Poll

• Do patients ever come to you complaining of intense burning or sharp pains in their feet?
Program Overview:

- This program focuses on information to help pharmacists advise patients on DPN.
- We give you valuable information on current methods of treatment and how these impact DPN.
- Special emphasis is placed on improving outcomes and giving you the knowledge to advise patients and other diabetes medical professionals on proper therapy choices and reasons for medication selection.

Objectives

At the end of this program the pharmacist should be able to discuss:

- The Neural Systems and how Neurotransmitters work
- The difference between Nociceptive and Neuropathic Pain
- Signs and symptoms of Diabetic Peripheral Neuropathy (DPN)
- Medical Management of DPN
- Advantage of newer medications for DPN
- Dosing recommendations, and Patient Safety Issues.

The Nervous System
Neurons – Functional Systems

- Sensory or Afferent
  - Collect info from organs or perception
  - Sends info to the brain
- Motor or Efferent
  - Carry the signal from the brain and spinal cord
  - Signal carries to the muscles, glands, blood vessels, organs

Neurotransmitters

- Acetylcholine
  - Transmits impulses that signal muscles to contract
  - Major Excitatory NT
- Glutamate
  - Major Inhibitory NT
  - GABA and Glycine

Neurotransmission

1. When an action potential is generated, it causes the calcium channels on the presynaptic axon terminal to open and calcium ions to flow into the presynaptic axon terminal.
2. The influx of calcium into the axon terminal causes the vesicles to release neurotransmitters.
3. Once released, the neurotransmitters act on the postsynaptic cell and bind to the receptors on the postsynaptic cell.
4. This causes the ion channels on the presynaptic cell to open, and ions to enter the postsynaptic cell. As a result, the cell is either activated to propagate the signal or inhibited to do so.
Nociceptive vs Neuropathic Pain States

- **Nociceptive**
  - Pain that arises from a stimulus that is outside of the nervous system
  - Proportionate to the stimulation of the receptor
  - When acute serves a protective function

- **Neuropathic**
  - Pain initiated or caused by a primary lesion or dysfunction in the nervous system
  - No nociceptive stimulation required
  - Disproportionate to the stimulation of receptor
  - Other evidence of nerve damage

Poll – True or False?

• An example of nociceptive pain would be arthritis.

Examples of Nociceptive and Neuropathic Pain

- **Nociceptive Pain**
  - Caused by activity in neural pathways in response to potentially tissue-damaging stimuli
  - Examples: Arthritis, Mechanical low back pain, Sports/exercise injuries, Sickle cell crisis

- **Mixed Type**
  - Caused by a combination of both primary injury and secondary effects
  - Examples: Postoperative pain, Central post-stroke pain

- **Neuropathic Pain**
  - Initiated or caused by a primary lesion or dysfunction in the nervous system
  - Examples: Postherpetic neuralgia (PHN), Trigeminal neuralgia, Diabetic neuropathy (PN), CRPS* (Complex regional pain syndrome)
Stimulus-Evoked Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allodynia</td>
<td>Painful response to a non-painful stimulus</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>Heightened response to a painful stimulus</td>
</tr>
<tr>
<td>Hyperpathia</td>
<td>Delayed, explosive pain to a painful stimulus</td>
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</tbody>
</table>

Mechanisms – Neuropathic Pain

- Ectopic impulse generation
  - Spontaneous neuronal firing
  - Common mechanism for DPN
- Peripheral/central sensitization
  - Lowers activation thresholds of nociceptors and increases firing rates
- Sympathetically maintained pain
  - Nerves release NE which stimulates C nerve fibers which are responsible for nociceptive input

Diabetic Peripheral Neuropathy (DPN): What Is It?

- Nerve damage and dysfunction secondary to diabetes mellitus type I or II
  - Consensus definition: “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes”
- A very common complication of diabetes
- A leading cause of neuropathic pain

Diabetic Peripheral Neuropathy

Distal Symmetric Polyneuropathy

• Most common form of DPN
• Gradual onset
• "glove-stocking" distribution
• Acute or chronic

Open-Ended Question

Please use the chat window to respond.

• What do you recommend OTC for your patients who complain of neuropathy?
• Treatment of DPN: Satisfaction with Medication is Inadequate

Patient Satisfaction With Prescription Medications

Few patients (22.3%) were extremely or very satisfied with their prescription medications.


• Management of Neuropathic Pain Associated With DPN and PHN

Belgrade MJ. Postgrad Med 1999;105:127-140
Orza et al. NeuroRehabilitation 2000;14:15-23
Ashburn and Staats. Lancet 1999;353:1865-1869

Poll

• Do you recommend prescription therapy for DPN to your patients who ask?
Management of Neuropathic Pain Associated With DPN and PHN

- Gabapentin 46.6%
- Opioids 19.8%
- TCAs 12.9%
- Cymbalta 3.9%
- Topamax 1.6%
- NSAIDs 1.3%
- Carbamazepine 1.2%
- Other AEDs 1.0%
- All Others 11.7%

Clinical Management - Anticonvulsants

- Mechanisms of Action
  - Block / modulate sodium, calcium channels
  - Decrease action potential frequency
  - Decrease excitation or decrease NT release
  - Increase GABA-ergic transmission
  - Increase inhibition
  - Decrease Glutamatergic transmission
  - Decrease excitation

Clinical Management – Anticonvulsant agents

- First generation
  - Carbamazepine
  - Phenytoin
  - Valproate

- Second generation
  - Gabapentin* (Neurontin)
  - Lamotrigine (Lamictal)
  - Topiramate (Topamax)
  - Pregabalin* (Lyrica)
Clinical Management - Anticonvulsant agents

- Gabapentin, Pregabalin
  - Modulate the release of excitatory neurotransmitters from the presynaptic cell
  - MORE ON THIS LATER!

Pharmacological Options: First-generation Anticonvulsants

- Phenytoin
  - Mechanism unclear; may stabilize sodium channels
  - Effectiveness less clear than with carbamazepine
  - May be limited by adverse effects and drug interactions
- Valproate
  - Increases CNS GABA concentrations
  - Limited evidence of efficacy in DPN
  - Generally well tolerated
- Carbamazepine
  - Inhibits sodium channels
  - Inhibits calcium channels
  - Blocks NMDA glutamate receptors
  - Increases extracellular serotonin levels

Carbamazepine: Efficacy

- Indicated for trigeminal neuralgia
- Significant pain relief compared with placebo shown in DPN trials
  - 4-week double blind cross-over (N=40)
  - 6-week double blind cross-over (N=30)

Safety and Tolerability

Black box warning for aplastic anemia and agranulocytosis
- Rare hypersensitivity reactions
- Hyponatremia
- Most frequent adverse events
  - Dizziness
  - Drowsiness
  - Unsteadiness
  - Nausea/Vomiting

References:
Carbamazepine: Dosing Recommendations

- Beginning dosage: 200 mg/d (2 divided doses)
- Titration: 100-mg increments every 12 hours
- Maximum dosage: 1200 mg/d

Pharmacological Options: Second Generation Anticonvulsants

- Lamotrigine
  - Interacts with sodium channels and inhibits glutamate release
  - Limited evidence of efficacy in DPN and PHN
  - Published data in other neuropathic pain states (i.e., HIV and trigeminal neuralgia)
- Gabapentin
  - α2δ ligand
  - FDA-approved for postherpetic neuralgia
  - Evidence for efficacy in DPN
  - Generally well tolerated
- Topiramate
  - Small study suggested efficacy

Clinical Management - Antidepressants

- Tricyclic Antidepressants
  - Block reuptake of NE, serotonin at presynaptic neurons
  - Block postsynaptic receptors
  - Thought to enhance the descending inhibitory pathway, and decrease pain signaling
  - Analgesic effects are independent of antidepressant effects
  - Low dose
**TCAs: Efficacy**

- Meta-analysis of 13 studies of TCAs across pain conditions
- Number needed to treat (NNT) for 50% pain relief: 2.9 (95% CI, 2.4-3.7)
  - Imipramine (4 reports): NNT=3.7 (2.3-9.5)
  - Desipramine (2 reports): NNT=3.2 (1.9-9.7)
- Analysis of DPN trials only: NNT=3.4 (2.6-4.7)
- Analysis of PHN trials only: NNT=2.1 (1.7-3.0)


**TCAs: Mechanism of Action**

- Block reuptake of noradrenaline and serotonin by presynaptic neurons
  - Raises synaptic neurotransmitter concentrations
- Analgesic effects independent of antidepressive effects
  - Analgesia usually occurs at a lower dose
- Inhibition of noradrenaline and serotonin reuptake is thought to enhance the descending inhibitory pathway


**TCAs: Safety and Tolerability**

- Up to 5% of patients experience significant adverse effects of TCAs
- Anticholinergic effects
  - Blurred vision
  - Dry mouth
  - Sinus tachycardia
  - Constipation
  - Urinary retention
  - Confusion/memory impairment
- Sedation, potentiation of CNS depressants
- Orthostatic hypotension, dizziness
- Hypotension
- Weight gain
- Reflex tachycardia

TCAs: Dosing Recommendations

- **Beginning dosage:** 10-25 mg every night
- **Titration:** increase by 10-25 mg/d every 3-7 days as tolerated
- **Maximum dosage:** 75-150 mg/d
- **Duration of adequate trial:** 6-8 wk with at least 1-2 wk at maximum tolerated dosage


Clinical Management - Antidepressants

**SNRIs**
- Venlafaxine (Effexor XR)
- Duloxetine* (Cymbalta)
- Specifically inhibit norepinephrine reuptake

**SSRIs**
- Sertraline (Zoloft)
- Fluoxetine (Prozac)
- Paroxetine (Paxil)
- Specifically inhibit serotonin reuptake

Poll

- Do you feel that clinicians are more likely to accept your recommendation for a topical product than for an oral medication?
Clinical Management - Topicals

- **Capsaicin**
  - OTC, PHN/DPN labeling
  - Depletes substance P from the peripheral nerve endings
  - Takes time for optimal response

- **Lidocaine Patch**
  - Blocks the movement of Na across neuronal cell membranes
  - Prevents the APs from being transmitted
  - Can be worn up to 12 hours a day

Local and Regional Treatment Measures

- **Lidocaine patch**
  - Indicated for PHN
  - Favorable side effect profile
  - Suggested efficacy in pilot studies in DPN have not been confirmed in controlled trials
  - Limitations
    - Topical route of administration
    - Application of the patch is painful

- **Capsaicin**
  - One study found effective pain relief compared with amitriptyline
  - Other studies have given mixed results

Pharmacological Options: Other Agents

- **Opioids**
- **NSAIDs**
- **Tramadol**
- **Baclofen**
  - Anecdotal reports suggest some benefit
- **Antiarrhythmics**
  - Mexiletine effective in some but not all trials

References:
**Opioids: Mechanism of Action**

- Bind to opioid receptors
  - G-protein linked cell signaling molecules
  - Endogenous ligands are the enkephalins, endorphins, and dynorphins
  - Physiological role not completely understood
- Opioid analgesia produced at the spinal and supraspinal levels
- Enhance activity of the descending pain modulation pathway


**Opioids: Efficacy**

- Efficacy in neuropathic pain remains controversial
- Some opioids have shown benefit in PHN

**Opioids: Dosing Recommendations**

- Extended-release opioids should be given by the clock, not on an as-needed basis
- Initiate at a low dosage
- Titrate based on response
- Maximum dosage based on adequate pain relief and tolerability

**Mechanisms of Action – AEDs**

*Multiple and overlapping Mechanisms*

- Block Na channels
  - Decreases frequency of the AP

- Block Ca channels
  - Decrease excitation, release of excitatory NTs

- Attenuation of Ca influx into Presyn. Terminal
  - Reduction of Ca influx decreases the release of excitatory NTs
  - Decrease # of APs

**Mechanisms of Action – AEDs**

*Decrease Glutamatergic Transmission*

- Inhibit glutamate receptor
- Decrease glutamate synthesis/release

*Increase GABA-ergic Transmission*

- Increase GABA receptor activity
- Increase GABA synthesis/release
- Decrease GABA reuptake

**Pregabalin and Gabapentin**

- Binds to the alpha2-delta subunit of voltage-gated calcium channels (N-type and P/Q-type)
  - Modulates the calcium channel and reduces calcium influx
  - Reduces the release of NTs from hyperexcited presynaptic neurons
Pregabalin and Gabapentin—Rationale for Newer Therapy

- Are NOT:
  - Calcium channel blockers!!
  - Calcium channel blockers (amlodipine) bind to the alpha1 subunit of L-type calcium channels
  - Directly blocks the channel pore
  - Effect the peripheral vascular smooth muscle

- DO NOT:
  - Bind to GABA
  - Augment GABA responses
  - Act like GABA uptake inhibitors

Different Chemical Structures

Gabapentin and Pregabalin Binds to the α₂-δ Subunit of Voltage-Gated Ca²⁺ Channels in the Central Nervous System

- Pregabalin selectively binds to α₂-δ subunit of calcium channels
  - Modulates calcium influx in hyperexcited neurons
  - Reduces neurotransmitter release
  - Pharmacologic effect requires binding at this site
  - The clinical significance of these observations in humans is currently unknown


Pharmacokinetic Profile
The Logic for a New Drug

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gabapentin</th>
<th>Pregabalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Food affects absorption</td>
<td>No food effect on dose absorption</td>
</tr>
<tr>
<td>Dosage increases</td>
<td>Various</td>
<td>Dose proportional</td>
</tr>
<tr>
<td>Exposure</td>
<td>Non-linear</td>
<td>Linear and predictable</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>BID or TID dosing</td>
<td>BID or TID dosing</td>
</tr>
<tr>
<td>Steady state</td>
<td>Slow dose adjustment</td>
<td>Fast dose adjustment</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Varied</td>
<td>Predictable levels</td>
</tr>
<tr>
<td>Metabolized</td>
<td>Yes</td>
<td>Predictable levels</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>Removed by dialysis</td>
<td>Adjust in renal impairment</td>
</tr>
</tbody>
</table>

Poll – True or False?

- A medication that has dose dependent absorption rates is safer for a patient than one that has linear absorption.
Open-Ended Question

Please use the chat window to respond.

• What do you recommend a patient do if they are not sure a medication is working?

Refractory Pain Study — Design Overview

Treatment period 1 = 3-month open-label treatment period with pregabalin 150-300 mg/day

Relapse

“How much has your pain worsened since discontinuing study medication?”

Not at all = 1
A little worse = 2
Moderately worse = 3
Much worse = 4
Very much worse = 5

Treatment period = 3-month open-label treatment period with pregabalin 150-300 mg/day

Dose Response

Pregabalin Versus Gabapentin

High Bioavailability

Linear PK Profile

**Pain Reported on Pregabalin Treatment**

- Drug holiday (DH) analysis
- 15-month open-label pregabalin treatment analysis

**Distribution of Pain Severity at Baseline and 15 Months**

- No/Mild Pain: 0 – 39
- Moderate Pain: 40 – 69
- Severe Pain: ≥ 70 on SF-MPQ pain VAS

**Dizziness / Somnolence**

- Mild, moderate
- Occurred soon after initiation of therapy
- Majority resolved before end of the study
- Most common reason for discontinuation:
  - Dizziness: 3%
  - Somnolence: 2%
In Conclusion

- DPN is a painful, debilitating complication of diabetes
- Patients have difficulty finding relief
- Current medications are somewhat effective and duration of effectiveness is varied
- Newer medications have been focused on improving outcomes without side effects
- Patients need to be counseled on medication expectations, dosing and side effects
- Pharmacists are in a unique position to counsel patients.