Help for Pain:
Treating Post-Herpetic Neuralgia (PHN)

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Help for Pain: Treating Post-Herpetic Neuralgia (PHN)

Accreditation: Pharmacists 798-000-08-048-L01-P
Pharmacy Technicians 798-000-08-042-L01-T
Nurses N-071708-322-L01

Target Audience: Pharmacists & Technicians, nurses & Nurse Practitioneers

Objectives:
• Describe the epidemiology and pathophysiology of post-herpetic neuralgia.
• Describe the pharmacological treatments for PHN to include comparative efficacy, pharmacokinetics and contraindications of agents used for the management of PHN.
• State the role of the pharmacist in providing medication therapy management services to patients with PHN.

Program Overview: This program will educate healthcare professionals on PHN pain treatment principles and current guidelines for use of pain medications so they can more comfortably respond to patients in their roles as pharmacists, techs, and nurses. The program includes information on pharmacologic treatments, patient counseling, and a question/answer period.

CE Credits:
1.0 Credit hour or 0.1 CEU for pharmacists/technicians
1.0 contact hours for nurses/nurse practitioner

Expiration Date: 08/15/2009

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Case of Mrs. Hendrickson

- Flossie Hendrickson is an 88 year old woman admitted to a residential hospice facility, with a terminal diagnosis of end-stage cardiac disease.
- Flossie has a history of three MI’s, the most recent about 2 months ago. She has a very limited prognosis, and significantly diminished functional capability.
- The nurse in charge of the residential facility notices one morning that Flossie has a vesicular rash across her right chest wall.
Case of Mrs. Hendrickson

• The nurse suspects that this is a burn, because Flossie insists the kitchen staff make her coffee extremely hot, then Flossie cuddles her cup against her chest, and falls asleep.

• When the Medical Director visits, the nurse asks that she visit Flossie and confirm the diagnosis of a burn. The nurses asks the Medical Director to have a stern talking-to with Flossie, and the “too hot coffee.”

• On physical exam, the Medical Director disagrees that the lesions are caused by a burn. Upon questioning Flossie, the Medical Director states that she believes Flossie has herpes zoster.
Objectives

1. Describe the physiologic processes, clinical presentation and management strategies of Herpes Zoster.

2. List pharmacologic options for the management of postherpetic neuralgia pain, including mechanism of action and adverse effects.

3. Provide pharmacotherapeutic recommendations for the management of PHN.
Herpes Zoster

• Most prevalent of all neurological diseases
  – 1 million people/year in the US

• Rate of occurrence
  – Occurs in 20-30% of the population at some point in their life
    • 1.2 to 4.8 cases per 1000 persons per year
    • 7.2 to 11.8 cases per thousand persons older than 60 years annually
  – Up to 50% of those living until age 85 years

• Marked increase in incidence with:
  – Aging
  – Drugs and diseases that impair cellular immunity
  – HIV, hematologic malignancies, organ transplants, immune-mediated diseases

Dormant chickenpox can cause shingles

A rash called shingles can attack anyone who has had chickenpox. The virus can lie dormant in the body and resurface years later. Initially causing a burning or tingling sensation on the skin, two to five days after symptoms first appear, a painful rash occurs. The process lasts four to five weeks.

A cluster of tiny bumps transform into blisters

Resembling chickenpox, they fill with pus

The blisters break open then crust over and disappear.

Skin surface

Nerve fiber

Reawakened virus

Dormant virus

A painful condition, post-herpetic neuralgia, caused by nerve damage sometimes occurs and can last years after the rash disappears

N. Rapp, J. O'Connell

SOURCE: Food and Drug Administration

AP
Patient Presentation

- Prodrome – precedes characteristic rash
  - Dermatomal pain
  - Abnormal sensations
  - May be accompanied by fatigue, headache, flu-like symptoms
- Rash usually appears within several days

http://www.medhelp.org/Medical-Dictionary/Terms/2/19687.htm
Schematic demarcation of dermatomes shown as distinct segments. There is actually considerable overlap between any two adjacent dermatomes.

Levels of principal dermatomes

- **C5**: Clavicles
- **C3, 6, 7**: Lateral parts of upper limbs
- **C8, T1**: Medial sides of upper limbs
- **C6**: Thumb
- **C6, 7, 8**: Hand
- **C8**: Ring and little fingers
- **T4**: Level of nipples
- **T10**: Level of umbilicus
- **T12**: Inguinal or groin regions
- **L1, 2, 3, 4**: Anterior and inner surfaces of lower limbs
- **L4, 5, S1**: Foot
- **L4**: Medial side of great toe
- **S1, 2, L5**: Posterior and outer surfaces of lower limbs
- **S1**: Lateral margin of foot and little toe
- **S2, 3, 4**: Perineum
Thoracic T4 Nerve

Flossie’s “burn”
FIGURE 2. Case of herpes zoster ophthalmicus

Photo/MN Oxman, University of California, San Diego

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e0515a1.htm
Acute Pain with HZ

- Pain may be accompanied by itch or other paresthesias or dysesthesias
- Can be described as constant burning, throbbing, intermittent shooting or stabbing, pain from innocuous stimuli (such as touch or clothing; known as “allodynia”)
- Acute pain usually resolves before or shortly after rash healing in most patients
- HZ affects QOL - Performing ALDs
  - Biggest impact seen 3rd to 4th week after rash onset
- Reduced health-related QOL
- Impaired mental and physical health
Treatment Goals in HZ
Therapeutic Interventions

- Immunocompetent patients - reduce pain
- Immunocompromised patients / ophthalmic HZ - Cessation of viral replication
- Non-pcol interventions
- Pharmacologic interventions
  - Antiviral agents, systemic corticosteroids, analgesics

## Treatment of HZ – Antiviral Tx

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Dose and frequency</th>
<th>Treatment Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir (Zovirax)</td>
<td>800 mg five times daily</td>
<td>7-10 days</td>
<td>$29.00</td>
</tr>
<tr>
<td>Famciclovir (Famvir)</td>
<td>500 mg q8h</td>
<td>7 days</td>
<td>$140.00</td>
</tr>
<tr>
<td>Valacyclovir (Valtrex)</td>
<td>1 gram q8h</td>
<td>7 days</td>
<td>$236.00</td>
</tr>
</tbody>
</table>

Other agents include: Corticosteroids, Analgesics, Neural blockade
Three Phases of Pain

1. HZ acute pain
   a. AKA acute herpetic neuralgia
   b. Pain that occurs within 30 days after rash onset

2. Subacute herpetic neuralgia
   a. Pain that persists beyond the acute phase but resolves before PHN is diagnosed

3. PHN
   a. Pain that persists 120 days or more after rash onset
   b. Stimulus-independent continuous pain
   c. Stimulus-independent intermittent pain
   d. Stimulus-evoked pain (brush-evoked dynamic allodynia)
   e. Paresthesias, dysesthesias and itching

Fig. 1: Man with postherpetic neuralgia in the left fifth and sixth thoracic dermatomes. Red lines delineate area of sensory loss, and black dashed lines delineate area of allodynia (touch-evoked pain). Extension of allodynia above and below the originally affected dermatomes is a feature of central sensitization.
Medications for PHN

• Approved for PHN
  – Gabapentin / Pregabalin
  – Transdermal lidocaine

• Systemic Agents
  – Tricyclic Antidepressants
  – Antiepileptic Drugs
  – Tramadol
  – Opioids
Antidepressants - TCAs

• Used to be considered first line gold standard for neuropathic pain
• Dose is 30-50% of antidepressant dose
• Tertiary amines (amitriptyline, imipramine, doxepin, clomipramine, trimipramine)
  – Inhibit reuptake of serotonin and norepinephrine
• Secondary amines (desipramine, nortriptyline, amoxapine, protriptyline)
  – Somewhat more selective at inhibiting reuptake of norepinephrine
  – Local anesthetic-like sodium channel blockade
Tricyclic Antidepressants

- Used to treat a variety of neuropathic pain states
- Meta-analysis of 4 RCT in PHN
  - Amitriptyline, nortriptyline, desipramine
  - Showed a number needed to treat (NNT) of 2.6
- Most data with amitriptyline
- Likely equal efficacy among TCAs
Tricyclic Antidepressants

- Amitriptyline (Elavil)
  - MOST anticholinergic adverse effects
    - Blurred vision
    - Urinary retention
    - Dry mouth
    - Constipation
    - Cognitive impairment
  - Orthostatic hypotension
  - Sedation
- Nortriptyline, despiramine
Tricyclic Antidepressants

• Use with caution in:
  – Cardiovascular disease
    • Screening EKG when beginning TCA after age 40 in non-EOL population
  – Glaucoma
  – Urinary retention
  – Autonomic neuropathy
  – Risk of suicide or accidental death from OD

Orthostatic hypotension, tachycardia, nonspecific EKG changes, changes in AV conduction, MI/CVA, heart block, arrhythmia, syncope, hypertension, palpitations
Tricyclic Antidepressants

- Analgesic effect independent of antidepressant effect
- Start TCA dose low – 10-25 mg qhs
- Increase every 3-7 days by 10-25 mg/day as tolerated
- Dose to 75-150 mg qd as tolerated
  - Blood level of about 100 ng/ml
- Adequate trial is 6-8 weeks with 1-2 weeks at maximally tolerated dosage
Antiepileptic Agents

• Used to treat a variety of neuropathic pains including PHN
• Gabapentin (Neurontin) and pregabalin (Lyrica)
• Mechanism of action
  – Believed to act at the $\alpha_2 \delta$ -1 subunit of voltage-dependent calcium channels to decrease calcium influx
  – This in turn inhibits the release of neurotransmitters such as glutamate from the central terminals of primary afferent fibers in the spinal cord
Antiepileptic Agents

Gabapentin Clinical Trials

- Gabapentin (up to 3600 mg/day) vs. placebo over a 4-week titration period in 229 patients with PHN
  - Gabapentin – pain score from 6.3 to 4.2
  - Placebo from 6.5 to 6.0
  - Gabapentin patients had more adverse effects

- 334 patients with PHN, gabapentin (1800 or 2400 mg/day) had a significantly greater improvement in pain scores from week 1 than those receiving placebo
  - Most common AE were dizziness and somnolence

Rowbotham MC et al. JAMA 1998; 280:1837-1842
Antiepileptic Agents

Gabapentin Clinical Trials

• Research suggests gabapentin dose should be titrated as quickly as possible to 1800 mg per day; some patients require up to 3600 mg

• Gabapentin plus an opioid may be preferred therapy
  – Lower doses of each
  – Fewer adverse effects with combination regimen

• Dose adjust in renal impairment
Antiepileptic Agents
Pregabalin Clinical Trials

• Similar mechanism of action to gabapentin
• RCT – pregabalin at 150 to 600 mg/day provided superior pain relief to placebo
  – Improved pain-related sleep interference in 3 double-blinded RCT in 776 patients with PHN
• Similar adverse effects
  – Dizziness, somnolence, peripheral edema
• Dose adjust in renal impairment

Frampton JE et al. Drugs 2005;65:111-118
Tramadol

- A norepinephrine and serotonin reuptake inhibitor with a major metabolite that is a mu opioid agonist.
- Evaluated in PHN and polyneuropathy from various causes (including PDM)
  - Effective when titrated to 400 mg/day
  - Effective vs. allodynia and improves QOL
- Adverse effects include:
  - Dizziness, nausea, constipation, somnolence, orthostatic hypotension
  - Occur more frequently with rapid dosage escalation and concurrent administration of medications with similar adverse effects
  - Increased risk of seizures in patients with history, or drugs that lower seizure threshold
Tramadol

- **Tramadol vs. placebo for PHN**
  - 127 patients with PHN
  - 6 weeks tramadol SR (100-400 mg/day)
    - Average dose was 275 mg
  - Reduced in pain and improved QOL
  - NNT was 4.8

- **Serotonin syndrome**

- **Older adults**

- **Adjust in renal/hepatic dysfunction**

- **Start with 50 mg once or twice daily; increase every 3-7 days**

- **Maximum dose 400 mg qd (300 mg qd older adults)**

Opioid Analgesics

- Role in neuropathic pain (PHN) debated
- Efficacy shown to be equivalent to TCAs and better than antiepileptics
  - Concerns include side effects, misuse and abuse
  - Tolerance
- Concerns have relegated opioids to second line status
- Cochrane Review - 23 trials met inclusion criteria for short-term therapy (< 24 hours) or intermediate-term (median 28 days)
- Short-term trials had contradictory results
- All intermediate trials demonstrated opioid efficacy for spontaneous neuropathic pain

Opioids for PHN

• Oral oxycodone PHN evaluated in a RCT
  – Placebo vs. oxycodone SR
  – Oxycodone SR group had a significant reduction in allodynia, steady pain, and paroxysmal spontaneous pain
  – Provided greater pain relief
  – Superior scores for global effectiveness, disability and masked patient preference vs. placebo

Opioids in PHN

• Opioids may be part of a comprehensive plan to treat PHN
  – Pain that is moderate to severe
  – Significant impact on QOL or function
• Consider abuse and diversion issues
• Prudent practice
• Consider adverse effects
Topical Local Anesthetics

• Local anesthetic – topical adhesive patch with 5% lidocaine
  – Treats neuropathic pain caused by accumulation of neuronal-specific sodium channels

• RCT of 5% lidocaine vs placebo for PHN
  – Preference was for patch 78.1% vs. 9.4%
  – No difference in adverse effects

• Two open-label trials showed 5% lidocaine patch reduced intensity of mod-to-severe PHN pain and improved QOL

Davies PS et al. Drugs 2004;64:937-947
Galer BS et al. Pain 1999;80:533-538
Topical Local Anesthetics

• Clinical trials suggest patient with PHN and allodynia will benefit from 5% lidocaine patch with minimal absorption and few AE
  – Mild skin irritation at site of application
• Apply to intact skin
• FDA approved labeling is 12 hours, 12 hours off

*NNH for major harm could not be calculated from available data.
Other agents

- Topical capsaicin
- NMDA receptor antagonists
  - Dextromethorphan, ketamine
- SNRI’s
  - Venlafaxine, duloxetine
- Other anticonvulsants
  - Carbamazepine, phenytoin, valproic acid
- Combination therapies
- Psychological interventions
- Interventional strategies
Treatment of neuropathic pain in primary care

Consider nonpharmacologic treatments (e.g., physiotherapy, psychological interventions) and, in some cases, early referral for nerve blocks to facilitate rehabilitation (e.g., complex regional pain syndrome).

If postherpetic neuralgia or focal neuropathy, initiate topical lidocaine treatment.

Ineffective, partial response or other diagnosis

Initiate first-line drug monotherapy (gabapentin or pregabalin OR tricyclic antidepressant [TCA] or serotonin-norepinephrine reuptake inhibitor [SNRI]).
Initiate first-line drug monotherapy (gabapentin or pregabalin OR tricyclic antidepressant [TCA] or serotonin-norepinephrine reuptake inhibitor [SNRI]).

If ineffective or not tolerated:
- Switch to alternate first-line drug monotherapy (TCA or SNRI OR gabapentin or pregabalin).
  - If ineffective or not tolerated, initiate monotherapy with tramadol or opioid analgesic.
  - If ineffective or not tolerated, refer patient to pain specialty clinic for consideration of third-line drugs, interventional treatments and pain rehabilitation programs.

If partial treatment response:
- Consider adding alternate first-line drug (TCA or SNRI OR gabapentin or pregabalin).
  - If partial treatment response, consider adding tramadol or opioid analgesic.
A Vaccination Reduces Incidence of Herpes Zoster

![Graph showing the reduction in cumulative incidence of herpes zoster with vaccination compared to placebo over 5 years of follow-up. The graph indicates a statistically significant difference (P<.001).]

B Vaccination Reduces Incidence of PHN

![Graph showing the reduction in cumulative incidence of postherpetic neuralgia (PHN) with vaccination compared to placebo over 5 years of follow-up. The graph indicates a statistically significant difference (P<.001).]
HZ Vaccine

• Indication – Individuals $\geq$ 60 years old
• Contraindicated in immunocompromised patients, children, pregnant women
• What is the duration of protection provided by the HZV?
• What is the utility of the HZV in patients < 60 years old?
• Does the HZV have benefits in patients who have already had HZ?
• Can HZV be used in patients with an unknown chickenpox history?
• Can the HZV be given concurrently with other vaccines?
• How do we define “immunocompromised” patients in whom HVZ is contraindicated?
• Can an adult receive the HZV is there is an immunocompromized VZV-seronegative individual living in the same household?

Gnann JW. J Pain 2008;S1:S31-36
Questions?