Pain in Multiple Sclerosis
A Biopsychosocial Approach

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Overview and Objectives

- Understanding pain as it exists in multiple sclerosis
- Discuss MS pain management from a biopsychosocial perspective
Pain… the ripples spread from the nervous system into the sufferer’s whole life. If you stub your toe or burn your finger, it hurts but its quickly over. Anything more complicated—and especially the kind of pain that is recurring or chronic—has an impact on the patient’s personality and relationship with the world. Pain does not happen in a laboratory. It happens to an individual, and there is a cultural context that informs the individual’s experience. What a pain is, and whether it matters, is not just a medical question. Hilary Mantel
Epidemiology of MS Pain

Pain in MS understood since 1875

“MS pain is concerningly common”-- affecting 63% (Foley, Vesterinen, Laird et al., 2013)

62% in past month; 65% > time frame

Linked to adverse disease outcomes

Pain is heterogeneous includes several pain syndromes and mechanisms

Mechanisms: neuropathic pain (28.5%) more prevalent than nociceptive pain (18.2%)

RRMS 50%; SPMS 69.8%; PPMS 70.3%

Most common pain syndrome: headache; extremity neuropathic pain (most common); back pain; painful tonic spasms; Lhermitte sign and trigeminal neuralgia

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**MS Pain is Complex**

(Foley et. al., 2013)

- No estimates of pain incidence; therefore rt to dz course is poorly understood
- No studies of pain prevalence prior to diagnosis
- One study of pain prevalence soon after diagnosis
- Neuropathic pain mechanisms more prevalent
- Demographic variables (mean EDSS, gender, MS subtype, dz duration) did not account for estimate heterogeneity
- Increase in headache pain associated with relapse
- Pain prevalence appeared to decrease over time
E.S.

- Female with RRMS; diagnosed in 2007
- Three sites of pain: migraine headaches; ‘icy cold to the bone’ pain in both legs; and, sharp, splintering feeling in both ankles
- May spend days in bed, avoiding friends and family
- Admits to excessive fatigue and depression
- Three ED visits in past year r/t severe pain
Pain Experience in MS

- Linked to adverse outcomes

  - Poorer quality of life and general poor health
  - Associated with relapse
  - Greater pain intensity, and poorer physical and emotional health
  - Insufficiently treated
  - Low satisfaction with treatment
  - Greater health-care utilization; greater medication use

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Pain Assessment

- **Self-report of pain** is the single most reliable indicator of pain.

- **Brief Pain Inventory** for pain interference:
  - 12-item: general activity; mood; mobility; normal work; relations; sleep; enjoyment of life; self-care; recreational & social activities; communication with others; learning new skills.

- Have patients maintain a pain diary (OLD CART).
MS Pain is Mixed

느 Nociceptive: Pain of the disability of living with MS

느 Caused by true or potential tissue damage stimuli: may be inflammatory
느 Example: pain of optic neuritis; postural anomalies, osteo r/t steroids; headache, treatment induced pain

느 Central neuropathic pain: Pain arising directly from a lesion or disease affecting the somatosensory system

느 may be intermittent or steady
느 may be spontaneous or evoked
느 Steady pain: burning, tingling, aching, throbbing (dysesthetic extremity pain)
느 Intermittent: shooting, stabbing, electric knife-like, searing (trigeminal neuralgia)
Mechanism-based Classification of MS Pain

(Truini et al., 2013)

- **Trigeminal neuralgia and Lhermitte’s** (paroxysmal neuropathic pain due to ectopic impulses along primary afferents (pons plaque vs neurovascular)

- **Ongoing extremity pain** (deafferentation pain due to a lesion in spino-thalamo-cortico pathways)

- **Tonic painful spasms and spasticity** (mixed pain secondary to lesions in central motor pathways but mediated by motor nociceptors)

- Pain associated with **optic neuritis** (neurogenic pain originating from nervi nervorum in 20%)

- **Musculoskeletal pain** (nociceptive pain)

- **Migraine** (nociceptive pain or midbrain lesion)
E.S.

- Treatments:
  - ED visits- given methylprednisilone for presumed MS attack
  - Dilaudid ineffective during hospitalizations
  - Past use…deemed ineffective: gabapentin, pregabalin, topiramate, nortriptyline, leviteracitam, lamictal, SSRIIs
  - Current use: duloxetine, memantine, tramadol as rescue
Pharmacologic Management

- **Topical agent**
- **Membrane stabilizing agents**
  - Antiepileptics
  - Antiarhythmic
  - Corticosteroids
- **Modulating agents**
  - Antidepressants
  - Opioids
  - Cannabis (*painful tonic spasms*)

- **Dorsal horn inhibition**
  - Antiepileptics
  - Antidepressants
  - GABA agonists-baclofen

- **NMDA antagonists**
  - Ketamine
  - Dextromethorphan
  - Methadone

- **Antispasticity Medications**
- **Antiinflammatory agents**
# Mechanism of Action

## A Case for Polypharmacy

<table>
<thead>
<tr>
<th><strong>Na+ channel modulators</strong></th>
<th><strong>Ca++ Channel Modulators</strong></th>
<th><strong>Inhibit reuptake of NE and 5HT</strong></th>
<th><strong>Gaba agonists</strong> (burning dysesthesias)</th>
<th><strong>NMDA agonist</strong></th>
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<tr>
<td>(TN and Lhermitte’s; tonic spasms)</td>
<td>(burning dysesthesias)</td>
<td>(Extremity dysesthesias)</td>
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Opioids in Neuropathic Pain

- No simple answers…consider ethical principles
- Neuropathic pain is sensitive to opioids
- Reasonable second line treatment
- BUT
  - MS – poor studies; effect at high doses
  - Risk of addiction (employ safeguards)
  - Risk of dose escalation
  - Risk of hyperalgesia/tolerance
  - Risk of ineffective doses, toxicity, overdose
- Do no harm
Cannabis
Useful as Medicine?

- Increasing anecdotal and clinical reports of potential benefit
- Greater understanding of the endocannabinoid system (CB1 regulates neurotransmission; role of CB2 on neuroinflammation, immunomodulation and neuroprotection)
- Approved for medical use in 19 states and the District of Columbia (eliminates criminal penalties)
- Legal: Colorado and Washington
- Federal Controlled Substance Act: **Scheduled I drug** with high potential for abuse and no currently accepted medical use (**criminalizes prescribing, dispensing, possession**)
Clinical Trials of Smoked Cannabis for Pain

- Statistically significant reduction in pain compared to placebo-THC content (9.4%) most effective

- Most showed improvement in pain (sharp, burning, aching, sensitive, superficial, deep) and stiffness, enhanced relaxation, feeling of well being

- AE: Generally well tolerated-somnolence, dry mouth, sedation, dizziness, tachycardia, conjunctival irritation, hypotension, numbness, cold, “high”... **cognitive effects**
Delta(9)-Tetrahydrocannabinol/Cannabidiol (THC/CBD)

synthetic orals

- 10-20mg THC=60-120mg codeine

- Dronabinol (Marinol®): 2.5,5,10mg cap; schedule III
  - Weight loss; N&V with chemo

- THC 2.5/CBD 1.25 (Cannador®) 2:1 cannabis extract 5-15mg capsule

- Nabilone (Cesamet®) schedule II
  - Synthetic CB1/CB2 receptor agonist
  - 0.5-1mg bid and 2mg tid

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Clinical Trial Data

- CAMS: 657 subjects – effects of Cannador (cannabis plant extract, 2.5THC/1.5CBD) vs placebo and Marinol vs placebo: subjective improvement in spasticity and pain and relapse rate; **significant decrease in CVLT** (Zajicek et al., 2003 & 2005)

- CUPID: 500 subjects/ disability outcomes on Δ-9-THC vs placebo-did not slow relapse or dz progression (Clinical neurology Research Group, 2009)

- MUSEC: (oral CE 2.5THC/1.25 CBD) superiority of CE over placebo for spasticity and pain (Zajicek et al, 2009; 2012)

- Meta-analysis: nabilone, dronobinol, nabiximols demonstrate statistically significant differences in pain intensity (Rog, 2010)

- **IASP (2007): level A evidence, but second line**
Cannabis Medicinal Extracts

Nabiximols (Sativex®): liquid extract from two strains of cloned Cannabis sativa chemovars in 1:1 sublingual spray

- Oromucosal spray containing THC (2.7 mg) and CBD (2.5 mg) in approximately equal amounts per spray; average 9.6 sprays; Max dose: 12 sprays a day (100mcl/spray; 33.8mg)

- Licensed in UK and Canada; New Zealand and 8 European countries as monotherapy or add-on tx

- For symptomatic relief of pain and spasticity in MS and as adjunctive analgesic in advanced cancer

- Found effective in MS pain resistant to pharmacologic intervention SE: dizziness, fatigue (10%); sedation; no withdrawal in RCT

- In US RCT in phase 3, with expected FDA approval Dec 2013
Sativex®

- Unique: no serious AEs; no evidence for tolerance; little withdrawal; not associated with sedative effect or memory impairment; rare intoxication and euphoria (Wade 2012; Argona, 2009)

- Collated RCT of 930 subjects with > than 455 days of extension data in 444 subjects (Constantinescue & Sarantis, 2006)

  - AEs: dizziness (27.5%); diarrhea (13.1%); fatigue (11%); nausea (10.8%); cannabis “high” (<1%)

  - Slow titration over 10 days resulted in fewer AEs

  - Benefit evident within 4 weeks of treatment

- Cost: may not be cost effective (10ml vial- $566.55 or $2.08/spray or $25.18 max daily sprays based on UK)

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A Look at Cognitive Function

Cannabis users performed significantly more poorly than nonusers on measures of information processing, working memory, executive function, and visuospatial perception.

Twice as likely to classified as globally cognitively impaired (Honarmand et al., 2011, Neurology).

Those receiving cannabis extract had a decrease in verbal learning and memory.

Trial of Sativex with decreased scores on selective reminding test.

“Use when conservative options have failed for fully informed patients treated in ongoing treatment relationships” (Bostwick, J., (2013). NEJM)
Pain Experience in MS

Psychosocial and psychological factors have greater impact than other variables on pain intensity:

- Associated with increased fatigue
- Anxiety
- Depression
- Associated with greater dysfunction and disability
- Social support enhanced pain coping
Pain Experience

- Different patients experience different levels of pain in response to comparable stimuli.
- Heredity, energy level, coping skills, prior pain experience—variation in tolerance.
- Patients with chronic pain are more sensitive to pain and other stimuli.
- Pain is a sensory, motivational and cognitive experience.
Pain is Multidimensional

- Sensory discriminative
- Motivational/Affective
- Cognitive/evaluative
Biopsychosocial Model

- Psychological and environmental factors are associated with pain intensity and interference with function
- Depression, anxiety, fear of pain influence intensity
- Pain beliefs influence intensity
- Provider is the key to cure
- External locus of control
- A life dictated by pain
- Pain-related catastrophizing; negative thinking

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Pain = suffering
Pain person = key to the cure
Shift the locus of control and responsibility
A life worth living despite pain
- External locus of control → increased depression, anxiety, and disease progression
- Internal health locus of control → greater disease knowledge, increased self-care, and more benign disease course
Self-Efficacy Theory
- Nearly all outcomes are mediated through the patient’s behavior (Bodenheimer et al., 2002).
Pain Coping

- Cognitive restructuring: recognizing maladaptive thinking and replacing with adaptive thoughts

- Adaptive
  - Develop an action plan (meaningful, specific, flexible, positive, write it down)
  - Rest and relaxation
  - Exercise
  - Reinterpreting pain sensation (burn = warmth)
  - Acceptance
  - Coping self-talk
  - Building self-efficacy for coping with pain
Building Self-Management Skills

- **Therapeutic Objectives:** Increase mastery and control over fear, anxiety, stress reaction, environmental pain triggers

- Acceptance and “living with”
  - Allowing some pain some of the time
  - Consists of both thinking and doing

- Two facets:
  - Willingness to experience pain
  - Engagement with life

- Activating resources: Mindfulness
  - Non-judgmental awareness of pain
  - Acting with intention
WHAT IS MINDFULNESS?

Consciously bringing awareness to the ‘here-and-now’ experience with openness, interest, and receptiveness

Primary elements:

- Living in the present moment
- Engaging fully in what you’re doing rather than ‘getting lost’ in your thoughts
- Allowing your feelings to be as they are, rather than trying to control them

Body Scan Exercise
ACCEPTANCE AND COMMITMENT THERAPY (ACT)

Termed ‘existential humanistic cognitive behavioral therapy’

‘Third wave’ of behavioral therapies

ACT gets its name from one of its core messages: accept what is out of your personal control, and commit to action that improves and enriches your life
TENETS OF ACT CONT’D

ACT breaks mindfulness skills down into 3 categories:

1) Defusion: distancing from, and letting go of, unhelpful thoughts, beliefs and memories

2) Acceptance: making room for painful feelings, urges and sensations, and allowing them to come and go without a struggle

3) Contact with the present moment: engaging fully with your here-and-now experience, with an attitude of openness and curiosity

http://contextualscience.org/
Activity Pacing & Goal-Setting

• Systematic increases in activity
• Activity scheduling
• Setting specific, measurable, & attainable goals
Goal Setting: Example Framework

“I will_____________________________(specific action) for ______

______________ (How long, How many, How far) on_______

___________(which day or days) at_______________(what time or times/what situation). I feel confident that I can do this, and even ________________________(barriers) come up, I will deal with them by________________________(solutions) and I will still work o my goals!”
Encourage the use of relaxation skills

Breathing

Imagery

Progressive muscle relaxation

Self-hypnosis
E.S

- Husband recently stateside after tour in Afghanistan
- Started coaching her daughters basketball team
- Swims three times a week
- Participates in acupuncture once a week
- Has not been hospitalized in over seven months
Summary and Conclusions

☞ Primary Goal of treatment: Improved quality of life
☞ A Biopsychosocial approach to pain management fosters satisfaction for both patients and providers
☞ The use of drugs in concert with nonpharmacologic modalities reduces the severity and intensity of pain
Resources

- National Multiple Sclerosis Society (Search terms “pain” or “fatigue”)  
  www.nationalmssociety.org

- Paralyzed Veterans of America  
  www.pva.org

- International Association for the Study of pain  
  www.IASP-pain.org

- American Chronic Pain Association  
  www.theacpa.org

- American Pain Foundation  
  www.painfoundation.org

- American Pain Society  
  www.ampainsoc.org

- Center for Mindfulness in Medicine, Health Care, and Society  
  (www.umassmed.edu/cfm)

http://health.ucsd.edu/specialties/psych/mindfulness/mbsr/audio.htm
http://students.georgiasouthern.edu/counseling/relax/OnlineRelax07.htm
http://www.olemiss.edu/depts/stu_counseling/relaxation.html
Thank you