Help for the Pain:
Treating Post-Herpetic Neuralgia

Ronnie DePue, R.Ph., CGP
Educational Objectives:

1. Describe the epidemiology and pathophysiology of post-herpetic neuralgia (PHN).

2. Describe the pharmacological treatments for PHN to include comparative efficacy, pharmacokinetics and contraindications of agents used for the management of PHN.

3. State the role of the pharmacist in providing medication therapy management services to patients with PHN.
Post-Herpetic Neuralgia

Definition:

Nerve pain that persists well after the rash associated with a Herpes zoster episode (Shingles) is resolved. This is generally recognized as at least 1-3 months.
Epidemiology

- Each year approximately 1,000,000 people in the U.S. develop shingles or herpes zoster. Of these, it is estimated approximately 10-20% will go on to develop PHN.

- The most established risk factor is age; this complication occurs nearly 15 times more often in patients more than 50 years of age.
Epidemiology

- It is estimated that at least 40% of all herpes zoster patients over age 50 and 75% of herpes zoster patients over age 75 will be affected by PHN\(^1\).

- The frequency 1 month after onset of shingles is 9-14.3%; at 3 months, about 5%; at 1 year, 3% continue to have severe pain\(^2\).

- PHN is the single most common neurologic condition in elderly patients\(^1\).
Pathophysiology

- Herpes zoster (HZ) is a viral infection that usually presents as a childhood infection of varicella (Chickenpox)
- Following the acute phase, the virus enters part of the sensory nervous system, dorsal root ganglia, where it lies dormant for decades
Pathophysiology

- Reactivation of the virus occurs following a decrease in virus-specific cell-mediated immunity
- Factors such as age, illness, stress or medications can cause reactivation the virus
Pathophysiology

- Once reactivated, the virus travels down the sensory nerves and is the cause of skin rash and lesions.

- It is hypothesized that damage done to the sensory nerve tracts by the virus is the cause of PHN.

- Although PHN is not fatal, patients may experience significant pain for a prolonged period of time.
The symptoms of postherpetic neuralgia are generally limited to the areas of outbreak. These symptoms include:

- Sharp and jabbing, burning, or deep and aching pain
- Extreme sensitivity to touch and temperature change
- Itching and numbness
Pharmacological Treatments

- FDA Approved for PHN
  - Lidocaine 5% Topical Patches
  - Gabapentin
  - Pregabalin

- Other Treatments
  - Antidepressants
  - NSAIDs
  - Opioid analgesics
Lidocaine 5% Topical Patches

- Lidocaine is an amide-type local anesthetic.
- It is believed to exert its pharmacological effect in PHN by stabilizing neuronal membranes through inhibition of ionic fluxes required for the initiation and conduction of impulses\textsuperscript{3}. 
Lidocaine 5% Topical Patches

- Lidocaine Patch is applied directly to the painful area. The lidocaine penetrates just enough to soothe the damaged nerves and exert its pharmacologic effect without significantly entering the bloodstream.
- Patch provides a physical barrier.
Absorption – minimal when dosed as directed

Distribution – At the low concentrations absorbed by the patch, it is 70% protein bound

Metabolism – Liver

Excretion – Kidney
Lidocaine 5% Topical Patches

- Should be applied to intact skin only with no blisters
- Lidocaine patches should be worn for no more than 12 hours in any 24 hour period. Applying the patches for a longer time or using more than 3 patches could cause increased absorption and potential adverse events
Lidocaine 5% Topical Patches

- Lidocaine toxicity will occur at blood levels above 5mcg/ml
- Average peak blood concentration when used as directed 0.13mcg/ml
- Potential dose related adverse events:
  - CNS excitation
  - CNS depression
  - Cardiac manifestations
Lidocaine 5% Topical Patches

- Contraindications
  - Contraindicated in those with allergies to amide type anesthetics
  - Should be used with caution in those with severe liver impairment and those taking class I antiarrhythmic medications (tocainide and mexiletine)
Lidocaine 5% Topical Patches

- Efficacy
  - In a pilot study, the lidocaine patch was effective in 81% of patients with various refractory neuropathic pain syndromes\(^4\)
  - Single-dose treatment of lidocaine 5% patches was compared to treatment with vehicle patch and no treatment in a double-blind, crossover clinical trial. The lidocaine patches performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours.
Gabapentin

- The mechanism by which gabapentin exerts its analgesic effects is unknown
- Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) although it does not modify GABA binding, is not converted to a GABA agonist and is not an inhibitor of GABA uptake or degradation
- The pharmacologic action is due to the activity of the parent compound
Gabapentin

- **Absorption** – Bioavailability decreases as dose increases. Food has minimal effect on absorption (increase)
- **Distribution** – Less than 3% protein bound
- **Metabolism** – Not appreciably metabolized in humans
- **Excretion** – Renal excretion as unchanged drug. Dosage adjustment required in patients with compromised renal function
Gabapentin

- Adverse events/precautions
  - Dizziness
  - Somnolence
  - CNS depression
  - Increased gabapentin levels when administered with morphine (up to 44%)
  - 20% decrease in bioavailability when administered with antacids
Efficacy

In a multicenter, double-blind study, patients received either gabapentin (n=109) titrated over 4 weeks to the maximum tolerable dose (maximum dose 3600 milligrams/day) or placebo (n=116). After 8 weeks, the average pain score (11-point Likert scale) was significantly decreased in the gabapentin group (33.3%) versus placebo (7.7%; p less than 0.001)\(^5\)

At the end of the study, 43.2% of patients treated with gabapentin categorized their pain as much or moderately improved versus only 12.1% of the placebo group.
Pregabalin

- CV controlled substance
- GABA analogue
- Shown greater potency than gabapentin in pain
- Binding of pregabalin to the alpha-2-delta subunit of voltage-sensitive calcium channels appears to be involved in the mechanism of action of the drug in neuropathic pain.
Pregabalin

- **Absorption** – Bioavailability is ≥ 90% and is independent of dose. Food has no effect on the total absorption.
- **Distribution** - Not bound to plasma proteins
- **Metabolism** – Negligible
- **Excretion** – 90% of administered dose excreted as unchanged pregabalin in the urine
Pregabalin

- Adverse events/precautions
  - Angioedema – Post marketing reports
    - Swelling of the face, mouth (tongue, lips and gums), and neck
  - Peripheral edema
  - Dizziness
  - Somnolence
  - Weight gain
Pregabalin

- **Efficacy**
  - In a 13-week, double-blind, randomized, placebo-controlled, parallel-group trial (n=368), pregabalin was superior to placebo in improving the endpoint mean pain score among patients with postherpetic neuralgia.
  - Patients treated with pregabalin experienced statistically significant improvement in mean pain scores at study end (primary endpoint) and pain-related sleep interference scores relative to placebo.
Pregabalin

- Efficacy
  - Pregabalin reduced pain and improved sleep in patients with postherpetic neuralgia in a multicenter, parallel-group, double-blind, placebo-controlled study
  - Patients (n=173) were randomized to pregabalin 600 or 300 milligrams/day or placebo for 8 weeks
  - Superior pain relief was found with pregabalin on the second day of the trial and the relief continued to be significant throughout all 8 weeks of the trial.
  - Pain reductions of 30% or more were reported in 63% and 25% of patients treated with pregabalin and placebo, respectively (p=0.001)\(^7\).
Other Agents

- Antidepressants
  - TCAs – ex. Amitriptyline
  - Used for various neuropathies
  - None are FDA approved for PHN
  - Works through inhibition of the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons
Other Agents

- Antidepressants (cont)
  - Side effects of TCAs
    - Dry mouth
    - Dry eyes
    - Constipation
    - Urinary retention
    - Orthostatic hypotension
    - Cardiac effects
Other Agents

- NSAIDs
  - Diclofenac, Indomethacin, Ibuprofen etc
  - None are FDA approved for PHN
  - Work through inhibition of cyclooxygenase activity, which causes a reduction in the formation of prostaglandin, prostacyclin and thromboxane, all of which are mediators of inflammation
Other Agents

- NSAIDs (cont)
  - Have not been shown to be an effective treatment for PHN pain
- Side Effects
  - GI Toxicity
  - Renal toxicity
  - Hepatotoxicity
  - Fluid retention
  - Increased BP
Other Agents

- Opioid Analgesics
  - Codeine, Morphine, Oxycodone, Hydrocodone etc
  - None are FDA approved for PHN
  - Bind to opioid receptors in the CNS and mimic the actions of enkephalins and endorphins which alters the rate of release of neurotransmitters.
Other Agents

- Opioid analgesics
  - In general effective analgesics, but many with neuropathic pain do not respond well
- Side Effects
  - Drowsiness
  - Sedation
  - Constipation
  - Addiction potential
Medication Therapy Management

- Pharmacist serves a resource for the patient
- Liaison between patient and physician
- Improve outcomes through integration of total Prescription and over-the-counter medication management across potentially multiple prescribers
Medication Therapy Management

- Full profile review
  - Look for:
    - Drug-Drug interactions
    - Therapeutic duplications
    - Early refills on opioids
    - NSAID use
    - Appropriate medication doses
Medication Therapy Management

- Counseling opportunities
  - Proper use of lidocaine patches
    - Wash hands after use, do not leave on more than 12 hours in a 24 hour period, do not apply more than 3 patches at a time
  - Gabapentin
    - Dizziness, Somnolence, CNS depression
    - Separate antacids and gabapentin by at least 2 hours
Medication Therapy Management

- Counseling opportunities
  - Pregabalin
    - Inform patient on the signs and symptoms of angioedema
    - Peripheral edema, dizziness, somnolence
Questions?


3. LIDODERM (Lidocaine Patch 5%) Prescribing Information. ENDO Pharmaceuticals, Chadds Ford, PA.

