PAINWEEK®

# Blurring the Lines: Pain and Demyelinating Conditions

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# Disclosures

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***Consulting Fee (e.g., Advisory Board):*** BDSI, Vertex, Teva, Amgen, Lilly, Neumentum, Collegium, Lundbeck, Gruenenthal, Redhill Pharma
***Contracted Research :*** Teva, Lilly, Amgen, Abbvie
***Speakers' Bureau:*** Abbvie, Amgen, Lilly, Teva, Lundbeck, Biohaven, Red Hill Pharma, Gruenenthal

# Learning Objectives

- Describe how commonly people diagnosed with multiple sclerosis experience chronic pain
- List painful conditions associated with multiple sclerosis and other demyelinating disorders
- Describe available treatments for pain associated with multiple sclerosis

# Pre-test question #1

- A 30 year old female with a 10 year personal as well as family history of migraine headaches presents to her primary care provider for an annual health assessment. She describes having episodes of severe, sudden shock-like pain over the right mandible lasting seconds to minutes. She often cannot brush her teeth without pain. Her dentist has evaluated her recently and no dental etiology has been determined. Here PCP notes several trigger zones over the affected area when examining her. What is the most appropriate step for this patient?

- A. PCP should advise the patient that her complaints and findings are consistent with migraine and discuss new treatments for her headaches.
- B. PCP should advise the patient that her complaints are consistent with trigeminal neuralgia and she should be referred to a Neurosurgeon for consideration of microvascular decompression surgery.
- C. PCP should advise the patient that her complaints are consistent with trigemeinal neuralgia and she is advised to undergo a MRI Brain with and without contrast.
- D. PCP should advise the patient that her complaints are consistent with temporomandibular joint dysfunction and she is advised to see a TMJ specialist.

# Pre-test question #2

- T/F:  20% of people diagnosed with multiple sclerosis experience associated chronic pain.

# Pre-test question #3

- T/F:  A recent study suggests that most pain associated with multiple sclerosis is neuropathic pain.

# Examples of Demyelinating Disorders Affecting the CNS

- **Multiple sclerosis**: potentially disabling disease of the brain and spinal cord in which the immune system attacks the myelin of the CNS
- **Transverse Myelitis**: acute inflammation of the spinal cord, most commonly in the thoracic region. Causes include multiple sclerosis, neuromyelits optica, directed related to infection or post-infectious, drug related or associated with vasculitis
- **Balo's concentric sclerosis**: rare disorder (some believe variant of multiple sclerosis), associated with a concentric circular pattern of sclerosis
- **Neuromyelitis optica (NMO/Devic's Disease):** an auto-immune, inflammatory condition associated with optic nerve and spinal cord attacks



Fabian MT, Krieger SC, Lublin FD. Multiple Sclerosis and Other Inflammatory Demyelinating Disease of the Central Nervous System, Chapter 80. In: DAroff RB et al. eds. Bradley's Neurology in Clinical Practice. Elsevier, 2016. 1159-1187.

# Pain in Multiple Sclerosis (and other demyelinating conditions)

- Multiple sclerosis:  demyelinating disorder affecting the central nervous system in which the immune system attaches the myelin sheath of the CNS
- The prevalence of pain in multiple sclerosis (MS) ranges from 50-86% (pooled prevalence from 17 studies is 62%)
- Pain, fatigue and depression are frequently noted within the first year of MS diagnosis
- Neuropathic pain, specifically trigeminal neuralgia has been noted to be an initial symptom of MS when a young person presents with this condition

Murphy KL et al.  Neuropathic Pain in MS-Current Therapeutic Intervention and Future Treatment Perspectives, In:  Multiple Sclerosis Perspectives in Treatment and Pathogenesis, Zagon I and Mclaughlin P, eds.  Codon Publications, Brisbane: 2017:53-69.  Valentine TR, et al.  Prevalence , co-occurrence and trajectories of pain, fatigue, depression and anxiety in the year following multiple sclerosis diagnosis.  MS Journal, June 2021 PMID:34132141, Foley PL et al.  Prevalence and natural history of pain in adults in multiple sclerosis:  Systematic review and meta-analysis.  Pain 154(2013):632-642.

# Painful Conditions in MS

- Neuropathic pain:  prevalence in MS has been reported to be as high as 86%
- Extremity pain and TN are common presentations
- Neuropathic pain in a patient with MS may signify a more severe disease course based upon number of lesions reported in such patients
- Neuropathic pain in MS is associated with a negative effect on QOL
- Lhrmitte's sign – occurs in as many as 40% of patients with MS
- Glossopharyngeal neuralgia- rare in MS
- Spasticity and spasms – frequently noted in MS patients can be painful

Urits I, et al.  Advances in the Understanding and Management of Chronic Pain in Multiple Sclerosis:  a Comprehensive Review.  Current Pain and Headache Reports(2019) 23:59, PMID 313421

# Characterizing Chronic Pain Phenotypes in MS: a Nationwide Survey Study

- Noting that pain heterogeneity may be associated with poor treatment outcomes, this study was designed to characterize pain phenotypes in people with MS
- A national web-based survey was used to collect data
- Measures included painDETECT (neuropathic pain), nociplastic pain (Fibromyalgia Survey Criteria), chronic overlapping conditions, pain medication use and pain relief
- 842 MS patients with chronic pain and MS
- 41% nociceptive pain, 27% mixed neuropathic/nociplastic pain, 23% nociplastic pain, 9% neuropathic pain
- Findings suggested need for multidimensional assessment of pain- improved characterization could help improve therapeutic approaches

Kratz AL, et al. Characterizing chronic pain phenotypes in multiple sclerosis: a nationwide survey study. Pain 162(2021):1426-1433

# Neuromyelitis Optica Spectrum Disorder

- Characterized by severe immune mediated demyelination  and axonal damage predominantly targeting the optic nerves and spinal cord as well as the brain and brainstem
- Symptoms include visual loss, paralysis and episodes of hiccups, nausea and vomiting
- Diagnostic tests include a blood test:  aquaporin-4 IgG antibodies – highly specific
- No specific medical therapies have been noted for the central neuropathic pain that is frequently associate with this condition
- A recent study notes that scrambler therapy (a type of TENS therapy)may improve pain in NMO

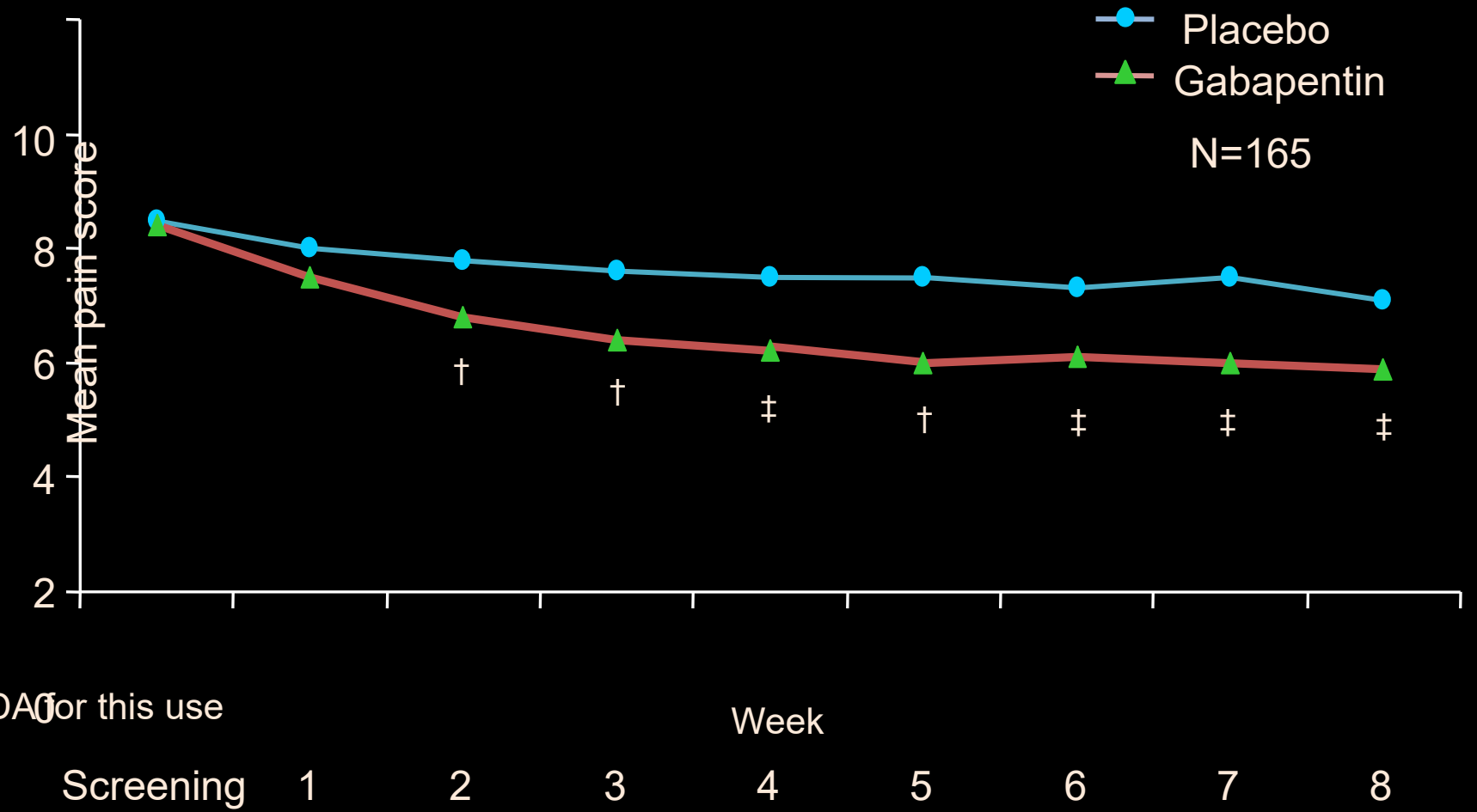
Mealy M, et al.  Scrmbler therapy improves pain in neuromyelitis optica.  Neurology 2020;94:e1900-e1907.

# Treating MS Related Pain is Not Equivalent to Treatingan Infection Caused by a Known Pathogen

| | | | |
|---|---|---|---|
| 07/15/10 1700 (COLLECTION TIME) | | 07/15/10 1733 (IN LAB TIME) | |
| -S BACTERIAL CULTURE | | FINAL ON 07/21/10 1517 | |
| - SPECIMEN TYPE | | WOUND | |
| - SOURCE-BODY SITE | | GROIN | |
| - ORGANISM 1 | | BETA STREPTOCOCCUS GROUP B | |
| - QUANTITATION | | MANY | |
| - ORGANISM 2 | | STAPHYLOCOCCUS LUGDUNENSIS | |
| - QUANTITATION | | MODERATE | |
| - SENSITIVITY SET-UP DATE: | | 07/20/10 | |
| - ORGANISM 3 | | CORYNEBACTERIUM SPECIES | |
| - QUANTITATION | | MODERATE | |
| - MIC in mcg/mL | COST/ | ORG 2 | |
| - *USUAL ADULT IV DOSAGE | DAY* | | |
| - CLINDAMYCIN | $ 24 | <=0.5 | S |
| - DOXYCYCLINE | $ 32 | <=1 | S |
| - ERYTHROMYCIN | $ 35 | <=0.5 | S |
| - OXACILLIN | $ 70 | 0.5 | S |
| - PENICILLIN | $ 38 | 0.06 | S |
| - RIFAMPIN | $ 33 | <=0.5 | S |
| - VANCOMYCIN | $ 21 | 1 | S |

- Erythromycin Susceptible STAPHYLOCOCCUS LUGDUNENSIS
- are susceptible to azithromycin and clarithromycin.
-
- Oxacillin-susceptible staphylococci are
- susceptible to cefazolin, cephalexin and ceftriaxone.

# Gabapentin in the Treatment of Painful Diabetic Neuropathy*




*Not approved by FDA for this use

† *P* <0.01; ‡ *P* <0.05

Adapted from Backonja M, et al. *JAMA*. 1998;280(21):1831-1836.

# Evidence Based Medicine

- Evidence-based medicine (EBM) has been defined as "the conscientious, explicit and judicious use of current best evidence in **making decisions about the care of individual patients**"
  Sackett, D. *Evidence-based Medicine - What it is and what it isn't. BMJ 1996; 312:71-72*
- Evidence-based medicine: The judicious use of the best current available scientific research in making decisions about the care of patients. Evidence-based medicine (EBM) is intended to **integrate clinical expertise** **with the research evidence and patient value**

**http://www.medterms.com/script/main/art.asp?articlekey=33300**

# Clinical Syndromes and Anticonvulsant Use

- Migraine – topiramate, divalproex sodium
- Postherpetic neuralgia
  - gabapentin
  - pregabalin
- Diabetic neuropathy
  - carbamazepine
  - phenytoin
  - gabapentin
  - lamotrigine
  - lacosamide
  - pregabalin
- Spinal cord injury- pregabalin
- HIV-associated neuropathy
  - lamotrigine
- Trigeminal neuralgia
  - carbamazepine
  - lamotrigine
  - oxcarbazepine
- Fibromyalgia
- - pregabalin
- Central post-stroke pain
  - lamotrigine

# Current pharmacotherapy considerations

- Acetaminophen
- NSAIDs
- TCA or SNRI antidepressant agents
- $Na^+$ blocker anticonvulsants
- $Ca^{2+}$ modulating anticonvulsants
- Tramadol
- Opioids
- TRPV1 topical agents
- Local anesthetic topical agents
- Botulinum toxin



Bannister K, et al. Neuropathic Pain" Mechanism-Based Therapeutics Annu Rev Pharmacol Toxicol 2020.60:257-274.

# TCA Antidepressant Agents

- Numerous studies have demonstrated the benefit of TCA agents (amitriptyline, nortriptyline) for NeP
- NNT ranges from 3-4.4
- The evidence is rated as strong and these are considered first line agents
- Common side effects include somnolence, constipation, dry mouth



Bannister K, et al. Neuropathic Pain" Mechanism-Based Therapeutics Annu Rev Pharmacol Toxicol 2020.60:257-274

# SNRI Antidepressant Agents

- Multiple studies demonstrate the analgesic benefit in NeP
- NNT ranges from 5.2-8.4
- The evidence is rated as strong
- Nausea is a common side effect especially for duloxetine



Bannister K, et al. Neuropathic Pain" Mechanism-Based Therapeutics Annu Rev Pharmacol Toxicol 2020.60:257-274

# $Ca^{2+}$ modulating anticonvulsants

- Multiple studies demonstrate the analgesic benefit of these agents for NeP
- Pregabalin is considered a first line agent with NNT ranging from 6.5-9.4
- Gabapentin is considered a first line agent with NNT ranging from 5.9-9.1
- Side effects include somnolence, dizziness and weight gain
- Recent labeling changes point out the enhanced risk of respiratory depression when used with opioids

Bannister K, et al. Neuropathic Pain" Mechanism-Based Therapeutics Annu Rev Pharmacol Toxicol 2020.60:257-274

Bannister K, et al. Neuropathic Pain" Mechanism-Based Therapeutics Annu Rev Pharmacol Toxicol 2020.60:257-274

# Opioids

- Opioids have demonstrated benefit in multiple NeP conditions
- NNT ranges from3.4-5.8
- The evidence for their benefit is considered weak and opioids are considered third line agents
- Side effects include constipation, nausea, emesis, pruritus

Bannister K, et al. Neuropathic Pain" Mechanism-Based Therapeutics Annu Rev Pharmacol Toxicol 2020.60:257-274

# Tramadol

- The evidence for the use of tramadol in NeP is weak
- NNT ranges from 3.6-6.7
- Tramadol is considered a second line agent for NeP
- Tramadol has tricyclic like acitivity and its metabolite has weak mu receptor activity
- Side effects include nausea, constipation, dizziness and dry mouth

Bannister K, et al. Neuropathic Pain" Mechanism-Based Therapeutics Annu Rev Pharmacol Toxicol 2020.60:257-274

# Topical capsaicin

- The 8% capsaicin patch may be considered for peripheral NeP
- It is now FDA approved for PHN and PDN
- The NNT ranges from 7.4-18.8 BUT recent studies suggest patients who do not benefit from initial application may benefit from repeated application
- Side effects include local pain and erythema

Bouhassira D, Attal N, Emerging therapies for neuropathic pain: new molecules or new indications for old treatments? Pain 159 (2018):576-582

# Botulinum Toxin

- Multiple animal studies and/or evaluations of known pain models in healthy subjects, have demonstrated that botulinum toxin (specifically onabotulinum toxin A) may result in analgesia independent of its effect on muscle
- Multiple single center RTC have evaluated the long term efficacy of subcutaneous or intradermal injections (50-200 units) in PHN, painful diabetic neuropathy of neuropathic pain following traumatic nerve injury
- A multicenter double-blind RTC has evaluated the effect of 2 subcutaneous treatments of onabotulinum toxin A, 12 weeks apart in 66 patients with PHN. Post-traumatic neuropathy or painful polyneuropathy- treatment resulted in improved average pain intensity compared to placebo and the second injection provided greater benefit- allodynia and paroxysmal pain was specifically helped
- The NNT ranges from 1.5-2.4
- Adverse events include local pain

# Botulinum Toxin/Capsaicin

- Botulinum toxin:  known benefit in chronic migraine/DPN
- In migraine, the effect is believed to be via a block of peripheral CGRP release
- However, no effect on peripheral CGRP levels has been seen in NeP
- Capsaicin is a TRPV1 agonist- application of the high concentration patch leads to local depletion of TRPV-1 and chemical denervation leading to reduced superficial nociceptive afferents in the skin- for several months after the application

Bannister K, et al.  Neuropathic Pain"  Mechanism-Based Therapeutics Annu Rev Pharmacol Toxicol 2020.60:257-274

# FDA-APPROVED INTRATHECAL ANALGESICS with different mechanisms

## Morphine

- μ-Opioid receptor agonist
- Most serious AE is respiratory depression
  - Risk increased with other agents that depress the CNS (eg, benzodiazepines)

## Ziconotide

- N-type $Ca^{2+}$ channel blocker
- Most serious AEs are neurocognitive
  - eg, confusion, dizziness, hallucinations
  - Urinary retention also can lead to treatment discontinuation

AE, adverse event; CNS, central nervous system.

Coffey RJ, et al. *Anesthesiology*. 2009;111(4):881-891; Deer TR, et al. *Neuromodulation*. 2012;15(5):436-466; Prager JT, et al. *Neuromodulation*. 2014;17(4):354-372; Webster LR, et al. *J Pain Symptom Manage*. 2009;37(3):363-372.

# OVERVIEW OF SYSTEMIC VS INTRATHECAL THERAPY

## Systemic drug delivery

- Drug distributed via bloodstream
- Drug interacts with receptors throughout the body
- Oral dosing produces peaks and troughs in plasma levels
- Relatively high daily dosages
  - High systemic side effect risk and drug-elimination load
- Concerns about adherence, abuse, and diversion

## Intrathecal drug delivery

- Implantable pump sends drug via catheter to intrathecal CSF
- Drug targeted to spinal receptors
- Steady-state around-the-clock dosing can be achieved
- Relatively low daily dosages
  - Reduced systemic side effects and low drug-elimination load
- Potential for better adherence and less diversion

**CSF, cerebrospinal fluid.**

Bagnall D. *Phys Med Rehabil Clin N Am.* 2010;21(4):851-858; Deer TR, et al. *Pain Physician.* 2010;13(3):E175-E213; Hayek SM, et al. *Pain Physician.* 2011;14(3):219-248; Onofrio BM, et al. *Mayo Clin Proc.* 1981;56(8)516-520; Prager J, et al. *Neuromodulation.* 2014;17(4):354-372.

# NEW PACC RECOMMENDATIONS

The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines

The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks

The Polyanalgesic Consensus Conference (PACC): Recommendations for Trialing of Intrathecal Drug Delivery Infusion Therapy

PACC, Polyanalgesic Consensus Conference.

Deer TR, et al. Neuromodulation. 2017;20(2):96-132; Deer TR, et al. Neuromodulation. 2017;20(2):133-154; Deer TR, et al. Neuromodulation. 2017;20(2):155-176

# Intraspinal baclofen and multiple sclerosis

- Intraspinal baclofen is considered for people with severe spasticity unresponsive to oral baclofen or other less invasive approaches to spasticity management
- In one study, spasticity management using intraspinal baclofen was associated with reduced spasticity as well as reduced pain for at least 76 months
- What about those instances in which baclofen alone is not effective enough?

Stampacchia G, Gerini A, Mazzoleni S. Effects of severe spasticity treatment with intrathecal Baclofen in multiple sclerosis patinets: Long term follow-up. NeuroRehabilitation 2016 Apr6;38(4): 385-393.

# Intraspinal Combination Therapy for Spasticity and Neuropathic Pain

- Clinical and preclinical studies support the use of ziconotide in combination with morphine, hydromorphone, clonidine or baclofen BUT no long term trials exist
- Specifically, in a case series, 7 patients experiencing both spasticity as well as neuropathic pain were treated with a combination of intraspinal baclofen and ziconotide- each person reported was treated with a different titration schedule and with different concentrations of each medication



Saulino M et al. Intrathecal ziconotide and baclofen provide pain relief in seven patients with neruopathic pain and spasticity: case reports. Eur J Phys Rehabil Med 2009;45: 61-67

# Additional Treatments to Consider

- **Physical therapy and exercise**: aerobic exercise, respiratory muscle training, resistance training, stretching, stability training
- Neuromodulation: IT baclofen for spasticity control, Deep Brain Stimulation (DBS), Spinal Cord Stimulation (SCS), and Transcranial Magnetic Stimulation have been utilized
- DBS may help MS related tremor and TN
- SCS has been used to treat bladder dysfunction and MS related pain

Urits I, et al. Advances in the Understanding and Management of Chronic Pain in Multiple Sclerosis: a Comprehensive Review. Current Pain and Headache Reports(2019) 23:59, PMID 31342191.

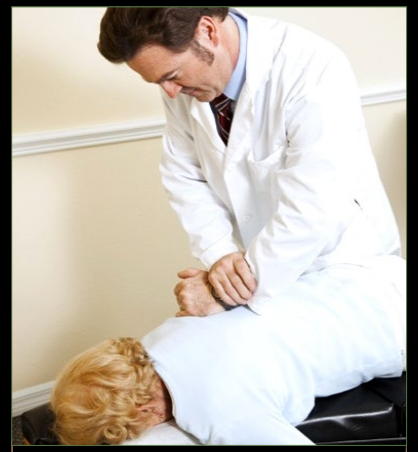
# Nonpharmacologic Treatment Modalities

**Psychological Support**

- CBT
- Biofeedback
- Relaxation training
- Supportive psychotherapy

**Lifestyle Change**

- Exercise
- Weight loss



**CAM**

- Massage
- Spinal manipulation
- Supplements
- Homeopathy
- Acupuncture

**Physical Medicine and Rehabilitation**

- Hot/cold presses
- Physiotherapy
- TENS
- Hydrotherapy

CAM, complementary and alternative medicine; TENS, transcutaneous electrical nerve stimulation.

Adams ML. *Clin Podiatr Med Surg*. 2008;25:409-429; Bruckenthal P. *Pain Manag Nurs*. 2010;11:S23-S31.

# Cannabinoids

- Neurotransmission via the endocannabinoid pathway is increasingly appreciated to regulate pain perception and modulation
- CB1 receptor plays an important role; analgesics effects are lost when CB1 antagonist (rimonabant) is given
- Both enandamide and NADA (N-arachidonyldopamine) activate the vanilloid receptor (TRPV-1) found on sensory nerves
- May promote analgesia through CB1 and CB2, but potentially increase pain via TRPV-1
- Progress is being made in the development of novel agonists and antagonists with receptor subtype selectivity which should help in providing a greater understanding of the physiological role of the endocannabinoid system and perhaps also in a broad number of pathologies.


Svízenská I, et al. *Pharmacol Biochem Behav*. 2008;90:501-511.

# MS- Oral Cannabinoids (Cannabis extract and THC)

- Neither oral cannabis extract (OCE) nor dronabinol had a greater effect in MS patients in reducing spasticity as measured by the Ashworth scale compared to placebo- this was the primary outcome measure of this study.
- HOWEVER:  for certain secondary outcome measures in this study, including pain associated with spasticity, muscle spasms and sleep both treatment groups demonstrated greater improvement than placebo treated patients

Yadev, V, Bever C, Bowen C, et al.  Summary of evidence-based guideline:  Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# MS- Oral Cannabinoids (Cannabis extract and THC)-2

- In a randomized controlled study (RTC) of 249 MS patients treated with OCE , muscle stiffness was more likely to occur in treated pts compared with placebo (29.4% vs. 15.7%) and secondary outcomes including spasms, pain and sleep were more likely to occur in the treated group
- Another RTC showed no difference in Ashworth scale scores OR subjective symptoms in each group
- A RTC assessing the effect of OCE for tremor and bladder symptoms in MS patients did not show a significant difference between pts treated with cannabinoids and placebo

Yadev, V, Bever C, Bowen C, et al. Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# MS- Oral Cannabinoids (Cannabis extract and THC)-3

- Based upon these findings the American Academy of Neurology (AAN) advises:

1. OCE is established as ***effective*** for reducing patient-reported spasticity symptoms and pain
2. THC is ***probably effective*** for reducing patient-reported symptoms of spasticity and pain
3. OCE and THC are ***probably ineffective*** for reducing objective spasticity measures and tremors

Yadev, V, Bever C, Bowen C, et al. Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# MS- Oromucosal Cannabinoid Spray

- A 6 week RTC including 160 MS pts evaluated the effect of the oromucosal cannabinoid spray (OCS) on spasticity:  no objective measured difference was seen between groups
- A 5 week RTC in 66 pts with MS related central neuropathic pain demonstrated that the OCS was superior in reducing mean pain intensity compared to placebo
- A 10 week RTC in 135 pts with MS related urinary incontinence did not show improvement with OCS; HOWEVER, the daily # of voids did decrease significantly in the treatment group

Yadev, V, Bever C, Bowen C, et al.  Summary of evidence-based guideline:  Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# MS- oromucosal Cannabinoid Spray-2

- Based upon these findings the American Academy of Neurology (AAN) advises:

1. OCS is ***probably effective*** for improving subjectuve spasticity symptoms, pain and urinary frequency
2. OCS is ***probably ineffective*** for reducing objective spasticity measures or bladder incontinence
3. OCS is ***possibly ineffective*** for reducing MS-related tremor

Yadev, V, Bever C, Bowen C, et al. Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# MS-Smoked Ccannabis

- 1 crossover study in 37 MS patients reported spasticity reduction- the primary outcome measure (using a modified Ashworth scale) in the cannabis group
- Pain, a secondary measure, also improved in the cannabis group
- Cognitive performance was measured and was REDUCED after cannabis treatment

Yadev, V, Bever C, Bowen C, et al. Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# MS-Smoked Cannabis-2

- In a separate study of 20 MS pts and normal controls, both groups demonstrated reduced measures of posture and balance after smoking one marijuana cigarette.

Yadev, V, Bever C, Bowen C, et al. Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# MS-Smoked Cannabis-3

- Based upon these findings the American Academy of Neurology (AAN) advises:

1. ***Data are not adequate*** to determine the safety or efficacy of smoked cannabis used for spasticity or pain relief.

Yadev, V, Bever C, Bowen C, et al. Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# MS – Additional Thoughts

- The reported studies were of short duration- longest 15 weeks
- Central side effects of the active agent could have unmasked subject
- The Ashworth scale may be insensitive to spasticity changes in these studies
- The cannabinoids were associated with serious adverse events including death- mild-moderate side effects were more common (50-80%) including dizziness, lightheadness, increased appetite, nausea, emesis, cystitis, dehydration, transient psychosis, hallucinations and cognitive impairment

Yadev, V, Bever C, Bowen C, et al. Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis Neurology 2014;82:1083-1092

# Randomized Controlled Trials of Smoked Cannabis in Pain

| N= | Indication | Duration/type | Outcome |
|---|---|---|---|
| 50 | HIV neuropathy | 5 days/DB | Decreased pain and hyperalgesia (Abrams, 2007) |
| 23 | Neuropathic pain | 5 days/DB | Decreased pain (Ware, 2010) |
| 38 | Neuropathic pain | Single dose/DBC | Decreased pain w/ highest dose, but significant psychoactive effects (Wilsey, 2008) |
| 34 | HIV neuropathy | 5 days/DB | Improved DDS, (Ellis, 2009) |
| 21 | Chronic pain on opioids | 5 days/DB | 27% decrease in pain (Abrams, 117) |

# Randomized Controlled Trials of Synthetic Cannabinoids in Pain

| Agent | N= | Indication | Duration/type | Outcome |
|---|---|---|---|---|
| Ajulemic acid | 21 | Neuropathic pain | 7 day crossover | Decreased pain (Karst, 2003) |
| Marinol | 24 | Neuropathic pain in MS | 15-21 days/DBC | Median numerical pain and relief improved (Svendsen, 2004) |
| Marinol | 40 | Postop pain | Single dose/DB | No Benefit (Buggy, 2003) |
| Marinol | 30 | Chronic pain | 3 doses, 1 day/DB | Total pain relief improved with 10 and 20 mg. AEs prominent, (Narang, 2008) |

# Randomized Controlled Trials of Synthetic Cannabinoids in Pain: Nabilone

| N= | Indication | Duration/Type | Outcome |
|---|---|---|---|
| 41 | Postop pain | 3 doses/24h, DB | No Benefit |
| 31 | Fibromyalgia | 2 weeks/DBC | Compared to amitriptyline, sleep/wakefulness improved, no effect on pain, (Ware, 2010) |
| 96 | Neuropathic pain | 14 weeks/DBC vs dihydrocodeine | DHC more effective with fewer AE (Frank, 2008) |
| 13 | Spasticity pain | 9 weeks/DBC | Decreased pain, (Wissel, 2006) |
| 40 | Fibromyalgia | 4 weeks/DBC | Decreased pain, FIQ, anxiety, (Skrabek, 2008) |

# Randomized Controlled Trials of Cannibis-Based Medicine in Pain: Sativex

| N= | Indication | Duration/Type | Outcomes |
|---|---|---|---|
| 20 | Neurogenic pain | Series of 2 wk N of 1 crossover blocks (CB) | Decreased pain, (Wade, 2004) |
| 24 | Chronic pain | 12 wks, series of N of 1 CB | Decreased pain in MS, (Notcutt, 2004) |
| 48 | Brachial Plex Avul | 6 wks in 3 two-week CB | Decreased pain, (Berman, 133) |
| 66 | Central neuropathic pain of MS | 5 weeks | Decreased pain, (Rog, 2005) |
| 125 | Peripheral neuropathic pain | 5 weeks | Decreased pain and allodynia, (Nurmikko, 135) |

# Randomized Controlled Trials of Cannibis-Based Medicine in Pain: Sativex

| N= | Indication | Duration/Type | Outcomes |
|---|---|---|---|
| 56 | Rheumatoid Arthritis | Nocturnal dosing for 5 weeks | Decreased pain and improved SF-MPQ, (Blake, 137) |
| 117 | Spinal cord injury pain | 10 days | No effect on pain, improved BPI, PGIC, (unpublished) |
| 117 | Cancer Pain | 2 weeks | Decreased pain, (Johnson, 138) |
| 135 | Lower urinary tract symptoms in MS | 8 weeks | Improved symptoms, (Kavia, 2010) |
| 360 | Cancer Pain | 5 weeks/DB | Decreased pain in low and middle dose, (Portenoy, 2012) |

# Randomized Controlled Trials of Cannabis-Based Medicines in Pain

| Agent | N= | Indication | Duration/type | Outcome |
|---|---|---|---|---|
| Cannador | 65 | PHN | 4 weeks | No benefit (Ernst, 2005) |
| Cannador | 419 | Pain in MS | 15 weeks | Decreased pain associated with spasm (Zajicek, 2003) |
| Cannador | 30 | Postop pain | Single dose | Decreased pain with increase dose (Holdcroft, 2006) |

# Conclusions: Pain in Demyelinating Disease

- Pain is common in MS and other demyelinating conditions
- Multiple treatments are available BUT very little primary as well as comparative literature
- No treatment works for most patients
- Some medications aren't appropriate for some patients
- Some patients only want procedures
- Some patients only want medications
- Some patients want alternative approaches
- Bottom line: care must be individualized and more data is needed!

# Post-test question #1

- A 30 year old female with a 10 year personal as well as family history of migraine headaches presents to her primary care provider for an annual health assessment. She describes having episodes of severe, sudden shock-like pain over the right mandible lasting seconds to minutes. She often cannot brush her teeth without pain. Her dentist has evaluated her recently and no dental etiology has been determined. Here PCP notes several trigger zones over the affected area when examining her. What is the most appropriate step for this patient?

- A. PCP should advise the patient that her complaints and findings are consistent with migraine and discuss new treatments for her headaches.
- B. PCP should advise the patient that her complaints are consistent with trigeminal neuralgia and she should be referred to a Neurosurgeon for consideration of microvascular decompression surgery.
- C. PCP should advise the patient that her complaints are consistent with trigemeinal neuralgia and she is advised to undergo a MRI Brain with and without contrast.
- D. PCP should advise the patient that her complaints are consistent with temporomandibular joint dysfunction and she is advised to see a TMJ specialist.

# Post-test question #2

- T/F:  20% of people diagnosed with multiple sclerosis experience associated chronic pain.

# Post-test question #3

- T/F:  A recent study suggests that most pain associated with multiple sclerosis is neuropathic pain.