Guidelines for General Practitioners on Treatment of Pain in Post-Herpetic Neuralgia

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SCOPE

The aim of this document is to provide guidance for General Practitioners on the drug treatment options for **post-shingles pain**. This is based on a review of the recent literature and tempered by the authors' usual practice.

What is post-herpetic neuralgia (PHN)?

An acute attack of shingles often causes pain. Pain usually ceases when the shingles rash clears up. It may continue after the shingles has resolved and it is then defined as PHN. The condition is common, occurring in half of patients with shingles over the age of 70 and the incidence increases with age[1]

What are the characteristics of pain in PHN?

Pain may be either **constant** or **intermittent** and is typically **burning, stabbing** or **itching** in character and located in the same dermatome distribution as the acute rash. **Allodynia** refers to the precipitation of pain by a non-painful stimulus, such as touch or pressure. It is often a distressing feature of PHN. **Sleep disturbance and clinical depression** are not uncommon.

TREATMENT DURING ACUTE PHASE

Does early treatment of acute shingles prevent post-herpetic neuralgia?

There is good evidence that prompt antiviral treatment can prevent development of PHN and reduce severity when it does occur. Options include aciclovir and the newer antiviral drugs valaciclovir (now a generic medication) and famciclovir. All three are equally effective though the newer agents appear to be better tolerated and have more evidence to support their use: demonstrated benefits include a **reduction in the incidence of PHN at 6 months and a faster resolution of pain symptoms.**

The early use of aciclovir has also been shown to reduce the incidence and severity of PHN[1]. The optimum window seems to be within 72 hours of appearance of the rash[2] but observational studies suggest even treatment outside 3 days may be of benefit[3]. This is particularly so for patients at high risk of morbidity such as those affected by herpes zoster ophthalmicus and HIV[4].

Table 1: Treatments used for prophylaxis of PHN

Drug	Dose regime	Duration of treatment (days)	% PHN at 6 months	Comments
Aciclovir	800 mg 5 times daily	7-10	25.5	Preferably start within 3 days of acute herpes zoster. All well tolerated. Latter two have simpler dosing regimens. Adjust doses if renal compromise.
Valaciclovir	1000 mg 3 times daily	7	19.3	
Famciclovir	500 mg TID	7	N/A	
Amitriptyline	25 mg nocte	90	Prevalence and severity of PHN reduced by 50% compared to placebo[5]	
Corticosteroids	N/A	N/A	N/A	Evidence does not support their use

TREATMENT OF ESTABLISHED PHN

SIMPLE ANALGESICS are unlikely to be effective on their own but may contribute to improved overall analgesia.

- **Paracetamol** (either alone or in combination with **codeine)** is recommended by two sets of guidelines but no evidence exists to support this. It is worth trying but do not expect more than modest benefit in isolation.
- **NSAIDs** have no evidence to support their use.

MAINSTAYS OF THERAPY

For many patients, pain control in PHN will involve the use of **tricyclic antidepressants (TCAs)** and/or **anticonvulsants**. Explain to patients why these apparently inappropriate drugs are being prescribed. Warn patients not to expect pain relief until tissue levels are established i.e. 2 to 3 weeks.

Off label use of a drug (use of a licensed drug for a condition for which it is not licensed) is common for neuropathic pain conditions. Many drugs used in PHN are not licensed for this purpose. This is particularly true for older drugs which were developed for and have licenses in other indications but have also demonstrated benefit in PHN, e.g. amitriptyline and nortriptyline – see next page.

What treatment should I start with?
This will depend on your patient (age, co-morbidity and frailty), phase of illness (acute zoster or established PHN), predominant symptom (allodynia or pain) and local prescribing preference (unlicensed versus licensed drugs).

The algorithm (see Appendix) is adapted from recent review articles[1,6] and based on our usual practice and offers one possible means of selecting therapy.

DRUGS WITH SPECIFIC LICENCE

1. GABAPENTIN

Gabapentin decreased pain and improved sleep in PHN[7]. The British National Formulary suggests gabapentin as an alternative to amitriptyline if the latter is ineffective or not tolerated. It is a reasonable first choice when a TCA is contraindicated.

- Start with a single bedtime dose of 300mg (100mg for frail elderly patients) and escalate as tolerated to a maximum of 3600mg (1200mg TID, or 800mg QID). Avoid abrupt withdrawal. Serious side-effects are rare but sedation, ataxia and weight gain may be treatment-limiting.

2. PREGABALIN

Pregabalin is in the same class of drug as gabapentin and is also effective in relieving pain and improving sleep in PHN[8]. There is no convincing evidence to recommend one over the other in terms of pain relief but pregabalin demonstrates a linear relationship between oral dosing and plasma levels and hence the dose required is not as variable as that of gabapentin. The half life is also longer so BD dosing is effective and compliance should be improved, compared to the more frequent dosing of gabapentin.

The side effect profiles are the same, most commonly they cause sedation and weight gain.

- 75mg 12 hourly is a reasonable starting dose for the average adult and may be increased up to 300mg BD if tolerated and required.

3. CAPSAICIN 0.075%

This topical treatment is licensed for the symptomatic relief of PHN **after lesions have healed[9]**. Two studies have demonstrated benefit over placebo in PHN. The preparation should be applied four times a day. Benefit may be delayed for up to 4 weeks. The commonest side-effect is a burning sensation; patients should be advised that this decreases with continued use, but if it remains problematical, lidocaine 5% ointment applied 10 minutes beforehand can alleviate this. Mixing the capsaicin with GTN paste or EMLA cream has proved useful10.

4. QUTENZA

Qutenza (a capsaicin 8% patch) is licensed for PHN, and is applied to the painful skin area for usually 60 minutes. [A – is this right here?] Transient increase in pain is usually seen within 48 hours of patch application (similar to a "sunburn") before the pain-relieving effect starts, which can last for 3 months. Systemic absorption of the drug is minimal and therefore general side effects are uncommon. [B] Currently the patch is applied by a healthcare professional in a Pain Clinic treatment setting, but because it is a relatively simple procedure, in future it is hoped that it could be used in primary care.

5. PLASTERS - 5% LIDOCAINE

Licensed for use in the UK by the MHRA and now approved by the Scottish Medicines Consortium as third line therapy for PHN, though several guidelines recommend its use earlier. It has to be applied over the painful area, and is used in a 12 hours on, 12 hours off regimen. If tolerated, clinical experience has found that some patients benefit from wearing the plasters 36 hours out of 48, reducing any pain associated with its application/removal.

In our practice, we use the plasters as 1st line where allodynia is prominent and distressing or where patients are particularly sensitive to side effects of systemic pharmacotherapy. In a study on pain resulting from PHN and diabetic neuropathy, the 5% lidocaine plaster had an incidence of drug related adverse events of under 6% (half were skin reactions) versus 42% for pregabalin[11].

DRUGS WITHOUT A SPECIFIC LICENSE

1. AMITRIPTYLINE and NORTRIPTYLINE

These drugs have proven efficacy[12] in reducing PHN as well as valuable additional benefits through their sedative and anxiolytic properties. **One Cochrane review concluded that amongst all antidepressants, TCAs have best evidence of efficacy for neuropathic pain**[13]**.**

While both are effective, nortriptyline seems better tolerated in elderly patients and this may be a reasonable first choice.

- Start with a single nightly dose of 10 mg for elderly (25mg for patients under 50) and titrate upwards in weekly increments of 10mg or 25mg respectively. Maximum benefit seems to require at least 3 weeks of treatment. 30-75mg daily may be effective depending on the patient. Maximum daily dosing is 100mg. If pain is uncontrolled at this level, other therapy is required.

Watch for side-effects such as dry mouth, fatigue, constipation, imbalance and urinary retention. Significant side-effects include cardiac dysrhythmias and hypotension. However, these are often dose-related and less severe when treatment is started at low dose and titrated slowly ("start low and go slow").

2. TRAMADOL

Tramadol is a weak opioid agonist but two thirds of its activity is by inhibition of noradrenaline and serotonin reuptake (similar to amitriptyline), which augments the body's own pain suppression pathway. One study suggests benefit in PHN[14] but the evidence is not strong enough to recommend tramadol as any more than an adjunct to therapy at the present time.

3. STRONG OPIOIDS

There is evidence that use of strong opioids in PHN is beneficial in relieving pain and is well tolerated. One study suggested strong opioids produced comparable pain relief and improvement in sleep compared to TCAs but with an increased risk of moderate or severe side-effects[15].

Clinicians are referred to the British Pain Society Guidelines on the Use of Opioids for Persistent Non-Cancer Pain[16]. In particular, it is important to screen patients for risk of addiction and drug diversion, agree treatment goals, monitor usage regularly and be vigilant for problems. Involvement of clinicians with expertise would be prudent.

DRUG COMBINATIONS

In clinical practice, in resistant cases, drugs with different mechanisms of action are often combined in order to produce an additive or synergistic effect. This has been clearly demonstrated to be beneficial in acute pain, but there is now emerging evidence of benefit in PHN. Drug combinations such as morphine and gabapentin, or oxycontin and gabapentin have demonstrated superior efficacy[17,18].

CHRONIC PAIN CLINICS

These offer additional treatments for PHN which include other more specialised drugs (such as opioids, ketamine, cannabinoids, etc), peri-neural local anaesthetic injections, physiotherapy, TENS and psychological coping strategies.

There is emerging evidence of the benefit of subcutaneous injections of botulinum toxin type A (BOTOX A) for the treatment of PHN. [C] Although its main pain relieving mechanism of action is not yet completely clear, BOTOX A is composed of a protein that blocks the release of several neurotransmitters and thus reduces pain nerve fibre activity. Its main advantage as a choice for chronic pain treatment is its long-duration of action (several months). However, the only pain condition BTX injections are licensed for are chronic migraine, and currently this treatment is only offered for PHN in some specialised pain clinics.

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