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Herpes Zoster and Postherpetic Neuralgia

Optimal Treatment

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Contents

Summary

Herpes zoster is a common disease primarily affecting the elderly. Although some individuals experience no symptoms beyond the duration of the acute infection, many develop chronic pain [postherpetic neuralgia (PHN)], which is the commonest complication of herpes zoster infection and remains notoriously difficult to treat once established. It may persist until death and has major implications for quality of life and use of healthcare resources.

Predictors for the development of PHN are present during the acute disease and should indicate the need for the use of preventive therapy. At the present time, use of antiviral and certain tricyclic antidepressant drugs, combined with psychosocial support, seem most effective, but are far from perfect. Sympathetic nerve blocks reduce acute herpetic pain but it is uncertain whether they prevent PHN. In the future, vaccines may have an important place in reducing the incidence of chickenpox in the population or, through the vaccination of middle-aged individ-

uals, in boosting immunity to varicella zoster virus, thus preventing or modifying the replication of the virus from its latent phase that results in herpes zoster.

Developments in the understanding of the pathophysiology of PHN indicate possible directions for improved drug management of established PHN, although no evidence yet exists for efficacy of the drugs concerned. Such agents include new generation anticonvulsants and *N*-methyl-D-aspartate antagonists.

Established postherpetic neuralgia (PHN) is remarkably intractable to therapy, leading to much distress and impaired quality of life for the patient, and significant costs to the healthcare provider. The benefits of preventive therapy and treatment for established PHN are difficult to assess, partly because there is no accepted definition of PHN, but also because there is a paucity of well designed clinical trials. Complications of herpes zoster (shingles) other than PHN, though less common, are also important. Dissemination, secondary infection, visual impairment and motor involvement are common; the latter two may be permanent.

This review summarises current beliefs, and evidence where available, regarding predictors for the development of PHN and preventive measures that can be taken during the acute phase of herpes zoster. Should PHN become established, a number of therapies offer some chance of benefit but none is universally effective. In this article, we give an overview of suggested treatments.

1. The Size of the Problem

Epidemiological studies have shown that the incidence of herpes zoster is between 1.31[1] and 4.8[2] per 1000 per year in the population overall, and increases significantly with advancing age.[1,3] Herpes zoster is caused by the reactivation and spread of latent varicella zoster virus that has been present since an earlier attack of varicella (chickenpox). It most commonly occurs because of a natural decline in cell mediated immunity, secondary to immunosenescence, but may occur in healthy young people (fig. 1).[3,4]

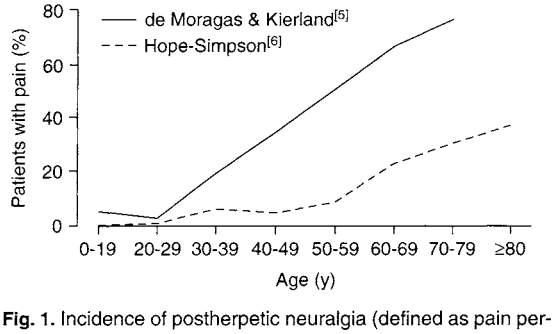


Fig. 1. Incidence of postherpetic neuralgia (defined as pain persisting for 1 month or more after rash onset) by age group. Derived from data originally reported by de Moragas and Kierland[5] (from a 916-patient survey) and Hope-Simpson[6] (a 321-patient survey), with permission.

Reduced immunity may also occur secondary to disease or its treatment. For example, lymphomas and their therapy, HIV infection, and the use of immunosuppressant drugs following organ transplant are commonly accompanied by herpes zoster. Long term use of anti-inflammatory steroids may also increase risk. Although immunosuppression is an important cause of herpes zoster, immunosuppressed patients form a small proportion of those developing the condition.

Pain is a feature of prodromal, acute-phase herpes zoster and a variable period of time following rash healing. Figure 2 shows an estimate of the incidence of pain during the continuum of zoster-associated pain (Z-aP).

2. Zoster-Associated Pain and Postherpetic Neuralgia (PHN)

PHN has been defined in many ways. Common definitions include:

- pain present after rash healing
- pain present 30 days after rash appearance
- pain present at 3 months
- pain present at 6 months.

Although a universally accepted definition has not been arrived at,[7] it is essential that all published work should state which definition has been

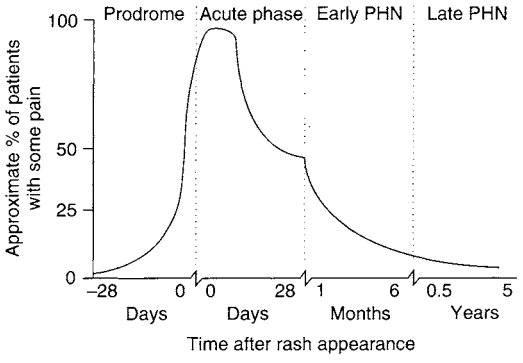


Fig. 2. Estimated incidence of zoster-associated pain with time before and after rash appearance.[26] By permission of Advanstar Communications, reprinted from *Neurology*. *Neurology* is a registered trade mark of the American Academy of Neurology. *Abbreviation:* PHN = postherpetic neuralgia.

used. Where possible, the data should be analysed using the commonly accepted definitions.[8]

Z-aP is a term of convenience that encompasses the continuum of pain at all stages of the disease.[9]

3. Risk Factors for PHN

Apart from increasing age,[1,10] studies have shown that prodromal pain,[11] the severity of acute-phase pain, and psychosocial factors are important predictors of ongoing pain.[12-14] Rash severity has been shown to be a predictor only in some studies.[15] Higa and colleagues[16] have analysed data from 1431 patients with respect to age, involved region and severity of skin lesions at the worst phase. They showed that the duration of acute herpetic pain was indeed longer in elderly patients and those with trigeminal zoster, but significantly more so in those with more severe skin lesions. Severity of skin lesions is suggested as an indicator of disease severity. However, patients with little or no acute pain and, similarly, those with insignificant rash may still develop PHN. It is not reliably known whether there is an increased risk of PHN in immunocompromised patients or those with ophthalmic zoster. Evaluation of predictors other than age is highly dependent on study design and methods of data collection. In some studies from which conclusions have been drawn, whether or not patients developed PHN may have been influenced by treatment rather than a reflection of the natural course of the illness.

4. Prevention of PHN

From our (incomplete) knowledge of the factors involved in Z-aP, it seems logical that limiting viral damage, reducing the inflammatory response and preventing ischaemic changes might prevent ongoing pain. Attention to the psychosocial factors associated with pain might help to place a patient on a more favourable curve of Dworkin's proposed diathesis stress model for zoster pain[17] (fig. 3).

Three preventive measures often applied are the acute-phase use of antiviral drugs, the acute-phase use of anti-inflammatory steroids and the early use of sympathetic nerve blockade (SNB). In addition, the early use of certain tricyclic antidepressants (e.g. amitriptyline) may prevent PHN (D. Bowsher, personal communication).

5. Treatment of Acute Herpes Zoster

5.1 Antiviral Agents

Herpes viruses are enveloped icosahedral structures containing double-stranded DNA. Viral replication may be aborted by the use of antiviral drugs. Early antiherpes drugs (vidarabine, idoxuridine) were of limited clinical use because of their toxicity. Newer drugs, such as aciclovir, are relatively

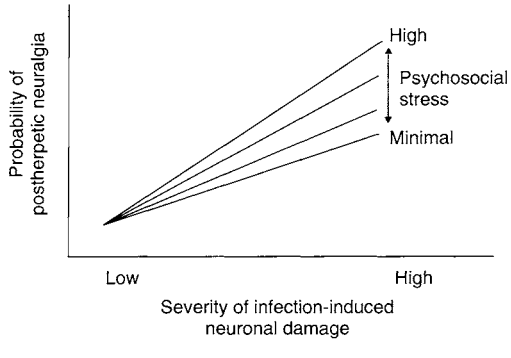


Fig. 3. Diathesis-stress model of postherpetic neuralgia, indicating the influence of psychosocial stress for a given extent of pathological damage.[17]

free of toxic effects at clinically relevant dosages, and are valuable in disease management. I shall only comment on their use in the management of herpes zoster and their effects on Z-aP.

Aciclovir, valaciclovir and famciclovir work via a similar mechanism. After absorption from the gastrointestinal tract, they are activated by phosphorylation by virus-specific thymidine kinase (which is present only in infected cells), and then further phosphorylated by cellular enzymes. They are then incorporated into viral DNA chains, preventing replication. The oral bioavailability of aciclovir is poor, hence the need for 5-times-daily administration of high doses. A prodrug of aciclovir, valaciclovir, is readily bioavailable and is converted to aciclovir after absorption. Similarly, famciclovir is a prodrug of the active agent penciclovir. Serum drug concentrations that are believed to be near-optimal are achieved with 3-times-daily administration of either famciclovir or valaciclovir.

Large multicentre studies comparing antiherpetic antiviral drugs with one another or with placebo have been undertaken.[11,18-23] In these studies, the exclusion criteria have varied, as have the definitions of PHN, making comparisons of the results difficult. Most studies excluded immunocompromised patients. Some included patients aged >18 years, while others included only patients aged >50 years, the latter being more likely to develop PHN. More unsatisfactory is the inclusion only of patients with significant pain at the time of the entry assessment: some patients would have developed pain during the next few days. Finally, for ethical reasons, ophthalmic zoster has been an exclusion criterion in most placebo-controlled studies.

Most significant is the way in which the data have been handled for analysis. Some studies have used intent-to-treat as the basis for outcome assessment; that is, data generated by all patients who satisfy the inclusion criteria and who undergo randomisation is used in the final analysis. In my view, this is appropriate. Other studies have included for analysis only those patients who had pain at the time of rash healing. This is certainly difficult to justify where a placebo control has been used, because antiherpetic drugs significantly hasten rash healing compared with placebo.

Others have analysed data only from patients with pain 30 days after rash appearance (one of the definitions of PHN; see section 2). This takes account of the fact that spontaneous resolution of pain is common up to this time. In a recent article,[8] Wood et al. discussed the ideal design of a clinical trial in herpes zoster infection. The authors agreed, among other things, the need for prospectively agreed definitions of all outcome measures and plans for data analysis. Studies of immunocompetent patients using pain as the major outcome measure should include only patients over the age of 50 years. Studies recruiting patients within 72 hours of rash onset should be designed (powered) to detect superiority over existing antivirals. They stated that evaluation of treatment effects on primary end-points should be based on intent-to-treat analysis, and subgroup analysis should be used only to support the findings of the intent-to-treat analysis.

Although studies comparing various combinations of placebo, aciclovir, famciclovir and valaciclovir have been published in peer-review journals,[11,22] there are no complete study reports of a head-to-head comparison of valaciclovir and famciclovir. All 3 drugs reduce acute pain, speed rash healing, shorten the period of viral shedding (infectivity) and shorten the duration of pain compared (sometimes indirectly) with placebo.

Wood et al.[24] worked with 2 statisticians to produce a meta-analysis of the results of 4 double-blind, randomised, placebo-controlled trials of aciclovir,[20,21,23,25] taking into account differences in study design and accepting intent-to-treat as the criterion for patient inclusion in the analysis. Various 'milestones' for pain cessation were analysed; my particular interest was in the percentage of patients with pain at 6 months, but only data from 3 of the studies could be used for this end-point because patients in the fourth[25] were not seen at 6 months if pain had ceased a month or more before this time. Data from the 3 remaining studies[20,21,23]

showed that 35% of placebo recipients aged ≥50 years still experienced pain at 6 months, compared with only 15% of aciclovir recipients in the same age group. The 95% confidence intervals showed that this difference was statistically significant.

It seems unlikely that further large studies of aciclovir versus placebo will be financially or scientifically viable and, whatever the shortcomings of meta-analyses may be, they do provide some guidance on efficacy. Valaciclovir appears to be significantly more effective that aciclovir.[11] Famciclovir is as effective as aciclovir, and has been shown to be more effective in some patient subgroups.[22] No doubt further studies will clarify the situation.

Demonstration of benefit in clinical rather than statistical terms depends on differentiation between 'any pain' and 'important pain',[26] and on any reduction in the number of patients with pain at 1 year and more. This remains uncertain.[27-30] In the UK, whether or not antiviral drugs are used depends on the perception of their value by general practitioners, and not all advice they receive has been encouraging.[31]

Further evaluation of patients in one study[27] has shed some light on this problem. McKendrick and coworkers have shown, in a retrospective long term follow-up study of patients after herpes zoster infection, that, of 160 patients aged >60 years who had zoster 9 years previously, 21% had experienced pain within the last year.[27] McGill and White[29,30] reported that, at a 5-year follow-up of 57 patients previously included in a placebo-controlled study of aciclovir,[27] PHN occurred in 37% and 6.6% of patients receiving placebo and aciclovir, respectively. These authors also reported that aciclovir had effectively prevented ocular complications.[29,30]

I believe that these drugs are well tolerated and preferable, at the present time, to other treatments (e.g. topical idoxuridine, steroids or analgesics alone) in patients with severe acute symptoms, those with ophthalmic zoster and those at high risk of developing PHN (table I). In my opinion, the more bioavailable drugs (valaciclovir and famciclovir) are now the drugs of choice in treating acute herpes zoster. Although there is some dissent, it is generally believed that ophthalmic complications of zoster are reduced by these agents.

Table I. Indications for the use of oral antiviral drugs (aciclovir, valaciclovir and famciclovir) in immunocompetent patients with herpes zoster infection[32]

Patient aged ≥60y presenting within 72h of rash appearance
Patients aged <60y presenting with severe acute pain within 72h of rash appearance
Ophthalmic involvement in patients of any age who present within 72h of rash onset
Active zoster affecting the neck, limbs and perineum (i.e. cervical, lumbar and sacral dermatomes)

The topical application of antiviral drugs probably has no useful place in the contemporary management of herpes zoster as far as pain control is concerned. Preparations of idoxuridine 5% in dimethyl sulphoxide are probably without beneficial effect,[33] and topical aciclovir is of no value in herpes zoster other than for ophthalmic involvement, but even this is controversial.[34,35]

Bowsher[36,37] has produced some evidence to suggest that residual pain in patients treated with aciclovir is more likely to respond well to the subsequent administration of amitriptyline (these results were presented before the advent of valaciclovir and famciclovir). He has also suggested that patients with high prediction scores for PHN should be treated with appropriate tricyclic antidepressants early on in the course of their disease (table II).[36,37] I agree with this view, but well designed studies are needed in this area.

5.2 Corticosteroids

The administration of systemic corticosteroids or corticotrophin (adrenocorticotrophic hormone; ACTH) during acute-phase zoster has been recommended to prevent PHN. Although these drugs carry a theoretical risk of reducing the immune response and allowing dissemination of the zoster virus, no reports of such an association exist. A number of small studies have shown benefit in terms of acute pain, but no long term protection from PHN.[39-42]

Table II. Proportion of 192 patients relieved of postherpetic pain as a function of time between onset of acute herpes zoster and commencement of treatment with an adrenergically active antidepressant. From Bowsher,[38] by permission of Advanstar Communications, as reprinted from *Neurology*. *Neurology* is a registered trademark of the American Academy of Neurology

Parameter	Months after onset		
	3-6	7-24	>24
No. of patients	65	85	42
Percentage relieved	83	49.4	35.7

Wood et al.[43] studied 400 immunocompetent patients with acute zoster and no contraindications to the use of aciclovir or short term high-dose prednisolone. Aciclovir plus placebo was compared with aciclovir plus prednisolone. Although there was some acute benefit in pain and rash healing, no protective effect was shown for PHN. Adverse events were more common in patients who received prednisolone.[43]

Whitley and colleagues[44] conducted a study of 208 patients aged ≥50 years in which they compared aciclovir plus prednisone, aciclovir plus prednisone placebo, prednisone plus aciclovir placebo, and placebos for both drugs. Prednisone was not shown to reduce the incidence of pain at 6 months; however, both acute and delayed aspects of quality of life (return to normal activities and sleep patterns) were improved in the steroid groups. Unlike the study by Wood et al.,[43] no excess of adverse events was shown in patients who received steroid treatment.[44]

Thus, steroids should not be given in the belief that they are protective against PHN. There may be some justification for their use where there are concerns about the patient's quality of life, although the risk of adverse effects, some serious, should indicate caution.

5.3 Sympathetic Nerve Blockade

A protective effect of SNB assumes either that ischaemic damage to nerve tissue is a significant factor in the development of chronic pain, or that sympathetic nerve activity is involved in both acute pain and the pathogenesis or persistence of chronic pain. Differences in susceptibility to damage between fibres of different diameter are possible; thus, it may be that the larger diameter (inhibitory) fibres are more at risk than small diameter nociceptor fibres and that, in accordance with gate control hypothesis of pain proposed by Melzack and Wall,[45] a mechanism for ongoing pain develops.

The role of SNB remains disputed. If *significantly* effective, such treatment should be available for patients predicted to be at high risk of developing PHN. This would not only be costly in terms of resource use but, possibly, significant morbidity.

When assessing studies, it is important to be aware of the natural history of zoster pain. There is a rapid recovery from pain at an early stage and a reduction in spontaneous resolution thereafter. It is hardly surprising that very early treatment with any modality may appear to be effective in preventing PHN. Only when large numbers of patients are investigated in a well designed study can the true value of such treatments be assessed. Reports are of case series (often selected) and important data, which might give an indication of the presence of risk factors for PHN, are often lacking. Some studies utilise prolonged, mixed (autonomic and sensory) block from continuous epidural local anaesthetic (LA) administration.[46]

Winnie and Hartwell[47] reported a retrospective assessment of 122 patients who had received SNB at various times after the development of shingles. SNB was achieved by LA stellate ganglion or epidural blocks at the appropriate segmental level. Patients were stratified according to time since the onset of symptoms. The number of blocks performed depended on response, and return of pain led to a further block. Results were analysed and it was concluded that early block prevented PHN, whereas late block was less effective. Allowing for the natural history of Z-aP, this would hardly be surprising since the longer pain persists, the more likely it is to be ongoing. No demographic data were given, although the authors[47] stated that they were collected. In my view, this report indicates that acute pain relief may be produced by SNB but no definite protective effect against PHN has been shown.

In a study involving 19 patients, Currey and Dalsania[48] claimed that LA stellate ganglion blocks (3 to 5 blocks during the acute stage) are effective in controlling acute pain and preventing PHN. 11 of the 19 patients were satisfied with the degree of pain relief produced, while 8 were not; this would fit with the natural history of the condition. Tenicela et al.[49] performed a randomised, double-blind, placebo-controlled crossover study of 20 patients who had had rash for less than 6 weeks. However, the power of this study is insufficient to allow confidence in any of the conclusions drawn. Higa et al.[50] elegantly discussed factors influencing the duration of treatment with sympathetic block, including some assessment of disease severity which, at that time, was assessed by his group using serial antibody titres to varicella zoster virus.

Ali[51] has recently re-evaluated 84 peer-reviewed original articles on the topic, and concluded that opinion for and against the value of SNB remained divided and that larger controlled trials were needed. Trial design for such studies may be difficult to formulate. Some workers believe that multiple blocks or continuous blockade for a significant period are necessary; others propose only a small number of blocks over a shorter period. The topic is of such importance that an international group should attempt to reach consensus on the design of a definitive study.

6. Economic Considerations

Various workers have looked at the cost of PHN, including the costs in terms of human suffering, lost earnings ability for both patients and caregivers, and healthcare provision. Davies and coworkers[52] estimated that the lifetime cost of managing PHN in a single patient in the UK was 770 pounds sterling (£), and that the annual national spending on PHN was between £4.8 million and £17.9 million (1994 values).[52] Oral antiherpetic drugs are considered by some to be expensive (approximately £100 for a week's course in the UK[53]) and SNBs even more so.

7. Assessment of PHN

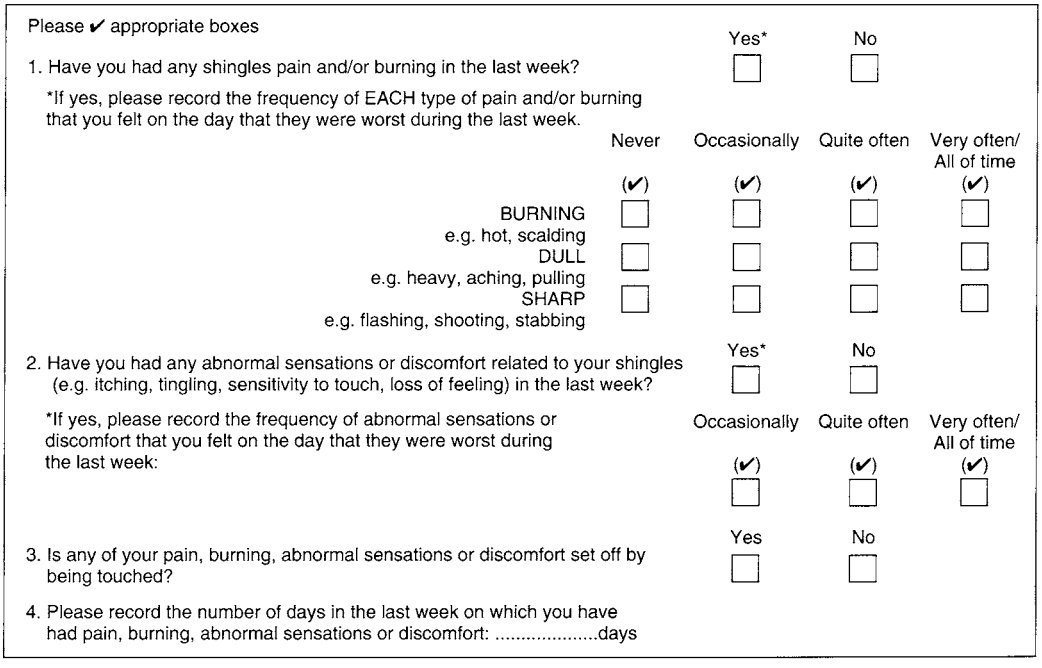
Pain and its effects differ markedly between patients, and detailed assessment of pain may offer improved opportunities to provide appropriate treatment. Apart from obtaining an accurate history, noting types of pain, the timing of pain, and its effects on quality of life and sleep, there may be value in performing a careful neurological examination, at any stage of infection, to include cold and heat thresholds, extent and type of allodynia (pain caused by a stimulus that does not normally provoke pain), and areas of altered sensation. A data collection chart has been devised and evaluated by the Aciclovir Study Group (fig. 4).[54]

During the assessment, patient compliance and the adequacy of earlier treatments should be noted. My experience with patients in a zoster clinic indicates that both are often suboptimal. Amitriptyline is frequently prescribed for PHN at a starting dosage that is too high and with no explanation of adverse effects and time course of benefit. Thus, patients often abandon treatment after a dose or two. In addition, treatments that do not afford pain relief in PHN (e.g. carbamazepine) are often continued, and may produce morbidity that adds to the patient's suffering.

Many people with PHN withdraw from social activity. This requires thorough evaluation and attempts at correction. Various assessment questionnaires are available, but the Hospital Anxiety and Depression scale is satisfactory.[55] More complex questionnaires may be difficult for elderly patients to follow. Psychosocial evaluation may indicate a need for counselling, support or encouragement to return to a 'wellness' situation, by encouraging the patient not to think of themselves as an invalid.

8. Management of Established PHN

Management of established PHN falls into early and late phases. All too often, patients are referred to Pain Management Clinics 2 or 3 years (and many unsuccessful trials of therapy) after the onset of established PHN. At this late stage it is unlikely that the condition will be cured, but it is



Please ✔ appropriate boxes

1. Have you had any shingles pain and/or burning in the last week? — Yes* ☐ No ☐

*If yes, please record the frequency of EACH type of pain and/or burning that you felt on the day that they were worst during the last week.

	Never (✔)	Occasionally (✔)	Quite often (✔)	Very often/ All of time (✔)
BURNING e.g. hot, scalding	☐	☐	☐	☐
DULL e.g. heavy, aching, pulling	☐	☐	☐	☐
SHARP e.g. flashing, shooting, stabbing	☐	☐	☐	☐

2. Have you had any abnormal sensations or discomfort related to your shingles (e.g. itching, tingling, sensitivity to touch, loss of feeling) in the last week? — Yes* ☐ No ☐

*If yes, please record the frequency of abnormal sensations or discomfort that you felt on the day that they were worst during the last week:

Occasionally (✔)	Quite often (✔)	Very often/ All of time (✔)
☐	☐	☐

3. Is any of your pain, burning, abnormal sensations or discomfort set off by being touched? — Yes ☐ No ☐

4. Please record the number of days in the last week on which you have had pain, burning, abnormal sensations or discomfort: .....days

Fig. 4. Zoster pain data collection instrument developed and evaluated by the Aciclovir Study Group in association with the Wellcome Foundation.[54]

possible to reduce the problem and improve the patient's quality of life. There is growing experience with the aggressive management of early PHN (from, say, 6 to 8 weeks after acute herpes zoster infection), and experienced clinicians are producing data that support such referral and care.

8.1 Physical Treatment

Sensory changes, abnormal sensations (e.g. formication) and allodynia are common symptoms in patients with PHN. Although much of the abnormality is located centrally, reduced nerve stimulation in the periphery may be valuable in ameliorating symptoms. For example, clothing made from natural fibres is preferable to that made from artificial fibres. A protective layer worn between the skin and provocative stimuli may be helpful: I use cling film, cut to size and shape and applied intermittently.

Transcutaneous nerve stimulation (TENS) is occasionally helpful in established PHN, but not often enough to warrant its routine use in early PHN.[56] Gerson[57] found no benefit of TENS in a study of 17 patients with PHN.[57] A few small series[58,59] have indicated that ultrasound is not effective in PHN, although it may be helpful for acute Z-aP. Acupuncture seems to provide little benefit in PHN,[60] although early treatment may be more effective.[61] Cold pack application often provides short term relief and is always worth trying.

8.2 Pharmacological Treatment

Many classes of drugs have been, and are, used in the management of PHN, although few have been evaluated by accepted contemporary standards. No doubt many drugs have helped some patients, but there are probably only a few drugs that have helped many patients.

8.2.1 Topical Treatment

Local Anaesthetics

Various LA preparations have been applied to hyperpathic skin, including lidocaine (lignocaine) and 'Emla' cream [eutectic mixture of local anaesthetics (prilocaine and lidocaine)]. They may be adsorbed onto various dressing materials, applied under occlusive dressings or administered by iontophoresis. Most publications report case studies or uncontrolled series and indicate a possible value of this approach.[62-64] Rowbotham and colleagues have reported the results of a double-blind, vehicle-controlled study.[65]

These authors' most recently reported study of 35 patients (PHN duration 4 to 318 months) showed that most patients gained some benefit from the application of a lidocaine 5% patch, compared with an observational period (i.e. no treatment) or the vehicle alone. The vehicle alone was found to be more effective than the observational period, possibly because the vehicle protected the skin from light mechanical stimuli.[66]

Lidocaine administered intravenously has been shown to produce pain relief equivalent to that of morphine and superior to that of placebo in patients with PHN, although the site of action is uncertain.[67] Subcutaneous lidocaine may reduce hyperpathia, and it is possible that this effect may be prolonged by the addition of a depot glucocorticoid. For patients in whom a few days' symptom relief follows, I cautiously offer 'pain holidays' for such events as weddings and christenings. Occasionally, the analgesic effects of systemic lidocaine may be reproduced by oral mexiletine or flecainide. These drugs may cause morbidity and are often rejected by patients because of their adverse effects.

Nonsteroidal Anti-Inflammatory Drugs

Topical nonsteroidal anti-inflammatory drugs (NSAIDs), formulated as creams, have been investigated in small studies of PHN. They may help some patients, but evidence is inconclusive.[68-70]

Capsaicin

Extract of *Capsicum frutescans* (a species of hot pepper) is widely prescribed to reduce the symptoms of PHN. It is relatively expensive, and long term use may be required to establish whether or not it offers benefit in an individual patient. The drug may need to be applied 4 times a day for up to 3 weeks to achieve an effect. Some patients reject it early on because of intense burning some minutes after application, but this may lessen with time. Capsaicin may induce selective C fibre substance P depletion following initial nociceptor stimulation. Whether transcutaneous absorption has effects that are equivalent to the direct application of capsaicin to naked nerve tissue is more doubtful.

Controlled studies of capsaicin are problematic because of difficulties related to blinding and placebo control. However, Watson et al.[71] performed a double-blind, vehicle-controlled study of 6 weeks' capsaicin therapy in 143 patients with PHN of >6 months' duration. Analysis of the whole group, and of a subset of 93 patients with PHN of >12 months' duration, showed a significant benefit of capsaicin in both groups. This beneficial effect was enhanced or maintained by ongoing (open label) use in 86% of patients.[71] Benefit may be derived from pharmacological effects, a response to counter-irritation or both.

Aspirin (Acetylsalicylic Acid) in Chloroform or Ether

Limited studies of aspirin (acetylsalicylic acid) in chloroform or ether have been reported.[72-75] A recent double-blind, placebo-controlled crossover study of 22 patients with PHN showed aspirin in ether to be significantly better, in terms of reduction of pain, than ether alone or diclofenac in ether, and to produce good to excellent results in 82% of patients. The best response was obtained in patients with trigeminal involvement, less severe pain or dysaesthetic quality of pain.[76] Despite this, there remains some doubt regarding the clinical benefit of such therapy and the mixtures are considered problematic by some pharmacists because of the effects of inhalation, potential fire hazard, and stability and disposal problems. As for so many other therapies, some patients have been helped. I have found this treatment to be very disappointing.

8.2.2 Oral Treatment

Antidepressants

Antidepressants are widely prescribed for chronic pain, and the analgesic effects of these drugs are considered to be independent of their mood elevating properties. Although blockade of noradrenaline (norepinephrine) reuptake seems to be the most important mechanism mediating this effect, most experience has been gained with amitriptyline, which has mixed noradrenergic and serotonergic effects and is effective in relieving pain in patients with PHN. The selective serotonin reuptake inhibitors (SSRIs) [e.g. zimeldine, paroxetine] seem to offer little relief in PHN although they have some activity in diabetic neuropathic pain.[77] The newer antidepressant venlafaxine also inhibits noradrenaline and serotonin reuptake but, unlike amitriptyline, lacks significant muscarinic adverse effects. It has not yet been investigated in the management of pain.

Max[78] has reviewed the evidence supporting the use of these drugs from 5 crossover studies in which drug therapy produced a reduction in the severity of PHN. Table III shows the numbers of patients who responded in each study. Definitions of response varied between the studies. Watson and coworkers[80] defined response as when most or all of the pain was gone and the patient was not disabled by pain, but Kishore-Kumar et al.[81] included relief that was moderate or greater at the end of treatment. Amitriptyline was shown to be effective in 4 of the studies, and desipramine in one. Maprotiline was less effective than amitriptyline, and zimeldine was ineffective.[82,83] Dose-response studies have not yet shown conclusively whether a direct dose-effect relationship exists, or whether there is a 'therapeutic window' below and above which pain control is suboptimal. In my experience desipramine should not be given at bedtime as it tends to result in insomnia.

Although some patients gain little benefit from tricyclic antidepressants, most patients experience pain relief if drug compliance is adequate. Compliance is most commonly lacking because of inadequate explanation of adverse effects and of the time course of expected benefit. In addition, drug dosage is often inappropriate. The physician should explain to the patient that the drug is being used for its central effect on pain, but that it is also used in other patients to treat depression. Failure to do so may make the patient angry when another party provides the information in a less acceptable way.

Adverse effects, and means of minimising them, should be fully explained. Dry mouth, constipation and sedation, which are anticholinergic effects of tricyclic antidepressants, can usually be attenuated through attention to diet, the use of artificial saliva, lozenges or chewing gum, once-daily administration before bedtime (except in the case of desipramine) and gradual dosage elevation. If the first drug prescribed does not produce adequate pain relief, a second or third may provide benefit.

Anticonvulsants

The anticonvulsants carbamazepine, phenytoin and valproic acid (sodium valproate) have been used for the management of neuropathic pain. Although these drugs may be significantly beneficial in trigeminal neuralgia and diabetic neuropathy, evidence

Table III. Summary of controlled trials of antidepressants in postherpetic neuralgia. (From Max,[78] with permission)

Reference	Drug	No. of patients	Response rate (%)	
			drug	placebo
Max et al.[78]	Amitriptyline	34	47	8
Watson et al.[79]	Amitriptyline	24	67	5
Kishore-Kumar et al.[80]	Desipramine	19	63	11
Watson et al.[81]	Maprotiline	32	18	
	Amitriptyline		44	
Watson & Evans[82]	Zimeldine	15	7	
	Amitriptyline		60	

for their effectiveness in PHN is lacking and their adverse effects, particularly in the elderly and frail, are unpleasant. McQuay and colleagues[84] reviewed the use of anticonvulsants in the management of pain and concluded that published studies offer no support for their use in PHN. Watson[85] concluded that studies have often been unimpressive,[86] or difficult to interpret because of the concomitant use of antidepressants.[57,87,88]

Newer anticonvulsants (e.g. lamotrigine and gabapentin) probably stabilise neuronal membranes via an effect on sodium channel function. They might logically be expected to be more useful. Studies of these agents are under way and the results are anticipated with interest. However, these drugs are not without adverse effects and, should they be shown to be effective in PHN, should not be used in an uncontrolled way. Prophylactic use (to prevent central sensitisation) might be more logical than use at a later stage.

Analgesics

Oral NSAIDs appear to be of little benefit in acute or chronic Z-aP. Paracetamol (acetaminophen) alone or combined with weak opioids is often considered useful by patients with acute zoster pain. Longer term benefit is less easy to assess because some of these drugs (paracetamol and weak opioids) may have minor dependency associations favouring their continued use.

Opioids are often avoided because of the risk of addiction and adverse effects in elderly patients. Traditionally, opioids have been considered to be unhelpful in neuropathic pain; however, like all such generalisations, this is not entirely true. Some patients benefit, but this should be assessed under controlled conditions with skilled observation of response and frequent review. Intravenous infusions of morphine have been shown to reduce pain and hyperalgesia in PHN patients.[89,90]

Pappagallo and Campbell[91] performed a study in 20 patients with PHN that had responded poorly to other therapy. 17 of the patients had been treated with 1 or more tricyclic antidepressants. Most patients received oral controlled-release morphine, and 2 received slow-release oxycodone. After 6 months, pain relief was described as excellent, good or slight to moderate by 5, 9 and 2 patients, respectively. There was no significant impairment of cognitive function, and adverse effects (drowsiness, nausea and constipation) were not found to be problematic.[91]

8.2.3 Ketamine and N-Methyl-D-Aspartate Antagonists

N-Methyl-D-aspartate (NMDA) receptors are involved in the development and maintenance of changes in neuronal excitability that might be relevant in the development of 'wind-up' (central sensitisation), allodynia and persistence of pain following damage to elements of the pain pathway resulting from herpetic infection. Ketamine is known to produce analgesia, at least in part, through blockade of these receptors. A limited number of studies of ketamine in PHN[92-95] have shown that elements of PHN are reduced or abolished in some patients, but with adverse effects and possibly other complications of ongoing use.[96]

The experimental NMDA antagonist CPP [3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid] appears to have similar effects to ketamine.[97] Dextromethorphan is also an NMDA antagonist and might mimic the beneficial analgesic effects of ketamine. However, no good evidence to support this exists: the dosage required and its long term adverse effects are largely unknown. At the dosages usually reported, dextromethorphan does not produce lasting analgesia in significant numbers of patients and may be rejected because of its adverse effects.[98]

8.2.4 Other

Numerous drugs have been found to be beneficial in at least some patients with PHN, and publications on their use range from single case reports to uncontrolled studies. I believe that most of these drugs can provide help to some patients. Such drugs include amantadine,[99-101] adenosine,[102,103] various phenothiazines, baclofen, haloperidol, noradrenaline-serotonin reuptake inhibitors and other antidepressants,[77] iontophoresis with vincristine,[104] and calcium antagonists.[105]

8.2.5 Nerve Blocks

Interpleural blocks have been used for acute[106] and chronic[107,108] herpetic pain. Subcutaneous injection of an LA, with or without a steroid, may produce a temporary reduction in allodynia. Peripheral blocks may reduce hyperpathia, but whether or not the temporary effects of LA block can be prolonged by neurolysis, be it chemical, heat- or cold-induced, is less certain; in addition, there is a risk of worsened pain following deafferentation. SNB is often effective in relieving acute pain and it may possibly have a role in preventing PHN, although it very rarely helps established PHN.

8.3 Psychosocial Treatment

Elderly patients are often lonely, and adverse major life events such as bereavement or loss of independence are common. They may have pre-existing anxiety or depression, or may develop these secondary to zoster and chronic pain. As in every other chronic pain situation, such factors should be evaluated. Re-establishment of social activities, in addition to giving the patient an understanding of the disease, are frequently helpful. An individual management strategy can be developed for each patient. Thomsen's book (see Recommended Reading) makes helpful reading for patients.

8.4 Neuroinvasive Measures

In 1959, Noordenbos[109] noted the intractability of PHN. He cited a case report, originally described by Sugar and Bucy,[110] of a patient with postherpetic pain in the eye, cheek and nose. The following methods were used in sequence, with appropriate intervals between them to enable the results to be evaluated: (i) injection of alcohol (ethanol) into the infraorbital nerve; (ii) x-ray irradiation of the Gasserian ganglion; (iii) partial division of the sensory root of the trigeminal nerve; (iv) total resection of the sensory root of the trigeminal nerve; (v) cocainisation of the sphenopalatine ganglion; (vi) procaine block of the stellate ganglion; (vii) excision of the contralateral sensory cortex for the face; (viii) excision of the ipsilateral sensory cortex for the face; (ix) electroconvulsive therapy; and (x) bilateral prefrontal leucotomy. Despite all of these interventions the patient still experienced pain, although it was less troublesome than it had been.

This cautionary tale should be heeded, and other reports of neurodestructive techniques do not much support the use of such invasive treatments. Pain is currently a justifiably feared complication of shingles, and may well be intractable in some patients.

8.5 Summary

Following thorough assessment (history, physical examination and psychosocial evaluation), a treatment plan should be prepared and discussed with the patient. At each stage, benefits and adverse effects should be quantified. Management should usually start with explanation and encouragement, accompanied by general advice on clothing, return to normal social activities and use of ice packs or protective film.

The mainstay of drug therapy is an appropriate tricyclic antidepressant, used in such a way that adverse effects are minimised while producing the required benefit. When using amitriptyline or nortriptyline in elderly or frail patients, the dosage should be started at 10 mg/day, taken 1 hour before bedtime, and increased by 10 mg/day at weekly intervals. Stronger and younger patients may tolerate a starting dosage of 25 mg/day. Adverse effects can usually be accommodated (see section 8.2.2). Capsaicin-containing cream may be offered to the patient, with careful explanation of the application technique and the required frequency and duration of treatment. Capsaicin should be applied 4 times daily for 4 weeks before response is evaluated.

Further management must depend on ongoing evaluation and the experience of the clinician, guided mainly by science and only partly by anecdote.

9. The Future

Eradication of varicella by effective immunisation would, presumably, be followed some generations later by the absence of zoster. It is possible that immunisation in middle age may boost immunity to the point where zoster is delayed until beyond an individual's life expectancy; trials in this area are ongoing.[111] Improved therapies may evolve both for the prevention and treatment of PHN. Unfortunately, humans do not respond to drugs in quite the same way as laboratory animals, and many promising therapies fail to achieve their potential. However, neurophysiological and neuropharmacological research continues to uncover more and more revelations on pain-related factors, and some of these must bear therapeutic fruit.

Recommended Reading

Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. Pain 1996; 67: 241-51
Glaser R, Gotleib-Stematsky T, editors. Human herpesvirus infections. Series: infectious diseases and antimicrobial agents. Vol. 2. New York: Dekker, 1982
Glaser R, Jones JF, editors. Herpes virus infections. New York: Dekker, 1994
Noordenbos W. Pain. Amsterdam: Elsevier, 1959
Rentier B, editor. Proceedings of the Second International Conference on the Varicella-Zoster Virus. Neurology 1995 Dec; 45 (12 Suppl. 8)
Thomsen TC. Shingles and PHN. Cross River (NY): Cross River Press, 1994
Watson CPN, editor. Herpes zoster and postherpetic neuralgia. Series: pain research and clinical management. Vol. 8. Amsterdam: Elsevier, 1993
Johnson RW. Aspects of postherpetic neuralgia: can we zap Z-aP? Pain Rev 1996; 3: 117-35

References

1. Ragozzino MW, Melton III LJ, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) 1982; 61: 310-6
2. McGregor RM. Herpes zoster, chicken-pox and cancer in general practice. BMJ 1957; I: 84-7
3. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med 1965; 58: 9-20
4. Weksler ME. Immune senescence. Ann Neurol 1994; 35: 35-7
5. de Moragas M, Kierland RR. The outcome of patients with herpes zoster. AMA Arch Dermatol 1957; 75: 193-6
6. Hope-Simpson RE. Postherpetic neuralgia. J R Coll Gen Pract 1975; 25: 571-5
7. Dworkin RH, Portenoy RK. Proposed classification of herpes zoster pain [letter]. Lancet 1994; 343: 1648
8. Wood MJ, Group HZCTC. How should zoster trials be conducted? J Antimicrob Chemother 1995; 36: 1089-101
9. International HMFCG. Reducing the burden of zoster-associated pain: update. IHMF Management Strategies Workshop. Worthing (England): PPS Europe Ltd, 1995
10. Boon R. Efficacy and safety of famciclovir in the treatment of herpes zoster [oral presentation]. The Second International Conference on the Varicella Zoster Virus: 1994 Jul 7-8; Paris
11. Beutner KR, Friedman DJ, Forszpaniak C, et al. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Antimicrob Agents Chemother 1995; 39: 1546-52
12. Dworkin RH, Hartstein G, Rosner HL, et al. A high-risk method for studying psychosocial antecedents of chronic pain: the prospective investigation of herpes zoster. J Abnorm Psychol 1992; 101 (1): 1-20
13. Rose MJ, Klenerman L, Atchison L, et al. An application of the fear avoidance model to three chronic pain problems. Behav Res Ther 1992; 30: 359-65
14. Leijon G, Boivie J, Rosberg M, et al. Sensory abnormalities accompanying herpes zoster and post-herpetic neuralgia. 7th World Congress on Pain; 1993 Aug: Paris. Seattle: IASP Press, 1993
15. Wilson JB. Thirty one years of herpes zoster in a rural practice. BMJ 1986; 293: 1349-52
16. Higa K, Mori M, Hirata K, et al. Severity of skin lesions of herpes zoster at the worst phase rather than age and involved region influences most the duration of acute herpetic pain. Pain. In press
17. Dworkin RH, Cooper EM, Walther RR, et al. Predicting the development of postherpetic neuralgia in acute herpes zoster patients: a diathesis-stress model [abstract/poster]. American Pain Society Annual Meeting. Los Angeles: American Pain Society, 1995
18. McKendrick MW, McGill JI, Bell AM, et al. Oral acyclovir for herpes zoster [letter]. Lancet 1984 Oct 20; II: 925
19. McKendrick MW. Oral acyclovir in herpes zoster. Scand Infect Dis 1985; 47: 76-9
20. Morton P, Thomson AN. Oral acyclovir in the treatment of herpes zoster in general practice. N Z Med J 1989; 102: 93-5
21. Huff JC, Bean B, Balfour HH, et al. Therapy of herpes zoster with oral acyclovir. Am J Med 1988; 85: 84-9
22. Degreef H, Group FHZCS. Famciclovir for herpes zoster. Int J Antimicrob Agents 1994; 4: 241-6
23. Harding SP, Porter SM. Oral acyclovir in herpes zoster ophthalmicus. Curr Eye Res 1991; 10: 177-82
24. Wood MJ, Kay R, Dworkin RH, et al. 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
25. Wood MJ, Ogan PH, McKendrick MW, et al. Efficacy of oral acyclovir treatment of acute herpes zoster. Am J Med 1988; 85: 79-83
26. Johnson RW. The future of predictors, prevention and therapy in postherpetic neuralgia. Neurology 1995; 45 Suppl. 8: S70-2
27. McKendrick MW, Care C, Wood MJ, et al. A retrospective review of herpes zoster and the development of chronic pain [oral presentation]. The Second International Conference on the Varicella Zoster Virus: 1994 Jul 7-8; Paris
28. McKendrick MW, Wood MJ. Acyclovir and post-herpetic neuralgia: two other participating study centres report different results [letter]. BMJ 1995; 310: 1005
29. McGill JI, White JE. Prevention of herpes zoster induced postherpetic neuralgia and ocular involvement with acyclovir

[oral presentation]. The Second International Conference on the Varicella Zoster Virus: 1994 Jul 7-8; Paris
30. McGill JI, White JE. Acyclovir and post-herpetic neuralgia and ocular involvement. BMJ 1994; 309: 1124
31. Lancaster T, Silagy C, Gray S. Primary care management of acute herpes zoster: systematic review of evidence from randomized controlled trials. Br J Gen Pract 1995 Jan; 45: 39-45
32. Johnson RW, Mandal BK. Brief summary of guideline for antiviral use. J Infect 1995; 30: 193-200
33. Juel-Jensen BE, MacCallum FO, MacKenzie AMR, et al. Treatment of zoster with idoxuridine in dimethyl sulphoxide: results of two double-blind controlled trials. BMJ 1970 Dec 26; 4: 776-80
34. Marsh RJ, Cooper M. Double-masked trial of topical acyclovir and steroids in the treatment of herpes zoster ocular inflammation. Br J Ophthalmol 1991; 75: 542-6
35. Neoh C, Harding SP, Saunders D, et al. Comparison of topical and oral acyclovir in early herpes zoster ophthalmicus. Eye 1994; 8: 688-91
36. Bowsher D. Acute herpes zoster and postherpetic neuralgia: effects of acyclovir and outcome of treatment with amitriptyline. Br J Gen Pract 1992; 42: 244-6
37. Bowsher D. The effects of acyclovir therapy for herpes zoster on treatment outcome in postherpetic neuralgia. Eur J Pain 1994; 15: 9-12
38. Bowsher D. Pathophysiology of postherpetic neuralgia: towards a rational treatment. Neurology 1995; 45 Suppl. 8: S56-7
39. Esmann V, Geil JP, Kroon S. Prednisolone does not prevent postherpetic neuralgia. Lancet 1987; II: 126-9
40. Eaglstein WH, Katz R, Brown JA. The effects of early corticosteroid therapy on the skin eruption and pain of herpes zoster. JAMA 1970; 211: 1681-3
41. Esmann V, Peterslund NA, Ipsen J. Systematic antiviral treatment of herpes zoster. In: Spitzy KH, Karrer K, editors. 13th International Congress of Chemotherapy: 1983 Aug 28-Sep 2; Vienna. Vol. 39, 1983
42. Keczkes K, Basheer AM. Do corticosteroids prevent postherpetic neuralgia? Br J Dermatol 1980; 102: 551-5
43. Wood MJ, Johnson RW, McKendrick MW, et al. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. N Engl J Med 1994; 330: 896-900
44. Whitley RJ, Weiss H, Gnann JW, et al. Acyclovir with and without prednisone for the treatment of herpes zoster: a randomised, placebo-controlled trial. Ann Intern Med 1996; 125: 376-83
45. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150: 971-9
46. Manabe H, Dan K, Higa K. Continuous epidural infusion of local anaesthetics and shorter duration of acute zoster-associated pain. Clin J Pain 1995; 11: 220-8
47. Winnie AP, Hartwell PW. Relationship between time of treatment of acute herpes zoster with sympathetic blockade and prevention of post-herpetic neuralgia: clinical support for a new theory of the mechanism by which sympathetic blockade provides therapeutic benefit. Reg Anesth 1993; 18: 277-82
48. Currey TA, Dalsania J. Treatment for herpes zoster ophthalmicus: stellate ganglion block as a treatment for acute pain and prevention of postherpetic neuralgia. Ann Ophthalmol 1991; 23: 188-9
49. Tenicela R, Lovasic D, Eaglstein W. Treatment of herpes zoster with sympathetic blocks. Clin J Pain 1985; 1: 63-7
50. Higa H, Dan K, Manabe H, et al. Factors influencing the duration of treatment of acute herpetic pain with sympathetic nerve block: importance of severity of herpes zoster assessed by the maximum antibody titers to varicella-zoster virus in otherwise healthy patients. Pain 1988; 32: 147-57
51. Ali NM. Does sympathetic ganglionic block prevent postherpetic neuralgia? Literature review. Reg Anesth 1995; 20: 227-33
52. Davies L, Cossins L, Bowsher D, et al. The cost of treatment for post-herpetic neuralgia in the UK. PharmacoEconomics 1994; 6: 142-8
53. British national formulary. 32nd ed. London: British Medical Association/Royal Pharmaceutical Society of Great Britain, 1996 Sep
54. Johnson R, Shukla S, Fletcher P, for the Aciclovir Study Group. Qualitative aspects of zoster-associated pain – evaluation of a new approach [abstract/poster]. 1st Scientific Meeting of the European Federation of IASP Chapters. Verona: European Federation of IASP Chapters, 1995
55. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression scale. Acta Psychiatr Scand 1983; 67: 361-70
56. Nathan PW, Wall PD. Treatment of postherpetic neuralgia by prolonged electrical stimulation. BMJ 1974; 3: 645-7
57. Gerson GR, Jones RB, Luscombe DK. Studies of the concomitant use of carbamazepine and clomipramine for the relief of postherpetic neuralgia. Postgrad Med J 1977; 54: 104-9
58. Jones RJ, Silman GM. Trials of ultrasonic therapy for acute herpes zoster. Practitioner 1987; 231: 1336-40
59. Payne C. Ultrasound for post-herpetic neuralgia. Physiotherapy 1984; 70: 96-7
60. Lewith GT, Field F, Machin D. Acupuncture versus placebo in postherpetic pain. Pain 1983; 17: 361-8
61. Dung HC. Acupuncture for the treatment of post-herpetic neuralgia. Am J Acupuncture 1987; 15: 5-14
62. Collins PD. EMLA cream and herpetic neuralgia. Med J Aust 1991; 155: 206-7
63. Stow PJ, Glynn CJ, Minor B. EMLA cream in the treatment of postherpetic neuralgia: efficacy and pharmacokinetic profile. Pain 1989; 39: 301-5
64. Wheeler JG. Emla cream and herpetic neuralgia [letter]. Med J Aust 1991; 154: 781
65. Rowbotham MC, Miller KV, Davies P. Topical lidocaine for post-herpetic neuralgia pain: results of a double-blind, vehicle controlled trial. Neurology 1992; 42 Suppl. 3: 390
66. Rowbotham MC, Davies PS, Verkempinck C, et al. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain 1996; 65: 39-44
67. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. Neurology 1991; 41: 1024-8
68. Alexander JI. Post herpetic neuralgia [letter]. Anaesthesia 1985; 40: 1133-4
69. Coniam SW, Hunton J. A study of benzydamine cream in postherpetic neuralgia. Res Clin Forums 1988; 10: 65-7
70. McQuay HJ, Carroll D, Moxon A, et al. Benzydamine cream for the treatment of post-herpetic neuralgia: minimum duration of treatment periods in a cross-over trial. Pain 1990; 40: 131-5
71. Watson CPN, Tyler KL, Bickers DR, et al. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. Clin Ther 1993; 15: 510-26
72. De Benedittis G, Besana F, Lorenzetti A. A new topical treatment for acute herpetic neuralgia and postherpetic neuralgia: the aspirin/diethyl ether mixture. An open-label study plus a double-blind, controlled clinical trial. Pain 1992; 48: 383-90
73. Haines DR. Topical aspirin in chloroform for post-herpetic neuralgia. J Intractable Pain Soc 1989; 7: 15-6

74. King RB. Concerning the management of pain associated with herpes zoster and of postherpetic neuralgia. Pain 1988; 33: 73-8
75. King RB. Topical aspirin in chloroform and the relief of pain due to herpes zoster and postherpetic neuralgia. Arch Neurol 1993; 88: 556-61
76. De Benedittis G, Lorenzetti A. Topical aspirin/diethyl ether mixture versus indomethacin and diclofenac/diethyl ether mixtures for acute herpetic neuralgia and postherpetic neuralgia: a double-blind crossover placebo-controlled study. Pain 1996; 65: 45-51
77. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992; 326: 1250-6
78. Max MB. Treatment of post-herpetic neuralgia: antidepressants. Ann Neurol 1994; 35: 50-3
79. Max MB, Schafer SC, Culnane M. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology 1988; 38: 1427-32
80. Watson CP, Evans RJ, Reed K, et al. Amitriptyline versus placebo in postherpetic neuralgia. Neurology 1982; 32: 671-3
81. Kishore-Kumar R, Max MB, Schafer SC. Desipramine relieves postherpetic neuralgia. Clin Pharmacol Ther 1990; 47: 305-12
82. Watson CPN, Chipman M, Reed K. Amitriptyline versus maprotiline in postherpetic neuralgia: a randomized double-blind, crossover trial. Pain 1992; 23: 387-94
83. Watson CPN, Evans RJ. A comparative trial of amitriptyline and zimelidine in post-herpetic neuralgia. Pain 1985; 23: 387-94
84. McQuay H, Carroll D, Jadad AR, et al. Anticonvulsant drugs for the management of pain: a systematic review. BMJ 1995; 311: 1047-52
85. Watson CPN. The medical treatment of postherpetic neuralgia. In: Watson CPN, editor. Herpes zoster and postherpetic neuralgia. Amsterdam: Elsevier, 1993: 205-19
86. Killian JM, Fromm GH. Carbamazepine in the treatment of neuralgia. Arch Neurol 1968; 19: 129-36
87. Raftery H. The management of postherpetic pain using sodium valproate and amitriptyline. Ir Med J 1979; 72: 399-401
88. Hatangdi VS, Boad RA, Richards ED. Postherpetic neuralgia: management with antiepileptic tricyclic drugs. In: Bonica JJ, Albe-Fessard D, editors. Advances in pain research and therapy. Vol. 1. New York: Raven Press, 1976: 583-7
89. Rowbotham MC, Fields HL. Topical lidocaine reduces pain in post-herpetic neuralgia. Pain 1989; 38: 297-301
90. Rowbotham MC. Managing post-herpetic neuralgia with opioids and local anesthetics. Ann Neurol 1994; 35: 46-9
91. Pappagallo M, Campbell JN. Chronic opioid therapy as alternative treatment for post-herpetic neuralgia. Ann Neurol 1994; 35: 54-6
92. Hoffmann V, Coppejans H, Vercauteren M, et al. Successful treatment of postherpetic neuralgia with oral ketamine. Clin J Pain 1994; 10: 240-2
93. Eide PK, Jorum E, Stubhaug A, et al. 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
94. Bushnell T, Vijay V, Thwaites R, et al. Ketamine is an analgesic in refractory postherpetic neuralgia. J Pain Soc 1996; 12: 93
95. Backonja M, Arndt G, Gombar KA, et al. Response of chronic neuropathic pain syndromes to ketamine: a preliminary study. Pain 1994; 56: 51-7
96. Kato Y, Homma I, Ichiyanagi K. Postherpetic neuralgia. Pain 1995; 11: 336-7
97. Kristensen JD, Svensson B, Gordh T. The NMDA-receptor antagonist CPP abolishes neurogenic 'wind-up pain' after intrathecal administration in humans. Pain 1992; 51: 249-53
98. 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
99. Galbraith AW. Treatment of acute herpes zoster with Symmetrel. In: Wink CAS, editor. Report of an International Clinical Symposium: 1971: 45
100. Galbraith AW. Treatment of acute herpes zoster with amantadine hydrochloride (Symmetrel). BMJ 1973; 4: 693-5
101. Parkes D. Amantadine. Adv Drug Res 1975; 8: 11-81
102. Sherlock CH, Corey L. Adenosine monophosphate for the treatment of varicella zoster infections: a large dose of caution. JAMA 1985; 253: 1444-5
103. Sklar SH, Blue WT, Alexander EJ, et al. Herpes zoster: the treatment and prevention of neuralgia with adenosine monophosphate. JAMA 1985; 253: 1427-30
104. Csillik B, Knyihar-Csillik E, Szucs A. Treatment of chronic pain syndromes with iontophoresis of vinca alkaloids to the skin of patients. Neuroscience 1982; 31: 87-90
105. Ikebe H, Miyagawa A, Mizutani A, et al. The effect of iontophoresis with several Ca channel blockers for PHN patients. Masui 1995; 44: 428-33
106. Reiestad F, Kvalheim L, McIlvaine WB. Pleural analgesia for the treatment of acute severe thoracic herpes zoster. Reg Anesth 1989; 14: 244-6
107. Reiestad F, McIlvaine WB, Barnes M, et al. Interpleural analgesia in the treatment of severe thoracic postherpetic neuralgia. Reg Anesth 1990; 15: 113-7
108. Thwaites BK, Powell DR. Interpleural block for acute combined cervical and thoracic herpes zoster [letter]. Reg Anesth 1995; 20: 255-6
109. Noordenbos W. Post-herpetic neuralgia. In: Noordenbos W. Pain. Amsterdam: Elsevier, 1959: 4-10
110. Sugar O, Bucy PC. Post-herpetic trigeminal neuralgia. Arch Neurol Psychiatry 1951; 65: 131
111. Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. Neurology 1995; 45: 41-6

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