Strategies for the Prevention of Postherpetic Neuralgia

( excluding herpes zoster vaccination)

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Dorsal horn atrophy, dorsal root ganglion fibrosis, and loss of epidermal nerve fibers on the affected side in PHN


### Proportion of patients developing PHN: famciclovir vs. placebo

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Days following</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>120</td>
<td>150</td>
</tr>
</tbody>
</table>

**Patients ≥ 18 yrs**

<table>
<thead>
<tr>
<th></th>
<th>Famciclovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41.3</td>
<td>44.1</td>
</tr>
<tr>
<td></td>
<td>38.2</td>
<td>39.5</td>
</tr>
<tr>
<td></td>
<td>27.9*</td>
<td>32.7</td>
</tr>
<tr>
<td></td>
<td>24.6*</td>
<td>29.6</td>
</tr>
</tbody>
</table>

**Patients ≥ 50 yrs**

<table>
<thead>
<tr>
<th></th>
<th>Famciclovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54.6</td>
<td>67.9</td>
</tr>
<tr>
<td></td>
<td>50.1</td>
<td>61.1</td>
</tr>
<tr>
<td></td>
<td>34.9*</td>
<td>49.2</td>
</tr>
<tr>
<td></td>
<td>28.8*</td>
<td>45.8</td>
</tr>
</tbody>
</table>

* denotes p < 0.05, famciclovir 500 mg tid vs. placebo.
Risk factors for PHN

1. Older age
2. More severe acute pain
3. Greater rash severity
7. Presence of a prodrome
8. Female sex
9. Trigeminal distribution
10. Greater sensory abnormalities in the affected dermatome
11. Generalized subclinical polyneuropathy
12. More pronounced immune responses
13. HIV infection, organ transplant, connective tissue disease
14. MRI brainstem and cervical cord abnormalities
15. Viremia
16. CSF interleukin 8 concentration (at rash healing)
17. HLA-A haplotype (*3303-B*4403-DRB1*1302)
18. Fever ≥ 38°C
Greater acute pain is a risk factor for PHN

1. Riopelle et al. 1984 72
2. Harding et al. 1987 71
3. Dworkin et al. 1992 19
4. Leijon et al. 1993 52
5. Cioni et al. 1994 52
6. Beutner et al. 1995 1141
7. Bruxelle 1995 301
9. Whitley et al. 1996 208
10. Wood et al. 1996 316
11. Dworkin et al. 1998 419
12. Meister et al. 1998 635
13. Söltz-Szöts et al. 1998 511
14. Harrison et al. (AIDS) 1999 170
15. Decroix et al. 2000 1897
16. Haanpää et al. 2000 113
17. Tyring et al. 2000 597
18. Zaal et al. 2000 81
19. Scott et al. 2003 165
20. Jung et al. 2004 965

Figure 1. Duration of zoster-associated pain according to pain severity at presentation in trial 5 patients, who were ≥50 (A) or trial 4 patients who were <50 (B) years old. A, For very mild vs. severe pain, hazard ratio (HR) = 3.00 (confidence limit [CI] = 2.26–3.99; *P* = .0001); for mild vs. severe pain, HR = 2.23 (CI = 1.69–2.95; *P* = .0001); for moderate vs. severe pain, HR = 1.58 (CI = 1.21–2.06; *P* = .0007). B, For mild vs. severe pain, HR = 1.69 (CI = 1.34–2.13; *P* = .0001).
If you come to a fork in the road, take it.

— Yogi Berra
Is severe acute pain a *modifiable* risk factor?

YES

Is severe acute pain a *causal* risk factor?

HAS BEEN A REASONABLE HYPOTHESIS, BUT MAYBE NOT...
Original Article

The Effects of Pre-Emptive Treatment of Postherpetic Neuralgia with Amitriptyline: A Randomized, Double-Blind, Placebo-Controlled Trial

David Bowsher, MD, PhD, FRCPed, FRCPath
Pain Research Institute, Walton Hospital, Liverpool, United Kingdom

![Bar chart showing percentage of patients with PHN at 6 months]
Peripheral nerve damage and dysfunction

Preventing PHN by attenuating nerve damage and acute pain in herpes zoster

VZV reactivation

VZV replication

ANTIVIRAL THERAPY

Peripheral nerve damage and dysfunction

Acute neuropathic pain

CENTRAL FUNCTIONAL AND STRUCTURAL CHANGES (E.G., CENTRAL SENSITIZATION, DAMAGE FROM EXCITOTOXICITY)

Acute nociceptive pain

Central functional and structural changes (e.g., central sensitization, damage from excitotoxicity)

Tissue damage and inflammation

PHN

VZV = varicella-zoster virus

A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster


Randomized subjects
(N = 87)

Allocated to CR-oxycodone plus famciclovir
(N = 29)

Discontinuations
(N = 8)
- Adverse events (5)
- Serious adverse event (1)
- Discontinued because of concerns that side effects might develop (1)
- Discontinued by investigator for noncompliance (1)

Completed (N = 21)

Allocated to gabapentin plus famciclovir
(N = 29)

Discontinuations
(N = 5)
- Adverse events (3)
- Serious adverse event (1)
- Discontinued by investigator for misdiagnosis (1)

Completed (N = 24)

Allocated to placebo plus famciclovir
(N = 29)

Discontinuations
(N = 2)
- Serious adverse event (1)
- Discontinued for elective surgery (1)

Completed (N = 27)
<table>
<thead>
<tr>
<th></th>
<th>LS mean difference*</th>
<th>&gt; 30% response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR-oxycodone vs. placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>days 1-8</td>
<td>-1.26</td>
<td>.01</td>
</tr>
<tr>
<td>days 1-14</td>
<td>-1.22</td>
<td>.02</td>
</tr>
<tr>
<td>days 1-28</td>
<td>-.78</td>
<td>.14</td>
</tr>
<tr>
<td><strong>Gabapentin vs. placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>days 1-8</td>
<td>-.75</td>
<td>.13</td>
</tr>
<tr>
<td>days 1-14</td>
<td>-.44</td>
<td>.37</td>
</tr>
<tr>
<td>days 1-28</td>
<td>.00</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

*Least squares mean difference between groups in mean daily diary worst pain. Intention-to-treat analysis with last observation carried forward in patients with at least one post-randomization diary.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Beginning dosage</th>
<th>Titration</th>
<th>Maximum dosage</th>
<th>Most common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Opioids</strong></td>
<td>5 mg every 4 h as needed; dosage can be converted</td>
<td>Increase by 5 mg 4 times daily every 2 days as</td>
<td>No maximum dosage with careful titration; consider evaluation by a pain</td>
<td>Nausea/vomiting, constipation, sedation, dizziness</td>
</tr>
<tr>
<td>or Tramadol</td>
<td>to long-acting opioid analgesic combined with short-acting</td>
<td>tolerated</td>
<td>daily; for patients &gt;75 years of age, 300 mg daily in divided doses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>medication continued as needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 mg once or twice daily</td>
<td>Increase by 50–100 mg daily in divided doses</td>
<td>400 mg daily (100 mg 4 times daily); reduce if renal function is impaired</td>
<td>Sedation, dizziness, peripheral edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>every 2 days as tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Gabapentin</strong></td>
<td>2 mg at bedtime or 100–300 mg 3 times daily</td>
<td>Increase by 100–300 mg 3 times daily every 2</td>
<td>3600 mg daily (1200 mg 3 times daily); reduce if renal function is impaired</td>
<td>Sedation, dizziness, peripheral edema</td>
</tr>
<tr>
<td>or Pregabalin</td>
<td></td>
<td>days as tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 mg at bedtime or 75 mg twice daily</td>
<td>Increase by 75 mg twice daily every 3 days as</td>
<td>600 mg daily (300 mg twice daily); reduce if renal function is impaired</td>
<td>Sedation, dizziness, peripheral edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. TCAs</strong></td>
<td>25 mg at bedtime</td>
<td>Increase by 25 mg daily every 2–3 days as</td>
<td>150 mg daily</td>
<td>Sedation, dry mouth, blurred vision, weight gain, urinary retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>daily for 7 days</td>
<td>After 60 mg daily for 7 days, decrease to 30</td>
<td>60 mg daily</td>
<td>Gastrointestinal distress, nausea, changes in mood, edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg daily for 7 days, then decrease to 15 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>daily for 7 days, and then discontinue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Consider lower starting dosages and slower titration for frail and elderly patients (e.g., 5 mg twice daily for oxycodone); dosages given are for short-acting formulations.

b Consider lower starting dosages and slower titration for frail and elderly patients (e.g., 10 mg at bedtime for tricyclic antidepressants).

^ Consider a screening electrocardiogram for patients >40 years of age.

Preventing PHN by attenuating nerve damage and targeting the TS in zoster

VZV = varicella-zoster virus

BOTTS (blockers of the transition state)

1. Glial cell modulators (PPF, AV-411)
2. GCH1 inhibitors
3. Pain sensitivity
4. Catastrophizing
5. Expectations
Shingles Trial of Oral Medication to Prevent Postherpetic Neuralgia (STOMP-PHN)

- Morphine or matching placebo for 28 days in herpes zoster patients all treated with famciclovir beginning within 5 days of rash onset.
- Primary endpoint: incidence of PHN defined as presence of any pain in the affected dermatome 120 days after rash onset.
- 95% power to detect a reduction in the incidence of PHN from 25% in the placebo group to 12.5% in the morphine group (80% power to detect a reduction of 25% to 15%).
- Requires 250 patients per group, inflated to 300 patients per group to account for the anticipated 16% withdrawal rate.
- Total sample size = 600 patients.
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- Total sample size = 600 patients.
Primary endpoints for PHN prevention RCTs:

1. Any pain 4 (or 6) months after rash onset.
2. Pain intensity (e.g., 0-10 scale) 4 (or 6) months after rash onset.
3. Clinically significant pain (e.g., ≥ 3/10) 4 (or 6) months after rash onset.
4. Time to resolution of any zoster-associated pain (ZAP).
5. Time to resolution of clinically significant ZAP.
6. Area under a pain intensity-by-duration curve.
7. Area under a “truncated” pain intensity-by-duration curve (e.g., Oxman burden of illness).
1. Topical local anesthetics
2. Subcutaneous local anesthetics and corticosteroids
3. Sympathetic blocks
4. Epidural blocks
5. Other invasive interventions
“As most studies were uncontrolled and often of limited size, we cannot conclude that the interventions resulted in a lower incidence of PHN than could be expected from the natural course of pain in HZ.

Moreover, differences in endpoints, PHN definition, and inclusion and exclusion criteria make the results of the studies almost impossible to compare.”

—Opstelten, van Wijck, Stolker, 2004
Optimum Pain Relief With Continuous Epidural Infusion of Local Anesthetics Shortens the Duration of Zoster-Associated Pain

Haruhiko Manabe, MD, * Kenjiro Dan, MD, †‡ Kazuhiko Hirata, MD, † Koichiro Hori, MD, † Shinjiro Shono, MD, † Shinichiro Tateshi, MD, * Hiroyuki Ishino, MD, * and Kazuo Higa, MD †

**FIGURE 1.** Time to resolution of zoster-associated pain for all patients. ZAP, zoster-associated pain; CEI, Continuous Epidural Infusion; IEB, Intermittent Epidural Boluses. *Comparison of effects between 2 groups, using the log-rank test.
The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial


Lancet 2006; 367: 219–24
See Comment page 186
Pain Clinic, Department of Anaesthesiology,
Figure 2: Proportion of patients with pain over time

Table 4. Logistic Regression Models for Presence of Postherpetic Neuralgia (n = 102)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>COEFFICIENT</th>
<th>STANDARD ERROR</th>
<th>P</th>
<th>ODDS RATIO*</th>
<th>95% CONFIDENCE INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster duration</td>
<td>-0.03</td>
<td>0.04</td>
<td>.554</td>
<td>0.98</td>
<td>0.90-1.06</td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>0.02</td>
<td>.115</td>
<td>1.04</td>
<td>0.99-1.08</td>
</tr>
<tr>
<td>Immune status</td>
<td>0.94</td>
<td>0.94</td>
<td>.320</td>
<td>1.39</td>
<td>0.05-3.20</td>
</tr>
<tr>
<td>Prodrome</td>
<td>0.72</td>
<td>0.61</td>
<td>.234</td>
<td>2.05</td>
<td>0.62-6.72</td>
</tr>
<tr>
<td>Physical health</td>
<td>0.15</td>
<td>0.07</td>
<td>.044</td>
<td>1.16</td>
<td>1.01-1.34</td>
</tr>
<tr>
<td>Acute pain intensity</td>
<td>0.24</td>
<td>0.13</td>
<td>.057</td>
<td>1.27</td>
<td>0.99-1.63</td>
</tr>
<tr>
<td>Measures of physical, role, social, and emotional functioning added to initial model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster duration</td>
<td>-0.03</td>
<td>0.05</td>
<td>.550</td>
<td>0.97</td>
<td>0.88-1.07</td>
</tr>
<tr>
<td>Age</td>
<td>0.06</td>
<td>0.03</td>
<td>.016</td>
<td>1.07</td>
<td>1.01-1.12</td>
</tr>
<tr>
<td>Immune status</td>
<td>0.52</td>
<td>1.09</td>
<td>.632</td>
<td>1.59</td>
<td>0.07-5.04</td>
</tr>
<tr>
<td>Prodrome</td>
<td>0.80</td>
<td>0.72</td>
<td>.273</td>
<td>2.21</td>
<td>0.54-9.15</td>
</tr>
<tr>
<td>Physical health</td>
<td>0.10</td>
<td>0.09</td>
<td>.237</td>
<td>1.11</td>
<td>0.93-1.32</td>
</tr>
<tr>
<td>Acute pain intensity</td>
<td>-0.05</td>
<td>0.16</td>
<td>.774</td>
<td>0.95</td>
<td>0.69-1.32</td>
</tr>
<tr>
<td>Role functioning</td>
<td>0.85</td>
<td>0.28</td>
<td>.003</td>
<td>2.34</td>
<td>1.34-4.08</td>
</tr>
<tr>
<td>Personality disorder symptoms</td>
<td>0.09</td>
<td>0.04</td>
<td>.021</td>
<td>1.09</td>
<td>1.01-1.18</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for other terms included in the model, and odds ratios for continuous variables reflect the multiplicative increase in odds for PHN for every one point change in the variable.