Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

Mechanism Based Treatment of Pain

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Disclosures:
- Course Director, "PPPM" 2000-2011, and "Headache and Facial Pain" 2004-2010
- Secretary, BOD, and FC, American Academy of Pain Medicine
- Contributor, UptoDate, Headache and Pain Sections
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

The Pain Textbook

PPPM-2012 and Headache Update-2012

- Principles and Practice of Pain Medicine 2012—Fairmont Copley Plaza, Boston, will be Monday—Friday, June 18th to June 22nd—Drs Bajwa, Abdi, and Warfield
- Headache and Facial Pain Update 2012 at the Fairmont Copley Plaza, Boston, Saturday, June 23rd 2012...Drs Bajwa, and Wootton

IASP Definition of Pain

“Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

Nociceptive vs. Neuropathic Pain

Nociceptive Pain
Caused by activity in neural pathways in response to potentially tissue-damaging stimuli

Mixed Type
Caused by a combination of both primary injury and secondary effects

Neuropathic Pain
Initiated or caused by primary lesion or dysfunction in the nervous system

FIBROMYALGIA
Postoperative pain
Mechanical low back pain
Sickle cell crisis
Sports/surgery injuries
Diabetic neuropathy (e.g., diabetic, HIV)

CRPS
Complex regional pain syndrome
Peripheral nerve injury
Postherpetic neuralgia
Neuropathic low back pain
Distal polyneuropathy
Central post-stroke pain

Mixed Type
Caused by a combination of both primary injury and secondary effects

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Distal polyneuropathy
Central post-stroke pain

Estimated Prevalence of Neuropathic Pain in the U.S.*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful diabetic neuropathy</td>
<td>600,000</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>800,000</td>
</tr>
<tr>
<td>Cancer-associated</td>
<td>200,000</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>120,000</td>
</tr>
<tr>
<td>Causalgia and reflex sympathetic</td>
<td>100,000</td>
</tr>
<tr>
<td>HIV-associated</td>
<td>100,000</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>50,000</td>
</tr>
<tr>
<td>Phantom pain</td>
<td>50,000</td>
</tr>
<tr>
<td>Poststroke</td>
<td>30,000</td>
</tr>
<tr>
<td>Trigeminal neuralgia (tic douloureux)</td>
<td>15,000</td>
</tr>
<tr>
<td>Low back pain—associated</td>
<td>2,100,000</td>
</tr>
<tr>
<td>Total (excluding back pain)</td>
<td>1,765,000</td>
</tr>
<tr>
<td>Total (including back pain)</td>
<td>3,865,000</td>
</tr>
</tbody>
</table>

*Based on population of 270 million; Adapted from: Bennett GJ. Hosp Pract (Off Ed). 1998(Oct 15);33(10): 95-98, 101-104, 107-

Physiology of Pain Perception

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior

Adapted with permission from WebMD Scientific American® Medicine.
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Pathophysiology of Neuropathic Pain
- Chemical excitation of non-nociceptors
- Recruitment of nerves outside of site of injury
- Excitotoxicity
- Sodium channels
- Ectopic discharge
- Deafferentation
- Central sensitization
  - maintained by peripheral input
- Sympathetic involvement
- Antidromic neurogenic inflammation

Impact of Acute and Chronic Neuropathic Pain
- Consequences of pain:
  - decreased quality of life
  - reactive anxiety and depression
  - weight loss
  - insomnia
- Require independent treatment

Acute Neuropathic Pain
- Does it exist?
- More Common Than Chronic Pain
- Offers a window of opportunity
- Pre-emptive Analgesia
- Importance of Regional Anesthesia
- Multimodal Anesthesia/Analgesia
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

Evolutionary Pharmacotherapy of Pain

- Anesthetics: The Ether Dome
- Analgesics
- Antihyperalgesics
- Sensory modulators

Treatment of Neuropathic Pain

- Efficacy against underlying cause
- Efficacy against pain characteristics
- Efficacy against putative pathophysiologic mechanisms

Clinical Trials in Neuropathic Pain

- Painful diabetic neuropathy/PDN
- Post-herpetic neuralgia/PHN
- Trigeminal neuralgia/TGN
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

**Treatment of Neuropathic Pain**

- Efficacy against underlying cause
- Efficacy against pain characteristics
- Efficacy against putative pathophysiologic mechanisms

**Characteristics of Neuropathic Pain**

- Lancinating, paroxysmal
- Burning, constant
- Cramping/Aching
- Hyperalgesia
- Allodynia
- Hyperpathia

**Treatment of Pain Characteristics**

- Burning, tingling, or aching pain: TCAs, oral local anesthetics, alpha 2 agonists
- Lancinating, shooting, stabbing: anticonvulsants, GABA agonists
- Sympathetically related pain: phenoxybenzamine, prazosin, propranolol, nifedipine, calcitonin, steroids

Adapted from Poretz and Kazim, 2000.
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

Treatment of Neuropathic Pain

- Efficacy against underlying cause
- Efficacy against pain characteristics
- Efficacy against putative pathophysiologic mechanisms

Pharmacologic Management of Neuropathic Pain

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, imipramine, desipramine, nortriptyline, SNRIs, SSRIs, Atypicals</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, oxcarbazepine, gabapentin, lamotrigine, phenytoin, topiramate, levetiracetam, pregabalin</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Mexiletine, Flecainide</td>
</tr>
<tr>
<td>Topical formulations</td>
<td>Aspirin, Capsaicin, Dosepin, Lidocaine</td>
</tr>
<tr>
<td>Analgesics</td>
<td>NSAIDs, Cox-2 inhibitors, tramadol, opiates/ opioids</td>
</tr>
<tr>
<td>Others</td>
<td>Levodopa, ketamine, dextromethorphan</td>
</tr>
</tbody>
</table>

Mechanistic Approach to Treatment

Central Sensitization
- TCAs
- SNRIs
- Atypicals
- Tramadol
- Opiates

Peripheral Sensitization
- NEF/5HT
- Opiate receptors
- NE/5HT

SPINAL CORD
- CBZ
- OXC
- PHT
- TCA
- TPM
- LTG
- Mesolamine
- Lidocaine

Others
- Capsaicin
- NSAIDs
- Levodopa
- ZOSTAVAX® Zoster Vaccine
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

Pharmacologic Treatment Options

- Classes of agents with efficacy demonstrated in multiple, randomized, controlled trials for neuropathic pain
  - Topical analgesics (capsaicin, lidocaine patch 5%)
  - Anticonvulsants (gabapentin, lamotrigine, pregabalin)
  - Antidepressants (nortriptyline, desipramine)
  - Opioids (oxycodone, tramadol)
- Consider safety and tolerability when initiating treatment

FDA-Approved Treatments for Neuropathic/Chronic Pain

- Carbamazepine: TGN
- Gabapentin: PHN
- Lidocaine Patch 5%: PHN
- Duloxetine: PDN, Fibromyalgia, C. Pain
- Pregabalin: PHN, PDN, and Fibromyalgia
- Milnacipran: Fibromyalgia
- Capsaicin 8% Patch: PHN

Importance of Randomized Clinical Trials

- Patient with trigeminal post-herpetic neuralgia treated with:
  - Alcohol injection into supra-orbital nerve
  - Division of the sensory root
  - Alcohol injection into trigeminal ganglion
  - Stellate ganglion block
  - Electroconvulsive therapy
  - Extirpation of contralateral then ipsilateral sensory cortex
  - Prefrontal lobotomy
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

**Mechanistic Approach to Treatment**
- **Descending Inhibition**
  - NE/FNT
  - Opiate receptors
- **Peripheral Sensitization**
  - Na⁺
  - CBZ, OXC, PHT, TCA, TPM, LTG
- **Central Sensitization**
  - Ca²⁺: GBP, OXC, NMDA: Ketamine, TPM, Dextromethorphan, Methadone
  - Others: Capsaicin, NSAIDs, Cox inhibitors, Levodopa

**Antidepressants in Painful Diabetic Neuropathy**
- Double-blind, placebo-controlled, cross-over trial of amitriptyline, desipramine, and fluoxetine
- Mean doses: amitriptyline 105 mg, desipramine 111 mg, fluoxetine 40 mg
- Moderate or significant pain relief in 74% of amitriptyline, 61% of desipramine, 48% of fluoxetine, and 41% of placebo-treated patients

**Antidepressants in PHN**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline vs placebo</td>
<td></td>
<td>P: 5%</td>
</tr>
<tr>
<td>Amitriptyline vs placebo</td>
<td></td>
<td>P: 8%</td>
</tr>
<tr>
<td>Kishore-Kumar et al (1980)</td>
<td>19</td>
<td>D: 63%</td>
</tr>
<tr>
<td>Desipramine vs placebo</td>
<td></td>
<td>P: 11%</td>
</tr>
<tr>
<td>Amitriptyline vs maprotiline</td>
<td></td>
<td>M: 18%</td>
</tr>
<tr>
<td>Watson and Evans (1985)</td>
<td>15</td>
<td>A: 60%</td>
</tr>
<tr>
<td>Amitriptyline vs zimeldine (SSRI)</td>
<td></td>
<td>Z: 7%</td>
</tr>
</tbody>
</table>
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

**Common Side Effects Associated With Tricyclic Antidepressants**

<table>
<thead>
<tr>
<th></th>
<th>Sedation</th>
<th>Anti-cholinergic effects</th>
<th>Hypotension</th>
<th>Cardiac effects</th>
<th>Seizures</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Desipramine</td>
<td>0+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Doxepin</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*From Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th edition.*

**Venlafaxine in Painful Diabetic Neuropathy**

- Randomized, placebo-controlled trial of 224 patients with PDN and no depression
- Venlafaxine (VLF) XR administered at 75 mg, 150 mg to 225 mg for up to 6 weeks
- Venlafaxine (150 mg to 225 mg) resulted in significantly better pain relief at weeks 2 to 6 and significantly decreased pain intensity at weeks 4 and 6
- At week 6, 58%, 39%, and 35% of patients on VLF 150 mg to 225 mg, VLF 75 mg, and placebo, respectively, reported significantly reduced pain intensity


**Tricyclic Antidepressants and Neuropathic Pain**

- Efficacy established in a number of small cross-over, placebo-controlled clinical trials
- Analgesic effect independent from effect on mood
- Start low and go slow. Usual dose range between 50-150 mg/day
- Analgesia starts to occur after a week and can take up to 3 weeks to reach maximum efficacy
Tramadol in Painful Diabetic Neuropathy

- Randomized, DB, PC, MC, 6-week clinical trial of 131 patients titrated up to 400 mg/day
- Significant reduction in pain intensity at week 6 for tramadol treated patients ($P < 0.001$)
- 15% drop-out rate due to adverse events

Opioid Efficacy Studies in Neuropathic Pain Disorders

- Nonmalignant neuropathic pain disorders
  - IV fentanyl, Oral Morphine, Methadone, Levorphanol
- Postherpetic neuralgia
  - IV morphine
  - Controlled-release oxycodone
- Phantom limb pain
  - Oral morphine, Methadone
- Diabetic neuropathy
  - Tramadol
  - Oxycodone

Oxycodone in Post-herpetic Neuralgia

- Randomized, DB, 8 weeks cross-over trial of 50 patients (32 evaluable)
- Oxycodone was titrated up to 30 mg BID
- Efficacy on a 100 mm VAS
- 76% of patients on oxycodone reported adverse events including constipation, nausea, and sedation
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Oxycodone in Post-herpetic Neuralgia

Tapentadol For Pain

- Novel Agent with Substantial Effects on Opioid And Norepinephrine Receptors
- Federally Scheduled Agent
- Studies In Acute And Chronic Pain Models
- Recent FDA Approval With Evolving Indications

Mechanistic Approach to Treatment
Perioperative Use of Neuropathic Analgesics

- Gabapentin: >20 published studies demonstrating perioperative analgesia, anxiolysis, and opiate-sparing effect
- Pregabalin: similar benefit from 50-300 mg preoperative dosing
- Antidepressants?
- Other Antiepileptics?

Tippenhauer et al. 2007. Anesthesia & Analgesia

Gabapentin in Painful Diabetic Neuropathy

- Multicenter, randomized, double-blind, 8-week, placebo-controlled, parallel design trial in 165 pts titrated up to 3600 mg/day
- Average daily pain score dropped from 6.4 to 3.9 on GBP compared to a drop from 6.5 to 5.1 for placebo (P < 0.001)
- Most common adverse events on GBP were dizziness and somnolence


Gabapentin in Post-herpetic Neuralgia

- Multicenter, randomized, double-blind, 8-week, placebo-controlled, parallel design trial in 229 pts titrated up to 3600 mg/day
- Average daily pain score dropped from 6.3 to 4.2 on GBP compared to a drop from 6.5 to 6.0 for placebo (P < 0.001)
- Somnolence, dizziness, ataxia, peripheral edema, and infection more frequent in gabapentin group

Dextromethorphan in Painful Diabetic Neuropathy

- Randomized, PC, CO trial; 14 pts
- Dextromethorphan titrated up to 960 mg/day
- Dextromethorphan (mean dose 381 mg) reduced pain by 24% compared with placebo
- Most common AEs were sedation, dizziness, and lightheadedness

Cymbalta provides rapid and significant reduction in daily average pain

- 3 randomized, double-blind, placebo-controlled, fixed-dose trials
- 1-week baseline phase, 5- to 8-week treatment periods
- Patients (N=729)
  - 600 mg/day pregabalin (n=164); 300 mg/day (n=157); 150 mg/day (n=79); 75 mg/day (n=77); placebo (n=252)
- Results
  - 300 and 600 mg/day significantly reduced endpoint mean pain scores from daily pain diaries (P<0.0001)
  - 50% responders: 43% of 300 mg/day group, 44% of 600 mg/day, vs 16% placebo
- Conclusions
  - Pregabalin at doses of 300 and 600 mg/day significantly improved painful diabetic neuropathy

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**Pregabalin: Percentage of Patients With >50% Reduction in Pain in Painful DPN**

![Graph showing percentage of patients with >50% reduction in pain for Pregabalin 75, 150, 300, and 600 mg/d vs placebo.](image)

*Last observation carried forward (LOCF) analysis. All pregabalin doses in mg/d.

**Pregabalin: Percentage of Patients With >50% Reduction in Pain in Painful PHN**

![Graph showing percentage of patients with >50% reduction in pain for Pregabalin 75, 300, and 600 mg/d vs placebo.](image)

*Last observation carried forward (LOCF) analysis. †Dose adjusted to 300 mg in cases of renal insufficiency. All pregabalin doses in mg/d.

**Incidence (%) of Most Common* Adverse Events With Pregabalin in All Controlled Studies**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregabalin 150 mg/d</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15.4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13.1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5.4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>4.8</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>4.2</td>
</tr>
<tr>
<td>Weight gain</td>
<td>3.5</td>
</tr>
<tr>
<td>Thinking abnormal</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Incidence >5% and at least twice the rate observed with placebo
†Includes all doses across all controlled studies.
‡Primarily difficulty with concentration/attention

Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

**Mechanistic Approach to Treatment**

- **BRAIN**
  - Descending Inhibition
  - NE/5HT
  - Opiate receptors

- **Central Sensitization**
  - Ca²⁺: GBP, OXC
  - NMDA: Ketamine, TPM
  - Others: Dextromethorphan, Methadone

- **PNS**
  - NE
  - CBZ
  - OXC
  - PHT
  - TPM
  - LTG
  - Mexiletine
  - Lidocaine

- **SPINAL CORD**
  - TCAs
  - SSRIs
  - SNRIs
  - Tramadol
  - Opiates

Trigeminal Neuralgia

- Attacks of pain in TGN represent paroxysmal activity in trigeminal pathway (Trousseau, 1853)
- First report of efficacy of DPH in TGN (Bergouignan, 1942)
- First report of efficacy of CBZ in TGN (Blom, 1962)
- Animal studies found that DPH and CBZ depress synaptic transmission in the spinal trigeminal nucleus to maxillary nerve stimulation (Fromm, 1969)

Carbamazepine in Trigeminal Neuralgia

- Efficacy established in three, double-blind, placebo-controlled, cross-over trials of 151 pts (Campbell, et al. 1966; Killian and Fromm 1968; and Nicol 1969)
- 70% to 80% of newly diagnosed patients have good initial response
- Efficacy correlates with serum levels
- Usual efficacious dose ranges between 400 mg/day and 1000 mg/day
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

**Carbamazepine in Trigeminal Neuralgia**

- Efficacy in 70-80% of patients within 24 to 48 h

**BUT**

- Poor tolerability (drowsiness, nausea, ataxia, and sedation)
  - number needed to harm: 3.4
- Hypersensitivity reactions necessitating discontinuation
- Numerous drug-drug interactions
- Up to 40% of initial responders become refractory to treatment

**Carbamazepine in Painful Diabetic Neuropathy**

- DB, PC, cross-over trial of 6 weeks (3 two-week periods); 30 pts
- Pain relief on a categorical scale
- 63% of patients on CBZ had moderate-complete relief versus 20% of patients on placebo ($P<0.05$)
- Median carbamazepine dose: 600 mg

Adapted from McQuay, et al. Pain. 1996.

**CBZ vs Antidepressants in Painful Diabetic Neuropathy**

- Graph showing % patients with pain relief on treatment vs patients with pain relief on placebo (%)

Adapted from McQuay, et al. Pain. 1996.
Oxcarbazepine in Trigeminal Neuralgia

- Comparative trial of OXC vs CBZ in a cross-over design; efficacy variable 11-point scale
- 15 pts titrated to OXC (900 mg/day to 2100 mg/day) or CBZ (400 mg/day to 1200 mg/day)
- Comparable analgesic effect in most patients
- OXC offers an alternative to CBZ for the treatment of trigeminal neuralgia
- CBZ, OXC, TPM, LMT (Per ZB)

Oxcarbazepine vs Carbamazepine in Trigeminal Neuralgia

3 double-blind randomized studies vs carbamazepine

Newly diagnosed trigeminal neuralgia
1 study
n=48
Oxcarbazepine 750 mg/day
Carbamazepine 500 mg/day

Refractory trigeminal neuralgia
2 studies
n=84
Oxcarbazepine 1050-1200 mg/day
Carbamazepine 700-900 mg/day

Beydoun et al. American Pain Society Meeting 2002
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

**Oxcarbazepine vs Carbamazepine in Trigeminal Neuralgia**

- **Global Efficacy**
  - OXC: 70%
  - CBZ: 50%

- **Global Tolerability**
  - OXC: 80%
  - CBZ: 60%

- **Ataxia**
  - Carbamazepine: 10%
  - Oxcarbazepine: 5%

- **Somnolence**
  - Carbamazepine: 15%
  - Oxcarbazepine: 8%

- **Nausea**
  - Carbamazepine: 20%
  - Oxcarbazepine: 15%

- **Dizziness**
  - Carbamazepine: 12%
  - Oxcarbazepine: 7%

- **Fatigue**
  - Carbamazepine: 9%
  - Oxcarbazepine: 4%

- **Vertigo**
  - Carbamazepine: 10%
  - Oxcarbazepine: 5%

Beydoun et al. American Pain Society Meeting 2002

- **Phenytoin in Painful Diabetic Neuropathy**

  - **CONFLICTING DATA**
    - Saudek, et al. 1977
      - DB, CO, PC trial of 4 weeks; 12 pts
      - Pain relief on linear analog scale
      - No significant difference between phenytoin and placebo

    - Chadda and Mathur 1978
      - DB, CO, PC, trial of 5 weeks; 38 pts
      - Categorical scale of improvement
      - Significant improvement on phenytoin

Beydoun et al. American Pain Society Meeting 2002
Lamotrigine in Trigeminal Neuralgia

- DB, PC, CO add-on trial of LTG (400 mg/day) in 14 pts with refractory trigeminal neuralgia
- 2 weeks treatment phases with intervening 3-day washout period
- Lamotrigine superior to placebo (P = 0.01) based on composite efficacy index

Lamotrigine in Neuropathic Pain

- Randomized, DB, PC, 8-week clinical trial in 100 pts
- Lamotrigine titrated to 200 mg/day
- No significant difference between lamotrigine and placebo for any variable
- Lamotrigine, at the dose used, had no effect on neuropathic pain

Lamotrigine in Diabetic Neuropathy

- Design and Dose Escalation of LTG and Placebo
**Mechanistic Approach to Treatment of Painful Peripheral Neuropathies**

### Lamotrigine in Diabetic Neuropathy

- **Graph:**
  - LTG
  - Placebo
  - Graph shows pain intensity (NPS) against dose of LTG (week).
  - Significant reduction in pain intensity.

- **Reference:**

### Topiramate in Painful Diabetic Neuropathy

- **Details:**
  - DB, PC (2:1) trial of 13 weeks duration in 27 patients
  - TPM titrated over 9 weeks up to 400 mg/day
  - Average daily pain score dropped from 6.9 to 4.1 on TPM compared to an increase from 6.5 to 7.0 for placebo ($P = 0.007$)
  - 5/18 patients (28%) on TPM vs 1/9 patients (11%) on placebo exited because of intolerable adverse events
  - 3 multicenter, randomized, placebo-controlled clinical trials in PDN were negative

- **References:**

### Mexiletene in Painful Diabetic Neuropathy

- **Details:**
  - 216 pts randomized to 3 dosages of mexiletine or placebo. Only significant reduction was in nighttime pain at the highest dose of 675 mg/day
  - 29 pts randomized to mexiletine 600 mg/day vs placebo for 3 weeks. No significant difference between the 2 groups
  - 95 pts randomized to 3 dosages of mexiletine or placebo. No significant difference in VAS score

- **Should be reserved for pts unresponsive or intolerant to standard therapy**

- **References:**
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

Lidocaine Patch

Topical Lidocaine in Post-herpetic Neuralgia

- Randomized, two-treatment period, vehicle-controlled, cross-over study
- Primary efficacy variable of 'time to exit'; subjects were allowed to exit either treatment period if pain relief score decreased by ≥2 categories on a 6-item pain relief scale for any 2 consecutive days
- All subjects had been successfully treated with topical lidocaine patches on a regular basis for at least 1 month prior to study enrollment
- The median time to exit with lidocaine patch phase was greater than 14 days vs vehicle (3.8 days; \( P < 0.001 \))

Adapted from Comer, Lamb.

Mechanistic Approach to Treatment

BRAIN
- Descending Inhibition
- NE/SHT
- Opiate receptors

PNS
- Peripheral Sensitization

SPINAL CORD
- Na+
- Ca++
- OXC
- PHT
- TCA
- TPM
- LTG
- Mexiletine
- Lidocaine

Central Sensitization
- Ca++: GBP; OXC
- NMDA: Ketamine, TPM
- Dextromethorphan, Methadone

Others
- Capsaicin
- NSAIDs
- Cox Inhibitors
- Levodopa
- ZOSTAVAX® [Zoster Vaccine]

Capsaicin Cream

Capsaicin in Painful Diabetic Neuropathy

- MC, DB, vehicle-controlled trial on topical 0.075% capsaicin cream applied 4x daily for 8 weeks; 225 pts
- Statistically significant pain improvement favoring capsaicin; significant placebo response
- Capsaicin caused transient burning, sneezing, and coughing
**Mechanistic Approach to Treatment of Painful Peripheral Neuropathies**

**Capsaicin 8% Patch for PHN**
- Recently FDA Approved
- Synthetic Capsaicin-Chili Peppers
- Single 60 Min. Application of Up To 4 Patches to the Most Painful Skin Areas May Provide 3 Months of Relief

**Aspirin/Diethyl Ether mixture (ADE) in Post-herpetic Neuralgia**
- Superior efficacy of topical 750 mg dose of ADE compared to single 500 mg oral dose of ASA in 19 patients*
- DB, PC, CO trial in 37 patients comparing ADE with indomethacin and diclofenac/diethyl ether mixtures in acute herpetic and post-herpetic neuralgias. Only ADE significantly superior to placebo**


**Levodopa and Painful Diabetic Neuropathy**
- Placebo-controlled, parallel-group trial of 25 patients
- Sinemet (25/100) administered on a TID schedule
- Significant improvement for the levodopa group by week 2

**Mechanistic Approach to Treatment of Painful Peripheral Neuropathies**

### Benzodiazepine Analogues
- Clonazepam
- Lorazepam
- Alprazolam
- Diazepam
- Other Benzopenic Subjects
- Hypnotics, Old, New and Reformulated

### Recommendations for First- and Second-Tier Agents for PDN-2006

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reason for Recommendation</th>
<th>Agent Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-tier</td>
<td>≥ 2 RCTs in DPN</td>
<td>Duloxetine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxycodone CR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregabalin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCAs</td>
</tr>
<tr>
<td>Second-tier</td>
<td>1 RCT in DPN; ≥ 1 in other painful neuropathies</td>
<td>Carbamazepine, Tramadol, Gabapentin, Lamotrigine, Venlafaxine</td>
</tr>
<tr>
<td>Topical</td>
<td>Mechanism of action</td>
<td>Capsaicin, Lidocaine</td>
</tr>
<tr>
<td>Other</td>
<td>≥ 1 RCTs in other painful neuropathies or other evidence</td>
<td>Bupropion, Paroxetine, Phenytoin, Topiramate, Citralogran, Methadone</td>
</tr>
</tbody>
</table>

### Zostavax- Vaccine for Herpes Zoster
- Indicated for prevention of shingles in age 60 or older
- Live vaccine-contraindicated in immuosuppressed patients
- Administered as a single SC injection

**ZOSTAVAX® [Zoster Vaccine Live [Oka/Merck]]** significantly reduced the risk of developing zoster compared with placebo: 315/19,254 cases (5.4 cases per 1,000 person-years) vs 642/19,247 cases (11.1 cases per 1,000 person-years). The protective efficacy was 51% (95% CI: 44%, 58%).

Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

**Zostavax - Vaccine for Herpes Zoster**

- Vaccine efficacy for the prevention of zoster was highest for those subjects 60 to 69 years of age and declined with increasing age.
- ZOSTAVAX reduced the incidence of zoster by
  - 64% in individuals 60 to 69 years of age (ZOSTAVAX, n=10,370; placebo, n=10,356)
  - 41% in individuals 70 to 79 years of age (ZOSTAVAX, n=7,62; placebo, n=7,559)
  - 18% in individuals 80 years of age or older (ZOSTAVAX, n=1,293; placebo, n=1,332).


**Pharmacologic Management of Neuropathic Pain**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, desipramine, imipramine, nortriptyline, SSRIs, SNRIs, Atypicals</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, oxcarbazepine, gabapentin, pregabalin, lamotrigine, topiramate, phenytoin</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Mexiletine, flecainide</td>
</tr>
<tr>
<td>Topical formulations</td>
<td>Capsaicin, lidocaine, aspirin</td>
</tr>
<tr>
<td>Analgesics</td>
<td>NSAIDs, COX inhibitors, tramadol, opioids</td>
</tr>
<tr>
<td>Others</td>
<td>Levodopa, ketamine, dextromethorphan</td>
</tr>
</tbody>
</table>

*drugs that have demonstrated efficacy in clinical trials*

**Symptomatic Treatment of Neuropathic Pain**

Treatment recommendations

- It is essential to start a given medication at a low dose, and to gradually titrate to efficacy
- If a patient experiences partial pain relief with one drug as monotherapy, a combination of two or more different classes of drugs can often yield better results in terms of efficacy
- In general, when a patient remains pain free for 3 months on a current treatment regimen, consideration to a slow taper should be given
Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

Rational Polypharmacy

- More comprehensive approach with better efficacy and tolerability
- Useful in patients responding poorly to single agents
- Require lower doses than medications used alone
- Fewer side effects
- Combination with opioids help to keep doses steady and manageable

Mechanistic Approach to Treatment

- BBP with NWRT
- Opiate receptors
- Descending Inhibition
- Peripheral Sensitization
- Central Sensitization

Morphine, Gabapentine Combination for Neuropathic Pain

- DB, PC, four-sided crossover trial of 5 weeks duration in 41 patients
- Patients received active placebo, sustained –release morphine, gabapentin, and a combination of gabapentin and morphine
- Mean daily pain at base line was 5.72 on VAS scale
- Mean daily pain dropped to 3.06 with gabapentin-morphine combination group compared with placebo 4.49, gabapentin 4.15 , morphine 3.70
- Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent
Serotonin Syndrome

- Serotonin Syndrome is a rare, but potentially life-threatening adverse drug reaction that results from inadvertent interactions between drugs (including herbal remedies).
- Sx: Nausea, tachycardia, agitation, confusion, myoclonus, mydriasis, tremor, headache, hyperthermia, hypertension, facial flushing, rigidity

New Treatments on the Horizon

- Adenosine agonists
- Cannabinoids
- EP antagonists
- Glycine agonists
- Nicotonic receptor agonists
- Thalidomide analogues
- Opioids
  - New preparations
  - Combinations
  - Transcranial Magnetic Stimulation Therapies

Adenosine Agonists

- Adenosine receptors found in the substantia gelatinosa of dorsal horn
- Decrease neurotransmitter release by decreasing calcium entry presynaptically
- Hyperpolarize postsynaptic membrane by increasing potassium conductance
- Analgesic effects of morphine may be mediated by local release of endogenous adenosine in the spinal cord

Mechanistic Approach to Treatment of Painful Peripheral Neuropathies

**Cannabinoids**

- CB1 receptors present in the CNS
- Both CB1 and CB2 receptors exist in certain peripheral tissues
- It is thought that the CNS effects of cannabinoids are mediated through the CB1 receptor


**Cannabinoids (Cont.)**

- Many studies currently underway in California (And Other Places) studying effects of inhaled cannabis on pain, nausea, spasticity, etc.
- Sublingual CB1 spray in clinical trials
- Other Studies Involving CB

**New Directions in Therapy: Delivery Systems and Expanded Indications***

- Gabapentin GR
- Newer AD and AE Analgesics
- Sufentanil (Chronogesic): nonbiodegradable implant
- E-TRANS fentanyl: iontophoresis-based patch
- Ketamine Protocols and Preparations