Neuropathic Pain: Overview and Management

Shyam Gelot, Pharm.D.
Assistant Professor
University of South Florida College of Pharmacy
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Disclosure

I have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Accreditation

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Technicians: 0165-0000-12-054-L01-T

Florida Pharmacist Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

By the end of this presentation one should be able to:

- Define neuropathic pain
- Describe the pathophysiology of neuropathic pain
- Discuss the clinical features of neuropathic pain
- Evaluate the pharmacologic treatment options

Patient Case

- CC: JS is a 65 yo retired vet with diabetes mellitus type 2. A year ago he noticed stabbing pain in his feet and now it has moved up to his shins. At times, each step feels like an “electric shock.” Pain is an 8/10. Claims to be compliant with meds, but “dent is another story…”
- PE: A&O X3. Good dorsalis pedis pulses. Decreased pinprick and temperature sensation to shins
- Home Medications: metformin 1000mg BID, lisinopril 10mg daily, insulin glargine 20 units QHS, simvastatin 20mg QHS
- PMHx: hyperlipidemia, hypertension, diabetes type 2 X 10 years
- Labs/Vitals: A1C 8%, HR 80, BP 115/78

Background
What is neuropathic pain (NP)?

- 1994 IASP “Pain initiated or caused by a primary lesion or dysfunction of the nervous system”
- 2008 IASP “Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”
- Not just one single etiology: autoimmune, metabolic, infection, trauma, and cancer.
- Several mechanisms can lead to NP
- Difficulty to treat: no more than 40-60% of patients obtain partial treatment of pain (Dworkin et al. 2007)
- Some treatment regimens are more effective for different pain mechanisms

Epidemiology

- Variable estimations 2-17.9% people suffer from neuropathic pain in the US
- Need “Gold Standard” definitions and assessment tools
- More information on prevalence and incidence of specific conditions, i.e. diabetic peripheral neuropathy
- To date no single study assessing overall economic impact on neuropathic pain

Etiology

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>Diabetes, Hypothyroidism, Nutritional Deficiency</td>
</tr>
<tr>
<td>Trauma</td>
<td>Amputation, Cancer, Entrapment Disorders, Spinal injury, surgery</td>
</tr>
<tr>
<td>Genetic</td>
<td>Fabry’s Disease</td>
</tr>
<tr>
<td>Immune Mediated</td>
<td>Guillain- Barre, Multiple Sclerosis</td>
</tr>
<tr>
<td>Infection</td>
<td>HIV, Herpes Zoster</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Chemotherapy, Alcohol, Isoniazid, nitrofurantoin, Thalidomide</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Lupus erythematosus, Sjogren’s Syndrome</td>
</tr>
</tbody>
</table>
Classification

Chronic Pain

Nociceptive --- Neuropathic

Somatic --- Visceral

Central --- Peripheral

Classification

Neuropathic Pain

Peripheral

<table>
<thead>
<tr>
<th>Peripheral Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phantom limb pain</td>
</tr>
<tr>
<td>Tingling</td>
</tr>
</tbody>
</table>

Central

<table>
<thead>
<tr>
<th>Central Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Traumatic nerve</td>
</tr>
</tbody>
</table>

Mixed

<table>
<thead>
<tr>
<th>Mixed Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS</td>
</tr>
<tr>
<td>Chronic low back pain with radiculopathy</td>
</tr>
</tbody>
</table>

Nociceptive Pain Circuit

| Brain |

| C fiber |
| Aβ fiber |

Transduction

| Peripheral |
| Dorsal horn |
Nociceptive Pain Circuit

Peripheral Mechanisms

- Collateral Sprouting: Neuroplasticity
- Ephaptic Conduction
- Coupling with sympathetic nervous system
- Alteration of channel expression

Peripheral Mechanism: Na Channels
Peripheral Mechanism: Na Channels

Peripheral Mechanism: Vanilloid Receptor (TRPV1)

Peripheral Mechanism: Vanilloid Receptor (TRPV1)
Peripheral Mechanism: TRP receptor family

Central Mechanisms
- Central Sensitization: hyperexcitability of central neurons
- Central Disinhibition
- Neuroplasticity

Central Mechanism: Central Sensitization

- N-type Calcium channel
- Substance P
- Glutamate
- NMDA receptor
- AMPA receptor
- CAMKII
- CA2+
- NA+
Quiz

Which of the following neurotransmitters are not involved in the descending inhibitory pathway?
A. Serotonin
B. Norepinephrine
C. Substance P
D. Endogenous opioids
E. All are involved in descending pathway

Assessment/Clinical Features

Clinical Descriptors of NP

Stimulus Dependent Pain
- Hyperalgesia: exaggerated response to a normally painful stimulus
- Allodynia: pain from a stimulus that does not normally evoke pain (mechanical or temperature)

Stimulus Independent Pain
- Paresthesias: abnormal sensations
- Dysesthesias: unpleasant or abnormal
  - Numbness (negative sign), tingling, lancinating, electric, shooting, burning
Recap

Ethiology
Metabolic, Trauma, Genetic
Immune, Infection, Toxicity

Mechanisms
Peripheral
Central

Symptoms
Stimulus Dependent
Stimulus Independent

Neuropathic Pain

Assessment

- Two types: Screening and Measurement
- Screening tools: reliable, self assessments to distinguish NP from Chronic Pain
  - ID Pain Tool
  - Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS)
  - painDETECT
- If NP pain is identified a referral to pain specialist who may use measurement tools, such as Neuropathic Pain Scale (NPS) or Neuropathic Pain Symptom Inventory (NPSI) to monitor pain over time

Assessment Screening: ID Pain

Mark "Yes" to the following items that describe your pain over the past week and "No" to the ones that do not. If you have more than one painful area, answer the question to the area most bothersome first:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does pain last less than 2 days?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2. Did the pain feel hot or burning?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3. Did the pain feel more sensitive?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4. Did the pain feel like electrical shock?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5. Is the pain inside or with the texture of clothing or fabric?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6. Is the pain limited to your joints?</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Assessment Monitoring: NPS

Diagnostic Challenges

- Do you diagnose and treat based on symptoms?
  - Signs and symptoms are diverse in one disease

- Do you diagnose and treat based on mechanism?
  - Disease states are associated with more than one mechanism and these mechanisms change over time
  - Each patient responds to medication differently

- Example: PHN has 3 mechanisms for peripheral and central pain: infectious, inflammatory, and ischemic. Each mechanism has a different signs and symptoms, each patient specific

Treatment
Treatment Principles

- Select treatment classes with efficacy demonstrated in multiple RCTs
- Individual variation
  - If a medication is well tolerated continue and titrate to effective pain relief
  - Can add a second medication with a different MOA if first medication provides partial relief but pain ≥ 4/10
  - Must consider SE, interactions, comorbidities (depression, anxiety or insomnia), cost, and abuse potential

Guidelines

- Attal et al, Eur J Neurol 2010; 17:1113-1123. EFNS, European Federation of Neurological Societies
- Dworkin et al, Pain 2007;133:210-220. IASP (International Association for the Study of Pain)

Guideline Recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>EFNS</th>
<th>CPS</th>
<th>IASP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SNRIs (venlafaxine and duloxetine)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gabapentin and Pregabalin</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lidocaine Patch</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Opioids and tramadol</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>NMDA antagonists</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Topiramate and valproate</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>2</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>
FDA approved drugs for NP conditions

- Diabetic peripheral neuropathy: duloxetine, pregabalin
- Postherpetic neuralgia: gabapentin, pregabalin, lidocaine patch 5%
- Trigeminal Neuralgia: Carbamazepine
- Neuropathic Spinal Injury: Pregabalin

Quiz Question

What would be a great first line agent for patient JS?
A. Valproic acid
B. Gabapentin
C. Capsaicin
D. Oxycodone

Tricyclic Antidepressants

- Not FDA approved for treatment of NP
- Two groups
- Tertiary amines: serotonin (5HT) and norepinephrine (NE) reuptake inhibitors
- Secondary amine only NE
- NNT of varied NP with 50% reduction in pain was 2.5*

* Moulin et al. 2007. Pain Res Manage
Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Pos</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inexpensive (30 day supply of amitriptyline $4)</td>
<td>Side effects: Ach, sedation, cardiac toxicity (doses &gt;150mg/day), weight gain, cognitive changes</td>
</tr>
<tr>
<td>Daily dosing</td>
<td>Can take 6-8 weeks for effect*</td>
</tr>
<tr>
<td>Great for dyesthesias (burning, electric shock, stabbing)</td>
<td>Not convincing evidence vs. placebo in HIV neuropathy, spinal cord injury, phantom limb pain, neuropathic cancer pain*</td>
</tr>
<tr>
<td>Benefits shown in PHN and DPN*</td>
<td></td>
</tr>
<tr>
<td>Use with co-morbid condition i.e. depression, insomnia, anxiety</td>
<td></td>
</tr>
</tbody>
</table>

*Data from: Jaffe J. Pain 2007

TCA guidelines

- Use secondary amines (nortriptyline, desipramine) over tertiary amines (amitriptyline and imipramine) due to adverse effects
- Use lowest effective dose and titrate up
- Avoid in elderly
- EKG baseline in patients 40 yo or greater
- 2D6 inhibitors i.e. SSRIs
SSNRI

- Mechanism similar to that of TCA, but increase NE and serotonin in descending pathway
- Duloxetine - FDA approved for DPN
  - NNT = 4.1 *
  - Start at 30mg/day and titrate to 60mg/day after 1 week
- Venlafaxine
  - NNT = 4.6 (2.9-10.6) *

*Namakula et al. Consultant Pharmacist 2009

SSNRI: Duloxetine

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief noted after 2 weeks (Raskin et al. Pain Med 2005)</td>
<td>Side effects: sedation, constipation, and nausea, but decreased if titrated after a week</td>
</tr>
<tr>
<td>Two large RCTs with similar 24 hr ave pain severity response 68% and 62% in vs. placebo shown in DPN.</td>
<td>60mg BID just as efficacious as 60mg QD *</td>
</tr>
<tr>
<td>Not much research in other NP conditions</td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions: anxiety and depression</td>
<td></td>
</tr>
</tbody>
</table>


SSNRI: Venlafaxine

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs vs. placebo shown DPN at higher doses (150-225mg/day) *</td>
<td>Side effects: EKG changes in 3% of patients in one trial **</td>
</tr>
<tr>
<td>Co-morbid conditions: anxiety and depression</td>
<td>Research in PHN and various other Peripheral and central conditions with mixed results (used lower doses) ***</td>
</tr>
<tr>
<td></td>
<td>Can take up to 4 weeks to reach effective dose. Titrate off as well **</td>
</tr>
</tbody>
</table>

** Dwoekin et al. Pain 2007
Calcium Channel α2-δ ligands

Gabapentin

- Considered first line agent by IASP guidelines (Dworkin)
- FDA approved for PHN
- Extended release gabapentin enacarbil (Horizant) 600mg postherpetic neuralgia
- NNT= 5.1 (Finnerup et al. Pain 2005)
- Starting dose 100-300mg at bedtime or 100-300mg TID
- Titrate by 100-300 mg TID every 1-7 days to max of 3.6 g (one study up to 6 g)

Gabapentin

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inexpensive (generic formulation) for immediate release</td>
<td>Side effects: sedation, dizziness, and unsteady gait</td>
</tr>
<tr>
<td>No clinically significant drug interactions</td>
<td>TID dosing generally; takes two weeks after a therapeutic dosage (1800-3600mg/day) achieved (8-12 weeks)</td>
</tr>
<tr>
<td>RCT gabapentin vs. placebo shown in PHN, DPN, phantom limb pain, neuropathic cancer pain and acute and chronic spinal cord injuries*</td>
<td>No benefit vs. placebo in HIV neuropathy and chemotherapy induced neuropathies*</td>
</tr>
<tr>
<td>Similar efficacy with nortriptyline**</td>
<td>Renal Adjustment</td>
</tr>
</tbody>
</table>

Kovacevic et al. Pain 2007
** Attal et al. European Journal of Neurology. 2010
Gabapentin

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>900 to 3400mg/day in 3 divided doses</td>
</tr>
<tr>
<td>30-59</td>
<td>400-1400mg/day in 2 divided doses</td>
</tr>
<tr>
<td>16-29</td>
<td>200-700mg/day given once daily</td>
</tr>
<tr>
<td>&lt;15 (HD)</td>
<td>100-300mg once daily</td>
</tr>
<tr>
<td>&lt;15 (HD)</td>
<td>Reduce daily dose in proportion to the CrCl</td>
</tr>
</tbody>
</table>

Source: Micromedex

Pregabalin

* First line agent by IASP
* FDA approved for DPN, PHN
* FDA recent approval: NP spinal injury
* NNT 4.2 in DPN and PHN*
* 7 fold higher affinity than gabapentin for calcium channel: Begin 50mg TID or 75mg BID
* Titrate to 300mg daily after 3-7 days, then by 150mg every 3-7 days for max dose of 600mg/day


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Pregabalin

<table>
<thead>
<tr>
<th>Pos</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>No significant drug interaction</td>
<td>Brand name only</td>
</tr>
<tr>
<td>Faster analgesic effects than gabapentin (Sweats)*</td>
<td>Side effects: sedation, dizziness, and unsteady gait Caution in patients with CHF</td>
</tr>
<tr>
<td>RCTs vs. placebo shown in PHN, DPN, spinal cord injuries*</td>
<td>BID/TID dosing</td>
</tr>
<tr>
<td>Analgesic effects (Schedule V)</td>
<td>renally adjust</td>
</tr>
<tr>
<td>Exhibits linear pharmacokinetics</td>
<td></td>
</tr>
</tbody>
</table>

*Badiani et al. J Pain 2007
Quiz

What is the difference(s) between gabapentin and pregabalin?

A. Pregabalin has higher affinity for the calcium channels than gabapentin
B. Pregabalin exhibits linear kinetics whereas gabapentin does not
C. Pregabalin does not have to be renally adjusted
D. There are no differences between the two agents
E. Both A and B

Topical Lidocaine

- Blocks sodium channels in periphery
- Not recommended for central NP and no efficacy in HIV neuropathy
- NNT 4.4 in PHN** most trials limited to 3 weeks
- FDA approval PHN: 3 patches applied for 12 hours on 12 hours off
- Recent data with 4 patches applied 18-24 hours considered safe
- Rash only side effect if used appropriately
- Avoid in patients taking oral Class I antiarrhythmics and severe hepatic dysfunction

*Dworkin et al. Pain 2007

Quiz

Can opioids be used as a first line agent to relieve neuropathic pain?

True
False
Opioids

- Can be used as a first line agent in patients with:
  - Neuropathic cancer pain
  - Acute neuropathic pain
  - During titration of a first-line medication to an effective dose
  - Used a second line due to side effects along with long term effects
  - Morphine and oxycodone in DPN and PHN 2.5*
  - “Start low and go slow”

* Moulin et al. 2007. Pain Res Manage

Opioids

<table>
<thead>
<tr>
<th>Pos</th>
<th>Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids (oxycodone, morphine, methadone, levorphanol) demonstrated efficacy in DPH, PHN and phantom limb pain short term*</td>
<td>Chronic Side effects: constipation, immunology changes, hypogonadism, hyperalgesia</td>
</tr>
<tr>
<td>Abuse/Addiction</td>
<td></td>
</tr>
<tr>
<td>Should not use in elderly</td>
<td></td>
</tr>
<tr>
<td>Long term data? (8 weeks)</td>
<td></td>
</tr>
</tbody>
</table>

*Dworkin et al. Pain 2007

Tramadol

- Weak µ antagonist, reuptake inhibitor of NE and 5HT
- Available in short acting and long acting form
- Caution in patients taking TCAs and SSNRIs
- Second line agent similar to opioids
- Start at 50mg QD to BID and titrate to max of 400mg/day
- Meta analysis NNT 3.8 95% CI (2.8-6.3)
### Tramadol

<table>
<thead>
<tr>
<th>Pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials demonstrated a reduction in pain in peripheral neuropathic syndromes such as PHN, DPN, and amputations.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects: Caution with concurrent use of SSRI, SNRI, lower seizure threshold.</td>
</tr>
</tbody>
</table>

- Abuse/Addiction
- Should not use in elderly
- Less efficacious than opiate.
- Dose reduction in hepatic and renal insufficiency

*Dworkin et. al Pain 2007*

### Capsaicin

- Constituents of chili pepper
- Regular application depletes the C fiber of substance-P
- Studies in DPN, PHN, post-mastectomy pain inconsistent
- 4 patches of 8% for 1 hour daily for 3 months
- SE: local burning and itching
  - Lidocaine 1 hour before
  - Nitrile gloves
  - Never place on broken skin
- Better than placebo, but overall poor efficacy (Mason et. al. BMJ 2004)

### NMDA receptor antagonist: Ketamine

- No mention in IASP guidelines (Dextromethorphan and memantine)
- Insufficient evidence to support use for chronic non-cancer pain (Bell et. al. Pain 2009)
- Refractory NP- reset opioid receptors
- No universal dosing, various protocols
- 0.25-0.5mg/kg or 10-25mg QHS. May be increased to 50mg TID.
Mexiletine

- Orally administered lidocaine analogue
- Class 1B antiarythmic
- Modest evidence to no evidence supporting use versus placebo*
- Evidence found at higher doses, but poorly tolerated due to SE

*Dworkin et al. Pain 2007

Antiepileptics

- Carbamazepine: Trigeminal neuralgia, inconsistent data in other NP conditions
- Valproic acid: Inconsistent data with DPN/PHN*
- Oxcarbazepine: Inconsistent data with DPN, some positive data with trigeminal neuralgia (better tolerability)
- Topiramate: not significant data in chronic lumbar radicular pain
- Lamotrigine: HIV polyneuropathy**, but inconsistent in DPN* risk of Steven Johnsons Syndrome

*Dworkin et al. Pain 2007
** Attal et. al European Journal of Neurology. 2010

Antidepressants

- Options after TCAs and SSNRI have failed
- Bupropion support in various NP conditions
- Citalopram, and paroxetine limited evidence in DPN*
- Fluoxetine no evidence

Combination Therapy

- Single drug unlikely to target multiple mechanisms of pain
- Avoid adverse effects by maxing out one agent
- Greater analgesic efficacy by using combination therapy

Combination Therapy

<table>
<thead>
<tr>
<th>Title</th>
<th>Morphine, Gabapentin or Their Combination for Neuropathic Pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>To investigate synergy of combination drug in treatment of NP</td>
</tr>
<tr>
<td>Methods</td>
<td>• Prospective, randomized, non-inferiority, double blinded study</td>
</tr>
<tr>
<td></td>
<td>• N=41; single center study</td>
</tr>
<tr>
<td></td>
<td>• Pt randomized to either gabapentin, morphine SR, both gabapentin and morphine, or placebo in patients with DPN or PHN</td>
</tr>
<tr>
<td></td>
<td>• Primary Outcomes: Mean intensity of pain (scale 1-10) TID</td>
</tr>
<tr>
<td></td>
<td>• Secondary Outcome: adverse effects, Short Form McGill Pain Questionnaire (0-45 scale), Brief Pain inventory (0-10), Beck Depression inventory (0-63), General Health Survey (0-100), MMSE (0-30), global pain relief</td>
</tr>
</tbody>
</table>


Morphine, Gabapentin or Their Combination for Neuropathic Pain.

Inclusion
- Daily moderate pain >3 months
- Age 18-89
- AST/ALT <1.5 ULN
- Appropriate language skills

Exclusion
- Hypersensitivity to medication
- Other pain conditions
- Recent MI
- Unstable angina
- Congestive heart failure
- Neurological disorders (seizures, mood disorders, substance abuse)
- Pregnancy
Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Morphine SR</th>
<th>Gabapentin</th>
<th>Dual Tx</th>
<th>Placebo (lorazepam)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: Numerical Pain (0-10) Baseline 5.72 ± 0.23</td>
<td>3.70±0.24</td>
<td>4.45±0.33</td>
<td>3.60±0.22</td>
<td>4.49±0.34</td>
</tr>
<tr>
<td>Maximum tolerated dose (mg)</td>
<td>45.38±3.9</td>
<td>54.4±2.6</td>
<td>34.4±2.6</td>
<td>4.58±0.55</td>
</tr>
</tbody>
</table>

Adverse Effects >10%:
- constipation
- sedation
- dry mouth
- pruritus
- nausea
- dizziness
- vomiting
- cognitive dysfunction
- insomnia


Trial Limitations
- Only 41 patients- insufficient statistical power
- Single center study
- Did not evaluate patients with renal insufficiency
- Used lorazepam as placebo, when alprazolam showed some benefit in NP

Non-cancer Combination Therapy Summary

<table>
<thead>
<tr>
<th>Drug Combo</th>
<th>NP Pain</th>
<th>Trial</th>
<th># of pts</th>
<th>Primary outcome</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin vs. nortriptyline vs. combo</td>
<td>DPN and PHN 6 week</td>
<td>56</td>
<td>Better pain control with combo</td>
<td>Less with combo</td>
<td></td>
</tr>
<tr>
<td>Gabapentin vs. venlafaxine vs. gabapentin + placebo</td>
<td>DPN 6 week</td>
<td>50</td>
<td>Better pain control with combo</td>
<td>Less in both groups</td>
<td></td>
</tr>
<tr>
<td>Gabapentin vs. morphine vs. combination vs. placebo</td>
<td>DPN and PHN 6 week</td>
<td>67</td>
<td>Better pain control with combo</td>
<td>Worse in combo</td>
<td></td>
</tr>
<tr>
<td>Gabapentin vs. oxycodone vs. gabapentin + placebo</td>
<td>DPN 6 week</td>
<td>53</td>
<td>Better pain control with combo</td>
<td>Opioid AE not exacerbated in combo</td>
<td></td>
</tr>
<tr>
<td>Pregabalin vs. oxycodone vs. combo</td>
<td>PHN, DPN, spinal stenosis, radiculopathy 90 day</td>
<td>409</td>
<td>Combo and oxy group better pain control</td>
<td>Less with combo</td>
<td></td>
</tr>
<tr>
<td>Pregabalin vs. 5% lidocaine vs. combo</td>
<td>DPN and PHN 8 week</td>
<td>229</td>
<td>Better pain control with combo</td>
<td>Fewest with lidocaine</td>
<td></td>
</tr>
</tbody>
</table>

Vorobeychik et al. CNS Drugs 2011: 25(12):1023-1034
Recap of Mechanism of Action

Perception
1. Lidocaine/mexilitine
2. TCA
3. Calcium Channel α2-δ ligands
4. Capsaicin

Modulation
Descendant inhibition
1. NMDA antagonist
2. TCA

Transmission
Dorsal horn
1. Opioids
2. Tramadol
3. TCA
4. Calcium Channel α2-δ ligands
5. Capsaicin
6. Cannabinoids

Conclusions
- NP is a complex disease with many questions to be answered
- More research is needed for large RCT, with head to head comparisons
- TCAs, SSNRI, calcium channel α2-δ ligands, and topical lidocaine should be considered first line agents
- If not adequate response can try combination or second/third line agents.

References
- Gilron I. Morphine, Gabapentin, or Their Combination for Neuropathic Pain. 2003; 332:1204-34.
References


Questions

Shyam Gelot, PharmD
sgelot@health.usf.edu