Multiple Sclerosis and Pain

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Disclosures

Official:

• Will discuss off label medication uses

• CONFLICTS:
  • Funded research and consulting: Teva.
  • Consulting: Kineta
  • Research: Pfizer, Vertex, Axsome

The Obvious: I am not a neurologist

OTHER Conflicts

• I am a clinician, not a basic scientist
• My preference it to see patients with neuropathic pain and/or CRPS
• I will express some opinions
Jean-Martin Charcot

First describes Multiple Sclerosis in 1868

- PubMed for “Pain Multiple Sclerosis” from 1868: first paper on the topic in English in 1969

Treatment of Pain in Multiple Sclerosis — Preliminary Report

Martin L. Albert, M.D.

My neurology rotation as an intern: “aside from trigeminal neuralgia and painful spasticity, MS isn’t a painful disease”

NOW

• A focus on quality of life, patient experience, and new treatments have dramatically increased awareness of pain in MS.

• A search at: https://clinicaltrials.gov/ for Multiple Sclerosis and Pain reveals:

  187 Studies found for: Pain | Multiple Sclerosis

• I anticipate our understanding of pain in MS and treatment options will expand dramatically in the next few years
Pain

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

International Association for the Study of Pain (IASP)

Chronic Pain: ongoing pain with no clear endpoint that impacts quality of life
Pain is connected to the Body

But Pain Is an Experience of the Brain

Everything is Consciousness
Beyond the ongoing pain

- Less Active → deconditioned, obese, injury-prone
- Altered Mood: irritable, depressed, anxious, angry
- Poor Sleep
- Loss of Energy
- Loss of Libido
- Work/Vocational Issues
- Legal Issues
Still more

- Financial Concerns
- Family Stress
- Decreased Self Esteem
- Frequent use of the health care system, with decreased satisfaction
- Use of Medications
- Fear of Injury
- Misconceptions
- Meaning, faith, Quality of Life
Pain in Multiple Sclerosis

A recent multi-site Italian study looking carefully for neuropathic pain in 1249 patients:

- 34% with pain, of those:
  - 67% with “nociceptive pain”, primarily MSK
  - 43% neuropathic, 7.6% TN


Pain in Multiple Sclerosis

- Heterogeneous
- Fluctuates
- Neuropathic pain is a subset
- Can be unrelated to Multiple Sclerosis diagnosis
- Treatments not studied very extensively
Pain in MS vs Other conditions

**Multiple Sclerosis**
- Depression, anxiety, distress predict pain
- More pain = poorer function
- Trigeminal neuralgia not infrequent
- Dramatically waxes and wanes
- Disease modification

**Everything else**
- Depression, anxiety, distress predict pain
- More pain = poorer function
- Trigeminal neuralgia is rare
- Major fluctuations unusual
- Disease modification = aspirational goal
What is Neuropathic Pain?

- Pain caused by a lesion or disease of the somatosensory nervous system.
  
  International Association for the Study of Pain 2011:  [www.iasp-pain.org/resources/painDefinition](http://www.iasp-pain.org/resources/painDefinition)

- In English: Pain originating from demonstrable damage or disease of the nerves, spinal cord, or brain. Not originating in the bones, muscles, organs.

Fig. 4. Anterior spinothalamic tract and the spinoreticular tract.
History and Symptoms Common to Neuropathic Pain

- Pain described as burning, tingling, electric, numb, or shooting, unusual
- Sensitive to cold, heat, or touch
- Changes in appearance
- Patient may guard and protect painful area
- Possible reports of neuro deficits

- History of injury, disease associated with nerve injury
- Impaired motor control or guarding
- History of other neuropathic pain
- May worsen at night
- Occasionally, neglect: “it doesn’t feel like my arm”
Assessing the Pain

- Number scale: 0 to 10, none to worst imaginable
- Ask about ALL the pain
- Also: impacts on function, mood, work, recreation, health, family, sleep, sex, etc
- Ask the patient: “what do you think is causing this pain?” “what do you think needs to be done?”
- Physical examination- complete = not limited to neuro exam
- Testing

The UW PainTracker™

Assess and graph core patient-reported outcomes of chronic pain management over time.

Displays relationships between chronic pain treatments and patient outcomes.

Identifies high-risk situations.

Pain Tracker Scores

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</tr>
<tr>
<td>Taper</td>
<td>Yes</td>
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Pain intensity & Interference (lower is better)

- Pain intensity: 9/10
- Pain interference: 9/10

Sleep (lower is better)

- Sleep Initiation: 5/10
- Sleep Maintenance: 6/10

ODI & Important Activity Difficulty (lower is better)

- ODI: 60/100
- Activity Difficulty: 8/10

QOL & Satisfaction

- Quality of Life: 9/10
- Treatment Satisfaction: 2/10

Days With Excess Meds (Last Month): none

Important Activity: putting on my shoes
Physical Examination

• Appearance
  • Guarding, loss of range of motion
  • Atrophic changes
• Loss: Sensory, motor, reflex
• Positive Sensory Findings:
  • Allodynia: painful response to normally nonpainful stimuli -- light touch, cold, vibration
  • Hyperalgesia: increased response to painful stimuli
  • Hyperpathia: repeated stimulus becomes more painful
• MSK: general screen for the entire body, more detailed of painful region
“Mixed” pain

• Neuropathic pain may coexist with other pain types
• Nociceptive or musculoskeletal pain may need different treatment than neuropathic component
• Therefore, it is not uncommon to need combination treatment to optimize outcome
Effectively treating pain often tied to improving mood, coping, sleep, and function while reducing distress.
Balancing Treatment: 
the sum is greater than the parts

**Mental Health:**
CBT, Self Management, Mindfulness, Acceptance, Control

**Medical:**
Disease management
Medication
Intervention
Coordination
Reinforcement

**Rehabilitation:**
Improve function
Overcome deconditioning
Independent exercise
Pacing

**Background:** Previous experiences, genetics, OVERALL HEALTH, insurance, work, disability, money, family, leisure, meaning
Mechanism based treatment

Rational, sounds good, and it is the future, BUT... we aren’t there yet

MS Specific Medication Trials for PAIN

Few

No 1\textsuperscript{st} line evidence
Medication Options for Neuropathic Pain

Best Evidence:
- Antidepressants:
  - TCAs: Nortriptyline, Desipramine (Amitriptyline, etc)
  - SNRIs: Duloxetine, Venlafaxine
- Gabapentin, Pregabalin
- Carbamazepine for TGN
- Opioids + Tramadol*
- Topical Lidocaine Patch

Second-line:
- Opioids and Tramadol*

Others:
- Other Antiepileptics
- Other Antidepressants
- Capsaicin (PHN)
- ETC: alpha 2 agonists, antiarrhythmics, etc

Attal N et al, Eur J Neurol. 17(9):1113-e88, 2010
Other treatments not well represented

• Mental health: cognitive behavioral approaches, mindfulness, hypnosis
• Physical activity/exercise: physical therapy, stretching, aerobic exercise, Yoga, Pilates, Tai Chi
• Diet, weight loss, sleep
• Alternative medicine approaches
• Interventions/Procedures
• Disease and comorbidity management
• New, developing medications
Medications that are used, but..............

• NSAIDs: for neuropathic pain:
  • Absent from ANY neuropathic guideline
  • Commonly used in the US and Europe in clinical practice
  • Despite being a wide-spread treatment for pain, there is a paucity of neuropathic NSAID clinical trial data, though suggestive animal data²
    Pain. 2009 Jun;143(3):169-71
  • Minimal evidence for many chronic pain conditions

• SSRIs: widely used, minimal positive data
  • Absent from ANY neuropathic guideline
Tricyclics

**The Good**
- Many trials for many conditions
- Recognized as first-line tx for neuropathic pain, headache, evidence in MSK
- Sleep
- Cheap
- Nortriptyline/Desipramine may be better tolerated

**The Bad**
- Many contraindications
- Excessive death
- Often underdosed (dose 50-150 mg)
- Often prescribed despite problems
- Check ECG/QT/interactions
- Anticholinergic effects

Attal N et al *Eur J Neurol* 2006
Salerno et al *Arch Int Med* 2002
Watson et al *Neurology* 1998

Gore M et al *Pain Pract* 2006
Duloxetine

• Selective serotonin norepinephrine reuptake inhibitor (SSNRI)\(^1\)

• Approved for “neuropathic pain associated with diabetic peripheral neuropathy” \(^2,3,4\)

• Also FDA approved for chronic MSK pain, fibromyalgia, GAD, depression

• Nothing better than duloxetine for low back pain


• Dosing: start 20-30 with food, effective dose most commonly 60 mg

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Gabapentin

• 1994: available, unknown mechanism, not for pain
• 1996: Case series in neuropathic pain suggestive of efficacy\(^1\)
• 1998: largest drug studies ever completed for neuropathic pain published\(^2,3\)
• Absorption decreases as dose increases
• Effective doses: 1200-2400 mg/day, max dose 3600 mg/day
• Doesn’t work for MSK pain without sensitization

**Pregabalin**

- Compared to gabapentin:
  - More potent, faster onset
  - Linear absorption (90% at all doses)$^{1,2}$
  - Increased bioavailability$^2$
  - BID or TID dosing$^2$
- Begins working in 1 day$^3$
- Reduces allodynia$^3$
- Potentially effective in treatment resistant patients$^4$
- May be opioid sparing$^5$

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2. Lyrica Package Insert
Low dose naltrexone

• Toll-like receptor 4 or TLR4 antagonist, other mechanisms possibly including opioid growth factor
  • Macrophages and microglia
  • Anti-inflammatory effect

• Studies in Fibromyalgia, Crohn’s Disease and MS

• Multiple Sclerosis:
  • Small studies with variable results: improvements in pain and QOL
  • Dose usually 4.5 mg/day or less

Trigeminal Neuralgia

- 5-10% of Multiple Sclerosis patients, can be presenting problem
- Medications: carbamazepine, oxcarbazepine, misoprotolol
- Surgery: lower success rate than non-MS TN
  - Radiosurgery
  - Decompression
  - Other neuro-destructive approaches
- Important to distinguish from neuropathy: Head and/or facial pain in the distribution of one or more branches of the trigeminal nerve caused by another disorder and indicative of neural damage.

Cannabis, Cannabinoids

- Much suggestive evidence in MS
- Mostly non-standardized dosing/delivery
  - Nabiximols (Sativex®) is a sublingual spray 2.7 mg THC and 2.5 mg CBD per dose approved in the UK and other countries for treatment of various aspects of MS
- Review of reviews: “Recent high quality reviews find cannabinoids may have modest effects in MS for pain or spasticity. Future research should include studies with non-cannabinoid comparators; this is an important gap in the evidence.”

Combination pharmacotherapy

2012 Cochrane Review: “Multiple, good-quality studies demonstrate superior efficacy of two-drug combinations...(limited data)...preclude the recommendation of any one specific drug combination for neuropathic pain”

More recent studies:

• Pregaballin + imipramine in painful polyneuropathy= better pain control, more side effects in a DBPCRT, crossover design vs either agent

• Pregabalin, duloxetine, or combo in pDPN: trends, but not clear superiority

• Morphine, nortriptyline, combo: superior efficacy with combo

Who is an interventional candidate?

**Green light:**
- Localized pain: one body region, one nerve, one area
- Pain consistent/persistent
- History, physical, and diagnostic testing consistent
- Distress, mood, medical illness under control
- Reasonable effort at initial conservative treatment
  - Medications
  - Rehabilitation = physical therapy
- Reasonable expectations

**LESS good candidate:**
- Diffuse/widespread pain
- Poorly managed anxiety, depression, substance use
- Pain with minimal stimulation
- Unrealistic expectations
- Unwilling to be active in their care
- Pain that fluctuates/migrates
- Others:
  - High dose opioids?
  - Smoking?
  - Severe deconditioning
  - Increased risk of complications
Summary

Pain in Multiple Sclerosis:

• Common
• Varied
• Can wax and wane or be stable/persistent
• Impacts QOL
• Focal or unimodal treatment for focused/persistent pain in patient otherwise doing well
• Comprehensive treatment: pain, mood, sleep, function, coping for difficult cases
Thank You!

Questions?