Classic diseases revisited

The management of postherpetic neuralgia

David Bowsher

Summary

Postherpetic neuralgia is defined as pain persisting, or recurring, at the site of shingles at least three months after the onset of the acute rash. Thus defined, at least half of shingles sufferers over the age of 65 years develop postherpetic neuralgia. In addition to increasing age, less important risk factors for postherpetic neuralgia are pain severity of acute shingles and trigeminal distribution. Postherpetic neuralgia accounts for 11–15% of all referrals to pain clinics and would, in fact, be far more effectively dealt with in primary care. Effective treatment of acute shingles by systemic antivirals at the appropriate time may have some effect in reducing the incidence of postherpetic neuralgia, making it easier to treat with tricyclics and greatly reducing scarring (25% of all cases affect the face). Pre-emptive treatment with low-dose tricyclics (ami- or nor-triptyline 10–25 mg nocte) from the time of diagnosis of acute shingles reduces the incidence of postherpetic neuralgia by about 50%. Established postherpetic neuralgia should be vigorously treated with adrenergically active tricyclics in a dose rising over two or three weeks from 10–25 mg to 50–75 mg. Positive relaxation should also be used. Carbamazepine, like conventional analgesics, is of little or no value. Failure of tricyclics to effect relief within eight weeks calls for specialist treatment. North American practitioners in particular believe that some opioids (eg, oxycodone) may be helpful in otherwise intractable cases.

Keywords: pain, postherpetic neuralgia

Postherpetic neuralgia is chronic pain in a dermatome(s) affected by herpes zoster, and is rated as one of the most severe of pains.¹ Postherpetic neuralgia is not a continuation of herpes zoster, but rather a separate disease caused by having had herpes zoster.² There is controversy about the time which must elapse after acute herpes zoster before the pain can be defined as postherpetic neuralgia. Some consider that pain continuing or recurring one month after acute herpes zoster should be classified as postherpetic neuralgia. The term 'zoster-associated pain' has been used to define a continuum of pain starting with the onset of acute herpes zoster; this term has been used particularly by investigators sponsored by some antiviral manufacturers, since it enables them to assert that (effective) treatment of herpes zoster with antivirals prevents or aborts ongoing pain, with the implication that the latter is postherpetic neuralgia. However, there is sometimes a pain-free interval between herpes zoster and postherpetic neuralgia³; the pains of herpes zoster and postherpetic neuralgia are described differently in McGill pain questionnaires,⁴ the former being mainly sharp and stabbing while the latter is constant and burning. Most importantly, Watson *et al*⁵ have shown that, in postherpetic neuralgia, there are degenerative changes in the dorsal horn of the spinal cord, while patients who have had herpes zoster which is not followed by postherpetic neuralgia, damage is limited to the dorsal root ganglion.

All are agreed that many cases resolve spontaneously within the first few months. For this reason, cases of less than three months post-rash duration should not be considered as postherpetic neuralgia, and some believe that a criterion of six months post-rash is safer. However, three months post-rash (four months post-onset) is what is now usually accepted,^{6,7} and a recent meta-analysis⁸ has reinforced this view.

Incidence and prevalence

The General Practice Morbidity Survey (1991) suggests that the annual incidence of shingles in the UK population at large is 4.5/1000, and of postherpetic neuralgia at least one tenth of this. Shingles itself is four times commoner at age 65 than it is at age 40,⁹ and it is well-known that postherpetic neuralgia follows shingles far more frequently in elderly than in younger subjects: 50% of those contracting herpes zoster at 60 years of age and 75% of those doing so at 70 subsequently developed postherpetic neuralgia.¹⁰ This means that there are over 25 000 new cases of postherpetic neuralgia in the UK every year. A meta-analysis¹¹ showed that 22% of placebo-treated cases of herpes zoster were in pain three months later, while another study showed that just over 20% of patients in pain one month after acute shingles continue to suffer for more than a year,¹² a considerable proportion of these still being in pain at three years.¹³ About half of patients developing shingles over the age of 75 are still in pain a year later.¹⁰ Thus the prevalence of postherpetic neuralgia in the UK may be approaching 50 000 cases per annum.

It is of interest that varicella tends to occur at a later age in the population of the Indian subcontinent; and postherpetic neuralgia as a sequela of herpes zoster in members of this population living in the UK is anecdotally said to be considerably less frequent than in the Caucasian population of the UK.

Between 1988 and 1990, 11% of all referrals to our Centre for Pain Relief were for postherpetic neuralgia.¹⁴ An unpublished survey of 13 pain clinics in North Wales and the former Mersey Region suggests that postherpetic neuralgia accounts for some 15% of all referrals, which is some 70 times as high as its prevalence as a proportion of all chronic pain. Such evidence indicates that treatment in primary care fails to provide relief from pain in a very large proportion of cases.

Pain Research Institute, Walton Hospital, Liverpool L9 1AE, UK
D Bowsher

Accepted 2 October 1996

Risk factors

As mentioned above, age is by far the most important risk factor, while severity of pain in acute zoster is to some extent a predictor of overall pain duration.¹⁵ Site of infection also appears to be a risk factor. Among 210 postherpetic neuralgia patients seen by the author, 25% had had acute shingles on the face, while among 590 acute herpes zoster patients observed in Rochester, Minnesota,⁹ only half this proportion (13.6%) had facial zoster.

Two groups^{16,17} have found psychometric differences between herpes zoster patients who develop postherpetic neuralgia and those who do not: individuals whose perception of spontaneous or inflicted pain and somatic perception is high are significantly more likely to have postherpetic neuralgia than those with lower scores for these parameters. This is a rare instance of a neurological condition with objective signs being correlated with 'psychological' factors.

Lowered immune status, caused by disease or medication, or both, may be a risk factor for herpes zoster, and thus for postherpetic neuralgia.

Features of postherpetic neuralgia

Postherpetic neuralgia is characterised by a history of herpes zoster (beware the rare zoster sine herpete) three or more months earlier, and pain. The pain is usually of a burning type in more than 75% of cases, and mainly throbbing, with burning reduced to 30% in patients whose acute zoster has been treated with acyclovir.⁴ Pain intensity is usually variable, and some patients may go for periods without any pain at all. Pain is exacerbated by physical or emotional stress, and alleviated by relaxation and distraction. There is no change in the ability to fall asleep.

There is a sensory deficit in the affected area^{18,19}: over 90% have a deficit for tactile sensation, which can be revealed by touching with a cotton wool wisp: the ability to distinguish between warm (eg, the examiner's finger) and cool (eg, a metal instrument), and/or the ability to detect that a pin is sharp (as opposed to touching the skin) is affected in all patients.

Allodynia (the production of pain by a non-noxious stimulus) affects over 90% of postherpetic neuralgia sufferers,^{19,20} and is the real bugbear of the condition so far as patients are concerned. In most instances, it is elicited by a low-intensity moving mechanical stimulus,²⁰ such as the movement of clothes over the skin, or a wind or draught on exposed areas; and in a smaller proportion by cold or some other sensory stimulus. Firm pressure usually alleviates the pain, thus distinguishing allodynia from tenderness (hyperalgesia) due to, eg, inflammation.

There is now a considerable body of evidence to show that neither allodynia nor the ongoing pain in postherpetic neuralgia are signalled or maintained by unmyelinated C nociceptors,^{18,19,21,22} or therefore, by implication, the central pathways by which impulses generated in them are transmitted towards the brain. However, an argument partly based on the therapeutic effectiveness of certain topical agents suggests that some role is nevertheless played by peripheral A β elements,²³ which seem to be entirely responsible for tactile allodynia.^{20,21}

Treatment

Before embarking on a description of treatments, a word should be said about the manner in which postherpetic neuralgia, like other neurogenic pains,²⁴ gets better. Allusion has already been made to the fact that the pain is inconstant in time and variable in intensity. When such pains begin to get better, the intervals during which pain is absent or minimal tend to increase in length; however, when the pain is present, its intensity tends to be as great as ever. Pain intensity only begins to diminish at a later stage. Thus great care must be taken in interrogating patients during surgery or clinic visits. A question such as 'For how many hours a day, when you are awake, are you in pain?' should precede measurement of pain intensity by the visual analogue scale; in patients able to make the distinction, the latter is best taken as the most intense and the least intense pain experienced over the previous 24 hours.

PREVENTION OR ABORTION OF POSTHERPETIC NEURALGIA

Many claims infer that antivirals prevent the development of postherpetic neuralgia. It is in order to 'prove' this statement that such contortions have been made in the definition of postherpetic neuralgia (see above). It does, however, appear from a recent meta-analysis,¹⁵ that adequate treatment of acute herpes zoster with acyclovir reduces the subsequent incidence of pain at three and six months by about 50%.

Figure 1

Figure 2

There is no doubt, of course, that antivirals rapidly relieve pain and bring about symptomatic relief of acute herpes zoster. One of their most important long-term benefits, especially considering that so much herpes zoster occurs on the face and (visible) neck, is that they greatly reduce, and often entirely prevent, scarring. For this reason alone, they should be prescribed in every case in which the disease is reported early enough for these valuable drugs to be effective.

Antiviral treatment of herpes zoster appears to facilitate the action of antidepressants in the relief of postherpetic neuralgia,^{25,26} in those cases in which the latter ensues (see further below).

There is some evidence,²⁷ from a small randomised double-blind trial, that the administration of low-dose (10–25 mg nocte) amitriptyline from the moment of diagnosis of herpes zoster reduces by half the number of patients still in pain six months after the onset of acute herpes zoster—irrespective of whether or not the herpes zoster is also treated with antivirals.

Sympathetic blockade relieves the pain of acute herpes zoster, at least temporarily; but there is no evidence that it prevents postherpetic neuralgia. The same is probably true for the subcutaneous infiltration of steroids. Systemic corticosteroids do not reduce the proportion of patients in pain at 6 or 12 months.^{28,29}

What does NOT work in postherpetic neuralgia?

Conventional analgesics of the milder variety are of little value in postherpetic neuralgia or any other neurogenic pain. Indeed, doctors should be warned off them, since valuable time during which the painful process becomes less reversible may be lost while ‘trying out’ analgesics. Failure of conventional analgesics is the greatest single cause of referral of postherpetic neuralgia to pain clinics.

There is disagreement, largely on a transatlantic basis, about the effects of strong opioids (morphine and diamorphine) on postherpetic neuralgia. Certainly the present author has had to detoxify agonised geriatric junkies, high on slow-release morphine and simultaneously in excruciating pain from postherpetic neuralgia, before undertaking hopefully more effective treatment; therapeutic studies³⁰ have demonstrated a lack of effect of opioids in neuropathic pains. The European consensus seems to be that opioids are largely ineffective in postherpetic neuralgia,³¹ even when administered epidurally.³² However, North American therapists claim that narcotics may help,^{33,34} at least to reduce pain severity to ‘an acceptable level’ for a few hours in cases refractory to all other treatments.³⁵ Oral oxycodone (5–10 mg four-hourly) in particular is recommended by Watson.³⁶

Anticonvulsant drugs have largely been used in combination with others, mainly antidepressants, which makes it difficult to evaluate their effect. A recent meta-analysis,³⁷ however, offers no support for their use in postherpetic neuralgia. It may be noted, with great sadness, that the ‘rationale’ for the (widespread) use of carbamazepine is that it is of known beneficial effect in trigeminal neuralgia, and postherpetic neuralgia also contains the word ‘neuralgia’.

Specific serotonin reuptake inhibitors (SSRIs) have not been shown to have any beneficial effect in postherpetic neuralgia or other neurogenic pains,^{38,39} although the combined noradrenaline- and serotonin-reuptake inhibitor venlafaxine has been found to be effective in some clinics (see below).

In established postherpetic neuralgia, there is no evidence that sympathetic or systemic nerve blockade (extremely expensive procedures) gives any relief beyond the duration of action of the local anaesthetic contained in the injectate.

Neurectomy and more heroic destructive procedures such as cordotomy should be avoided at all costs; they replace (or supplement) postherpetic neuralgia with anaesthesia dolorosa.⁴⁰ Acupuncture is also ineffective.⁴¹

What DOES work in postherpetic neuralgia?

Amitriptyline has been in use since the 1960s, and was shown to be effective in a placebo-controlled trial published in 1982.⁴² Since that time, other noradrenergically active antidepressants (nortriptyline, desipramine, and maprotiline) have also been shown to be effective. Their analgesic action is independent of their antidepressant action; the time to effect in the two conditions is different, as is the minimum dose required.

As stated above, SSRIs are ineffective, but the combined noradrenaline- and serotonin-reuptake inhibitor venlafaxine has been found to be effective in the relief of postherpetic neuralgia in a number of clinics.

Even taking into account the spontaneous recovery rate, it has been shown that amitriptyline is more effective the sooner it is started (after the three-month criterion level),^{43,44} such that some 75% of patients beginning treatment

between three and six months after rash onset gain relief, whereas only one third of those beginning treatment between 12 and 24 months after lose their pain.

How can these figures be improved? The fact that the earlier treatment is begun the more effective it is suggested that prophylactic treatment with amitriptyline might improve the situation. As stated above, immediate treatment with low-dose amitriptyline for three months, starting as soon as shingles is diagnosed in patients over the age of 60 halves the number of patients (from 35% to 18%) still in pain at six months.²⁷ Among the author's patients, comparison of 35 patients who received systemic acyclovir within 72 hours of rash appearance, as the only therapy, with 29 patients who received low-dose amitriptyline starting within 72 hours of rash appearance, and no antiviral, reveals that six months later, 31.4% (11 patients) of the former, but only 17.25% (5 patients) of the latter were still in pain. This would appear to indicate that amitriptyline is more effective than acyclovir in the prevention of postherpetic neuralgia, though ideally both antidepressants and antivirals should be given at the earliest possible stage (see below). Comparison of same-age same-interval (to commencing amitriptyline after acute herpes zoster) patient groups showed that treatment of acute herpes zoster with acyclovir halved the time from beginning amitriptyline to 75% fall in visual analogue pain intensity score.²⁶

In patients not apparently responding to amitriptyline, it has been found that the addition of (not the substitution by) dexamphetamine 5 mg mane for a month has led to successful pain relief in seven out of eight cases.⁴⁵ This is attributed to enhancement of the noradrenergic effect of amitriptyline.

Amitriptyline produces a number of undesirable side-effects, the commonest of which is dry mouth. This can be overcome by the co-prescription of artificial saliva spray. Response is very idiosyncratic, and it may be better to use another tricyclic (nortriptyline, desipramine, maprotiline). It is essential to explain to the patient that the drug is not being used as an antidepressant, but that it has a separate and independent analgesic action; and that pain relief is unlikely to begin (by increased pain-free or low-intensity pain periods) until the patient has been on the full dose for a few weeks. Dosage should start at 25 mg (10 mg in the enfeebled) daily, and be increased by 25 or 10 mg a day every week until a maximum dose of 75 (50) mg is reached. In this author's experience, little is to be gained by increasing the dose beyond this level unless a partial effect is seen. McQuay *et al*⁴⁶ have argued that the effect is dose-dependent, although it is believed that therapeutic effectiveness is not related to plasma concentrations.⁴⁷ Dosage reduction should not start until the patient has been pain-free for at least two months, and should be increased again if pain returns. Some patients need to stay on low-dose amitriptyline for life.

It has recently been shown that neuropathic pain is, at least in part, transmitted via *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system,⁴⁸ and that the receptor antagonist ketamine produces effective relief of postherpetic pain³¹; this was reinforced by several sources reporting at the recent (August 1996) International Pain Congress. Dextromethorphan, which is a less effective, but less toxic, NMDA-receptor antagonist, also produces some relief.⁴⁹ This promising avenue is most likely to yield an effective future treatment for postherpetic neuralgia.

Because the tactile allodynia of postherpetic neuralgia is mediated by A δ primary afferents,²⁰ it had been hoped that analogues or facilitators of gamma-aminobutyric acid, which mediates inhibition from these fibres in the dorsal horn, would prove effective. A number of reports from different centres at the recent (August 1996) International Pain Congress indicated that the new drug gabapentin is in fact effective in postherpetic neuralgia, and has few side-effects. The recommended dose is 100–600 mg (usually 300 mg) three times a day by mouth.

Johnson⁵⁰ states that mexiletine, successful in painful diabetic neuropathy⁵¹ and central post-stroke pain,⁵² may sometimes be helpful in postherpetic neuralgia; the present author's experience has been disappointing.⁴⁵

Topical preparations galore have been used in the attempt to relieve postherpetic neuralgia. None of these have been shown to have any significant effect, with three exceptions: (a) Capsaicin cream, even in the most recalcitrant cases, may help after assiduous application for some eight weeks.^{53,54} This is much longer than would be predicted if it acted by destroying peripheral C fibres, known not to be involved in the pain of postherpetic neuralgia^{21,22}; it must be assumed that capsaicin, when it works, acts transsynaptically within the spinal grey matter following centripetal transport up peripheral C fibres. (b) Lignocaine (Lidocaine) patches have been shown to be effective in the treatment of postherpetic neuralgia.⁵⁵ This could be due to a central effect⁵⁶ following transdermal absorption, although Rowbotham and his colleagues

Postherpetic neuralgia: treatment

- don't waste time seeing if conventional analgesics will work; they won't! Nor will anticonvulsants on their own
- in patients over 60 years, commence amitriptyline* 10 or 25 mg at night as soon as shingles is diagnosed
- see patients six weeks after shingles onset. If pain still present, commence or increase amitriptyline dose by weekly increments until maximal daily dose of 50 or 75 mg reached; prescribe relaxation tape
- see patients every two months. If adequately improved, reduce amitriptyline gradually and cautiously. If not, consider other measures described in text

* or other tricyclic antidepressant

argue for a purely peripheral effect,⁵⁵ based on very low blood lignocaine levels following topical application. Many patients find that the application of an ice pack to the painful area gives temporary relief.

Some success has been obtained in some cases with transcutaneous nerve stimulation.⁵⁷ It is a form of treatment well worth trying. Often the application of electrodes to the affected area is not tolerated because of the allodynia it elicits. In such cases, stimulation of the contralateral mirror-image area for 10–15 minutes will make it possible subsequently to stimulate the affected area.

A review by Loeser⁵⁸ concludes that deep brain (thalamic or periventricular grey) stimulation may be successful, but that other central stimulation sites (eg, spinal cord) are ineffective.

PSYCHOSOCIAL TREATMENT

Reference has been made to the facts that individuals with particular psychometric features are more likely to develop postherpetic neuralgia following shingles; and that postherpetic neuralgia, like all other neurogenic pains, is alleviated by relaxation. It is not surprising, therefore, that positive relaxation therapy can play an important part in the treatment of postherpetic neuralgia. It does not need to be complicated, or professionally labour-intensive; an audiotape, used in the privacy of the patient's own home, can be exceedingly effective, and should be used as a complement to other treatment in every case.

Conclusions

The mainstay of postherpetic neuralgia therapy is amitriptyline or other adrenergically active antidepressant. While it should be given to every patient who is still in pain 12 weeks after rash onset, there is a strong case for commencing low-dose amitriptyline immediately herpes zoster is diagnosed in high-risk groups (particularly the elderly), as well as for treating the herpes zoster itself with a suitable antiviral drug. Patients with postherpetic neuralgia should also use a relaxation tape. There may be a place for oral oxycodone in recalcitrant cases.

In the future, NMDA receptor antagonists and gabapentin will undoubtedly play an increasingly important role. In the meanwhile, a number of other adjuvant therapies are suggested, some of them peripherally applied, such as lignocaine patches, capsaicin cream, and TENS.

- Cossins L, Bowsher D, Wells C, Wiles JR. Comparison of pain characteristics in 6 diagnoses in 3118 successive pain clinic cases. (abstract), 5th International Congress: The Pain Clinic, Jerusalem, 1992.
- Bowsher D. Pathophysiology of postherpetic neuralgia: towards a rational treatment. *Neurology* 1995; 45 (suppl 8): 56–7.
- Dworkin R, Portenoy R. Pain and its persistence in herpes zoster. *Pain* 1996; 67: 241–52.
- Bowsher D. Acute shingles and postherpetic neuralgia: effects of acyclovir and outcome of treatment with amitriptyline. *Br J Gen Pract* 1992; 42: 244–6.
- Watson CPN, Deck JH, Morshead C, van der Kooy D, Evans RJ. Postherpetic neuralgia: Further postmortem studies of cases with and without pain. *Pain* 1991; 44: 105–17.
- Dworkin RH, Portenoy RK. Proposed classification of herpes zoster pain (letter). *Lancet* 1994; 343: 1648.
- Wood MJ (for HZCTC Group). How should zoster trials be conducted? *J Antimicrob Chemother* 1995; 36: 1089–101.
- Wood MJ. Herpes zoster and pain. *Scand J Infect Dis* 1991; 80: 53–61.
- Ragozzino MW, Melton MJ, Kurland LT. Population-based study of herpes zoster and its sequelae. *Medicine* 1982; 61: 310–6.
- De Moragas JM, Kierland RR. The outcome of patients with herpes zoster. *Arch Dermatol* 1957; 75: 193–6.
- Crooks RJ, Jones DA, Fiddian AP. Zoster-associated chronic pain: an overview of clinical trials with acyclovir. *Scand J Infect Dis* 1991; 78 (suppl): 62–8.
- Ragozzino MW. The epidemiology and natural history of herpes zoster and postherpetic neuralgia. In: Watson CPN, ed, *Herpes zoster and postherpetic neuralgia*. Amsterdam: Elsevier, 1993; pp 27–36.
- Watson CPN, Watt VR, Chipman M, Birkett N, Evans RJ. The prognosis with postherpetic neuralgia. *Pain* 1991; 46: 195–9.
- Cossins L. Features of commonest diagnoses in 1017 successive pain clinic cases. *Pain* 1990; 5 (suppl): S350.
- Wood MJ, Kay R, Dworkin RH, Soong S-J, Whitley RJ. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. *Clin Infect Dis* 1996; 22: 341–7.
- Dworkin RH, Hartstein G, Rosner HL, Walther RR, Sweeney EW, Brand L. A high-risk method for studying psychosocial antecedents of chronic pain: the prospective investigation of herpes zoster. *J Abnorm Psychol* 1992; 101: 200–5.
- Rose M, Klennerman L, Atchison L, Slade P. An application of the Fear Avoidance Model to three chronic pain problems. *Behav Res Ther* 1992; 30: 359–65.
- Nurmikko T, Bowsher D. Somatosensory findings in postherpetic neuralgia. *J Neurol Neurosurg Psychiatry* 1990; 53: 135–41.
- Bowsher D. Sensory change in postherpetic neuralgia. In: Watson CPN, ed, *Herpes zoster and postherpetic neuralgia*. Amsterdam: Elsevier, 1993; pp 97–107.
- Nurmikko T, Wells C, Bowsher D. Pain and allodynia in postherpetic neuralgia: role of somatic and sympathetic systems. *Acta Neurol Scand* 1991; 84: 146–52.
- Barone R, Saguer M. Postherpetic neuralgia: are C-nociceptors involved in signalling and maintenance of tactile allodynia? *Brain* 1993; 116: 1477–86.
- Barone R, Saguer M. Mechanical allodynia in postherpetic neuralgia: evidence for central mechanisms depending on nociceptive C-fiber degeneration. *Neurology* 1995; 45 (suppl 8): 63–5.
- Rowbotham MC, Fields HL. The relationship of pain, allodynia and thermal sensation in postherpetic neuralgia. *Brain* 1996; 119: 347–54.
- Bowsher D. Neurogenic pain syndromes and their management. *Br Med Bull* 1991; 47: 644–66.
- Bowsher D. Post-herpetic neuralgia in older patients. Incidence and optimal treatment. *Drugs Aging* 1994; 5: 411–8.
- Bowsher D. The effects of acyclovir therapy for herpes zoster on treatment outcome in postherpetic neuralgia: a randomised study. *Eur J Pain* 1994; 15: 9–12.
- Bowsher D. Pre-emptive treatment of postherpetic neuralgia: a randomised double-blind placebo-controlled trial. *J Pain Symptom Manage* 1997; 13: 327–31.
- Post BT, Philbrick JT. Prevention of postherpetic neuralgia by corticosteroids. In: Watson CPN, ed, *Herpes zoster and postherpetic neuralgia*. Amsterdam: Elsevier, 1993; pp 159–72.
- Whitley RJ, Weiss H, Gnann JW, et al. A randomised, placebo-controlled trial of acyclovir with and without steroids for the treatment of herpes zoster. *Ann Intern Med* 1996; 125: 376–83.
- Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain* 1988; 33: 11–23.
- Eide PC, Jörum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994; 58: 347–54.
- Watt JWG, Wiles JR, Bowsher D. Epidural morphine for postherpetic neuralgia. *Anaesthesia* 1996; 51: 647–51.
- Rowbotham MC. Managing post-herpetic neuralgia with opioids and local anaesthetics. *Ann Neurol* 1994; 35: 46–9.
- Papagallo M, Campbell JN. Chronic opioid therapy as alternative treatment for post-herpetic neuralgia. *Ann Neurol* 1994; 35: 54–6.
- Watson CPN, Evans RJ, Watt VR, Birkett N. Postherpetic neuralgia: 208 cases. *Pain* 1988; 35: 289–98.
- Watson CPN. The treatment of postherpetic neuralgia. *Neurology* 1995; 12 (suppl 8): 58–60.

- 37 McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for the management of pain: a systematic review. *BMJ* 1995; **31**: 1047–52.
- 38 Watson CPN, Evans RJ. A comparative trial of amitriptyline and zimeclidine in post-herpetic neuralgia. *Pain* 1985; **23**: 387–94.
- 39 Kishore-Kumar R, Schafer SC, Lawlor BA, Murphy DL, Max MB. Single dose of the serotonin agonists buspirone and m-chlorophenylpiperazine do not relieve neuropathic pain. *Pain* 1989; **37**: 223–7.
- 40 White JC, Sweet WH. *Pain and the neurosurgeon*. Springfield, IL: CC Thomas, 1969.
- 41 Lewith GT, Field F, Machin D. Acupuncture versus placebo in postherpetic pain. *Pain* 1983; **17**: 361–78.
- 42 Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology* 1982; **32**: 671–3.
- 43 Bhala BB, Ramamoorthy C, Bowsher D, Yelnoorker KN. Shingles and post-herpetic neuralgia. *Clin J Pain* 1988; **4**: 169–74.
- 44 Bowsher D. Acute shingles and postherpetic neuralgia: Effects of acyclovir and outcome of treatment with amitriptyline. *Br J Gen Pract* 1992; **42**: 244–6.
- 45 Bowsher D. Postherpetic neuralgia and its treatment: a retrospective survey of 191 patients. *J Pain Symptom Manage* 1996; **12**: 290–9.
- 46 McQuay HJ, Carroll D, Glynn CJ. Dose-response for analgesic effect of amitriptyline in chronic pain. *Anaesthesiology* 1993; **48**: 281–5.
- 47 Rascol O, Tran M-A, Bonneville P, et al. Lack of correlation between plasma levels of amitriptyline (and nortriptyline) and clinical improvement of chronic pain of peripheral neurologic origin. *Clin Neuropharmacol* 1987; **10**: 560–4.
- 48 Seltzer Z, Cohn S, Ginzburg R, Beilin B. Modulation of neuropathic pain behaviour in rats by spinal disinhibition and NMDA receptor blockade of injury discharge. *Pain* 1991; **45**: 69–75.
- 49 McQuay HJ, Carroll D, Jadad AR, et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind, randomised controlled crossover trial with integral n-of-1 design. *Pain* 1994; **59**: 127–33.
- 50 Johnson RW. Herpes zoster and postherpetic neuralgia: optimal treatment. *Drugs Aging* 1997; **10**: 80–94.
- 51 Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. *Lancet* 1988; **1**: 9–11.
- 52 Bowsher D. The management of central post-stroke pain. *Postgrad Med J* 1995; **71**: 598–604.
- 53 Watson CPN, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Ther* 1993; **15**: 510–26.
- 54 Rowbotham MC. Topical agents for post-herpetic neuralgia. In: Watson CPN, ed, *Herpes zoster and postherpetic neuralgia*. Amsterdam: Elsevier, 1993; pp 185–204.
- 55 Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: a double-blind controlled study of a new treatment method for postherpetic neuralgia. *Pain* 1996; **65**: 39–44.
- 56 Boas RA, Covino BG, Shanharian A. Analgesic responses to iv lignocaine. *Br J Anaesth* 1982; **54**: 501–5.
- 57 Bates JAV, Nathan PW. Transcutaneous electrical nerve stimulation for chronic pain. *Anaesthesia* 1980; **35**: 817–22.
- 58 Loeser JD. Surgery for postherpetic neuralgia. In: Watson CPN, ed, *Herpes zoster and post-herpetic neuralgia*. Amsterdam: Elsevier, 1993; pp 221–38.