (IASP), neuropathic pain is a pain condition initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system (CNS) (Table 1).¹³ The term neurogenic pain is sometimes used if the dysfunction causing pain is reversible. Hence, neuropathic pain always indicates permanent abnormality. The neuropathic pain states are distinguished according to the site of the lesion: central or of CNS origin (e.g. central post stroke pain, spinal cord injury pain), peripheral or of peripheral nervous system origin (e.g. painful polyneuropathies, painful sequelae of peripheral nerve injuries) or a combination of these (e.g. post-herpetic neuralgia, nerve root avulsions). However, it must be remembered that this division is only neuroanatomical; the pathophysiological phenomena always comprise both central and peripheral mechanisms also in peripheral neuropathic pain states.

The prevalence of neuropathic pain varies according to lesion sites and patient groups. Only 5% of patients with traumatic nerve injury suffer from pain,¹⁴ while about 75% of patients with syringomyelia have chronic pain.¹⁵ It is not known why seemingly similar nerve injuries are painful in some patients and painless in others. Animal studies have suggested

Table 1. Pain and sensory terms

Nociceptor	A receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged
Nociceptive pain	Pain caused by irritation of the nociceptors by a noxious stimulus
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system (irreversible)
Neurogenic pain	Pain initiated or caused by a primary lesion, dysfunction, or <i>transient perturbation</i> in the peripheral or central nervous system (reversible)
Paraesthesia	An abnormal sensation, whether spontaneous or evoked
Dysaesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
Allodynia	Pain due to a stimulus, which does not normally provoke pain
Hyperalgesia	An increased response to a stimulus which is normally painful
Hypoalgesia	Diminished pain in response to a normally painful stimulus
Hyperaesthesia	Increased sensitivity to stimulation, excluding the special senses
Hypoaesthesia	Decreased sensitivity to stimulation, excluding the special senses

that the risk of developing neuropathic pain following peripheral nerve damage may have a genetic basis.¹⁶ Due to multiple pathophysiological mechanisms the possible role of genetic factors in different pain states remains unsettled.

The mechanisms of neuropathic pain have not yet been fully established. The plasticity of the nervous system, i.e. its ability to undergo functional and structural changes in association with various disease processes, is a key issue in the development of neuropathic pain states. Several types of peripheral mechanisms have been described in animal models of peripheral nerve injury.¹⁷ Abnormal neuronal activity has been reported in primary afferents and in the dorsal root ganglion, and appears at least partly related to the increased number of sodium channels in the nerve cell membrane. These abnormal discharges are called ectopic, since they do not originate from nociceptors. Other peripheral mechanisms include pathological fibre interactions, referring to the formation of abnormal connections between individual afferents, and nociceptor sensitization, which is characterized by an ongoing discharge in nociceptors, even in the absence of noxious stimulation.¹⁷ An increase in the sensitivity of nociceptor endings also means that weak, previously non-noxious stimuli may activate nociceptors, and elicit pain.¹⁸ Human studies on peripheral nerve function are limited, but single nerve fibre studies have recently documented increased activity and sensitization in patients with a chronic painful condition.¹⁹

Another characteristic feature of neuropathic pain is the relative weakness of the central inhibitory mechanisms. Descending inhibitory pathways from the brain stem and midbrain nuclei modulate signal transmission in dorsal horn. Both monoaminergic and adrenergic systems are involved in this modulation.²⁰ Sensitization also occurs at the level of the CNS where the activation of N-methyl-D-aspartate (NMDA) receptors plays a central role. Central sensitization means that pain results from increased gain in central processing circuits, including spontaneous impulse initiation.¹⁸ It inevitably leads to anatomic reorganization and hyperexcitability of central nociceptive neurons.¹⁷ In the presence of central sensitization, input via non-nociceptive afferent fibres may trigger pain. Apoptosis seems to induce neuronal sensitization and loss of inhibitory systems, and its irreversibility is in accordance with the chronic character of many neuropathic pain states.²¹

Nervous system damage or dysfunction leads to the production of only two types of phenomena: negative and positive. Both phenomena depend on the functional system affected. Hence patients with neuropathic pain always present a variety of negative and

positive sensory and motor symptoms, as well as autonomic symptoms.¹² Hypoaesthesia, for example, is a negative sensory phenomenon while pain, paraesthesias and dysaesthesias are positive sensory phenomena. The pain may have various components. It may be continuous, often burning or aching, or intermittent and lancinating. The pain may be spontaneous (stimulus-independent) or provoked by different stimuli (stimulus-dependent). When provoked by a normally pain-free stimulus, it is called allodynia. Mechanical allodynia is divided into dynamic and static subtypes, provoked by moving tactile stimulus and light compression, respectively, and thermal allodynia is divided into heat and cold allodynias. If a painful stimulus causes an exaggerated pain, the term hyperalgesia is used.

Neuropathic pain in leprosy

Since leprosy causes severe sensory loss, it is assumed that pain is uncommon in leprosy. However, peripheral nerve pain, dysaesthesias and paraesthesias may complicate leprosy both during and after treatment. Data on consumption of analgesics by patients with neuropathic pain gives some indication of the extent of the problem. In a Malaysian study with 235 leprosy patients, neuritic pain was the main reason for consumption of analgesic preparations. In 46 patients (19.5%), an overall total intake had been more than 2 kg of analgesics. The duration of intake ranged from 2 to more than 20 years.²²

PERIPHERAL NERVE TRUNK PAIN

Acute pain in one or several nerves may be the presenting feature in leprosy. Pain is a familiar symptom of reactions and neuritis, due to entrapment of the oedematous inflamed nerve in fibro-osseous tunnels.^{2,23,24} Neuritis of cutaneous nerves may also be painful.²⁵ Peripheral nerve abscesses occur in all types of leprosy and a variety of nerve trunks and cutaneous nerves.²⁶ They are often associated with severe acute pain. Acute pain in leprosy patients is usually reversible, i.e. it can be relieved by steroids or other therapeutic measures such as anti-inflammatory drugs and immobilization or surgical intervention. Because pain in these cases is not an irreversible phenomenon, the term neurogenic pain is appropriate.

As pain moves from neurogenic to neuropathic, it becomes chronic and irreversible. The biological value of pain is lost; it no longer informs of ongoing tissue damage. Even though recognized by many leprologists, chronic pain in leprosy has received scant attention in medical literature. Hietaharju *et al.*³ reported on moderate or severe chronic neuropathic pain in 16 patients with treated multibacillary leprosy. In 10 patients the pain had a glove and stocking-like distribution and in two patients it followed the course of a specific nerve. The quality of pain was burning in nine, biting in three, pricking in three, cutting in two, and electric-shock-like in two patients. The occurrence of pain was continuous in 50% of patients.

In a recent evaluation of 303 patients from a Brazilian referral centre, 174 (57%) patients complained of neuropathic pain.^{5,6} In 84 patients (48%) pain manifested as bursts. Pain affected one or more peripheral nerve territories; ulnar nerve in 101 (58%) patients and tibial nerve course in 48 (28%). There was a polyneuropathic distribution as glove-like in 47 patients (27%) and sock-like in another 47 patients. At the time of evaluation, pain was present in 47 (27%) patients.

SENSORY DISTURBANCES

There is little data on the occurrence of sensory disturbances such as dysaesthesias, paraesthesias or allodynia in patients with leprosy. In a study by Hietaharju *et al.*,³ four patients complained of tingling sensation which was considered as unpleasant and painful, i.e. they had dysaesthesia. Dysaesthesia followed a glove and stocking-distribution in two patients, the course of the femoral cutaneous nerve in one patient, and was located in both legs below mid-thigh in one patient. Allodynia, pain due to a stimulus that does not normally provoke pain, was noticed in two patients. In both of these patients, enlargement and tenderness of the nerves (cutaneous femoral, common peroneal and posterior tibial) without abscess formation was found out in clinical examination.⁴

ASSUMED PATHOGENESIS OF NEUROPATHIC PAIN IN LEPROSY PATIENTS

Hietaharju *et al.*³ found that the most typical sensory abnormalities were severely impaired perception of tactile stimuli and mechanical and thermal pain, indicating damage of A β , A δ and C fibres at the painful site. The cases with sensory loss associated with pain suggest peripheral deafferentation, i.e. pain due to loss of sensory input into the central nervous system, as occurs with different types of lesions of peripheral nerves. However, in a considerable proportion of the patients with pain the sensory function was quite well preserved suggesting other pathophysiological mechanisms.

Different pathophysiological mechanisms leading to persistent neuropathic pain in patients with leprosy can be invoked. First of all, these patients may have small-fibre sensory neuropathy (SFSN). In early cases of leprosy, pain and temperature sensation are strikingly decreased, followed later by loss of tactile and pressure senses.² This chain of events in sensory deterioration suggests early involvement of small fibres due to mycobacterial invasion. Pain and dysaesthesia are also the most common symptoms of both acquired and idiopathic SFSN.²⁷ In these patients, morphometric analysis of cutaneous nerves by immunohistochemistry has demonstrated either absence or marked reduction of intraepidermal nerve fibres.²⁸ Reduced numbers of intraepidermal fibres are seen in other conditions, either as the result of selective small fibre neuropathies or as part of a process that involves both large and smaller fibres. Examples of these are diabetic neuropathy,²⁹ Fabry disease,³⁰ systemic lupus erythematosus,³¹ and HIV infection.³²

Other possible explanations for the occurrence of neuropathic pain in leprosy patients include the impact of previous episodes of reactions, neuritis and inflammation, which may leave the nerve fibrosed, and at risk of entrapment.³³ Some patients may have a chronic ongoing neuritis manifesting clinically with pain. The histological correlates of the peripheral nerve in such patients have not been described. Lockwood *et al.*³⁴ have shown that *M. leprae* protein and lipid antigens are present in skin and nerve at the time of acute reversal reactions. Persisting antigen could be the cause of late chronic neuritis. Inflammation along nerve trunks has been shown to produce ectopic activity in nerves and therefore past or present inflammatory conditions represent a source for central sensitization, which may manifest as chronic neuropathic pain.³⁵ A delayed vasculitic neuropathy, probably precipitated by persisting mycobacterial antigen, is a rare complication of leprosy.³⁶ Vasculitic neuropathies, such as HIV and rheumatoid disease related neuropathies are known to be painful.

In the acute phase, the above-mentioned pain states are combinations of nociceptive and neurogenic types of pain. Patients with irreversible course of pain will remain with chronic

neuropathic pain and permanent sensory abnormalities. It is not known how often an acute painful peripheral nerve lesion in leprosy recovers completely and how often chronic neuropathic pain remains as an aftermath. The profiles of sensory abnormalities in patients with neuropathic pain are not known, either.

Diagnosis of neuropathic pain

The diagnosis of possible neurogenic or neuropathic pain should be a logical process combining information from the medical history, clinical findings and if needed, additional methods to identify the site of a process or lesion and the reason for it. With reversible problems such as nerve entrapment, nerve compression or a local inflammatory process an early and correct diagnosis affords the possibility of curative treatment.

The cornerstone of good diagnosis is a meticulous medical history. The onset and progress of symptoms should be established, as well as possible temporal associations with current diseases. Trauma and exposure to toxic agents should be specifically asked about.

The location of the pain is easy to document using the pain drawing; the patient marks the distribution of various types of pain on a template body map. The pain intensity can be measured by visual analog scale (VAS), numerical rating scale (for example, Likert scale 0–10) or verbal rating scale (for example mild–moderate–severe–intolerable). VAS involves the use of a 10 cm straight line on a piece of paper labelled at the left end as ‘no pain’ and at the right as ‘worst imaginable pain’.³⁷ To use the VAS the patient is simply asked to mark on the line the amount of pain that he or she is feeling. The VAS is one of the oldest, most simplified and best-validated measures to assess pain, but it may be difficult for some patients to comprehend it. In addition to the intensity (i.e. sensory component of the pain), the unpleasantness (i.e. the affective component) can be coded by using for example a verbal scale annoying–unpleasant–distressing.

Severe neuropathic pain can disturb sleep, affect mood and cause deterioration of functional capacity and quality of life. These aspects should be evaluated in the medical history, i.e. what kind of functional impairment does the pain cause to the patient or how has the pain changed the patient’s life. The previous treatment efforts and patient’s response to them should be inquired. For neuropathic pain, simple analgesics (i.e. NSAIDs and paracetamol) are typically ineffective.

A comprehensive clinical examination is essential to diagnose or to rule out neuropathic pain. It includes the assessment of sensory, motor and autonomic signs. In neuropathic pain, the localization of pain and abnormal sensory findings should be neuroanatomically logical, i.e. they should be in accordance with the distribution of the injured nerve or, as in case of radiculopathies, the dermatomal boundaries. It is advisable to do the main neurological examination first and end with the sensory examination. Tactile sense can be assessed by a piece of cotton wool, the pinprick sense by a wooden cocktail stick or toothpick, the thermal sense by warm and cold objects, and the vibration sense by a tuning fork (128 Hz). In the sensory examination the intensity, quality, spatial and temporal responses should be noted, as there may be aberrations in all of them (Table 2).³⁸

In cases with a clear aetiology such as post-herpetic neuralgia, further examinations are often not needed. In individual cases, however, it may be necessary to use laboratory, neurophysiological or imaging methods to establish the cause of the symptoms. If there is need to quantify the sensory functions in a more detailed way, quantitative somatosensory

Table 2. Quantitative, qualitative, and the most common spatial and temporal aberrations found during sensory examination of pain patients (adapted from Hansson³⁸)

Quantitative	Qualitative	Spatial	Temporal
Hypoesthesia	Allodynia	Delocalization	Abnormal latency
Hyperaesthesia	Paraesthesia	Radiation	Abnormal aftersensation
Hypoaesthesia	Dysaesthesia		Abnormal summation
Hyperaesthesia			Habituation
			Abnormal adaptation

testing (QST) can be employed. QST may be defined as the analysis of perception in response to external stimuli of controlled intensity. Detection and pain thresholds are determined by applying stimuli to the skin in an ascending and descending order of magnitude. Mechanical sensitivity for tactile stimuli is measured using von Frey hairs or Semmes–Weinstein monofilaments,³⁹ pinprick sensation with weighted needles,⁴⁰ and vibration sensitivity with an electronic vibrometer.⁴¹ Thermal perception and thermal pain are measured using a probe that operates on the Peltier principle.⁴²

Semmes–Weinstein monofilaments are well known to all leprologists. These consist of 20 monofilaments of increasing diameter calibrated to deliver a specific force on the skin (0.0045–447 g). The filaments are applied in an ascending and descending order of magnitude and the appearance and disappearance thresholds are recorded using the up-down paradigm. Two to three successive stimuli may be applied for 1.5 to 3 s at 5-s intervals per filament. Detection thresholds may be defined as the weakest stimulus felt within 3 s or as the middle between the strongest stimulus not felt in three trials and the weakest stimulus.

The measurement of pinprick sensation using weighted needle apparatus is also appropriate for field conditions.⁴⁰ It consists of 12 weighted 23 gauge disposable needles (0.2–5.2 g). They are applied perpendicularly to gently contact the skin so that pinprick sensation is produced only by the weight of the needle resting on the skin. The procedure is equal to that of measuring touch detection thresholds. The pinprick threshold may be defined as the lightest weighted needle, which consistently (at least three stimuli) produces a sharp sensation. The equipments for the assessment of thermal and vibratory responses are too expensive for field conditions.

In the early stages of an abnormal process, such as diabetic neuropathy, QST can identify subclinical changes,⁴³ and in any neuropathic pain syndrome, QST can measure the magnitude and type of sensory abnormalities (i.e. is there hypo- or hypersensitivity to different stimuli). QST has also several limitations. Tests are usually lengthy and not always easy to use in clinical practice. Several sources of bias in the testing and interpretation of results have also been emphasized. For a more detailed view of QST, the IASP handbook is recommended.⁴⁴

Treatment of neuropathic pain

In some patients with neuropathic pain, the symptoms may be mild and diagnosis and explanation of the pain may suffice without recourse to drug treatment. If the pain disrupts the patient's everyday life, medical treatment should be tried. A 50% pain relief has been the

Table 3. Mechanism of action of the drugs with proven efficacy for neuropathic pain in randomized controlled trials

Drug	Mechanism(s) of action
Tricyclic antidepressants	Blocking of the reuptake of norepinephrine and serotonin
Carbamazepine	Blocking of sodium channels
Tramadol	Blocking of reuptake of norepinephrine and serotonin μ -opioid agonism
Gabapentin	Blocking of calcium channels (?)
Lamotrigine	Blocking of sodium channels Inhibition of the release of glutamate
Oxycodone	μ -opioid agonism
Topical lidocaine	Blocking of sodium channels in the free nerve endings

‘gold standard’ criterion used in meta-analyses to calculate the NNT (number needed to treat).⁴⁵ With data from 2700 patients participating in a phase III study, Farrar *et al.* compared the 11-point Likert numerical rating scale (NRS) and a validated measure, Global Impression of Change reported by the patient (PGIC). They found that a 50% pain reduction in the NRS corresponded to ‘very much improved’ in the PGIC, whereas even a 30% reduction in the NRS was clinically important.⁴⁶ Hence the 50% criterion for good pain relief may be too stringent. In clinical work, the intensity of pain and magnitude of pain relief compared to the initial stage should be evaluated at every visit or phone call.

The choice of medication depends on the patient’s previous experience of locally available drugs, other diseases and associated medication, motivation to try the suggested medication, and the price of the medication. Drugs with proven efficacy for neuropathic pain have several different mechanisms of action, which are logical in view of pathophysiological mechanisms (Table 3). Of these drugs, tricyclic antidepressant and anticonvulsant drugs are the most appropriate for use in developing countries.

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants are the corner stone of neuropathic pain treatment. Their efficacy is proven in randomized controlled studies,^{45,47} and using the NNT calculations, they are currently the most effective drugs for neuropathic pain. In diabetic neuropathy, for example, the NNT for TCAs is 3.⁴⁷ There are no major differences between different drugs, but nortriptyline is better tolerated than amitriptyline.⁴⁸ Alleviation of pain is independent of the effect on the mood, its onset is more rapid and relief can be attained at lower doses.

The drug is started at a low dose, 10–25 mg in the evening, and the dose is escalated with the steps of 10–25 mg after 3–7 days to an adequate level of pain relief, with a maximal tolerated dose up to 150 mg/day. To avoid sedation the drug should be taken early on in the evening. With the dose escalation, the daily dose can be divided into two different doses, the evening dose being higher.

As the patient’s sleep is often disturbed, the first effect is usually undisturbed sleep at night. The total benefit can be assessed once the drug has been used for a couple of weeks without changing the level of the dosage. The commonest adverse effects include tiredness, dry mouth, constipation, disturbances of micturition and orthostatic hypotension. Disturbances of sexual functions and arrhythmias may also occur. In a meta-analysis of tricyclic

antidepressants for chronic pain, NNT for minor adverse effects was 3.7 (meaning that one needs to prescribe tricyclic antidepressants for 3.7 patients in average to achieve minor adverse effects to one patient). The NNT for major side effects (demanding cessation of the medication) was 22.⁴⁵ Patients with narrow-angle glaucoma, prostatic hyperplasia and heart disease should be treated with caution.

CARBAMAZEPINE

Carbamazepine is a drug of choice in lancinating neuropathic pain such as trigeminal neuralgia. It has also been found effective in treating of neuropathic pain in other conditions.⁴⁵ The same dosage regimens are used as in epilepsy, i.e. starting with 100 mg at bedtime and escalating the dose by 100 mg after 3–5 days. The maintenance dose in neuropathic pain is usually 400–600 mg/day, divided into two doses when a slow-release preparation is used and into three doses when an ordinary preparation is used. The evaluation of the response is mainly based on clinical judgment but in case of the appearance of side effects with low doses of carbamazepine or the lack of response with adequate doses, the determination of serum drug concentration may be useful. Blood count and the transaminase levels should be monitored, at least at the start of treatment. The most common adverse reactions include tiredness, vertigo and hyponatraemia. Liver enzyme-induced interactions with many drugs, including combined oral contraceptives, should be borne in mind.

GABAPENTIN

Gabapentin has been found effective in randomized controlled trials for diabetic neuropathy⁴⁹ and post-herpetic neuralgia.⁵⁰ It is administered 3 times a day, and the target dose in the treatment of pain is 900–3600 mg/day. The initial dose is 300 mg at bedtime, and the dose can be escalated with 300 mg in 1–3 days. The response to treatment can be assessed within a couple of days after reaching the target dose. Vertigo, tiredness and oedema are the most common adverse reactions of gabapentin.

LAMOTRIGINE

The efficacy of lamotrigine has been proven in both central and peripheral neuropathic pain.^{51,52} The dose should be increased very slowly to avoid rash. Monitoring by laboratory tests is not necessary, and adverse reactions of central nervous system origin are fewer than with conventional antiepileptic agents. Due to the slow titration of the dose, the use of lamotrigine is restricted to the cases where drugs with easier administration have not brought adequate relief.

OPIOIDS

The effect of tramadol is exerted via both the opioid receptors and the serotonin and noradrenaline systems. Tramadol, classified amongst the weak opioids, causes distinctly less dependence and tolerance than strong opioids do. Its efficacy has been proven in polyneuropathic pain and post-herpetic neuralgia.^{53,54} The most common adverse reactions include nausea, vertigo, tiredness and headache. Interactions with antidepressants, especially the serotonin syndrome, should be kept in mind.

Pure opioids were previously considered to have no effect on neuropathic pain, but a proportion of patients with neuropathic pain were later shown to benefit from their use. Oral oxycodone with long-term effect has been proven to be effective in both post-herpetic neuralgia and diabetic neuropathic pain.^{55,56} The doses used in the studies were relatively small, 20–80 mg/day. The most common adverse reactions include tiredness, constipation and pruritus. The status of strong opioids in the treatment of neuropathic pain remains unsettled, since only a proportion of patients benefit from these drugs. Furthermore, due to the risk of dependence, considerate patient selection and regular follow-up are necessary.

Need for further research

This review has illustrated that neuropathic pain is a problem in leprosy. However, studies are required in several areas to document the extent of the problem, the underlying pathological mechanisms and assessment of potential treatments.^{3,5} First, multicentre epidemiological studies are needed to determine the prevalence of the neuropathic pain problem among leprosy patients. These should include patients with all types of leprosy to determine if pain is over represented in any subgroup; and also the assessment of pain intensity, unpleasantness and quality of life. Second, clinical studies to characterize the profiles of sensory abnormalities with and without pain are required. These should imply an appropriate use of currently used pain terminology (Table 1) and analysis of quantitative, qualitative, spatial and temporal aberrations of sensation (Table 2). Furthermore, studies to characterize neuropathological findings in leprosy patients with and without pain and randomized placebo-controlled clinical trials to test the efficacy of symptomatic treatment of neuropathic pain are essential.

Information from such studies will help us to understand and manage the chronic pain conditions seen in leprosy patients and give an important contribution to care after cure.

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