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Therapy of Zoster Pain, Postherpetic Neuralgia and Other Neurological Complications

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Treatment of Acute Herpes Zoster

In most cases acute herpes zoster is a self-limiting disease and will resolve without complications with time. Analgesic drugs, i.e. NSAIDs and weak opioids or in severe cases strong opioids, in combination with local antiinflammatory ointments are used to establish adequate control of acute pain during healing of the rash. Furthermore, antiviral therapy (e.g. acyclovir, famciclovir, valacyclovir and brivudin) should be initiated as soon as possible, especially in older patients. If neurological complications, i.e. motor paresis, clinical signs of myelitis or encephalitis or dermatological complications (involvement of the cornea, zoster generalisatus) have developed as well as in immunocompromised patients an intravenous therapy of virostatic drugs should be applied.

The pain in acute herpes zoster may have a sympathetically maintained component, i.e. some percentage of the pain depends on the efferent sympathetic innervation to the affected skin area. If the zoster is located in the face, the upper or lower extremity diagnostic sympathetic blocks at the stellate ganglion or the lumbosacral chain can be performed particularly in severe cases. In case of a sympathetically maintained pain component a series of several sympathetic blocks may reduce acute pain. The important question whether sympathetic blocks are capable of reducing the risk of chronic PHN is still unresolved.

Prediction of Postherpetic Neuralgia

Despite the similarity of the acute symptoms only a subgroup of zoster patients are at risk for the development of postherpetic neuralgia (PHN). Until now there are no firm indicators the clinician can rely on in setting the prognosis for the patient with acute herpes zoster. However, some interesting associations have started to emerge. In general, patients of older age have a higher risk to be left with PHN [1–3]. In acute herpes zoster there is a positive correlation between elevation of T-lymphocyte CD4/CD8, indicative of the impairment of cell mediated immunity, and duration of pain [4]. Several psychosocial antecedents of the development of chronic pain could be established in herpes zoster, i.e. disease conviction and depression [2]. Furthermore, neurophysiological measures, i.e. elevation of thermal thresholds within the acutely affected skin area, were associated with reports of pain at 3 months duration but the small number of patients precluded assessment of association with chronic established PHN [5]. By analogy with other chronic pain syndromes, i.e. phantom limb pain [6] and chronic back pain [7], many investigators suggested that the acute pain intensity, indicative of the severity of the herpes zoster infection and nerve damage, may predict the development of PHN [2, 3]. In addition, it was shown that patients with a preexisting large fiber polyneuropathy were at higher risk to develop PHN [8].

Prevention of Postherpetic Neuralgia

Recent results from the shingles prevention study shows that vaccination of adults is effective in prevention of PHN [9]. If vaccination of adults is adopted, and shows similar long-term effects, it is possible that there could be a dramatic reduction of PHN in decades to come. Combining this effect with the long-term effect (40+ years) of childhood vaccination against varicella, future generations might be immune to the sometimes devastating results of PHN.

Early antiherpetic therapy, in particular with modern antiviral drugs [10] significantly reduced the development of PHN [11].

The immediate treatment objective during the acute zoster phase is to shorten as much as possible the duration of the pain phase. Although only few controlled studies are available that assessed the effect of acute pain therapy on development of PHN all modern concepts of pain generation suggest that every acute pain input to the nervous system will lead to chronification.

According to the pathophysiological mechanisms several therapeutical interventions to prevent PHN can be hypothesized: (1) an adequate analgesia should be established in the acute phase with e.g. analgesics, anti-depressants

or epidural or sympathetic blocks and (2) C-fiber degeneration should be prevented by reducing the inflammatory reaction with e.g. antiviral drugs. So far one controlled study performed so far demonstrated that the incidence of PHN can be reduced by half if 50 mg amitriptyline is administered within the acute zoster phase [12]. Furthermore, gabapentin showed promising results in animal experiments [13].

Taken these data together, a combination of an antiviral agent, analgesics (NSAID or opioids), antidepressants and anticonvulsants and in selected cases sympathetic blocks to treat the sympathetically maintained pain component seems to be appropriate to minimize the risk of pain chronification and development of PHN.

Treatment of Postherpetic Neuralgia

The number of treatment options for PHN has expanded greatly in the last few years [14, 15]. Of particular note are the results of randomized, controlled clinical trials that now confirm the efficacy of anti-depressants, opioids, anticonvulsants and topical analgesics in relieving the symptoms of PHN.

Antidepressants

Tricyclic antidepressants (TCAs) are effective in the treatment of postherpetic pain [16–18]. These compounds are inhibitors of the reuptake of monoaminergic transmitters. They are believed to potentiate the effects of biogenic amines in CNS pain modulating, in particular pain-inhibiting pathways projecting from the brain stem to the spinal cord. In addition, they block voltage dependent Na-channels and alpha adrenergic receptors. However, it may be that the effectiveness of TCAs in neuropathic pain has to do with their broad range of pharmacological actions.

Of the TCAs, amitriptyline is currently the most widely prescribed and best studied compound for the treatment of chronic pain. There is extensive evidence that amitriptyline produces pain relief in PHN [17]. All components of neuropathic pain such as stimulus-independent continuous burning or shooting pain as well stimulus-induced allodynia may be improved. The mean dose required for pain reduction (75–150 mg/day) is usually smaller than doses necessary to achieve anti-depressant effects.

Amitriptyline and other TCAs, however, have significant side-effects. They can produce orthostatic hypotension, largely due to an α -adrenergic blocking action. Due to its histamine receptor blockade, amitriptyline is also a potent sedating drug, which can be a desirable action if patients are having difficulty sleeping. Other significant problems include urinary retention, memory loss and

cardiac conduction abnormalities (largely due to the muscarinic anti-cholinergic actions of the drug). Patients, especially the elderly, who are to be treated with this drug should be started at a very low dose (e.g. 10 mg), and built up slowly.

Desipramine and nortriptyline, both of which have predominant norepinephrine reuptake blocking action, appear to be as effective as amitriptyline in PHN [17]. Patients respond to desipramine and nortriptyline at doses comparable to those of amitriptyline but with fewer anti-cholinergic side-effects and significantly less sedation. Still, the side effect profile of the TCAs as a class will continue to represent a significant limitation to their use in the treatment of PHN.

The selective serotonin reuptake inhibitors (SSRI) are an alternative class, but there are as yet no controlled clinical trials with these agents in PHN. In other neuropathic pain states the results with SSRI are disappointing.

There are some newer antidepressants that are neither TCAs nor SSRIs. Venlafaxine and duloxetine block both serotonin and norepinephrine reuptake and have demonstrated efficacy in painful diabetic neuropathy [19, 20].

Based on available data, amitriptyline is still a first-line antidepressant agent in the treatment of PHN. If it is effective but produces intolerable side effects, a cautious trial of nortriptyline or desipramine may be appropriate. Alternatively, a lower dose of amitriptyline may still provide benefit, especially when combined with other types of agents.

Anticonvulsants (Na-Channel Blockers)

Carbamazepine and oxcarbazepine are very effective in trigeminal neuralgia. However, there are no controlled studies in PHN [17]. Newer anticonvulsants like lamotrigine also have some utility in the treatment of peripheral and central neuropathic pain, however, the evidence supporting their use in PHN is currently missing.

Anticonvulsants (Ca-Channel Modulators)

There is a large body of clinical evidence for the efficacy of gabapentin in a variety of neuropathic pain syndromes. Placebo-controlled trials show that gabapentin is effective in PHN [21]. Its relatively benign side effect profile compared to other options have encouraged many physicians to use it frequently for nerve injury pain.

Pregabalin, the successor drug of gabapentin was shown to be efficacious in PHN, DPN and spinal cord injury (until now 7 published studies) [22, 23]. Its mechanism of action has now been solved: a modulating action on the $\alpha 2\delta$ -subunit of central Ca-channels located presynaptically at the nociceptive terminal in the dorsal horn spinal cord. Pregabalin has a low potential for drug-drug interactions, and no negative impact on cardiac function. In addition, pregabalin was noted considerably to improve sleep disturbances in neuropathic pain

patients. Furthermore, overall mood and other measures of quality of life were positively affected. All these features make it suitable first-line therapy than TCAs or traditional anticonvulsants especially for the elderly, a population very often suffering from several comorbidities that need multiple drug therapies. One advantage over gabapentin is its superior bioavailability which makes it easier to use without the need of long titration periods. Dizziness and somnolence are the most commonly reported adverse events, especially during upward titration to targeted doses.

Opioid Analgesics

Opioids are clearly effective in postoperative, inflammatory and cancer pain. However, the use of opioids for patients with chronic neuropathic pain is controversial, even among experts in the field of pain management, primarily due to a perceived lack of efficacy, and concern about the potential for drug tolerance and addiction.

However, double-blind placebo controlled studies have now demonstrated that acute infusions of morphine or fentanyl give significant pain relief to patients with PHN [24]. Furthermore, recent controlled trials have demonstrated sustained efficacy for several weeks of oral oxycodone [25] and tramadol [26] in PHN. In one study oral morphine was analyzed in a group of PHN patients comparing the effect of antidepressants in the same cohort. Both drugs were similar effective. However, there was no correlation in the response rate between both drugs indicating that different mechanisms are active in these PHN patients [27].

All data on opioid use in chronic nonmalignant pain collected so far are insufficient to address the long-term efficacy of opioids and the development of adverse effects that might only arise during long-term use, e.g. their effect on the immune system. However, many patients with pain due to central and peripheral nerve injury can be successfully and safely treated on a chronic basis with stable doses of strong opioids without signs of tolerance. The use of opioids requires caution in patients with a history of chemical dependence or pulmonary disease. We recommend using long-acting opioid analgesics (e.g. sustained release morphine preparation) when alternative approaches to treatment have failed. An opioid trial should be tested before invasive therapies are instituted. Furthermore, a trial of opioids should not be delayed to a 'last resort' status. Prophylactic treatment of common side effects notably nausea or constipation is necessary and improves patients' compliance.

NMDA-Receptor Antagonists

These drugs block excitatory glutamate receptors in the CNS that thought to be responsible for the increased central excitability (central sensitization)

following noxious stimuli. Clinically available substances with NMDA receptor blocking properties include ketamine, dextromethorphan, memantine and amantadine. Typical side effects include sedation, nausea, disagreeable psychological disturbances or even frank hallucinations. Dextromethorphan, memantine and amantadine have fewer side effects.

Studies of small cohorts have generally confirmed the analgesic effects of ketamine in patients suffering from PHN [28]. However, studies with oral NMDA-antagonists formulations (e.g. dextromethorphan) showed positive results in painful diabetic neuropathy but the drug was without beneficial effect in PHN [29, 30].

Topical Medications

Topical Capsaicin: Capsaicin is an agonist of the vanilloid receptor which is present on the sensitive terminals of primary nociceptive afferents. On initial application it has an excitatory action and produces burning pain and hyperalgesia, but with repeated or prolonged application it inactivates the receptive terminals of nociceptors. Therefore, this approach is reasonable for those patients whose pain is maintained by anatomically intact sensitized nociceptors.

Capsaicin extracts are available in a 0.025 and 0.075% preparation. The 0.025 and 0.075% preparations have been reported to reduce the pain of PHN [31, 32]. Capsaicin preparations often produce intolerable burning so that many patients discontinue their use.

Topical Lidocaine: A second topical medication for neuropathic pain are local anesthetics. Local anesthetics block voltage-dependent Na-channels. Although the site of action of membrane-stabilizing drugs for relief of pain has not been proven in patients, *in vitro* studies have shown that ectopic impulses generated by damaged primary afferent nociceptors are abolished by concentrations of local anesthetics much lower than that required for blocking normal axonal conduction.

Controlled studies report pain relief with topically applied special formulations of local anesthetic. Lidocaine patches (5%) were evaluated in several controlled studies [33–35]. Pain relief was statistically significant compared with the control group between 4 and 12 h following application of the patch. Blood levels of lidocaine were at least an order of magnitude below those required for an anti-arrhythmic effect, and therefore there were only minor adverse effects associated with application of the patch itself. Lidocaine patch therapy is a safe and well-tolerated supplemental modality for PHN pain relief.

Intrathecal Administration of Drugs

Intrathecal administration of lidocaine and methyl prednisolone combined appear to be associated with remarkable benefit in PHN patients [36]. However,

the therapy has potentially dangerous side effects and the trial has not yet been replicated. Therefore, it is suggested to wait for further high-quality controlled trials for this therapy before definite recommendations can be made [15].

Stimulation Techniques

Transcutaneous electrical nerve stimulation (TENS) may be effective in some cases and has minimal side effects. It should be avoided to place the electrodes within skin areas with allodynia since pain may be exaggerated. Alternatively the electrodes may be fixed at adjacent dermatomes or even contralaterally.

Invasive stimulation techniques, epidural spinal cord stimulation and deep brain stimulation (sensory thalamus, motor cortex), have been reported to be effective in selected cases of PHN.

Treatment Guideline

In summary, adult vaccination seem to be effective for prevention of shingles and PHN. In acute herpes zoster early antiviral therapy is recommended and immediate pain treatment should be initiated. The following treatment algorithm for PHN (fig. 1) is based on the results of available controlled trials in PHN, several recent meta-analyses of therapy of neuropathic pain and clinical experience (table 1) [14, 15, 17, 37]. The medical management of PHN consists of four main classes of oral medication (serotonin/norepinephrine reuptake blockers, Na-channel-anticonvulsants, Ca-channel-anticonvulsants, opioids) and several categories of topical medications for patients with cutaneous allodynia and hyperalgesia (capsaicin and local anesthetics). However, it should be noted that so far no controlled trials exists for carbamazepine, oxcarbazepine, lamotrigine, duloxetine and venlafaxine and most opioids in PHN (table 1).

Since more than one mechanism of PHN is at work in most patients, a combination of two or more analgesic agents to cover multiple types of mechanisms will generally produce greater pain relief and fewer side effects. Therefore, early combinations of two or three compounds out of different classes may be more appropriate for some patients instead of a stepwise proceeding with a successive monotherapy. This is indicated in the circles in figure 1. Indeed, in a recent controlled four-period crossover trial gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent with constipation, sedation and dry mouth as the most frequent adverse effects [38].

In particular cases intrathecal administration of lidocaine and methyl prednisolone combined or invasive stimulation techniques like epidural spinal cord

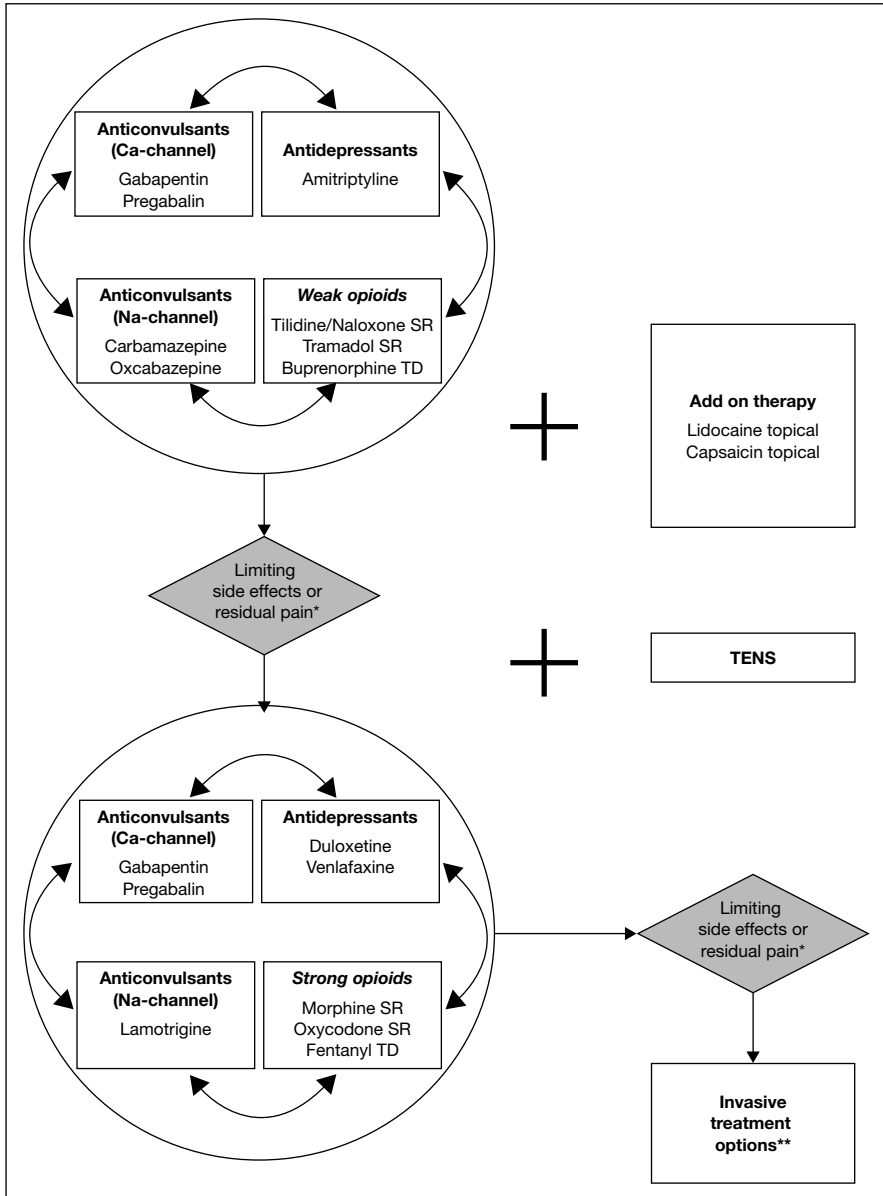


Fig. 1. Algorithm for the treatment of neuropathic pain. An early combination of two or more agents to cover multiple types of mechanisms will generally produce greater pain relief and fewer side effects. This is illustrated in the circles. *Pain level significant and persistent for at least 2–4 weeks. **Spinal cord stimulation, deep brain stimulation or motor cortex stimulation. TENS = transcutaneous electrical nerve stimulation.

Table 1. Pharmacological therapy of postherpetic neuralgia (doses for adults)

Compound	Efficacious dose (maximal dose) [mg/day]	Dose interval	Evidence
Anti-depressants			
Amitriptyline	50–75 (150)	0–0–1	↑↑
Anti-convulsants (Ca-channel)			
Gabapentin	1,200–2,400 (3,600)	1–1–1	↑↑
Pregabalin	150 (600)	1–0–1	↑↑
Long-acting opioids			
Tramadol SR	Titration (600)	1–(1)–1	↑
Morphine SR	Titration no	1–(1)–1	↑
Oxycodone	Titration no	1–(1)–1	↑
Topical therapy			
Capsaicin cream	–	4 × die	↑
Lidocain-patch	–	(3 patches/die) 1 × die	↑↑

Levels of evidence.
↑ = at least 1 RCT; ↑↑ = Several RCT or metaanalyses.

stimulation may be indicated. Transcutaneous electrical nerve stimulation may be effective in some cases and has minimal side effects.

However, beyond these treatment approaches the importance of the biopsychosocial model of chronic pain should be considered by additional management of psychological and social aspects [15, 39].

The treatment of neuropathic pain is currently still unsatisfactory. The hope is that in the future novel drugs will be developed that address specifically the relevant combination of mechanisms in one particular patient leading to an optimal individual polypragmatic therapy [40].

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