Understanding and Treating Post-Herpetic Neuralgia (PHN)

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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

- Describe epidemiology and etiology of PHN in the United States.
- Identify the pharmacological treatment options for patients suffering from PHN, to include their mechanisms of action, efficacy, safety, and tolerability profiles.
- Outline the pharmacist’s role in counseling and educating patients on drug treatment strategies for 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

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

Thoracic T4 Nerve

Flossie’s “burn”

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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>
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<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>
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<tr>
<td>Famciclovir (Famvir)</td>
<td>500 mg q8h</td>
<td>7 days</td>
<td>$140.00</td>
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<tr>
<td>Valacyclovir (Valtrex)</td>
<td>1 gram q8h</td>
<td>7 days</td>
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</tbody>
</table>

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

**HZ acute pain**
- AKA acute herpetic neuralgia
- Pain that occurs within 30 days after rash onset

**Subacute herpetic neuralgia**
- Pain that persists beyond the acute phase but resolves before PHN is diagnosed

**PHN**
- Pain that persists 120 days or more after rash onset
- Stimulus-independent continuous pain
- Stimulus-independent intermittent pain
- Stimulus-evoked pain (brush-evoked dynamic allodynia)
- Paresthesias, dysesthesias and itching


**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, desipramine

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

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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 α,δ-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

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

Rowbotham MC et al. JAMA 1998; 280:1837-1842
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 JL 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 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 placebos 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 J Pain 1999;0:0;113-136
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

Other agents

- Topical capsicain
- NMDA receptor antagonists
  - Dextromethorphan, ketamine
- SNRI’s
  - Venlafaxine, duloxetine
- Other anticonvulsants
  - Carbamazepine, phenytoin, valproic acid
- Combination therapies
- Psychological interventions
- Interventional strategies
Understanding and Treating Post-Herpetic Neuralgia

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]).

- Partial treatment response.

- Consider adding alternate first-line drug (TCA or SNRI or gabapentin or pregabalin).

- Refer patient to pain specialty clinic for consideration of third-line drugs, interventional treatments and pain rehabilitation programs.

HZ Vaccine

- Indication – Individuals > 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 “immunocompromized” patients in whom HZV is contraindicated?
- Can an adult receive the HZV if there is an immunocompromized VZV-seronegative individual living in the same household?
The Role of the Pharmacist

• Be knowledgeable about the risk factors for HZ
• Recognize the prodromal state
• Educate the patient on treatment goals
• Appropriately recommend antiviral agents
• Recognize PHN, recommend drug therapy, monitor/adjust therapy