

# Neuropathic pain Differential Diagnosis and Management

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# Outline – Neuropathic pain

Etiology of neuropathic pain

Common neuropathic pain syndromes

Management of neuropathic pain

Beyond the guidelines

# What is Neuropathic Pain

# Background – what is neuropathic pain?

Pain caused by a **lesion** or **disease** of the somatosensory nervous system

**Not** originating from bones, muscles or organs (somatic or visceral pain)

Can be associated with **nociplastic pain** - central pain sensitization without structural damage of the nervous system

# What Makes Neuropathic Pain **Different**?

- **Semiology:**
  - Burning, tingling, electric, numb, shooting
- **Provoking factors:**
  - hypersensitivity to temperature or touch (allodynia), NOT often worse with activity or movement, repeated stimulus becomes more painful (hyperpathia)
- **Timing:**
  - worse with INACTIVITY and often worse at NIGHT
- **Severity:**
  - fluctuating, moving, episodic

# Neuropathic pain can be MIXED with somatic pain

- Careful not to miss combined pain syndromes
- May need multiple different types of treatment

# Common Neuropathic Pain Syndromes

- Headaches
  - Facial pain / Trigeminal autonomic cephalgias
- Central thalamic pain
- Myelopathic pain
- Peripheral neuropathy
  - Small fiber neuropathy
- Fibromyalgia

# Headaches / Trigeminal Autonomic Cephalgias

A very large set of pain disorders, not directly included in this talk but can be linked to other neuropathic pain disorders and genetic susceptibility

- Migraine has a 30-60% heritable rate (twin studies)
- Migraines associates with chronic hypersensitivity to sensory stimuli and or abnormal processing of sensory information
- Some shared genetic risk for ADHD, Tourette's, and major depressive disorder

# Central Thalamic Pain Syndrome

Mantra “Stroke’s don’t cause pain”

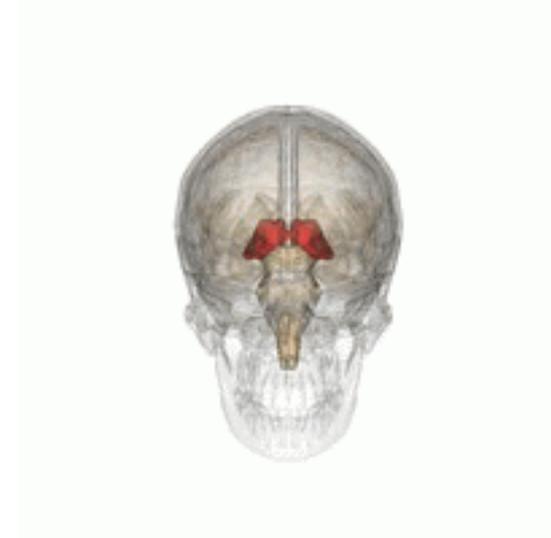
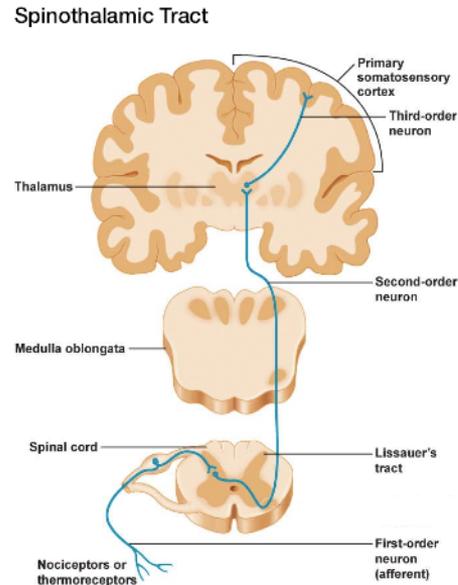
Historically, it was known as Dejerine–Roussy syndrome (1960’s)

Thalamus acts as a relay station for all sensory information within the brain

Thalamic pain syndrome, this process becomes damaged, interpret tactile information accurately, then the afferent pathway longer functions correctly with light touch causing pain (Allodynia)

# Central Thalamic Pain Syndrome

Any injury along the spinothalamic tract can cause this type of centralized pain  
Stroke, Multiple Sclerosis, Myelopathy...



# Myelopathic Pain

Similar to thalamic pain syndrome

Examples:

- Spinal stenosis with compressive myelopathy
- Multiple Sclerosis with transverse myelitis

# Radicular Pain

Chronic radiculopathy, similar to peripheral neuropathy in etiology

Less studies on medication management

Discussed elsewhere



# Peripheral Neuropathy

Most common neuropathic pain syndrome - 10-26% cross sectional studies of diabetics with painful neuropathy; More than 40 million Americans

Pain is a symptom of small fiber involvement

Best studied for medication treatments – diabetic neuropathy



# Peripheral Neuropathy

## - Isolated Small Fiber Neuropathy

Small myelinated and unmyelinated fibers

Does NOT show up on EMG/NCS test!

### Symptoms

- pain and tingling without numbness
- autonomic dysfunction – prominent – orthostatic hypotension, heat intolerance

### Etiology

- similar causes of large fiber peripheral neuropathy (DM, B12 deficiency...)
- also: amyloidosis, MGUS, Sjogren's, HIV, Lupus, Paraneoplastic neuropathy

# Fibromyalgia

## What is it?

- Considered a central neurologic pain syndrome (nociceptive pain), a functional disorder of the nervous system

## How common?

- Between 2 – 8% lifetime prevalence; Women > Men 3:1; Age 30 – 50yrs

## How is it diagnosed?

- Often delayed (>2 years since symptoms onset and 3.7 avg different physicians before diagnosis)
- American College of Rheumatology 2010 Criteria (updated from 2002)
- American Pain Society 2019 Criteria

## Who diagnosis, manages and follows this condition?

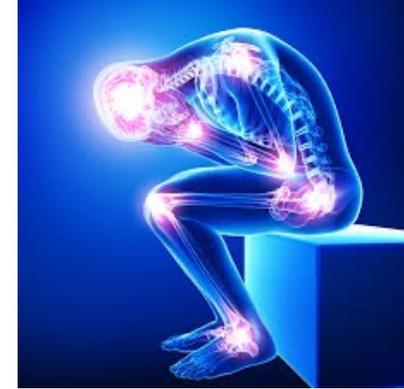
- Primary Care, PMR, Rheumatology, Pain specialists, Neurology

# Fibromyalgia – what is it?

A pain processing disorder without a known structural injury

Central neurologic amplification of pain perception (nociplastic pain)

- Allodynia - a heightened sensitivity to stimuli that are not normally painful
- Hyperalgesia - an increased response to painful stimuli



Associated with neuroimaging functional abnormalities

- FM is associated with aberrant processing of painful stimuli in the central nervous system

## What it is NOT

- Unknown, Autoimmune, Inflammatory, Muscle/Tissue disorder, a “grab bag” diagnosis

- **Arnold et al.** Improving the Recognition and Diagnosis of Fibromyalgia. *Mayo Clinic Proceedings*. 2011
- **Nebel and Gracely.** Neuroimaging of fibromyalgia. *Rheum Dis Clin North Am*. 2009
- **Gracely et al.** Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum*. 2002

# Fibromyalgia associated conditions

## **Risk factors / Associated Conditions:**

- Family history (8x higher risks)
- Female sex (7x higher diagnostic rate)
- Mood disorders
  - Anxiety 35-62% of FM patients
  - Major Depressive Disorder 58-86%
  - Bipolar Disorder 11%
- Other comorbid pain disorders
  - Irritable bowel syndrome (IBS), migraine, interstitial cystitis, chronic prostatitis, temporomandibular disorder (TMJ), chronic pelvic pain, and vulvodynia
- Prior physical or psychologic trauma
- Peripheral Neuropathy / Small fiber neuropathy

# Fibromyalgia diagnostic criteria (ACR 2010)

**Chronic Widespread Pain** in  $\geq 7$  areas (or  $\geq 3$  areas) over last 1 weeks

- **no longer need “tender points” as of 2010 guideline statement**
- 19 locations of possible pain - Shoulder (L/R), Upper arm (L/R), Lower arm (L/R), Hip (L/R), Upper leg (L/R), Lower leg (L/R), Jaw (L/R), Chest, Abdomen, Upper back, Lower back, Neck)

**Multiple Systemic Symptoms**  $\geq 5$  score (or  $\geq 9$  score)

- Fatigue (0-3) 0= none, 1 = mild, 2= moderate, 3 = severe
- Waking Unrefreshed (0-3)
- Cognitive Symptoms (0-3)
- PLUS: Somatic Symptoms (0-3) 0= none, 1= few, 2= moderate, or 3= a great deal of the following: muscle pain, IBS, headaches, abdominal pain, numbness/tingling, dizziness, insomnia, depression, constipation, nausea, nervousness, blurred vision, fever, diarrhea, wheezing, dry mouth, itching, Raynaud's, heartburn, vomiting, loss of appetite, shortness of breath, frequent urination, painful urination, bladder spasms...

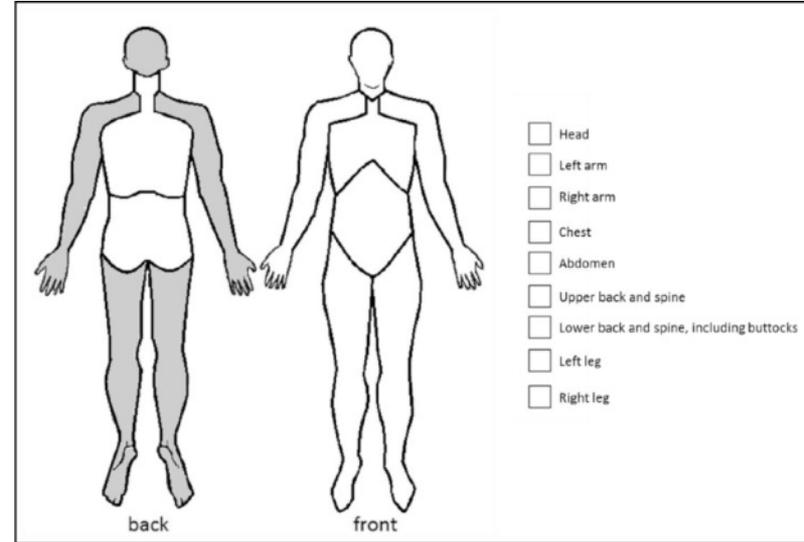
**3 months duration**

**AND... No other better explanation of symptoms**

# Fibromyalgia – updated simplified criteria

## Diagnostic Criteria (APS 2019)

- **Multisite pain**,  $\geq 6$  pain sites from 9 total (figure)  
Head, Arm (L/R), Chest, Abdomen, Upper Back, Lower Back, Leg (L/R)
  - **Sleep Problems** - moderate to severe
- OR
- **Fatigue** – moderate to severe (physical or mental)
  - **>3 months in duration** (both symptoms)
  - No other better explanation
- Common associated features:
    - Tenderness
    - Dyscognition (forgetfulness, disorganized thinking)
    - Stiffness
    - Environmental sensitivity (photo/phonophobia, smell sensitivity)



Arnold et al. "AAPT Diagnostic Criteria for Fibromyalgia". Journal of Pain.

# Fibromyalgia – case examples

37yo woman with 6 months of aching pain in bilateral shoulders (2), abdomen (1), hips (2), and legs (2), severe fatiguability, cognitive fogging and insomnia.

- No other characteristic diagnosis, normal physical exam otherwise, history of IBS-d
- +7 areas of chronic pain, +6 Systemic Symptoms (+3 severe fatigue, +3 cognitive symptoms)
- Classic Fibromyalgia diagnosis

# Fibromyalgia – case examples

37yo woman with 6 months of moderate fluctuating aching pain in bilateral hips (2), and legs (2). Moderate fatigue (2), moderate cognitive fogging (2), moderately un-refreshing sleep (2) and many other symptoms (3), headaches, numbness/tingling, dizziness, depression, constipation, nausea, nervousness, blurred vision, fever, diarrhea, dry mouth, itching, Raynaud's, heartburn... “pan-positive ROS”.

- No other characteristic diagnosis, normal physical exam without structural etiology of leg and hip pain, extensive workup with normal L spine MRI, labs, EMG, xrays and consult with Rheumatology and PMR
- +4 areas of chronic pain, +9 Systemic Symptoms
- Fibromyalgia diagnosis (ACR 2010 criteria) - **but only lower extremity chronic pain!**

# Fibromyalgia – case examples

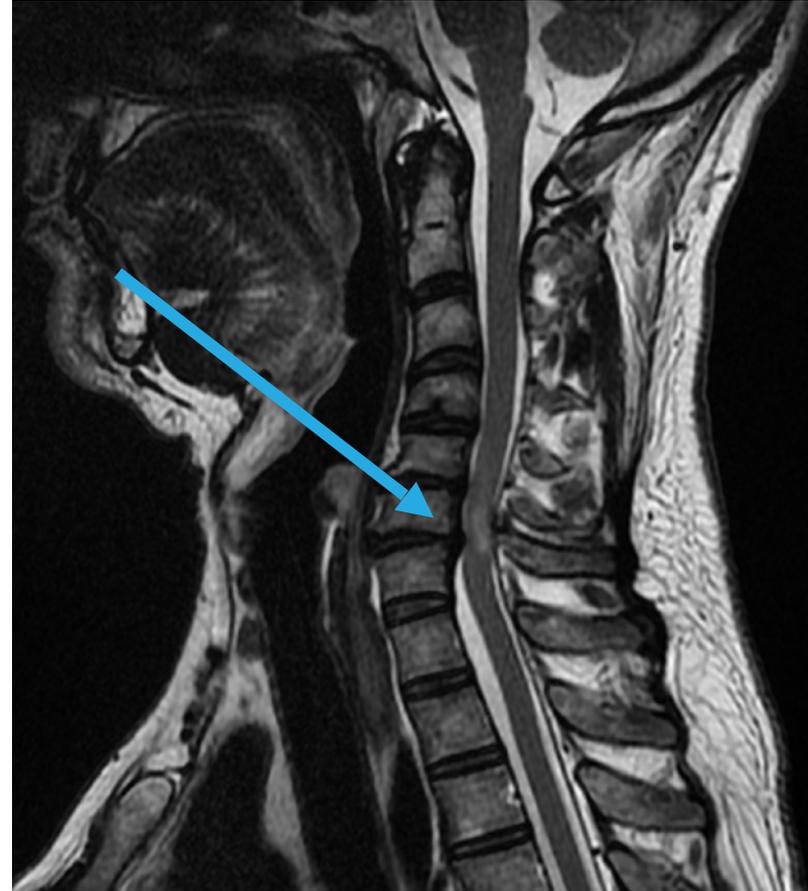
37yo woman with 6 months of progressive pain in neck, arms, chest, abdomen, legs, tingling/aching pain, with stiffness, muscle spasms, urinary urgency/frequency, constipation, tingling/numbness, mild imbalance, insomnia.

- Exam notable for mild diffuse hyper-reflexia, mild low distal vibration sense, mild difficulty with tandem walking
- **Possible** Fibromyalgia diagnosis

# NOT Fibromyalgia – case examples

37yo woman with 6 months of progressive pain in neck, arms, chest, abdomen, legs, tingling/aching pain, with stiffness, muscle spasms, urinary urgency/frequency, constipation, tingling/numbness, mild imbalance, insomnia.

- Possible Fibromyalgia diagnosis
- MRI C-spine done for prominent neck pain and mild distal sensory loss found  
**severe cervical stenosis and myelopathy**
- **NOT Fibromyalgia**
- **Neuropathic pain from chronic myelopathy**



# Fibromyalgia Workup Questions

- Have you had pain in your muscles or joints that has lasted 3 months or more?
- Do you have pain all over?
- Do you become fatigued during the day so that you must stop normal activities?
- Do you wake up in the morning and feel more tired than when you went to bed?

# Fibromyalgia Workup Questions

- Have you had pain in your muscles or joints that has lasted 3 months or more?
  - **chronic myofascial pain**
- Do you have pain all over?
  - **widespread pain**
- Do you become fatigued during the day so that you must stop normal activities?
  - **moderate/severe fatigue**
- Do you wake up in the morning and feel more tired than when you went to bed?
  - **non-restoring sleep**

# Is Fibromyalgia a Diagnostic Dilemma?

”No one can tell me what is wrong with me”

“I have been to multiple doctors who give me different answers”

## Why make a diagnosis fast?

**Improved satisfaction:** Diagnosis of FM has no negative effect on clinical outcomes, and those newly diagnosed with FM report improved satisfaction with health and fewer long-term symptoms<sup>1</sup>

**Reduced costs:** Utilization of medical resources and the associated costs decline after a diagnosis of FM<sup>2</sup>

*\*Don't “Turn off your brain” once diagnosis made – maintain differential diagnostic vigilance*

<sup>1</sup>White et al. Does the label “fibromyalgia” alter health status, function, and health service utilization? *Arthritis Rheum.* 2002

<sup>2</sup>Annemans et al. Health economic consequences related to the diagnosis of fibromyalgia syndrome. *Arthritis Rheum.* 2008

# Fibromyalgia Take-Home Points

- Fibromyalgia is common (at least 1 in 20 lifetime prevalence)
- Under-diagnosed / Delayed Diagnosis
- Diagnosis shouldn't take 3+ doctors and >2 years
- Primarily Neurologic etiology – Central pain sensitization (nociceptive pain)
- Many associated conditions (21% of RA patients with fibromyalgia<sup>1</sup>)
- Association with small fiber neuropathy and other pain syndromes

# Treatment of Neuropathic pain

# Treatment of Neuropathic pain

## Treatment

Effectively treating pain often tied to improving mood, coping, sleep, and function while reducing distress (holistic management)

## Mechanism based treatment

Sounds reasonable, treat differently based on etiology (peripheral neuropathy, post-herpetic neuralgia, Central thalamic pain, Myelopathic pain...) sounds good, and it is the future, BUT... **we aren't there yet**

# Treatment of Neuropathic pain

## Many Medication Options for Neuropathic Pain

- TCAs : Nortriptyline, Desipramine, Amitriptyline
- SNRIs: Duloxetine, Venlafaxine, Milnacipran
- Gabapentinoids: Gabapentin, Pregabalin, Gabapentin Enacarbil
- Topical Lidocaine or Capsaicin
- Sodium channel blocking anti-seizure medications: Valproate, Lamotrigine...

Other Antiepileptics

Other Antidepressants

Others: Alpha 2 agonists, Antiarrhythmics, Devices, Botox...

# Treatment of Neuropathic pain

Non-Medical Treatments – IMPORTANT and UNDERUTILIZED

- **Mental health:** cognitive behavioral approaches, mindfulness, hypnosis
- **Physical activity:** PT, stretching, aerobic exercise, Yoga, Pilates, Tai Chi
- **Behavior Modification:** Diet, weight loss, sleep
- **Complementary approaches:** massage, acupuncture

Specific disease and comorbidity management



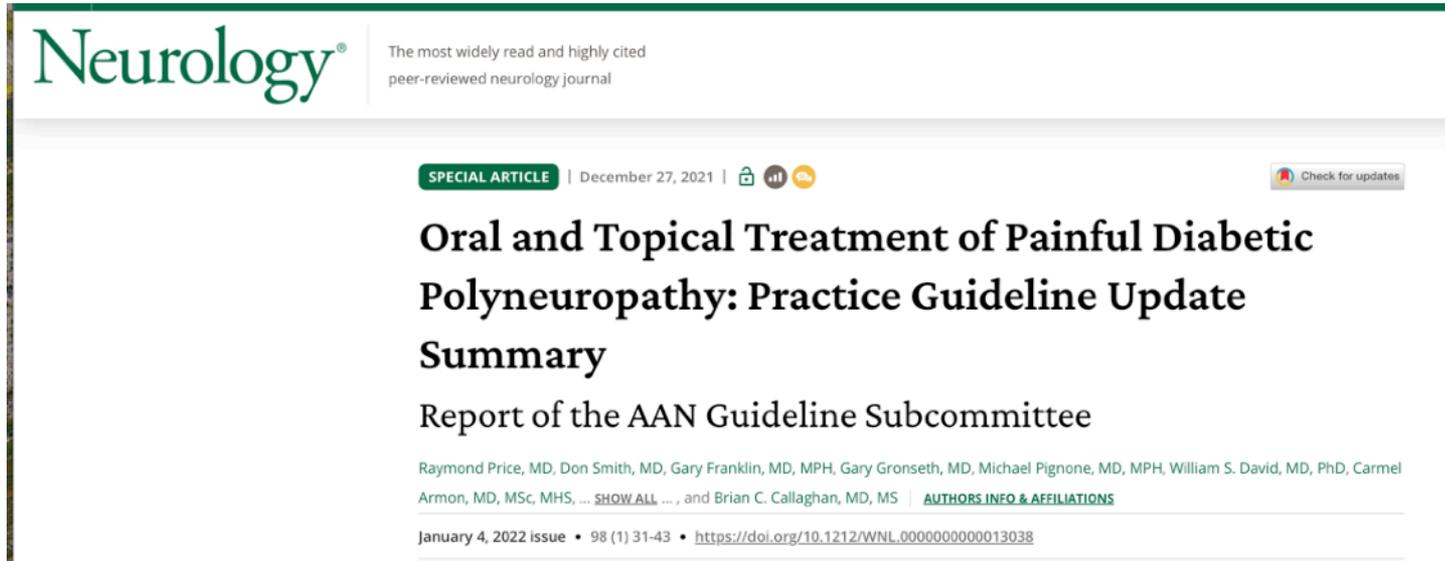
# Treatment of Neuropathic pain

## What is UNLIKELY Helpful

### Absent from Neuropathic Pain Treatment Recommendations:

- NSAIDs: low likelihood of benefit
- SSRIs: widely used, minimal positive data

# Are there recommendations for treatment of neuropathic pain (DM neuropathy)?



The screenshot shows the top portion of a Neurology journal article page. The journal logo "Neurology" is in green on the left, with the tagline "The most widely read and highly cited peer-reviewed neurology journal" to its right. Below this is a navigation bar with a "SPECIAL ARTICLE" badge, the date "December 27, 2021", and icons for a lock, a person, and a speech bubble. A "Check for updates" button is on the right. The main title is "Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary" in bold black text. Below the title is the subtitle "Report of the AAN Guideline Subcommittee". The authors are listed as "Raymond Price, MD, Don Smith, MD, Gary Franklin, MD, MPH, Gary Gronseth, MD, Michael Pignone, MD, MPH, William S. David, MD, PhD, Carmel Armon, MD, MSc, MHS, ... SHOW ALL ... , and Brian C. Callaghan, MD, MS" with a link to "AUTHORS INFO & AFFILIATIONS". At the bottom, it says "January 4, 2022 issue • 98 (1) 31-43 • <https://doi.org/10.1212/WNL.0000000000013038>".

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SPECIAL ARTICLE | December 27, 2021 |    [Check for updates](#)

## Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary

Report of the AAN Guideline Subcommittee

Raymond Price, MD, Don Smith, MD, Gary Franklin, MD, MPH, Gary Gronseth, MD, Michael Pignone, MD, MPH, William S. David, MD, PhD, Carmel Armon, MD, MSc, MHS, ... [SHOW ALL ...](#) , and Brian C. Callaghan, MD, MS | [AUTHORS INFO & AFFILIATIONS](#)

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# Are there recommendations for treatment of neuropathic pain (DM neuropathy)?

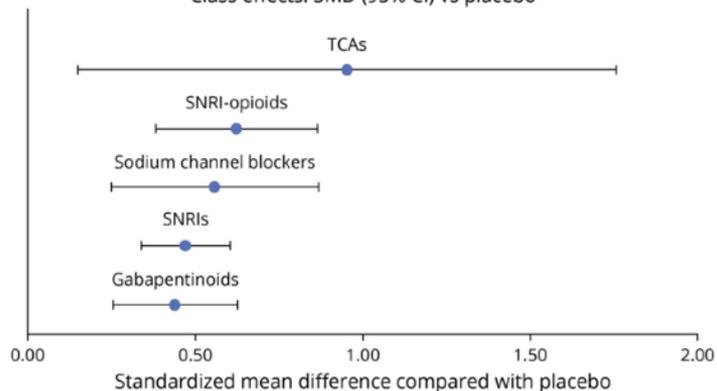
**Table 3** Efficacy of Oral Medications for Painful Diabetic Neuropathy by Class Effect

Medication class	SMD <sup>a</sup>	LCL	UCL	Number of articles	Number of patients	Conclusion	Confidence
<b>Gabapentinoids</b>	0.44	0.25	0.63	16	3,550	Probably more likely than placebo to improve pain	Moderate
<b>Sodium channel blocker</b>	0.56	0.25	0.87	5	566	Probably more likely than placebo to improve pain	Moderate
<b>SNRI</b>	0.47	0.34	0.60	9	1,884	Probably more likely than placebo to improve pain	Moderate
<b>SNRI-opioid</b>	0.62	0.38	0.86	4	775	Probably more likely than placebo to improve pain	Moderate
<b>TCA</b>	0.95	0.15	1.75	3	139	Possibly more likely than placebo to improve pain	Low

Abbreviations: LCL = lower confidence limit; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants; UCL = upper confidence limit.

<sup>a</sup> SMD >0 indicates intervention is clinically better than placebo.

Class effects: SMD (95% CI) vs placebo



**Table 1** Medication Dosage and Duration Information

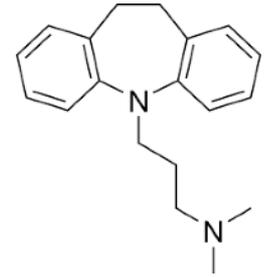
Medication class	Medication	Dosage, mg/d	Duration, wk
<b>SNRI</b>	Duloxetine	40–60	12
<b>SNRI</b>	Venlafaxine	150–225	6
<b>SNRI</b>	Desvenlafaxine	200	13
<b>Gabapentinoid</b>	Gabapentin	900–3,600	4–8
<b>Gabapentinoid</b>	Pregabalin	300–600	5–12
<b>Gabapentinoid</b>	Mirogabalin	15–30	5
<b>Sodium channel antagonist</b>	Oxcarbazepine	1,400–1,800	16
<b>Sodium channel antagonist</b>	Lamotrigine	200–400	6
<b>Sodium channel Antagonist</b>	Lacosamide	400	12
<b>Sodium channel blocker</b>	Valproic acid	1,000–1,200 or 20 mg/kg/d	4–12
<b>TCA</b>	Amitriptyline	75–150	6
<b>Capsaicin</b>	Capsaicin	8% for 30 min/ application or 0.075% 4 times per day	12

Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

# Are there recommendations for treatment of neuropathic pain (DM Neuropathy)?

- Goal of therapy to reduce, not eliminate pain
- Assess concurrent sleep or mood disorders and treat
- Should offer TCA's, SNRI's, gabapentinoids, and/or sodium channel blockers to reduce pain
- Should not prescribe Valproic Acid unless multiple other medications have failed
- Dose should be escalated to efficacy/tolerability and tried for at least 12 weeks before claiming failure
- Should NOT use opiates / tramadol for the treatment of neuropathic pain

# Tricyclics for neuropathic pain



## Benefits

- Many trials show significant benefits for multiple neuropathic pain types
- FIRST LINE option for neuropathic pain, headache
- Some benefits for Insomnia
- Very inexpensive
- Can be combined with Gabapentinoids or others

# Tricyclics for neuropathic pain

## Drawbacks

- Do have significant **side effects** and **risks** - worse with age
- Many contraindications – cardiac risks in elderly, drug-drug interactions
- Excessive death
- Often underdosed – recommended for neuropathic pain - dose 50-150 mg
- Consider checking ECG prior with at risk patients
- Anticholinergic effects – urinary retention, dry mouth, constipation, orthostatic hypotension, delirium

# Tricyclics for neuropathic pain

## Whom to use

- Younger patients
- Prefer once daily dosing
- Additional comorbidities: Migraine, Insomnia, IBS-d, Interstitial Cystitis
- Lower risk for metabolic syndrome, constipation, dry mouth
- Not on significant doses of other anti-cholinergic or serotonergic medications
- Start low and increase – 10mg or 25mg -> 50-100mg over 2-4 weeks
- Nortriptyline and Desipramine<sup>1</sup> probably better tolerated than Amitriptyline with equal efficacy

# SNRIs – Duloxetine, Venlafaxine

Selective serotonin norepinephrine reuptake inhibitor (SSNRI)

FDA approved for: diabetic neuropathic pain, fibromyalgia, GAD, Depression, and chronic musculoskeletal pain

## **Benefits:**

- Modest response
- Helpful at standard dosing for **many conditions** in addition to neuropathic pain
- Low anti-cholinergic side effects

Dosing: Duloxetine - start 20mg-30mg with food, effective dose mostly 60mg daily, max 120mg daily

# SNRIs – Duloxetine, Venlafaxine

## Drawbacks

- Nausea main side effect, can be stimulating (sweating, insomnia also)
- Venlafaxine has higher cardiac risks and risks for withdrawal symptoms than Duloxetine
- More expensive - Duloxetine – \$124<sup>1</sup>, Venlafaxine - \$71<sup>1</sup>, newer agents much more expensive: milacipran (savella) - \$508<sup>1</sup>, desvenlafaxine (generic Pristiq) - **\$26<sup>1</sup>**
- Drug-drug interactions, some
- May provoke RLS
- Withdrawal symptoms – should be tapered slowly – 2-4 weeks

# Gabapentin

Widely used (overused) since 2000's for neuropathic. OFF LABEL (not FDA approved) use for neuropathic pain other than post-herpetic neuralgia. Does NOT increase GABA, but is structurally similar this, but binds  $\alpha 2\delta$ -1 voltage gated calcium channels and also interacts with key excitatory synaptic proteins, including N-methyl-D-aspartate (NMDA) receptors and AMPA receptors.

## Benefits:

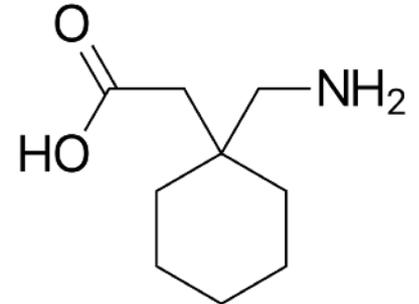
- Renally cleared (not metabolized)
- low drug-drug interactions
- Relatively fast onset of action
- Helpful for RLS (1st line) and Essential Tremor
- Possibly helpful for anxiety and insomnia
- Inexpensive



# Gabapentin

## Drawbacks

- Renally cleared – watch for CKD
- Peripheral edema and weight gain
- BID/TID dosing required for optimal benefits
- Fatigue and Depression worsening
- Dizziness



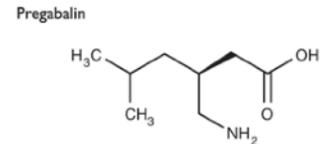
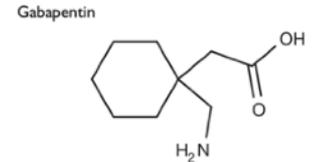
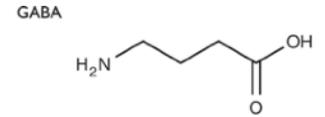
# Pregabalin

## Benefits:

- Compared to gabapentin - More potent, faster onset (1hr vs. 3hr peak)
- BID dosing typically – 50mg BID -> 150mg BID = Gabapentin 300mg -> 900mg
- Fast onset of effect, within 1-2 days
- Now generic and cheap, \$12 with goodrx coupon – 50mg x60pills
- Similar benefits to Gabapentin

## Drawbacks:

- Probably more risk for peripheral edema and CHF than Gabapentin



# Low dose naltrexone (LDN)

- Toll-like receptor 4 or TLR4 antagonist, other mechanisms possibly including opioid growth factor
- Studies in Fibromyalgia, Crohn's Disease and MS
- Dose usually 4.5 mg/day or less
- Must be compounded \$30-50 per month
- Mild benefits in small trials only
- Limited side effects

# How to treat neuropathic pain?

## Based on Comorbidities:

- Depression / Anxiety – SNRIs
- Chronic Musculoskeletal Pain – SNRIs
- Insomnia – TCA's
- Migraine - TCA's or SNRIs
- IBS-d - TCA's
- RLS – Gabapentinoids
- Fibromyalgia - SNRIs, LDN

## Based on Risks:

- Dementia - not TCA's
- Constipation / Sjogren's - not TCA's
- Long QT / Vent Arrhythmia - not TCA's
- CHF - not Pregabalin
- Depression / Fatigue - not Gabapentinoids
- RLS - not SNRIs or TCAs
- Nausea - not SNRIs

# RCT on Diabetic Neuropathy Treatments

## OPTION-DM RCT for Diabetic Neuropathy Pain in the UK<sup>1</sup>

130 patients randomized to one of 3 monotherapies x 6 weeks, then if needed additional randomized to dual therapy x 10 weeks

Largest and longest ever, head-to-head, crossover neuropathic pain trial

Amitriptyline to 75mg daily,  
Pregabalin to 300mg BID,  
Duloxetine to 120mg Daily

<b>Monotherapy</b>	Amitriptyline	Pregabalin	Duloxetine
<b>&gt;50% reduction at 6 weeks</b>	40%	35%	40%
Top side effects	Dry Mouth (21%) Sedation (18%) Fatigue (17%)	Dizziness (18%) Edema (13%) Fatigue (10%)	Nausea (19%) Fatigue (17%) Diarrhea (10%)
<b>Dual Therapy</b>	Amitriptyline + Pregabalin	Pregabalin + Amitriptyline	Duloxetine + Pregabalin
<b>&gt;50% reduction at 16 weeks</b>	48%	46%	44%

# How to treat neuropathic pain

Start low, go up to maximally effective dosing quickly as tolerated

Choose agent with best benefit / risk profile for individual

Consider multi-modal treatment from the start

	TCA	SNRI	Gabapentinoid
NNT	4.6	7.4	8.9
NNH	17.1	13.9	26.2

# Neuropathic Pain

- Many different etiologies for neuropathic pains
- Current treatment algorithms are similar regardless of source currently
- FDA approval does not equate to efficacy / safety
- Consider other co-morbidities when treating with medications
- ALWAYS consider non-medication management (holistic care)
- Be weary of side effects and contraindications

Thank you for your time!