Innovative Solutions for Diabetic Neuropathy Pain

Nilesh Patel
Advanced Pain Management
npatel@apmhealth.com
941-744-6960
March 16, 2018. 3:45 - 5:00. Chula Vista Resort. 2501 River Rd. Wisconsin Dells, WI 53965

Disclosures
• No paid relationship with ANY industry
• Not on any paid medical advisory boards
• Speaker Bureau for Electro Core (Vagal Stimulator)
• I am employed by Advanced Pain Management and they have Research Funded by Boston Scientific, Nevro, Abbott, Semnur; Registry Enrollment with VertiFlex for Lumbar Stenosis

Objectives:
• Understand the most current literature pertaining to pathophysiology and treatment of diabetic neuropathy
• Understand the innovations in dealing with Pain from Diabetic Neuropathy (PDN)
ADA specified...

• “With the ADA Standards of Care, we do not recommend opiates for pain management. Would you be able to present on the safer approaches to pain management for people with neuropathy? You can still touch on the topic of opioids, as we do recognize that they are effective for pain, but we want to make sure the information is presented as they are not the first line of defense for treating diabetic neuropathy...
• ...and also ensure our audience has a strong understanding of prevention of neuropathy as well as those other treatment options”

Heidi Dietrich
Associate Manager – Midwest Division 1/3/18

CDC 2016 article quote

• “Several guidelines agree that first- and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and SNRIs.”

• Broadly, ADA agrees with the CDC

Agency for HealthCare Research and Quality

Prevent Complications:
• Intensive glycemic control is more effective than standard control for prevention of amputation
• Home monitoring of foot skin temperature, therapeutic footwear, and integrated interventions are effective for preventing incidence and/or recurrence of foot ulcers.

Recent CDC estimates of diabetes in the US:
- 29.1 million people with diabetes = 9.3% of the population
- Another 86 million people are pre-diabetic (>1 in 3 people)
- Costs: $245 billion (Direct medical costs = $176 & Indirect costs = $69 billion)

Estimates of painful diabetic neuropathy (PDN) prevalence:
- 20% to 26% of those with diabetes have PDN
- ~5.8 to 7.6 million people in the US with PDN

Painful Diabetic Neuropathy: Why Bother?

Painful neuropathy leads to:
- Impaired ability to perform daily activities
- Decrease in quality of life such as general activity, mood, mobility, self-care, recreational and social activities

Sad Reality about lack of effectiveness (PDN medications)

Most patients STOP MEDS with 12 months due to ineffectiveness and/or side effects
Most patients do not switch to a different medication
Questions

Q1. What is the NNT for Gabapentanoids (Gabapentin, and Pregabalin)

• 1
• 2-5
• 4-6
• >6

Questions

Q2. The most effective group of medications for neuropathic pain, based on NNT

• Tricyclic antidepressants (e.g. amitriptyline)
• Gabapentanoids (e.g. Pregabalin and gabapentin)
• Opiates (e.g. Oxycodone, hydrocodone, morphine)
• SSRI/SNRI (e.g. Venlafaxine and Duloxetine)

Questions

Q3. The CDC and State Board guidelines suggest the following

• Lowest possible opiate dose not to exceed 90mg morphine equivalent
• Prescription on Naloxone if patient at high risk for overdose and deaths
• Checking PDMP on patients at initiation of opiate therapy and at least once every three months
• All of the above
### Questions

Q4. Spinal stimulation effectiveness for neuropathic pain, which of the following are true statements?

- For focal neuropathic pain (e.g. foot pain) dorsal root ganglion stimulation is the most optimal option
- For peripheral sensory motor neuropathic pain, High Frequency stimulation has been shown to decrease pain, improve function, and decrease opiate use at 24onth follow up
- For lumbar post laminectomy and CRPS the long term data supports use
- All of the above

### Questions

Q5. Lumbar epidural steroids are effective for which of the following conditions

- Diabetic Neuropathic pain
- Lumbar stenosis with claudication pain when used, as part of a multimodal therapy
- Axial non radicular pain due to lumbar spondylosis
- Post-surgical pain in a patient who has undergone thyroidectomy

### Neuropathic Pain

To better understand the application of these medications, we must first understand:

1. Neurophysiology of Pain
2. Neuro-Modulatory Systems
3. Classes of Medications, Sites of Actions

Then we will tackle clinical use:

1. Effectiveness Data
2. How to use these clinically
But how do these medications provide pain relief?
That requires understanding of some very basic normal physiology and abnormal physiology.

- Signal transduction to conduction to Synaptic transmission
- Ascending and Descending modulation

• 1st 2nd 3rd order
But how do these medications provide pain relief?

That requires understanding of some very basic normal physiology and abnormal physiology.

- Signal transduction to conduction to Synaptic transmission
- Ascending and Descending modulation
- 1st 2nd 3rd order

But how do these medications provide pain relief?

That requires understanding of some very basic normal physiology and abnormal physiology.

- Signal transduction to conduction to Synaptic transmission
- Ascending and Descending modulation
- 1st 2nd 3rd order
- Lateral and Medial Systems


Lateral system, neurons are projected to the somatosensory cortex; Records pain intensity and the site of transmission;

Medial system projects to the anterior cingulate cortex and insular cortex. Thus pain-associated anxiety and fear
Primary afferent nociceptors convey noxious information to projection neurons within the dorsal horn. A subset of these projection neurons transmits information to the somatosensory cortex via the thalamus, providing information about the location and intensity of the painful stimulus. Other projection neurons engage the cingulate and insular cortices via connections in the brainstem (parabrachial nucleus) and amygdala, contributing to the affective component of the pain experience. This ascending information also accesses neurons of the rostral ventral medulla and midbrain periaqueductal gray to engage descending feedback systems that regulate the output from the spinal cord.

• Let us summarize these events as pain comes from Viscera, Joints, Lower Back etc.

• The information reaching the brain needs amplification initially

• But once we determine context and that it is NOT a matter of life and death matter you can focus elsewhere.

Under normal conditions: Eudynia

1. Normally pain is carried by A-delta and c-fibers
Under normal conditions: Eudynia

1. Normally pain is carried by small fibers: A delta and c fibers
2. Touch and proprioception are carried by the larger A beta fibers

Abnormal Pain sensation: Maldynia “Central Hypersensitization” due to:

1. Glutamate/NMDA receptor-mediated sensitization
2. Dis-inhibition: Interneurons and Descending inhibitory pathways
3. Microglial activation: Morphine Hyperalgesia
4. Immune Activation

At 1st order nerve terminals (in the spinal cord dorsal horn) activation of the calcium channels release excitatory neurotransmitters, such as glutamate and substance P, act on 2nd order postsynaptic receptors.

This step is regulated by both local inhibitory interneurons and descending projection neurons from the brainstem to the spinal cord, which is a pharmacologically important target site.
Major inhibitory neurotransmitters include, norepinephrine, serotonin, glycine, opioid peptides, and γ-aminobutyric acid (GABA)

- Norepinephrine acts on α2-adrenergic receptors.
- Serotonin acts on several types of receptors, including 5-HT2a receptors.
- Opioid peptides act on the postsynaptic μ receptors.

So anything that increases serotonin and norepinephrine will dampen the signals.

Likewise, opioid peptides act at μ opioid receptor plays an important role in the analgesic action of morphine.

WHY NORTRIPTYLINE and SEROTONIN? DESCENDING INHIBITORY CONTROL SYSTEMS

Norepinephrine is a principal neurotransmitter facilitating the “descending inhibitory systems”

Norepinephrine is released from the projection neurons descending from the brainstem to the spinal cord and acts on α2-adrenergic receptors.

Serotonin is also released from these descending projection neurons and is thought to act on several types of receptors, including 5-HT2a receptors.
Norepinephrine is a principal neurotransmitter facilitating the "descending inhibitory systems"


61 RCT, 2005 Cochran Review:
TCA of NNT 3.6 for "moderate pain relief"
Venlafaxine (3 RCT): AVG NNT of 3.1
Diabetic neuropathy: NNT 1.3

NNH:
Amitriptyline 6 to 28
Venlafaxine: 9.2 to 16.2

1. Increasing norepinephrine in the spinal cord by reuptake inhibition directly inhibits neuropathic pain through α₂-adrenergic receptors.
2. Increasing norepinephrine acts on the locus coeruleus and improves the function of an impaired descending noradrenergic inhibitory system. Serotonin and dopamine may reinforce the noradrenergic effects to inhibit neuropathic pain.


Major inhibitory neurotransmitters include opioid peptides, norepinephrine, opioid peptides glycine, and γ-aminobutyric acid (GABA). Opioid receptors are G proteinc coupled receptors that are categorized into three subtypes (μ, δ, and κ receptors). μ opioid receptor plays an important role in the analgesic action of morphine. Opioids act not only on the central end of the primary sensory neuron, but also on the brain, brainstem, and spinal cord.

μ opioid receptor stimulation in the spinal cord is a very efficacious mechanism to block synaptic transmission, limiting the number of nociceptive stimuli that reach thalamus and eventually the cortex where conscious perception of pain occurs.

70% of μ opioid receptor are presynaptic and 30% post synaptic

The activation of presynaptic μ receptors (on 1st order C and Aδ fibers) causes the inhibition of calcium ion channel, preventing the release of excitatory neurotransmitters.

The activation of postsynaptic μ receptors (on 2nd order neurons) causes potassium ion channels activation with consequent efflux of potassium ions and hyperpolarization of the projecting cells.

Main actions of Opioids at the dorsal horn

- **μ opioid receptor stimulation** in the spinal cord is a very efficacious mechanism to block synaptic transmission, limiting the number of nociceptive stimuli that reach thalamus and eventually the cortex where conscious perception of pain occurs.
- 70% of μ opioid receptor are presynaptic and 30% post synaptic
- The activation of presynaptic μ receptors (on 1st order C and Aδ fibers) causes the inhibition of calcium ion channel, preventing the release of excitatory neurotransmitters.
- The activation of postsynaptic μ receptors (on 2nd order neurons) causes potassium ion channels activation with consequent efflux of potassium ions and hyperpolarization of the projecting cells.

Major inhibitory neurotransmitters include opioid peptides, norepinephrine, opioid peptides glycine, and γ-aminobutyric acid (GABA).

Gabapentin and pregabalin are GABA analogs that have structural similarity to GABA, bind to the voltage-dependent calcium channel auxiliary subunit α2δ, with a high affinity. These α2δ ligands exert an analgesic effect by suppressing the presynaptic calcium influx and inhibiting the release of excitatory neurotransmitters. Both agents have been found to be effective for the treatment of the numbness and pain associated with PHN and DPN.
Major inhibitory neurotransmitters include opioid peptides, norepinephrine, opioid peptides, glycine, and γ-aminobutyric acid (GABA).

Tramadol and Tapentadol are centrally-acting analgesics with broad activity achieved by combining two established analgesic principles (μ-opioid receptor agonist and noradrenaline reuptake inhibition) in a single molecule. These molecules offer a better balance between efficacy and tolerability than classical opioids and they cause less respiratory depression than traditional opiates.

Not only are these safer, but they are appropriate for acute and chronic settings:

Use of antagonist shift the curve to the left, showing that the greater effect of Tapentadol in acute setting is from Opiates agonist as opposed to NE reuptake inhibition which dominates the action in chronic setting.

Tramadol and Tapentadol are centrally-acting analgesics with broad activity achieved by combining two established analgesic principles (μ-opioid receptor agonist and noradrenaline reuptake inhibition) in a single molecule.


Topentadol

Acute Pain: More Opiate Analgesia
Chronic Pain: More NE mediated analgesia
Multiple Medications Used

- Duloxetine
- Valproic Acid
- Lamotrigine
- Imipramine
- Anticonvulsants
- Antidepressants
- Sodium Channel Blockers
- NMDA- Receptor Antagonists
- Opioids
- Baclofen
- Topicals
- NNT

Peripheral neuropathic pain drugs: NNT

- Tricyclic antidepressants
- Valproic Acid
- Lamotrigine/Phenytoin/Carbamazepine
- Opioids
- Tramadol
- Gabapentin/pregabalin
- SNRIs
- Capsaicin
- NMDA antagonists
- SSRI
- Topiramate
- NNT to achieve pain relief >50%

Peripheral neuropathic pain drugs: NNT

- Tricyclic Antidepressants
- Tramadol
- Gabapentin/pregabalin
- SNRIs Duloxetine, Venlafaxine
- NNT to achieve pain relief >50%
### Gabapentin and Pregabalin: NNT 7

<table>
<thead>
<tr>
<th>Strong for</th>
<th>Weak for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Capsaicin +amate</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Lidocaine patch</td>
</tr>
<tr>
<td>None</td>
<td>Tramadol</td>
</tr>
<tr>
<td>None</td>
<td>RBS-A (SC)</td>
</tr>
<tr>
<td>None</td>
<td>Topical</td>
</tr>
</tbody>
</table>

#### Conclusion

Both gabapentin and pregabalin are effective in reducing pain severity in neuropathic pain conditions. Gabapentin is associated with a lower NNT of 7 compared to pregabalin, indicating a slightly better efficacy. However, both are safe in polypharmacy and do not undergo significant metabolism by phase I or II enzymes. They are excreted unmodified by the kidneys, making them a safe option for patients with renal dysfunction. Gabapentinoids have been proven effective in various neuropathic conditions such as post-herpetic neuralgia, painful diabetic neuropathy, and low back pain.

---


Gabapentin and Pregabalin: NNT 7

Adverse Effects:

- **Pregabalin** is dizziness, followed by somnolence, dry mouth, edema, and blurred vision, with treatment discontinuation due to somnolence occurring in 4% of patients.

- **Gabapentin**, dizziness and somnolence occur in more than 20% of patients and are the most commonly reported adverse effects; other adverse effects include confusion and peripheral edema.

- **For both drugs**, adverse effects are dose-dependent and reversible.

---

**Membrane stabilizers for pain control**

<table>
<thead>
<tr>
<th>Membrane stabilizer</th>
<th>Starting dose/day</th>
<th>Target dose/day</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine Tegretol®</td>
<td>200</td>
<td>600-1200</td>
<td>Sedation, ataxia, diplopia, leukopenia, ↓Na, ↓Platelet</td>
</tr>
<tr>
<td>Valproate Depakote®</td>
<td>400-500</td>
<td>1000-3000</td>
<td>weight ↓, liver failure</td>
</tr>
<tr>
<td>Pregabalin Lyrica®</td>
<td>75</td>
<td>300-600</td>
<td>weight ↑</td>
</tr>
<tr>
<td>Gabapentin Neurontin®</td>
<td>100-300</td>
<td>1800-3600</td>
<td>weight ↑, headache, twitching</td>
</tr>
<tr>
<td>Lamotrigine Lamictal®</td>
<td>50</td>
<td>300-500</td>
<td>rash, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Levetiracetam Keppra®</td>
<td>1000</td>
<td>3000</td>
<td>recurring infections</td>
</tr>
<tr>
<td>Oxicarbamazepine/Unera®</td>
<td>300</td>
<td>600-2400</td>
<td>↓Na</td>
</tr>
<tr>
<td>Topiramate Topamax®</td>
<td>40</td>
<td>30-50</td>
<td>nervousness, flu-like symptoms</td>
</tr>
<tr>
<td>Zonisamide Zonegran®</td>
<td>100</td>
<td>600</td>
<td>weight ↓, renal calculi</td>
</tr>
</tbody>
</table>

---

**Anti epileptics: Dose and AEs**

- **Carbamazepine Tegretol®**: Starting dose/day 200, Target dose/day 600-1200, Side effects Sedation, ataxia, diplopia, leukopenia, ↓Na.
- **Valproate Depakote®**: Starting dose/day 400-500, Target dose/day 1000-3000, Side effects weight ↓, liver failure.
- **Pregabalin Lyrica®**: Starting dose/day 75, Target dose/day 300-600, Side effects weight ↑.
- **Gabapentin Neurontin®**: Starting dose/day 100-300, Target dose/day 1800-3600, Side effects weight ↑, headache, twitching.
- **Lamotrigine Lamictal®**: Starting dose/day 50, Target dose/day 300-500, Side effects rash, Stevens-Johnson syndrome.
- **Levetiracetam Keppra®**: Starting dose/day 1000, Target dose/day 3000, Side effects recurring infections.
- **Oxicarbamazepine/Unera®**: Starting dose/day 300, Target dose/day 600-2400, Side effects ↓Na.
- **Topiramate Topamax®**: Starting dose/day 40, Target dose/day 30-50, Side effects nervousness, flu-like symptoms.
- **Zonisamide Zonegran®**: Starting dose/day 100, Target dose/day 600, Side effects weight ↓, renal calculi.

---

The most effective TCAs for pain are Desipramine and Amitriptyline and their metabolites Nortriptyline and Imipramine. TCAs have been proven to be efficacious in several neuropathic conditions, including painful polyneuropathy, post-herpetic neuralgia, peripheral nerve injury.
The most effective TCAs for pain are Desipramine and Amitriptyline and their metabolites Nortriptyline and Imipramine. TCAs have been proven to be efficacious in several neuropathic conditions, including painful polyneuropathy, post-herpetic neuralgia, peripheral nerve injury, and painful diabetic neuropathy. Adverse Effects:

- **Anticholinergic** effects are a major concern
- Dry mouth, orthostatic hypotension, constipation, and urinary retention
- **Cardiotoxicity**
- **Weight Gain**
- Limits the dosage to less than 100 mg/day

Duloxetine has shown consistent efficacy in painful diabetic neuropathy and low back pain.

Dosing of duloxetine: 30-60 mg 1-2 times daily

Nausea is the most common adverse effect of duloxetine (Decreased by lowering the dosage to 30 mg once daily for 1 week then to 60 mg daily).

Duloxetine and Venlafaxine NNT 6.4

- Duloxetine has shown consistent efficacy in painful diabetic neuropathy and low back pain
- Dosing of duloxetine: 30-60 mg 1-2 times daily
- Nausea is the most common adverse effect of duloxetine (Decreased by lowering the dosage to 30 mg once daily for 1 week then to 60 mg daily)


Tramadol (sufficient data in 2015), Toprentadol

Norepinephrine binds to α₂-adrenergic receptors, localized on presynaptic (nociceptors) and postsynaptic (spinothalamic) neurons, thus inhibiting synaptic transmission with mechanisms identical to those described for μ receptors: blockade of presynaptic calcium ion channels and activation of postsynaptic potassium ion channels.

Tramadol and Taprentadol allows norepinephrine to accumulate in the spinal cord synapses and are μ agonists.


Tramadol (sufficient data in 2015), Topentadol

Because of simultaneous stimulation of $\mu_1 + \alpha_2$:

- Consistent reduction of adverse events (N, V, C)
- Better control of mixed pain, very frequent in several clinical conditions, such as low back pain, in which neuropathic and nociceptive components co-exist
- Better response to norepinephrine and opioids
- Potentially fewer overdose and deaths

Hartrick CT, Roos RA. Tapentadol in pain management: a $\mu_4$-opioid receptor agonist and norepinephrine reuptake inhibitor. CNS Drugs. 2011 May;25(5):359-70.


Studies involving 5% Topical Lidocaine for Painful Diabetic Neuropathy

Lidocaine can penetrate no deeper than 8–10 mm, thus indicated in well-localized neuropathic pain. Minimal Absorption.

Efficacy has been documented in different types of localized neuropathic pain: post-herpetic neuralgia, painful diabetic neuropathy, post-surgical and post-traumatic pain related to incision of the skin.

The most common adverse effects of lidocaine are mild local reactions due to its topical application. Expensive, approved for PHN

Table 3. Summary of GRADE recommendations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect大小</th>
<th>Evidence</th>
<th>Strength</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>Postop</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>Preop</td>
<td>Medium</td>
<td>High</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Postop</td>
<td>Medium</td>
<td>High</td>
<td>Strong</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Note: GRADE criteria refer to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria. This table provides a summary of the GRADE recommendations for each agent, with effect size categorized as low, medium, or high, and evidence quality as low, moderate, or high. Strength of recommendations ranges from weak to strong, with weak being less compelling evidence and strong being more compelling evidence.
Peripheral neuropathic pain drugs: NNT

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>NNT 3.6 and NNH 11.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic</td>
<td></td>
</tr>
<tr>
<td>Oxycodone 10-120/MS 90-240mg</td>
<td>NNT 5.3 and NNH 12.6</td>
</tr>
<tr>
<td>Tramadol up to 400mg</td>
<td>NNT 7.7 and NNH 13.9</td>
</tr>
<tr>
<td>Gabapentin/pregabalin</td>
<td></td>
</tr>
<tr>
<td>SNRs Duloxetine, Venlafaxine</td>
<td>NNT 4.7 and NNH 12.6</td>
</tr>
</tbody>
</table>

Finnerup et al. Lancet 2015 NNT to achieve pain relief >50%

- Although tricyclic antidepressants have long been recommended as a secondary treatment option for chronic low back pain, Duloxetine appears to be more effective than tricyclic antidepressants, as well as being associated with a more favorable safety profile, which could impact the selection of drugs within the antidepressant class.

- Anticonvulsant medications, such as gabapentin and pregabalin, are being prescribed more for radicular low back pain than other back pain, despite the lack of evidence showing that they are effective.

- NSAIDs Small benefits

- Benzodiazepines and acetaminophen ineffective


Single drugs have high NNTs, thus combination therapy common

**Combined gabapentin and nortriptyline is more efficacious than either drug given alone for neuropathic pain**, therefore these Canadian authors recommend use of this combination in patients who show a partial response to either drug given alone and seek additional pain relief.


**Ample RCTs data for Combination therapy**


**“Central Hypersensitization” due to….”**

Microglial and Immune Activation:
What can be done about this?
LBP: Combination therapy show improvement in pain, and function

**TOPENTADOL** = Opiate AGONIST + NE increase
**PEA** = Mast Cell Stabilizer plus **Micgrolia**

**Palmitoylethanolamide (PEA)**, a member of the N-acylethanolamine family, produced by most mammalian cells and which is particularly abundant in brain tissues. PEA exerts its effects on cellular targets involved in the generation and maintenance of pain [13] by down-modulating

Newer RCTs data for Combination therapy
Combination therapy show improvement in pain, and function as well reduction in dose of Topenadol

Post lumbar Laminectomy Syndrome:
(Combination therapy TPD + PGB then PEA added)

Newer RCTs data for Combination therapy show improvement in pain, and function in Post lumbar Laminectomy Syndrome: (Combination therapy TPD + PGB then PEA added).

Studies involving 5% Topical Lidocaine for Painful Diabetic Neuropathy


Lidocaine can penetrate no deeper than 8–10 mm, thus indicated in well-localized neuropathic pain. **Minimal Absorption.**

**Efficacy** has been documented in different types of localized neuropathic pain: post-herpetic neuralgia, painful diabetic neuropathy, post-surgical and post-traumatic pain related to incision of the skin.

The most common adverse effects of lidocaine are mild local reactions due to its topical application.


**FDA Approved for PDN**

Drugs approved for pain in diabetic neuropathy:
- Duloxetine
- Pregabalin
- Tapentadol

Agency for HealthCare Research and Quality

- **SNRI** (Duloxetine, Venlafaxine): Moderate
- **AEDs** (Pregabalin, Gabapentin, Oxcarbazepine): Low
- **TCAs** ( Amitriptyline, Nortriptyline): Low
- Atypical opioids, botulinum; alpha-lipoic acid
- Spinal cord stimulation are more effective than placebo but with low SOE.


Currently used Therapies

1. **Anticonvulsants**: Gabapentin, Pregabalin (66.6%)
2. **Antidepressants**: Amitriptyline, duloxetine, Nortriptyline, Venlafaxine, Desipramine (17.4%)
3. **Opioids and Atypical Opiates**: Tramadol, Tapentadol oxycodone, morphine (12.7%)
4. **Topical Agents**: lidocaine, capsaicin (3.3%)
5. Mindfulness, CBT, Modalities: Unknown
6. **Conventional low frequency spinal cord stimulation**

AHCPR: Pregabalin

Figure 7. Standardized mean difference in pain scores comparing pregabalin with placebo stratified by studies found in the published literature versus those found only in ClinicalTrials.gov

AHCPR: Tramadol and Topentadol

Figure 5. Meta-analysis of calculated standardized mean differences for studies comparing an allopregol opioid with placebo for pain outcome

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Outcome</th>
<th>Follow-up weeks</th>
<th>Tramadol n/N</th>
<th>Placebo n/N</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakayama 2011</td>
<td>PE 6</td>
<td>Tramadol 85</td>
<td>65</td>
<td>-1.10 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Freeman 2007</td>
<td>VE 8</td>
<td>Tramadol 100</td>
<td>90</td>
<td>-0.30 (0.13)</td>
<td></td>
</tr>
<tr>
<td>Nakayama 2011</td>
<td>VE 6</td>
<td>Topentadol 12</td>
<td>12</td>
<td>-1.10 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Yoon 2014</td>
<td>VE 12</td>
<td>Topentadol 150</td>
<td>150</td>
<td>-0.46 (0.22)</td>
<td></td>
</tr>
<tr>
<td>Sato 2009</td>
<td>VE 12</td>
<td>Topentadol 100</td>
<td>100</td>
<td>0.70 (0.30)</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td></td>
<td></td>
<td>-1.10 (0.05)</td>
<td></td>
</tr>
</tbody>
</table>

Sad Reality about effectiveness and use of PDN medications

Most patients STOP MEDS with I 12 months due to inefficacy and/or side effects
Most patients do not switch to a different medication


AHCPR: Tramadol and Topentadol

Figure 5. Meta-analysis of calculated standardized mean differences for studies comparing an allopregol opioid with placebo for pain outcome

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Outcome</th>
<th>Follow-up weeks</th>
<th>Tramadol n/N</th>
<th>Placebo n/N</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakayama 2011</td>
<td>PE 6</td>
<td>Tramadol 85</td>
<td>65</td>
<td>-1.10 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Freeman 2007</td>
<td>VE 8</td>
<td>Tramadol 100</td>
<td>90</td>
<td>-0.30 (0.13)</td>
<td></td>
</tr>
<tr>
<td>Nakayama 2011</td>
<td>VE 6</td>
<td>Topentadol 12</td>
<td>12</td>
<td>-1.10 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Yoon 2014</td>
<td>VE 12</td>
<td>Topentadol 150</td>
<td>150</td>
<td>-0.46 (0.22)</td>
<td></td>
</tr>
<tr>
<td>Sato 2009</td>
<td>VE 12</td>
<td>Topentadol 100</td>
<td>100</td>
<td>0.70 (0.30)</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td></td>
<td></td>
<td>-1.10 (0.05)</td>
<td></td>
</tr>
</tbody>
</table>

Sad Reality about effectiveness and use of PDN medications

Most patients STOP MEDS with I 12 months due to inefficacy and/or side effects
Most patients do not switch to a different medication
AHCPR: Spinal Stimulation
(Failed conventional Rx, Multicenter RCT; N=96, >6 mo f/u European studies)


• N= 60: RCT 20 CMP and 40 CMP plus SCS.
• Netherlands, Denmark, Belgium & Germany from 11/08 and 10/12. Refractory diabetic neuropathic pain >5/10 >1 year 6 month post in the Netherlands, Denmark, Belgium and Germany


Conventional Spinal Stimulation versus Conventional Medical Practice

• N= 60: RCT 20 CMP and 40 CMP plus SCS.
• Netherlands, Denmark, Belgium & Germany from 11/08 and 10/12. Refractory diabetic neuropathic pain >5/10 >1 year 6 month post in the Netherlands, Denmark, Belgium and Germany

Conventional Spinal Stimulation versus Conventional Medical Practice

- **N= 60: RCT 20 CMP and 40 CMP plus SCS.**
- **Netherlands, Denmark, Belgium & Germany from 11/08 and 10/12.**
  Refractory diabetic neuropathic pain >5/10 >1 year 6 month post in the Netherlands, Denmark, Belgium and Germany

1. **Because “over 50% pain relief after 3 years of SCS therapy was reported by five out of six patients with PDN in a non-randomised studies (Daousi 2005), …long-term follow-up of the cohort of this RCT is required to verify if these results are corroborated in patients with PDN”**

2. **Since then the technology has improved dramatically**


**Major inclusion criteria**
- Clinical diagnosis of peripheral polyneuropathy (PPN) of the upper or the lower limb(s)
- Refractory to conservative therapy for >3 months
- Mean upper or lower limb VAS 25 out 10 cm

**Major exclusion criteria**
- Mononeuropathy or neuropathies of the trunk
- Failed prior SCS trials for chronic intractable pain

PDN Study HF 10: Pain Relief (N=25 3 mo follow up at NANS 2018; 18 LE 7 UE):

- Clinical diagnosis of peripheral polyneuropathy (PPN) of the upper or the lower limb(s)
- Refractory to conservative therapy for >3 months
- Mean upper or lower limb VAS 25 out 10 cm

**Major exclusion criteria**
- Mononeuropathy or neuropathies of the trunk
- Failed prior SCS trials for chronic intractable pain
PDN Study HF 10: Pain Relief
(N=25 3 mo follow up at NANS 2018; 18 LE 7 UE:

**Videos**

- N:\Marketing\Patient Testimonials\2018\angela-diabetes\angela--diabetic-neuropathy.mp4
- [https://www.youtube.com/watch?v=kqEgHQHAMqM&sns=em](https://www.youtube.com/watch?v=kqEgHQHAMqM&sns=em)
- [https://www.youtube.com/watch?v=FRpCWB_Eh4Y](https://www.youtube.com/watch?v=FRpCWB_Eh4Y)
- [https://youtu.be/Zy1hTemOf8k](https://youtu.be/Zy1hTemOf8k)
- [https://www.youtube.com/watch?v=tvPuHLK6W8&sns=em](https://www.youtube.com/watch?v=tvPuHLK6W8&sns=em)

**Current Multi-Center US PDN HF-10 SCS Study**

**Inclusion:**
- Diagnosis of diabetic neuropathy (PDN) of the lower limbs.
- Minimum of 12 mo conservative Rx including failed trial of Pregabalin (just need to have tried Lyrica)
- Average VAS > 5 average over 7 days at the time of enrollment.
- Pain Meds stable for at least 30 days prior to enrollment.

**Exclusion:**
- Diagnosis of lower limb mono-neuropathy, lower limb amputation, gangrenous ulcers of lower limbs (>=3cm).
- Hgb A1C > 9%.
- BMI > 40.
- MEDD greater than 120mg.
- Failed prior SCS Trial or Explanted Permanent Implant.
- Existing drug pump or implanted device.

**Responder Rate (%)**

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>EOT</th>
<th>1 Wk</th>
<th>1 Mo</th>
<th>3 Mo</th>
<th>6 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAS (cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Responder Rate (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All Implanted Subjects (N=18)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Implanted PDN Subjects (N=7)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Answers**

Q1. What is the NNT for Gabapentanoids (Gabapentin, and Pregabalin)

- 1
- 2-5
- 4-6
- >6

*Answer d.*


**Answers**

Q2. The most effective group of medications for neuropathic pain, based on NNT

- Tricyclic antidepressants (e.g. amitriptyline)
- Gabapentanoids (e.g. Pregabalin and gabapentin)
- Opiates (e.g. Oxycodone, hydrocodone, morphine)
- SSRI/SNRI (e.g. Venlafaxine and Duloxetine)

*Answer a.*


**Answers**

Q3. The CDC and State Board guidelines suggest the following

- Lowest possible opiate dose not to exceed 90mg morphine equivalent
- Prescription on Naloxone if patient at high risk for overdose and deaths
- Checking PDMP on patients at initiation of opiate therapy and at least once every three months
- All of the above

*Answer d.*

Answers

Q4. Spinal stimulation effectiveness for neuropathic pain, which of the following are true statements?
• For focal neuropathic pain (e.g. foot pain) dorsal root ganglion stimulation is the most optimal option
• For peripheral sensory motor neuropathic pain High Frequency stimulation has been shown to decrease pain, improve function and decrease opiate use at 24 onth follow up
• For lumbar post laminectomy and CRPS the long term data supports use
• All of the above
• Answer d.

Kapural L et al. Comparison of 10-MHz High Frequency and Traditional Low Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multi-center, Randomized Controlled Trial Trial. Neurosurgery. 0: 1–10, 2018

Answers

Q5. Lumbar epidural steroids are effective for which of the following conditions
• Diabetic Neuropathic pain
• Lumbar stenosis with claudication pain when used, as part of a multimodal therapy
• Axial non radicular pain due to lumbar spondylosis
• Post-surgical pain in a patient who has undergone thyroidectomy
• Answer: b.


Answers

Q1. What is the NNT for Gabapentanoids (Gabapentin, and Pregabalin)
• 1
• 2-5
• 4-6
• >6

Answer d.

Answers

Q2. The most effective group of medications for neuropathic pain, based on NNT

- Tricyclic antidepressants (e.g. amitriptyline)
- Gabapentenoids (e.g. Pregabalin and gabapentin)
- Opiates (e.g. Oxycodone, hydrocodone, morphine)
- SSRI/SNRI (e.g. Venlafaxine and Duloxetine)

Answer a.


Answers

Q3. The CDC and State Board guidelines suggest the following

- Lowest possible opiate dose not to exceed 90mg morphine equivalent
- Prescription on Naloxone if patient at high risk for overdose and deaths
- Checking PDMP on patients at initiation of opiate therapy and at least once every three months
- All of the above

Answer d.


Answers

Q4. Spinal stimulation effectiveness for neuropathic pain, which of the following are true statements?

- For focal neuropathic pain (e.g. foot pain) dorsal root ganglion stimulation is the most optimal option
- For peripheral sensory motor neuropathic pain: High Frequency stimulation has been shown to decrease pain, improve function and decrease opiate use at 24 month follow up
- For lumbar post laminectomy and CRPS the long term data supports use
- All of the above

Answer d.

- Kapural L et al. Comparison of 10 kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. Neurosurgery 0: 1–10, 2016
Answers

Q5. Lumbar epidural steroids are effective for which of the following conditions

- Diabetic Neuropathic pain
- Lumbar stenosis with claudication pain when used, as part of a multimodal therapy
- Axial non radicular pain due to lumbar spondylosis
- Post-surgical pain in a patient who has undergone thyroidectomy

- Answer: b.