CLINICAL REVIEW

# Diagnosis and management of neuropathic pain

R Freynhagen,[1] M I Bennett[2]

[1]Department of Anaesthesiology, Critical Care Medicine, Pain Therapy & Palliative Care, Pain Center Lake Starnberg, Benedictus Krankenhaus Tutzing, 82327 Tutzing, Germany
[2]International Observatory on End of Life Care, School of Health and Medicine, Lancaster University, Lancaster LA1 4YT
Correspondence to: R Freynhagen r.freynhagen@krankenhaus-tutzing.de

Cite this as: *BMJ* 2009;339:b3002
doi: 10.1136/bmj.b3002

Neuropathic pain arises from damage, or pathological change, in the peripheral or central nervous system. It is usually a chronic condition that can be difficult to treat because standard treatment with conventional analgesics does not typically provide effective relief of pain. Patients with neuropathic pain commonly present to primary care professionals, but making a diagnosis may be difficult. Neuropathic pain is usually associated with substantially greater impairment of quality of life compared with other types of chronic pain, and the disorder is a large cost burden on healthcare services. In this review, we provide an overview of published evidence to help clinicians recognise and manage patients with neuropathic pain.

**Box 1** | 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)

**Complex neuropathic disorders**
Complex regional pain syndrome types I and II

## What is neuropathic pain and who gets it?

A group of specialists of the International Association for the Study of Pain defines neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[1] In contrast to inflammatory or nociceptive pain, which is caused by actual tissue damage or potentially tissue damaging stimuli, neuropathic pain is produced either by damage to, or pathological change in, the peripheral or central nervous system, the system that normally signals pain. As such, the term neuropathic pain represents a varying set of symptoms rather than a single diagnosis.

Damage to the somatosensory system can provoke a range of responses; an absence of sensation and pain is probably a more common response than new onset of pain. Sensitisation of peripheral nerves with ectopic or spontaneous activity and hyperexcitability in the modulatory pathways of the central nervous system are possible mechanisms that could cause neuropathic pain.[2 3]

Neuropathic pain can be caused by several different disease processes, which can often overlap, but currently there is no universally accepted classification for the disorder. However, four broad classes of diseases are recognised based on aetiology and anatomy[2]: focal and multifocal lesions of the peripheral nervous system; generalised polyneuropathies of the peripheral nervous system; lesions in the central nervous system; and complex neuropathic disorders (box 1).

## SUMMARY POINTS

Neuropathic pain commonly presents in primary care and is often unrecognised
Diagnosis is based on characteristic symptoms, altered sensation, and a clinical history that matches a neuroanatomical or dermatomal pattern
Less than half of patients achieve significant benefit with any single drug
Management includes making pain tolerable and maintaining emotional and physical functioning
Non-pharmacological approaches can be effective, but referral for specialist help is indicated if pain persists or remains uncontrolled

**Box 2 | Common side effects of first line drugs for neuropathic pain**

**Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine)**
Drowsiness
Confusion
Dry mouth
Orthostatic hypotension
Weight gain
Urinary retention
Screening electrocardiography is recommended before beginning treatment in patients over 40 years

**$\alpha_2$-δ anticonvulsants (gabapentin and pregabalin)**
Drowsiness
Dizziness, cognitive or gait impairment
Peripheral oedema

**Serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine)**
Nausea
Dizziness
Dry mouth
Sexual dysfunction

**Topical 5% lidocaine patch**
Mild skin reactions (such as redness or swelling under patch, erythema)

## How common is neuropathic pain?

Estimates of neuropathic pain associated with specific aetiologies are well described. A 2008 study reported age standardised 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.[4] The prevalence of neuropathic pain typically rises with age and severity of the underlying condition.[5 6]

By contrast, the overall prevalence of neuropathic pain in the general population is difficult to quantify, and exact data are lacking because of the large number of underlying causes and the lack of standardised measurement methods. Nevertheless, epidemiological surveys suggest that 6-8% of the general population report chronic pain with neuropathic characteristics.[7 8] Neuropathic back pain with radiating pain to the arm or leg, and post-traumatic neuropathic pain (from accidental or surgical injury) are probably the most common causes. Among every 1000 patients registered with a general practitioner, about 60-80 patients will have symptoms of chronic neuropathic pain; in half of these patients, pain will require medication and regular support.[9]

## How does neuropathic pain present in clinical practice?

Abnormal responses to nerve damage can account for many of the clinical characteristics of neuropathic pain. Symptoms can be unusual and are unlike more common pain symptoms that patients will have previously experienced (see the box "A patient's perspective"). Painful symptoms arising in an area of altered sensation (numbness or hyperexcitability) are the hallmark of neuropathic pain.

Cardinal symptoms can be spontaneous pain (pain arising without stimulus) and abnormal responses to non-painful or painful stimuli. In the clinic patients can complain of dysaesthesias (unpleasant and strange sensations in the skin, such as tingling and pins and needles), deep seated gnawing pain, and abnormal thermal sensations (burning, on fire, or ice cold). Less commonly, patients complain of paroxysmal pains classically described as shooting, stabbing, or electric shocks. Patients may complain that the painful area is abnormally sensitive to any innocuous mechanical or thermal stimulus; sometimes clothes brushing against the area or a cold draught of air can be intensely painful.

Features of neuropathic pain may be evident within days of nerve damage or can take months to develop. Sometimes, a minor insult to an area of previous injury that had healed without problem can trigger neuropathic pain.

## How is neuropathic pain diagnosed?

There is no standard diagnostic procedure for neuropathic pain, so making a diagnosis is based on clinical judgment. The essential elements of this process are to identify painful symptoms, altered sensation, and a clinical history that all match a neuroanatomical or dermatomal pattern.[10] Screening methods for neuropathic pain consist mostly of characteristic verbal descriptors, though some have simple bedside tests in addition. Examples of the latter are the Leeds assessment of neuropathic symptoms and signs (LANSS) pain scale[11] or the painDETECT questionnaire,[5] which have an approximate accuracy of 80% compared with expert clinical judgment in identifying patients with neuropathic pain. Screening methods, however, are not a substitute for good clinical assessment and are not intended to be diagnostic methods.[12]

Bedside examination is straightforward; the aim is to identify altered sensation in the painful area, and so responses should be compared with a non-painful adjacent or contralateral area. A painful response to lightly stroking the skin with a finger or cotton wool is a sign of allodynia (pain caused by a stimulus that does not usually provoke pain), a common characteristic of neuropathic pain. Numbness (hypoalgesia) or an exaggerated painful response (hyperalgesia) to pin prick testing with

**A patient's perspective—neuropathic facial pain resulting from oropharyngeal cancer**

As far as I can remember my pain started during the second week of the radiotherapy and chemotherapy. In total I had six chemotherapy and 30 radiotherapy sessions over a six week period. I found the radiotherapy was the most painful. Not during treatment—it was the after effects. The headache seemed to get worse on a daily basis.

Trying to explain the pain is difficult. It is like hundreds of needles inside my head. I ended up trying to relate it to other pain I have suffered over my lifetime. For instance, ear infection at its worst, very bad migraine, tonsillitis. If you could imagine all this pain in one blast it is about right, maybe even worse. At this time of my life I was lucky if I managed to have an hour or two of undisturbed sleep. Now 10 months down the line, I am finding it much easier to cope as my nerve ends are healing. The medication as a pain patch has definitely been a great help with the nerve pain.

a monofilament or sharp object confirms an altered pin prick threshold. Finally, inability to distinguish warm from cold objects suggests an altered thermal threshold. A combination of characteristic painful symptoms in an area of altered sensation on bedside testing is usually enough to make a diagnosis of neuropathic pain. When there is doubt, more detailed examination using quantitative sensory testing is helpful though not commonly available, and it is costly and time consuming.[13]

Patients usually present with a spectrum of features (mixed pain) and it is more helpful to ask yourself the question "does this pain have any neuropathic component?"[14] It is important to identify neuropathic components because different classes of analgesic drugs are usually required to manage this type of pain effectively. Recently, criteria for categorising neuropathic pain as definite, probable, or possible have been proposed; this would better indicate the reality of clinical practice than a simple "nociceptive versus neuropathic" dichotomy.[1]

## What are the personal and societal costs of neuropathic pain?

Patients with chronic neuropathic pain usually report poorer physical and mental health compared with patients with other types of chronic pain, even when adjusting for pain intensity.[5 15 16] This association with poor physical and mental health suggests that the nature, and not simply the intensity, of neuropathic pain adversely affects quality of life and that successful management requires more than drug treatment alone. The cost of neuropathic pain to society is not known, but recent economic modelling of neuropathic low back pain in Germany estimated the annual cost to be about €7.6bn (£6.4bn; $10.9bn).[17]

### TIPS FOR NON-SPECIALISTS

- Make sure that the chronic pain type has been diagnosed correctly: a neuropathic pain screening tool may help (such as painDETECT, the LANSS pain scale)
- In general, start with monotherapy, but consider combination therapy from early on (for example, start with amitriptyline or duloxetine but then add gabapentin or pregabalin, or vice versa)
- Provide adequate time for any drug trial (two to eight weeks; at least one to two weeks at maximum tolerated dosage)
- Address physical and emotional aspects, as well as pain, by encouraging physical activity, improving poor sleep, and treating depression and anxiety
- A multidisciplinary approach to treatment is often the most successful; this includes seeking specialist help if your patient is not improving despite initial treatment

## What is a sensible therapeutic approach for patients with neuropathic pain?

Combination therapy with drugs that result in additive or synergistic effects to target different pain mechanisms is a logical approach because less than half of all patients will achieve a significant benefit with any single medical treatment for neuropathic pain.[18] The evidence, however, to support the idea that combination therapy is likely to be more efficacious and safer than each drug alone is less developed than that for single drugs (see the box "Tips for non-specialists").[18]

**Table 1** | Treatment recommendations for peripheral neuropathic pain adapted from recent guidelines and algorithms[19-22]

| Medication class/drug | Recommended stage of treatment | Dose range (mg/day) for maintenance | Combined NNH for study withdrawal (range) | Combined NNT for 50% pain relief (range) |
|---|---|---|---|---|
| **Antidepressants** | | | | |
| Tricyclics (nortriptyline, desipramine, amitriptyline, imipramine) | First | 25-150; secondary amine tricyclic antidepressants are in favour (nortriptyline, desipramine) | 14.7 (10.2-25.2) | 2.1/2.5/3.1 (1/8-3.7) |
| Duloxetine | First or second | 60-120 | Relative risk not significant | 4.1/5.2 (2.9-8.5) |
| Venlafaxine | First or second | 150-225 | Relative risk not significant | 4.6 (2.9-10.6) |
| Paroxetine, citalopram, bupropion | Third | | Relative risk not significant | 6.8 (3.4-441) |
| **Anticonvulsants** | | | | |
| Pregabalin | First | 150-600 | 11.7 (8.3-19.9) | 4.2/4.9 (3.7-7.6) |
| Gabapentin | First | 1200-3600 | 17.8 (12-30) | 4/4,4 (3.3-6.1) |
| Carbamazepine | First (only for trigeminal neuralgia) | 200-1200 | 21.7 (12.6-78.5) | 2.0 (1.3-2.2) |
| Lamotrigine | Second or third | 200-400 (slow titration) | Relative risk not significant | 4.9 (3.5-8.1) |
| Oxcarbazepine | Second (only for trigeminal neuralgia) | 600-1800 (fewer safety concerns) | Relative risk not significant | NA |
| Topiramate | Third | 200-400 | 6.3 (5-8) | 7.4 (4.3-28) |
| Valproate | Third | 1000 | Relative risk not significant | 2.8 (2.1-4.2) |
| **Opioids*** | | | | |
| Oxycodone | Second or third | 10-120 | Relative risk not significant | 2.6 (1.9-4.1) |
| Morphine | Second or third | 15-300 | Relative risk not significant | 2.5 (1.9-3.4) |
| Tramadol | Second or third | 200-400 | 9 (6.0-17.5) | 3.9/4.8 (2.6-26.9) |
| Methadone | Second or third | 15 | NA | NA |
| **Miscellaneous** | | | | |
| Topical lidocaine (patch 5%; gel) | First or second (only for localised areas of pain, focal neuropathy, allodynia) | 1-3 patches/day applied for 12 h | Relative risk not significant | 4.4 (2.5-17.5) |
| Cannabinoids | Third | 5-15 | Relative risk not significant | 9.5 (4.1-∞) |
| Topical capsaicin | Third | | 11.5 (8.1-19.8) | 6.7 (4.6-12) |

NNH=number needed to harm on the basis of withdrawal from neuropathic pain studies owing to adverse effects.
NNT=number needed to treat on the basis of 50% pain relief from baseline.
*The combined NNH for study withdrawal (range) for opioids overall = 17.1 (10-66).

**Table 2** | Treatment recommendations for central neuropathic pain adapted from current evidence based literature[19-22 26]

| Medication class/drug | Recommended stage of treatment |
|---|---|
| **Antidepressants** | |
| Tricyclics (amitriptyline) | First or second |
| Serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine) | First or second |
| Anticonvulsants | |
| Pregabalin | First or second |
| Gabapentin | First or second |
| Lamotrigine | Second or third (in pain after stroke) |
| Valproate | Third |
| **Opioids*** | |
| Levorphanol | |
| **Miscellaneous** | |
| Cannabinoids | Second (in multiple sclerosis) |
| Mexiletine | Third |

*Second or third (no specification).

## What are the recommendations from clinical guidelines and algorithms?

Unfortunately, there is no absolute consistency from the four most recently published guidelines and algorithms regarding the assessment of first, second, and third line drug treatments for neuropathic pain, although consistency exists for the classes of medication.[19-22] There are several limitations of this evidence. The evidence is focused on a limited range of peripheral neuropathic pain disorders (in particular, post-herpetic neuralgia and painful diabetic peripheral neuropathy) rather than central neuropathic pain (box 1); past studies have usually examined monotherapy rather than sequential or parallel combinations; priorities in guidelines are not derived from head to head studies but from comparisons of separate and heterogenous controlled trials; and the duration of studies is usually limited to six to eight weeks, which tells us little about managing chronic neuropathic pain that lasts for many years. Table 1 shows data for different classes of treatments.

### First line approaches

A sensible first line approach is to use an anticonvulsant that binds on the $\alpha_2$-$\delta$ subunit of presynaptic, voltage-gated calcium channels (gabapentin or pregabalin) or a tricyclic antidepressant. Comparisons of tricyclic antidepressants did not show any significant difference between them, but tertiary amine tricyclic antidepressants (amitriptyline, imipramine, clomipramine) are usually associated with more severe side effects than with other tricyclic antidepressants, and secondary amine tricyclic antidepressants (nortriptyline and desipramine) are better tolerated (box 2). The newer mixed serotonin and norepinephrine reuptake inhibitors (such as duloxetine and venlafaxine)[20-22] are recommended as either first or second line treatment, as is the use of topical 5% lidocaine patches (for localised small areas of pain).[19-22] Meta-analyses show that tricyclic antidepressants are more efficacious and more cost effective than serotonin and norepinephrine reuptake inhibitors, although the latter have a better side effect profile and may therefore be more suitable for elderly patients or those with cardiac disease (box 2).[19] As new studies on serotonin and norepinephrine reuptake inhibitors emerge, these drugs may soon replace the use of tricyclic antidepressants. Topical lidocaine patches can be used preferentially for localised small areas of peripheral neuropathic pain with mechanical allodynia (such as in post-herpetic neuralgia) or for focal neuropathy, but not for patients with central neuropathic pain. As systemic side effects are extremely rare with topical treatments, they are safe particularly for elderly patients. Data about impact on quality of life and comorbidities are only available for newer drugs such as gabapentin, pregabalin, and duloxetine, which have all shown positive effects.[9 16 19]

### Second line approaches

Randomised controlled trials have shown that controlled release opioid analgesics, such as morphine, oxycodone, and tramadol, are effective in neuropathic pain.[18-22] There is no evidence that one opioid is any more effective than another, or less effective than other drug classes for neuropathic pain, however, due to potential safety concerns such as tolerance, addiction, cognitive impairment, these drugs are usually recommended as second or third-line treatments.

Opioids can be considered as a first-line approach in selected clinical circumstances, such as intractable pain, episodic exacerbations of severe pain, acute neuropathic pain, and neuropathic cancer pain.[20] The treatment of trigeminal neuralgia has distinct recommendations: carbamazepine (stronger evidence) or oxcarbazepine (better tolerability) should be offered as first-line treatment for patients with this disorder, but are otherwise not recommended for the management of neuropathic pain.[23] There are encouraging results from studies regarding cannabinoids, but their future role in the treatment of neuropathic pain has still to be determined.[24]

### Third line approaches

Even with well established drugs, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed, and dose limiting adverse effects are common. So patients who are refractory to any first or second line treatment may benefit from other drugs, but recommendations are based on much weaker evidence or only expert clinical opinion. There is insufficient support for the use of non-steroidal anti-inflammatory drugs such as aspirin, diclofenac, naproxen, or ibuprofen.

### Central neuropathic pain

The treatment of central pain is even more controversial. The evidence base is limited, and responders typically experience only partial pain relief at tolerable doses. Based on recent evidence,[25 26] the first line approach that

### SOURCES AND SELECTION CRITERIA

We searched PubMed and Medline for articles whose titles included the keywords "neuropathic pain" with the limits "meta-analysis, review and randomised controlled trial", and we restricted the search to articles published in English in the previous five years. We individually reviewed the titles of the resulting articles to identify major themes. We identified all systematic reviews in the Cochrane Controlled Trials Register with the same terms. Finally we checked recent recommendations and published clinical guidelines from different international pain associations and societies and reviewed contemporary textbooks and personal files.

**ADDITIONAL EDUCATIONAL RESOURCES**

- Special Interest Group on Neuropathic Pain of the IASP (NeuPSIG) (www.neupsig.org)—Leading professional forum for science, practice, and education in the field of neuropathic pain; news, guidelines on diagnosis and treatment; international educational meetings and symposiums
- German Research Network on Neuropathic Pain (DFNS) (www.neuro.med.tu-muenchen.de/dfns/e_index.html)—Provides excellent information about neuropathic pain and ongoing research (the central Integrative Network Project of the DFNS is a large neuropathic pain data bank funded by the German Federal Ministry of Education and Research)
- Neuropathic Pain Network (NPN) (www.neuropathicpainnetwork.org/english/coalition/index.asp)—Coalition of organisations and patient support groups actively supporting people with neuropathic pain
- International Association for the Study of Pain (IASP) (www.iasp-pain.org)—Large multidisciplinary organisation focused specifically on pain research and treatment
- Oxford Pain Internet Site (Bandolier) (www.medicine.ox.ac.uk/bandolier/booth/painpag/#Chronic)—Based on the principles of evidence based medicine, this site has pulled together systematic reviews with pain as an outcome

is recommended for peripheral neuropathic pain conditions can be used for central pain; $\alpha_2$-δ anticonvulsants, tricyclic antidepressants, and serotonin and norepinephrine reuptake inhibitors are considered to be first or second choice. Table 2 gives data for therapeutic options in detail.

## Is there a role for non-pharmacological treatments?

Surgical and chemical sympathectomy have been used to treat neuropathic pain, but the evidence base is weak and complications may be substantial.[27] Microvascular decompression is a recognised treatment for some types of trigeminal neuralgia. The use of neurodestructive procedures to treat painful disorders that are due to nerve damage is misguided and can lead to even more pain.

Recent systematic reviews have shown that neurostimulation, including the use of transcutaneous electrical nerve stimulation, electroacupuncture, and repetitive transcranial magnetic stimulation, were all found to be better than placebo, though these recommendations were not based on high grade evidence.[28 29] The evidence for spinal cord stimulation supports its use in patients with refractory neuropathic back and leg pain (particularly in failed back surgery syndrome) and complex regional pain syndrome.[30] Although the role of traditional acupuncture in neuropathic pain is not supported by current evidence, it is popular among patients, and as it is relatively harmless it is often used in addition to drug treatment.

## Questions for future research

Important areas for future research include developing a specific diagnostic method for neuropathic pain; identifying associations between symptoms, signs, and pathology to guide mechanism based treatment strategies; comparing combination treatments with monotherapy; and conducting pharmacogenomic studies to guide prescribing.

**Contributors:** RF and MIB contributed equally to the article. Both authors read and approved the final manuscript and are guarantors.

**Competing interests:** In the past three years RF has received research support and consulting or speaking fees from Grünenthal, Janssen-Cilag, Lilly/Boehringer, Mundipharma, Organon, Pfizer, and Schwarz Pharma. MB has received honorariums, consultancy fees, and research grants from Pfizer, NAPP, and Cephalon.

**Provenance and peer review:** Commissioned; externally peer reviewed.

1 Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008;70:1630-5.
2 Baron R. Mechanisms of disease: neuropathic pain: a clinical perspective. *Nat Clin Pract Neurol* 2006;2:95-106.
3 Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. *Nat Neurosci* 2007;10:1361-8.
4 Hall GC, Carroll D, McQuay H. Primary care incidence and treatment of four neuropathic pain conditions: a descriptive study, 2002-2005. *BMC Fam Pract* 2008;9:26.
5 Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006;22:1911-20.
6 Gustorff B, Dorner T, Likar R, Grisold W, Lawrence K, Schwarz F, et al. Prevalence of self-reported neuropathic pain and impact on quality of life: a prospective representative survey. *Acta Anaesthesiol Scand* 2008;52:132-6.
7 Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population study. *J Pain* 2006;7:281-9.
8 Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008;136:380-7.
9 McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM. The burden of neuropathic pain: results from a cross-sectional survey. *Eur J Pain* 2006;10:127-35.
10 Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jørum E, et al. EFNS guidelines on neuropathic pain assessment. *Eur J Neurol* 2004;11:153-62.
11 Bennett M. The LANSS pain scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 2001;92:147-57.
12 Bennett MI, Attal N, Backonja MM, Baron R, Bouhassira D, Freynhagen R, et al. Using screening tools to identify neuropathic pain (topical review). *Pain* 2007;127:199-203.
13 Rolke R, Baron R, Maier C, Tölle TR, Treede RD, Beyer A, Binder A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006;123:231-43.
14 Bennett MI, Smith BH, Torrance N, Lee AJ. Can pain be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians. *Pain* 2006;122:289-94.
15 Smith BH, Torrance N, Bennett MI, Lee A. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. *Clin J Pain* 2007;23:143-9.
16 Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. *Neurol* 2007;68:1178-82.
17 Schmidt CO, Schweikert B, Wenig CM, Schmidt U, Gockel U, Freynhagen R, et al. Modelling the prevalence and cost of back pain with neuropathic components in the general population. *Eur J Pain* 2009; Feb 5. (Epub ahead of print)
18 Gilron I, Max MB. Combination pharmacotherapy for neuropathic pain: current evidence and future directions. *Expert Rev Neurother* 2005;5:823-30.
19 Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005;118:289-305.
20 Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132:237-51.
21 Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag* 2007;12:13-21.
22 Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;13:1153-69.
23 Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol* 2008;15:1013-28.
24 Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin* 2007;23:17-24.
25 Finnerup NB. A review of central neuropathic pain states. *Curr Opin Anaesthesiol* 2008;21:586-9.
26 Tzellos TG, Papazisis G, Amaniti E, Kouvelas D. Efficacy of pregabalin and gabapentin for neuropathic pain in spinal-cord injury: an evidence-based evaluation of the literature. *Eur J Clin Pharmacol* 2008;64:851-8.
27 Mailis A, Furlan A. Sympathectomy for neuropathic pain. *Cochrane Database Syst Rev* 2003;(2):CD002918.
28 Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur J-P, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007;14:952-70.
29 Pittler MH, Ernst E. Complementary therapies for neuropathic and neuralgic pain: systematic review. *Clin J Pain* 2008;24:731-3.
30 Boswell MV, Trescot AM, Datta S, Schultz DM, Hansen HC, Abdi S, et al. Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain. *Pain Physician* 2007;10:7-111.