Management of Neuropathic Pain

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Disclosures

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What has been your experience managing neuropathic pain?
Managing Neuropathic Pain (NP)

The Broader Context and Mechanisms of NP
The Diagnostic Approach to NP
Data-Based Approach to Treatment for NP

The Context of NP

Afflicts millions of people worldwide (exact numbers unknown)

Significant Impact on:
- QoL
- Emotional Functioning
- Substantial Societal Cost
- Challenging Pain Syndrome to Treat

Only 40-60% will have a partial response
Can be Uniquely Challenging in Palliative Care Setting

Causes of Neuropathic Pain are Numerous

- Diabetic Neuropathy (DPN)
- Post-Herpetic Neuralgia (PHN)
- Lumbar Radiculitis
- Auto-Immune Related
- Vitamin B12 Deficiency
- Alcohol Related
- Trigeminal Neuralgia
- Central (Post-Stroke/MS)

Palliative Care Related:
- Chemotherapy-Induced
- Post-Surgical
- Radiation-Induced
- Tumor Infiltration of a Plexus
- Multiple Myeloma
- HIV Neuropathies
What is Neuropathic Pain?

“Pain caused by a primary lesion or dysfunction in the nervous system”

IASP

Difference between Nociceptive and Neuropathic Pain

What is Happening on the Molecular Level?
Concepts of Peripheral and Central Sensitization

The Normal Functioning Pain System
PNS: Increased Peripheral Activation
*The Alarm Doesn't Turn Off*

CNS: Inputs are Amplified and Sustained
*The Flood Gates are Open*

CNS: Loss of Descending Inhibition
*The Off Switch is Switched Off*
Diagnosing Neuropathic Pain

History, History, History!
- Characterize the Pain (burning, electrical)
- Location/Distribution of Pain
- ‘Medication History

Exam Findings (Allodynia, Hyperalgesia, Hyperpathia)
Diagnosing Neuropathic Pain

Lab Eval: Glu, B12, TSH, ANA, RF, HCV, SPEP/UPEP, etc
*Paraneoplastic Panel if fits clinically

EMG --> ? biopsy for small fiber PN if EMG (-)

MRI Imaging if indicated

Pharmacologic Management of Neuropathic Pain

Treating Neuropathic Pain is a Real Pain!

Only 40-60% will have a partial response
Why is it hard to treat?

- So Many Causes, Mixed Neuropathies,
- Meds Not Fast Acting
- Unpredictable Efficacy
- Medication Side Effects
- Data is Not Great
**Significant Limitations of NP Data Exist**

- Few Head-to-Head; Most Drug x v Placebo
- Indirect Comparisons btw Trials
- Variation in Outcome Measures
- Limited follow-up intervals (<3 mos)
- Most RCTs focus on PHN or DPN
- Extrapolate to other types of NP? Few Cancer Studies

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**Why keep treating NP?**

"Fall seven times, stand up eight."

~Japanese Proverb

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**Treating Neuropathic Pain**
Treating NP: Match the Drug to the Patient

Matching Drug to Patient is a Balance:
→ Consider Drug and Patient Factors
→ Can you treat pain + another illness?
→ Avoid an agent that may put pt at risk

Eg: TCA in young pt with depression or insomnia
Avoid in elderly patient or those w/ heart dz

First Line Therapies

Anti-Depressants with Norepinephrine and Serotonin Activity

Increase concentration of NE and SHT in synaptic Cleft

Tricyclic Antidepressants (TCAs)

Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
Tricyclic Anti-Depressants:

No FDA approval for NP; Numerous RCTs w/ Benefit in NP
- PHN, DPN, Post-Mastectomy Pain

Benefits: Inexpensive, Once Daily, Mood Effects

Downside: Side effects
- Orthostasis, Sedation/Confusion, Dry Mouth, Constipation, Urinary Retention, Cardiac

Tricyclic Anti-Depressants:

Secondary v Tertiary Amines
Nortriptyline <<< Amitriptyline

Qhs Dosing / “Start low, Go slow”

Goal of 50mg-100mg Qhs; 6-8 Weeks for Effect

Qtc Monitoring - Caution w/ Heart Disease, Ekg >40 yrs

Tricyclic Anti-Depressants: Data

Best data for:
- DN (NNT 1.3)
- PHN (NNT2.2)
- Post-mastectomy pain (NNT 2-3)

Side Effects:
- Nausea (NNH minor 6)
- Somnolence (NNH minor 11)
- Constipation, and reduced appetite

NNH major SAE:15
SNRIs: Duloxetine

FDA approved for DPN, Fibromyalgia, Chronic MSK Pain
3 studies w/ DN: NNT ~5
Benefits: Mood effects and chronic pain, once-daily dosing, ease of titration
Dose to 60mg/day (Higher doses ≠ More Benefit)
Most common SE: Nausea (NNH minor 6), somnolence, constipation, and reduced appetite
Caution w/ other 5HT agents and if Liver dysfunction
Recent Data for Chemotherapy-Induced PN

Gabapentin & Pregabalin

Do not bind to GABA receptor!
Bind to Ca+ Channel in dorsal horn -> decrease pain neurotransmission

Gabapentin

FDA Approved for: PHN
Data for DPN, Neuropathic Cancer Pain but not for CIPN or HIV-assoc neuropathy
Initiation 100mg TID or 300mg qhs
Increase by 300mg/d q3-7 days
Goal of 1,800-3,600/d divided in TID dosing
Main SE: Somnolence, dizziness, edema
Caution in renal dysfxn or medically frail
*Data Controversy
Pregabalin

FDA Approved for PHN, DPN, and Fibromyalgia
- Initiate at 50mg po BID or TID
- Increase q3-5d to goal of 300-450mg/day divided in BID or TID dosing
- Less if renal dysfunction or medically frail
- Side effects similar to Gabapentin
- May reach analgesia faster than Gabapentin
- NNT for PHN & DPN : 4.2

Topical Lidocaine

- Blocks Na+ channels = Block pain signaling
- Best data/indication is for localized neuropathic pain; minimal central effects
- First Line for PHN
- Limited systemic effects = ideal in med frail, elderly

Topical Lidocaine

- Pros
  - NNT 4-6, NNH 40
  - Good for localized neuropathies (FDA approved for PHN)
- Cons
  - Not as effective in widespread neuropathies
  - Expensive in patch form (consider 5% ointment)
Second Line Therapies

Tramadol & Opioid Analgesics

Efficacy in multiple RCTs w/ multiple NP
Concern long-term safety: Used if no response to 1st line agents

However: considered first-line for those with:

- Acute NP
- Temporizing Measure while titrating First Line Agent
- Exacerbations of Severe NP
- NP due to Cancer

Tramadol

Binds mu receptors weakly, as well as inhibiting NE and serotonin uptake
50-100mg q4-6hrs pm, max 400mg/day
Special considerations: Sz Threshold, SHT Syndrome
Lower risk of addiction
Data:
- NNT 3.8, studies for PHN, DN, phantom
- NNH major 8.3
Opioids and NP

- Multiple RCTs showing efficacy similar to TCAs and Gabapentin
- Double-Edged Sword: Potent and Fast Onset, but...
- Issues when used chronically:
  - Tolerance
  - Hormone and Immune Effects
  - Opioid-Induced Hyperalgesia
  - Addiction & Aberrancy
- Less of concern w/ patients with malignant cancer

A Word on Methadone and NP...

- The NMDA receptor has been implicated in NP
- Methadone blocks the NMDA receptor
  - Perhaps More Impact on NP
  - Not shown widely in human studies
- Methadone can be tricky!

Third Line Therapies
### Third Line Agents

- **Anti-Epileptics**
  - eg, Carbamazepine, Lamotrigine, Oxcarbazepine, Topiramate, & Valproic Acid
- **Low-Concentration Topical Capsaicin**
- Dextromethorphan
- Memantine
- Mexiletine

* Exception: Carbamazepine/Oxcarbazepine 1st line for TGN


### Cannabinoids and NP

Extracts w/ Some Efficacy in MS Pain and Possibly Cancer

Benefit Appears Modest

May be Helpful if Concomitant Nausea, Appetite issues

Risks of Abuse and Altered Mental Status

### More Advanced Therapies:

- **IV Lidocaine**
  - Blocks Na+ Channels
  - Chronic Pain: Cochrane Review 2011
    - Better than placebo but marginal
  - Cancer Pain: Sharma JPSM 2009
    - 50pt X-over RCT, 68% w/ Neuropathic Pain
    - Improvement in pain: 75% vs 25% in placebo group
    - Effect ~9 days
More Advanced Therapies:

Ketamine
- NMDA antagonist, also NE & 5HT effects
- Subanesthetic Doses, IV or PO
- Small RCTs w/ benefit
- Recent large RCT w/ SubQ w/o benefit for Cancer Pain
- Need more studies

Combination Therapies for NP

Data Suggest Combination Regimen Better than Single Agents
- Gabapentin + Morphine ER: RCT of PHN/DPN (NEJM 2005)
- Gabapentin + Nortriptyline: X-Over RCT of PHN/DPN
  (Lancet 09)
  Better Effect with Lower Doses, No Change in Adverse Events
Cochrane Review: Good Data thus Far, Not for Particular Combo
  Need More RCT for both Placebo and Single Agent

Newer/Interventional Therapies

- Qutenza: 8% High Concentration Topical Capsaicin, used for PHN
- Tapentadol: Weak-mu agonist + NE, similar potency to Oxycodeone, No Studies in NP
- Milnacipram: FDA Approved for Fibromyalgia, No studies in NP
- Botox Inj for PHN: Mixed data
- Spinal Cord Stimulator
- Intrathecal Pump w/ Bupivacaine/Clonidine
- Deep Brain/Motor Cortex Stimulation
Non-Pharmacologic Therapies

- TENS unit*
- Acupuncture
- Mind-Body Techniques
- Physical Therapy (Desensitization, Gait Stability)

Consensus Guidelines for NP

IASP Consensus Guidelines

1. Initiate treatment with:
   - Secondary-amine TCA or SNRI
   - Gabapentin or Pregabalin

   If localized, consider Topical Lidocaine w/ above

   Consider Tramadol or Opioids for:
   - Acute NP
   - Cancer Pain
   - Exacerbations
   - While Titrating above Agents
IASP Consensus Guidelines

2. Reassess pain and QOL
   → If substantial improvement (≤3/10): continue treatment
   → If partial relief at adequate dose: add a second 1st line agent
   → If no or inadequate relief (<30%) despite adequate dose: switch to another 1st line agent

3. If trials of 1st line agents fail, consider 2nd/3rd line, or referral to multidisciplinary pain center

The Take Home Points

Neuropathic Pain is Challenging Pain Syndrome
Sustained and Amplified by Peripheral/Central Sensitization
Match Drug to Patient
Keep Trying! Cycle through agents
Consider Combination Regimens
Consider Pain Consult for Advanced Therapies if Pain Remains Refractory
Thank You! Questions?