Pharmacological Treatment of Pain in Multiple Sclerosis

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Disclosures

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No financial conflicts
Presentation reflects my personal opinion, and not the opinion of my employer or the Dept of Veteran Affairs
Presentation includes the discussion of off-label use of medical drugs, in addition to *FDA approved indications

"Ask your doctor if taking a pill to solve all your problems is right for you."
Overview

1) General approach to pharmacological therapy in pts with chronic pain
2) Pain types in MS
3) Approach to
   • Dysesthetic extremity pain
   • Trigeminal neuralgia
4) What to do with patients on opioid medication?

Case: 35 y/o woman with RRMS and abdominal and back pain

• 35 y/o woman with RRMS, dx in 2005, using cane for walking
• Longstanding h/o constipation and abdominal pain, with dx of neurogenic bowel
• Presents with c/o worsened abdominal pain and new report of lower back pain x 4 days “as if intestines are bursting through”
• Exam reveals tenderness in lower T-spine around T10
• Workup: Xray with evidence of constipation and subileus.
  CT abdomen shows 4 mm ovarian cyst
  MRI T-spine w/o cord hyperintensities
  MRI L-spine no significant spondylosis
  Ultrasound abdomen/pelvis no other lesion
Case: 35 y/o woman with RRMS and abdominal and back pain

- Two weeks later she returns with report of worsened pain that is now in abdomen, lower back and in particular a tightness/pressure sensation that extends from mid- to lower back around the abdomen “like a band squeezing my body”. Maximal pain around T8
- Bowel function is improved with bowel regimen
- Pain is worse at night
- Treatment trial with gabapentin 300 mg TID for neurogenic pain
- One week later she develops weakness in L arm/leg; on exam worsened ataxia
- Diagnosis of MS exacerbation, treatment with IV methylprednisolone improves neurological function and back pain resolves completely

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**Pain Types in MS**

- Central neuropathic pain
  - Chronic/steady (fluct/remitting)
  - Dysesthetic extremity pain 26%
  - Thalamic pain
- Intermittent (paroxysmal)
  - Trigeminal neuralgia 4%
  - Lhermitte 16%
  - Paroxysmal limb pain
- Muscle spasm and spasticity
  - Spasticity pain
  - Painful tonic spasms 15%
- Headache 43%
  - Migraine
  - Tension type
  - Unclassified

**Treatment induced pain**

- Visceral pain
- Back pain 20%
- Musculoskeletal pain due to postural abnormalities

**Optic neuritis pain**

**Musculoskeletal or Nociceptive pain**

O’Connor et al. 2008, Pain 137: 96-111
Truini et al. 2013, J Neurol 260:351-367
Möhre, Kropp, Zettl 2013, PloS One; 8(8): e69570
Foley et al. 2013, Pain 154: 632-642

--> pooled data of 17 studies, 5319 subjects. Overall pain prevalence in MS pts was 63%
Medication therapy should be in the context of non-pharmacological treatment

- Medications are typically symptomatic
- Rarely a treatable cause is identified
- Discuss realistic expectations
- “Collaborative Self-Management” provider as partner or “coach”
- Set measurable functional goals
- Pain psychology therapies:
  - Cognitive behavioral therapy (CBT)
  - Coping measures
  - Stress reduction, Relaxation
  - Meditation
  - Sleep hygiene
- Physical Therapy/Paced activities
- Acupuncture, and other CAM Approaches
- Interventional procedures

Medications for Chronic Pain: Approach

- Individual variation in response to medications is substantial
- Stepwise process to identify the medications that provide the greatest relief with fewest adverse effects.
- Change only one medication at a time and give it adequate trial
- If medication is not effective or causes severe side effects, stop it
- If medication provides partial relief and is well tolerated, add on second agent with different mechanism of action.

("Rationale Polypharmacy")

- Additive analgesic benefits with less side effects
- Combine agent with rapid benefit with one that requires weeks
- but: - added cost
  - lower compliance
  - drug interactions
  - less clear what works

Dworkin et al; Pain 2007, *Chisaz et al; Clin J Pain 2009*
**Medications for Chronic Neuropathic Pain**

*FDA approval

- **Antidepressants**: TCA, SNRI  → “broad spectrum”
  - duloxetine* for DPN, FM, chronic musculoskeletal pain incl. OA and lbp
- **Antiepileptics (AEDs)**  → Neuropathic pain
  - carbamazepine* for TN
  - gabapentin* for PHN, pregabalin* for DPN, PHN, FM
- **Opioids**  → primarily for short term use
- **Tramadol/Tapendatol**
- **Cannabinoids**
- **Antispasticity agents**: baclofen, tizanidine
- **Muscle relaxants**
- **Topical**: Capsaicin, Lidocaine 5%, Diclofenac 1% gel, Methylsalicylate
- **NSAID, Cox-2, aspirin, acetaminophen - only minor effectiveness**
- **Clonidine**
- **Benzoazepines - use only with caution, avoid combination with opioids**
- **Botulinumtoxin injections**  → for TN in MS
- **Misoprostol**
- **Local anesthetics**: Mexiletine, Lidocaine injection
- **Naltrexone**
- **NMDA-receptor antagonists**: Dextromethorphan, Memantine, Ketamine

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**Medications for Chronic Pain**

**How do I decide what agent to use?**

- What works for the underlying disorder?
  - Musculoskeletal/nociceptive vs. neuropathic pain
- What works for the patient’s pain symptoms?
  - Sharp stabbing vs. electrical vs. burning vs. aching pain
- What are the co-existing symptoms?
  - depression, anxiety, sleep disturbance
- What are the co-morbidities?
  - Medical: cardiac, renal, hepatic, bladder/bowel fct
  - Psychiatric co-morbidities, substance abuse
- What is the patient’s level of functioning?
  - Occupation? Walking ability? Sexual fct?
- What are the characteristics of my potential drugs?
  - Side effects (adverse or beneficial), interactions, ease of use, cost, abuse potential, risk of overdose, etc.

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Case: 29 y/o woman with RRMS and pain in lower extremities

- 29 y/o woman with RRMS, dx in 2007
- Sites of pain:
  - Headaches with migraine features
  - Leg pain that is constant/steady, described as ‘icy cold to the bone’ pain in both legs
  - Sharp, splintering feeling in both ankles
- May spend days in bed, avoiding friends and family
- Admits to excessive fatigue and depression
- Multiple ER visits in the last year with c/o severe pain
- Failed multiple medication trials in the past, including methylprednisolone for presumed MS exacerbation
Case: 29 y/o woman with RRMS and pain in lower extremities - Treatment

- Prior treatments without benefit:
  - Hydromorphone
  - Anticonvulsants gabapentin/pregabalin, topiramate, levetiracetam and lamotrigine
  - Antidepressants nortriptyline and fluoxetine.
- Treatment approach: trial of duloxetine, with tramadol as “rescue” medication for prn use
- In addition, weekly acupuncture and physical therapy
- 7 months later: doing well, husband returned from deployment in Afghanistan, she swims 3 x per week, recently began coaching her daughter’s basketball team

Dysesthetic Extremity Pain in MS

Dysesthetic extremity pain
= steady extremity pain, continuous central neuropathic pain in MS
- Dysesthesia indicates an “unpleasant abnormal sensation, whether spontaneous or evoked” (IASP)
- Constant, often burning pain; less commonly deep and muscular aching pain
- Predominantly affects trunk and legs distally – often bilateral
- Lifetime prevalence rates range between 12 and 28 %
- More common in primary progressive or the progressive-relapsing MS
- Pathophysiology is poorly understood
  → Demyelinating lesions in central pathways mediating pain signaling

O’Connor AB, et al. 2008; J Pain 137; 96-111
**Dysesthetic Extremity Pain (cont’d)**

Hypothesis: arises from lesions in the pain signaling pathways

Correlation between lesion location and pain in MS is poor

Bilateral and relatively distal (legs) distribution presumably explained by

• length of the spinothalamic tract to the lower extremities

• somatotopic location in the spinal cord (more superficial) and brain (periventricular), i.e. sites with predilection to MS plaques

Truini A et al 2013; J Neurol 260(2):351-6


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**Guidelines for Neuropathic Pain (IASP)**

For Neuropathic Pain in general, in adults

• Excludes trigeminal neuralgia and fibromyalgia

**First line agents:**

• Secondary amine tricyclic antidepressants (TCA): nortriptyline, desipramine

• Serotonin and norepinephrine reuptake inhibitor (SNRI) duloxetine, venlafaxine

• Calcium channel alpha 2-delta ligand: gabapentin, pregabalin

• For localized np pain: topical lidocaine

• If acute, cancer-related, or episodic exacerbation of severe pain, and when prompt pain relief is required: opioid analgesic or tramadol

Dworkin et al. for the IASP. Pain 2007

Dworkin et al. Mayo Clin Proc 2010

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Rating of Recommendations

First line: efficacy in multiple RCTs (grade A) and c/w clinical experience
Second line: grade A, but reservations based on clinical experience
Third line: grade B, reasonable alternatives based on clinical experience

Oxford grading system
A: “Established” - consistent level 1 studies
B: “Probable”- consistent level 2 or 3 studies; inconsistent level 1 studies, or extrapolations from level 1 studies
C: “Possible” - level 4 studies, or extrapolations of level 2 or 3 studies.

Rating of strength of evidence:
Class I 1: Randomized controlled trials (with homogeneity)
Class II 2: Cohort studies (with homogeneity)
Class III 3: Case-control studies
Class IV 4: Case series, poor quality cohort or case control studies; 5: “Expert opinion”

Treatment of Neuropathic Pain:
Antidepressants

– Tricyclic Antidepressants (TCA)
  • Nortriptyline, Desipramine, Amitriptyline, Imipramine

– SSRIs
  • only inconsistent benefit on pain, NNT of 6.7 (Sindrup 2000)

– SNRIs:
  • Dual uptake inhibition; multiple receptor affinities
  • Better tolerated than TCAs
  • For pain not more effective than TCAs
  • Duloxetine*, venlafaxine, milnacipran ‘FDA approval

– Bupropion inhibitor of NE and dopamine reuptake

– Mirtazapine noradrenergic and specific serotonergic

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Antidepressants: TCAs

Amitriptyline
• classic TCA in pain treatment
• metabolized to nortriptyline

Nortriptyline
• Secondary amine, more selective for NE re-uptake inhibition
• less anticholinergic and less sedation

Desipramine
• Even less anticholinergic or sedating
• Higher cardiac toxicity – high risk with overdose; avoid in pts with arrhythmia

• > 10 placebo contr. studies with efficacy in neuropathic pain
  – NNT of 2.6 overall, in high dosage 1.4 (Sindrup 2000)

• Crossover study nortriptyline vs amitriptyline in PHN
  – equally effective, but side effects greater with amitriptyline
  – Unless the sedating effect of amitriptyline is specifically desired, the lesser anticholinergic agents are preferred

Antidepressants: TCAs

• Mechanisms:
  – Blocking of reuptake of serotonin (5-HT) and norepinephrine (NE)
  – Independent of antidepressant effect
  – Improve sleep

• Indications: “Broad spectrum”
  – Neuropathies with burning, aching pain, but also sharp, stabbing pain, incl. diabetic np, PHN
  – Central pain: post-stroke
  – Headache (migraine, tension-type headache)
  – Chronic musculoskeletal pain

• In MS:
  – First line (level A) for chronic dysesthetic pain
  – limited direct evidence, no class 1 studies
  – Uncertain for TN

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Antidepressants: TCAs

• Dosage:
  – Starting dose is 10 - 25 mg at bedtime, increase weekly as tolerated
  – Maximal therapeutic daily dose of
    - Amitriptyline 75 - 150 mg
    - Nortriptyline 50 - 100 mg
  – Last dose 2-3 hours before bedtime to reduce hangover
  – Dosages needed lower than in treatment of depression
  – Blood level to monitor treatment and compliance

• Time course:
  – Faster than in treatment of depression: 1 - 2 weeks at therapeutic doses
  – Delayed response possible (up to a year)

• Side Effects of TCAs
  – Cardiac:
    • Risk of sudden cardiac death. Avoid, if h/o MI, arrhythmia incl. BBB
    • BASELINE EKG in pts > 40 yrs, assess QTc interval, PR interval
  – Anticholinergic side effects:
    • Dry mouth
    • Urinary retention
    • Constipation
    • Blurred vision
    • Rapid pulse
  – Peripheral anticholinergic effects may be reversed by pyridostigmine
  – Sedation and drowsiness: often dose-limiting
  – Weight gain
  – Decrease in seizure threshold (at higher dosages)
  – Suicide risk (like all antidepressants), in addition toxic overdose
  – Avoid in elderly: orthostatic hypotension, falls, impaired cognition
  – Side effects usually improve within 2 - 3 weeks
Antidepressants: SNRI

**Duloxetine***

*FDA approval for depression, painful diabetic np (DPN), FM, musculoskeletal pain including low back pain and osteoarthritis pain

- Improvement in painful physical symptoms incl. back pain, abdominal pain, and musculoskeletal pain
- Study in 38 pts with MS dyesthetic pain randomized to placebo (x 6 wk)
  - On duloxetine 39% ↓ in avg pain vs placebo 10%
  - 78% of pts on duloxetine completed study
  
  Brown et al, CMCS 2013, abstract only

- CI: alcohol abuse, renal ds, liver ds (black box); monitor LFTs
- Begin 30 mg, after one week 60 mg QD (target dosage for pain)
  - max 60 mg bid (depression)

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**Venlafaxine, Desvenlafaxine**

- FDA approval for depression. Use for pain is “off-label”
- Low dose like SSRI, higher dosage NE reuptake inhibition (>150 mg/d)
- ADE: BP increase. ECG monitoring is recommended (5% change)
- Dosing: begin 37.5 mg QD to BID, increase gradually to 300-375 mg/d, over 2-4 weeks. Generic is BID dosing, but less tolerated (GI)

**Milnacipran**  
FDA approval for FM, not depression (→ outside US)

- FM: 25 mg/d x 4 days, then titrate to 50 mg BID. May be increased to 200mg/d.
Antidepressants: SNRI

- **SNRIs: Side Effects** – generally well tolerated
  - Nausea (often disappears in 1-2 wks, avoided by low beginning dosage)
  - Sleepiness, dizziness, fatigue
  - Constipation, dry mouth
  - Increased sweating, hot flashes
  - Decreased appetite/anorexia, occasionally weight loss
  - Sexual dysfunction (decreased libido, anorgasmia)
  - Withdrawal syndrome: Dizziness, nausea, headache
  - CI: MAOI, uncontrolled narrow-angle glaucoma
  - Duloxetine: liver disease, renal insufficiency
  - Venlafaxine: BP increase

AEDs for Common Neuropathic Pain Ds

**Postherpetic neuralgia**
- Gabapentin*/Pregabalin*

**Diabetic neuropathy**
- Gabapentin*/Pregabalin*
- Carbamazepine and Oxcarbazepine
- Lamotrigine
- Topiramate

*FDA approval

**Central pain: poststroke**
- Gabapentin/Pregabalin
- Lamotrigine

**Central pain: SCI**
- Gabapentin/Pregabalin
- Lamotrigine

**Trigeminal Neuralgia**
- Carbamazepine* and Oxcarbazepine
- Lamotrigine
- Pregabalin

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Gabapentin

AEDs: Gabapentin

**Gabapentin**

- **Mechanism of action:**
  - binds to α2-δ subunit of voltage gated calcium channel (NMDA)
  - ↓ calcium influx in presynaptic nerve terminals
  - ↓ release of glutamate, noradrenaline and substance P
- **FDA-approvals:** in partial seizures, postherpetic neuralgia
- **Class I studies** in PHN, DPN, phantom limb, SCI, GBS
- **MS:** first line for painful dysesthesias
  - case studies: 15/22 pts mod to excellent improvement, 7 pain free x 6 mo
  - One patient had dramatic improvement on 900 mg/d
  - second line for trigeminal neuralgia
  - case studies: 5/6 pain free, 1 impr; 6/7 pain free, 1 impr
    - allowed dosage reduction of CBZ or lamotrigine in 10/11 pts
  - Reduction in both spontaneous and evoked pain
  - Relieves allodynia, burning, shooting pain and hyperesthesia
  - Poor response for dull aching pain

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**Side effects:**

- CNS depression: dizziness, somnolence, confusion, unsteadiness (particularly in the elderly)
  - often subsiding within 10-14 d of treatment
- Peripheral edema
- Rarely gastrointestinal symptoms: nausea
- Weight gain (higher dosage, esp in comb with TCAs)

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### Good safety profile

- **TID administration (generic):**
  - Begin 300 mg tid (or slower), target 600-900 mg TID
  - Once daily formulation is available
- **Renal elimination, adjust dosage for renal impairment**
- **No significant drug interactions**

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**AEDs: Gabapentin**

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AEDs: Pregabalin

**Pregabalin**
- Mechanism of action is similar to gabapentin:
  - binds to α2-δ subunit of voltage gated calcium channel (NMDA)
  - binding affinity is 6x more potent than gabapentin
- FDA approval for epilepsy, painful diabetic neuropathy, postherpetic neuralgia, fibromyalgia
- has anticonvulsant, analgesic and anxiolytic activity
- Controlled drug: Schedule V low potential for abuse, and a limited dependence liability
- MS: first line for painful dysesthesias
  second line for trigeminal neuralgia
  - Case report of in MS pts with paroxysmal pain: 9/16 improved, 3 discont’d due to SE


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AEDs: Pregabalin

**Pregabalin**
- Pharmacokinetics is linear, good absorption
- Renal excretion
- Fast titration possible
- For painful neuropathies: approved at up to 300 mg/d (given as 100mg tid or 150 mg bid), dosages for FM up to 450 mg/d
  - BID to TID regimens are approved, consider QHS only
- Side effects: well tolerated, most common are dizziness (26%), somnolence (17%), and peripheral edema (9.4%)
- Weight gain may limit long term use
- Withdrawal headache and nausea

Dworkin et al 2003, Sabatowski et al 2004
Rosenstock et al 2004, Lesser et al 2004

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### Pain Types in MS

**Central neuropathic pain**
- Chronic/steady (fluct/remitting)
- Dysesthetic extremity pain 26%
- Thalamic pain

**Intermittent (paroxysmal)**
- Trigeminal neuralgia: 4%
- Lhermitte: 16%
- Paroxysmal limb pain

**Musculoskeletal or Nociceptive pain**
- Headache: 43%
  - Migraine
  - Tension type
  - Unclassified

**Muscle spasm and spasticity**
- Spasticity pain
- Painful tonic spasms: 15%

**Visceral pain**
- Back pain: 20%
- Musculoskeletal pain due to postural abnormalities

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**Case: 40 y/o man with SPMS and facial pain**

- 60 yo M with SPMS, dx in 1998, on IFN beta 1B
- Longstanding mild left facial pain (years) treated with gabapentin
- Now presents to clinic with excruciating left cheek and jaw pain x 2 days
- Intermittent (paroxysmal) pain lasting up to 5 min, almost hourly in the last 24 hours
- Characteristic: intermittent, excruciating, stabbing
- Aggravating factors: talking, moving, eating, brushing teeth
- Relieving: holding perfectly still
- “I am desperate”
Trigeminal Neuralgia in MS

Trigeminal Neuralgia (classic)
• (Typical) TN: pain syndrome without a clinically manifest sensory deficit
• Classic TN: no cause other than a vascular contact/compression of the trigeminal nerve (CN V)

Trigeminal Neuralgia in MS
• TN in MS (2-6%) more frequent than in general population (10-20x)
• More frequent bilateral (11-31%)
• Affects younger patients than in classic TN
• Usually V2 or V3 branch (90%), less likely ophthalmic (V1) distribution
• Plaque theory: Demyelinating lesion at the root entry zone (REZ) of the trigeminal nerve root and the brainstem (pons)
  • Transition zone between myelin derived from Schwann cells and oligodendrocytes
  • Vascular contribution in some?

O’Connor AB, et al. 2008; J Pain 137; 96-111

-Trigeminal Neuralgia in MS (cont’d)-

“Dual mechanism”
1) MS plaque at root entry zone (pons) -- inflammatory demyelination
2) Vascular contact/compression of the TN -- mechanical demyelination
• Imaging study of 130 pts with MS including 50 with TN
• Pts with TN had R/L asymmetry and sx onset at older age than others
• MS pts with TN benefit from vascular decompression surgery, but less than pts with classic TN

MRI in 50 pts
Red = area of maximal lesion probability
(Cruccu 2009)

1)

1) 49 y/o with TN as initial sx of MS
2) Athanasiou TC et al. 2005; Br J Neurosurg 19:463–468
Cruccu G et al 2009; Pain 143:186–191

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Recommendations for TN: Classic TN

- Carbamazepine * Level A recommendation
  FDA indication
  NNT = 1.8; NNT 1.7
- Oxcarbazepine Level B rating
- Lamotrigine 400 mg/d Class I study, NNT 2.1
- Baclofen 30-80 mg/d Class I and II studies

Other options with lower level of evidence:
  phenytoin, pregabalin, gabapentin, clonazepam, valproic acid, intranasal lidocaine

* CMSC 2014

Case: 40 y/o man with SPMS and facial pain (TN) - Treatment

- Current dosage of gabapentin at 600 mg BID ineffective → 2nd line drug, consider increased dosage
- Patient “desperate” to get on effective treatment
- Treatment with carbamazepine (CBZ) as first line agent for TN
- Target dosage is about 600 to 1200 mg CBZ per day, with higher dosage likely more effective
- Rx was begun on target dose of 600 mg BID (longacting CBZ) with goal to get therapeutic dosage level fast
- In addition, tramadol as prn “rescue” medication 50 mg QID prn
- 2 days later, his wife calls, as patient is dizzy, drowsy and has unsteady gait

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AEDs: Carbamazepine

Carbamazepine

– First line drug in Trigeminal Neuralgia, FDA approved
– Sodium channel blocker
  • Injured nerves have high amount of Na⁺ channels
  • Prevents spontaneous firing, reduces triggering of damaged neurons
  • Reduces firing in polysynaptic neurons within the CNS that process nociceptive signals
– Indication:
  • *paroxysmal, sharp, lancinating, electric-shock and lightning-like pain*
– MS patients with Trigeminal Neuralgia:
  • Case series: 27 pts, 10 pain free, 10 impr; 4/27 d/c due to SEs
– Possible advantage: mood stabilizing benefit (anger outbursts)

Pöllman and Feneberg, CNS Drugs 2008; 22 (4)

AEDs: Carbamazepine

Carbamazepine

• Dosage:
  – Starting dose 100 mg TID or 200 mg BID (slow release)
  – Increase gradually (weekly intervals) as tolerated
  – Target therapeutic daily dose of 600 - 1200 mg or higher (200 - 400 mg TID)
  – Slow-release carbamazepine allows BID dosing
  – Blood level to monitor treatment and compliance: 5 - 12 µg/ml
• Time course:
  – Relief often within 1 - 2 weeks of therapeutic dosage

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AEDs: Carbamazepine

**Carbamazepine – Side effects**
- Contraindication: Liver disease, bone marrow suppression, allergy
- Leukopenia (20%), thrombocytopenia common
- Rare: aplastic anemia, agranulocytosis
- Hepatotoxicity
- Sedation, dizziness (improves with time), unsteadiness – ataxia if dosage is increased too fast!
- Hyponatremia
- May worsen hypercholesterinemia
- Drug rash (2nd week or later)
- Enzyme induction: drug-drug interactions, OC effectiveness
- Pregnancy cat. D

• Labs
  - CBC, LFTs, Creatinine, electrolytes (Na+), (cholesterol)
  - at baseline, after 2 weeks, then 2-3 months, for a year

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**Case: 40 y/o man with SPMS and facial pain (TN) - Follow-up**

- CBZ toxicity due to high starting dosage resulting in ataxia and drowsiness
- Dosage held, then resumed at lower dosage 400 mg bid
- At this dosage no side effects, and TN pain reduced in frequency, then stopped completely and
- Serum Drug level therapeutic on this lower dosage
- Pain free, pt does not need to use tramadol anymore
AEDs: Oxcarbazepine

**Oxcarbazepine**

- Similar to Carbamazepine
  - Class IV study for TN: 9/12 completely pain free, 1/12 partial, 2/12 d/c due to SE
  - Sodium channel blocker
  - Not enzyme inducer; Pregnancy cat. D
  - ADEs: overall better tolerated than CBZ
  - More common: Hyponatremia
  - MS: primarily for Trigeminal Neuralgia (level B)
    - Possible advantage: mood stabilizing benefit (anger outbursts)

AEDs: Lamotrigine

**Lamotrigine**

- Blocks voltage-sensitive sodium channels, inhibits presynaptic release of glutamate; GABA agonist
- MS: Third line medication (level B) for TN.
  - Class IV studies for TN: 16/18 pain free, 5/5 completely pain free,
    Add on 2/15 good improvement, 6/15 partial
    Combination with gabapentin 5/5 complete relief
  - Poor evidence for use in for painful dysesthesias
    - Two RCTs showed no clear benefit (N=125 and N=96)
  - Possible advantage: mood stabilizing effect
  - Side effects
    - CNS: advantage is absence or low cognitive impairment
    - Dizziness, ataxia, headaches
    - Hepatotoxicity
    - Rash (5-10%) incl. Stevens-Johnson syndrome – d/c if any rash
  - Dosage/titration depends on concurrent medication
  - Slow titration over months: begin with 25 mg QD or QOD, increase up to max 400 mg/d (BID)

Pöllman and Feneberg, CNS Drugs 2008; 22:291-324
1 Leandi et al 2000, 2 Lunardi et al 1997, 3 Cianchetti et al 1999
4 Solaro et al. 2000, 5 Breuer et al. 2007 6 Silver et al. 2007
AEDs: Topiramate

**Topiramate**
- Blocking Na+, Ca++ channels, blocks glutamate, potentiates GABA
- **Indication:** FDA approved for Migraine; neuropathic pain?
- **MS:** Level C for painful dysesthesias, level C for TN
  - Class IV study for TN: 6/6 pain free, 1 improved\(^1\); 4/4 improved\(^2\) on fairly low dosage
  - Class IV study for painful dysesthesias: case report of pt completely pain free x 8 mo\(^3\)

- **Side effects**
  - CNS depression and cognitive impairment, incl. word finding
  - Paresthesias in hands
  - Kidney stones
  - Weight loss – often desired
  - Reduces “craving” – may be advantage

- **Interactions:**
  - Carbonic anhydrase inhibition, avoid with acetazolamide (black box), monitor electrolytes
  - Reduced OC effectiveness

- **Dosing:** 25 mg qhs to 200 mg bid, titrate slowly
  - Consider QHS only keep <200mg/d

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AEDs: Levetiracetam

**Levetiracetam**
- Ca++ channel blocker; binding to the SV2A prot. on presynaptic vesicles
- **Indication:** neuropathic pain? – not helpful in peripheral neuropathies
- **MS:** painful dysesthesia pain level C:
  - Class 2 study\(^1\) of MS pts (12 pts active Rx, 8 placebo) x 3 mo
    - Reduced pain scores and improved quality of life
  - Class 1 study\(^2\) of 30 MS pts (cross-over) x 6 mo, up to 4000 mg/d
    - No difference in pain relief or total pain intensity
    - Pain reduction in subgroup with lancinating pain

- **Side effects:**
  - Generally well tolerated
  - Agitation, depression/anxiety, psychosis, suicide

- **Renal clearance**
- **Dosage:** BID, begin with 500 bid, max 1500 mg bid
- **Avoid abrupt cessation**

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\(^1\)Rossi et al, Eur J Neurol 2009
\(^2\)Falah et al, Eur J Pain 2012
\(^3\)Jorn et al, Eur J Neurol 2009
**Additional Option for TN in MS**

**Misoprostol**
- Prostaglandin E1 analogue
- FDA approved for NSAID-induced gastric ulcer prophylaxis (GI protection)
- Off-label use in gynecological conditions and transplant rejection prophylaxis
- Regulates immunologic cascades, and inhibits T-lymphocyte function
- In MS: benefit in Trigeminal Neuralgia in several case series (level C):
  - 6/7 pts with good relief (complete or partial)\(^1\)
  - 8/18 complete pain relief after 2 weeks, 6/18 partial relief\(^2\)
  - Case series of 3 pts with good benefit\(^3\)
- Side effects:
  - Generally well tolerated
  - Diarrhea reported in 14—40%, usually self-limiting (first 2 weeks)
  - Abdominal pain, nausea/vomiting and flatulence
  - Headache
  - GYN side effects rare (spotting, cramps)
- Dosage: available as 100 and 200 mcg tablets, typically TID or QID

\(^1\)Reder and Arnason, Neurology 1995
\(^2\)DMKG Study Group, J Neurol 2003
\(^3\)Pfau et al, Pain Med 2012

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**Medications for Chronic Neuropathic Pain**

- **Antidepressants**: TCA, SNRI
- **Antiepileptics (AEDs)**
- **Opioids**
  - Tramadol/Tapendatol
- **Cannabinoids**
  - Antispasticity agents: baclofen, tizanidine
  - Muscle relaxants
  - Topical: Capsaicin, Lidocaine 5%, Diclofenac 1% gel, Methylsalicylate
  - NSAID, Cox-2, aspirin, acetaminophen - only minor effectiveness
  - Clonidine
  - Benzodiazepines - use only with caution, avoid combination with opioids
  - Botulinumtoxin injections
- **Misoprostol**
- **Local anesthetics**: Mexiletine, Lidocaine injection
- **Naltrexone**
- **NMDA-receptor antagonists**: Dextromethorphan, Memantine, Ketamine

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Opioids for Chronic Pain Patients

No clear long-term benefit from opioids in chronic neuropathic pain

- All opioids have similar effectiveness and side effects in equianalgesic dosages
- “Central” analgesics (action CNS > PNS).
- RCTs documenting “effectiveness” in neuropathic pain provide poor guidance for long-term opioid therapy:
  - usually short term (<4 mo)
  - small sample sizes (<300 pts)
  - modest pain relief (14/100 points in meta-analysis)
  - no clear functional improvement

Opioids for Chronic Pain Patients

No clear long-term benefit from opioids in chronic neuropathic pain

- Pain reduction is usually short-term only: “take the edge off”
- Tolerance and physical dependence develops in all pts on regular opioids in higher dosage
- Epidemiological studies suggest that opioid patients have higher levels of pain, utilize health care at higher rates and demonstrate lower activity levels
- Opioids increase passivity, validate the patient’s "sick role", and decrease autonomy
- Long-term opioid-induced morbidities related to endocrinopathies, immune suppression, sleep disorders
- Opioid therapy may worsen anxiety and depression
- Increasing concern about “opioid-Induced hyperalgesia” → sensitization, with worsened ability to tolerate pain
Fatal Drug Overdoses

2007 in the US:
27,658 deaths from accidental drug poisoning replacing MVA as the leading cause of accidental deaths in 15 states and DC
11,499 deaths from prescription opioids more than heroin and cocaine combined


Fatal Drug Overdoses

2008 in the US:
36,450 deaths from overdoses = 11.9/100,000 population
27,153 deaths from an identified drug
20,044 deaths from one or more prescription drugs
14,800 deaths from opioid medications equivalent to 74% of all identified prescription drug deaths

Drug Overdoses

In the US: 14,800 deaths from opioids in 2008
For every unintentional overdose death related opioid analgesic, there are ... 
... 9 persons admitted for substance abuse treatment, 
... 35 visits emergency departments, 
... 161 patients with report of drug abuse or dependence, 
... 461 patients with report of nonmedical use of opioids

CDC: MMWR, Nov 2011

For VHA:
• Pts on opioids in 2004/5 followed to 2008: 
  -- fatal overdose rate of 0.04%, equivalent to about 1 in 2500 pts
• Risk directly linked to dosage: 
  -- hazard ratio 7.18 with ≥100 mg/d vs. 1-20 mg/d

Bohnert et al, JAMA 2011

Opioids in MS Patients

“Clearly, insufficient evidence exists for the use of morphine for neuropathic pain in MS.”

Solaro et al; Curr Neurol Neurosci Rep. 2013

Morphine responsiveness in a group of well-defined multiple sclerosis patients: a study with i.v. morphine
• 14 pts with constant, chronic pain caused by MS (single blind study).
• Only 4 patients were “opioid responders” (defined as minimal placebo effect, 
  >50% pain↓ after morphine and >25% pain↑ after naloxone given i.v. after morphine)
• Response required high doses of morphine (mean 41 mg)
• 10 patients non-responders

Kalman et al, Eur J Pain. 2002

Rowbotham et al, NEJM 2003
• 81 pts with neuropathic pain (incl. 8 MS) treated with levorphanol
• Central pain less responsive than peripheral neuropathic pain (36%↓ high dose)
**Opioids for Chronic Pain Patients**

*If opioids are used...*

- Avoid new starts for chronic opioid therapy (COT) for long-term use
- **Realistic expectations:** only short-term benefit of opioids
- Use opioids only for time-limited (temporary) intervention, as a “trial” with exit strategy; for intermittent use during flare-ups in selected patients
- Use opioids as only **one component** of a long-term rehabilitation plan
- **Safety is primary concern**
  - **a) Patient Risk:** medication misuse/abuse/death  
  - **b) Public risk:** diversion
- **Individual risk analysis, tailored monitoring** (ORT, structure therapy to match perceived risk incl. visits/quantities, access PDMP, single pharmacy, etc)
- **Measure pain control and functioning (social, physical, emotional)**
- Document “4 As”: Analgesia, Activities, Adverse effects, Aberrant behavior
- Aberrant behaviors require intervention

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**Opioids for Chronic Pain Patients**

*If you have patients on chronic opioid therapy (COT)...*

- If patient transfers to you on chronic opioid medication, establish goal of coming off right from the beginning, before taking the patient on
- Educate all pts about risks/benefits of opioids.
- Document an “informed consent”
- Reduce/keep dosage below 60-100 mg of morphine equiv daily dosage (MEDD)
- If patient is on benzodiazepine (often for anxiety ds), require MH input

**Risk assessment:**

- Assess psychosocial factors and medical co-morbidities to determine risk
- High risk are pts with
  - Psychiatric disease: psychiatric instability, substance abuse
  - Medical disorders: sleep apnea, pulmonary ds, cognitive impairment
- Assess risk of misuse using an established tool such as ORT

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### Opioid Risk Tool

<table>
<thead>
<tr>
<th>Family history (parents and siblings):</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
<td>(3)</td>
<td>(1)</td>
</tr>
<tr>
<td>Illegal drug use</td>
<td>(3)</td>
<td>(2)</td>
</tr>
<tr>
<td>Prescription drug abuse</td>
<td>(4)</td>
<td>(4)</td>
</tr>
</tbody>
</table>

| Personal history:                      |      |        |
| Alcohol abuse                          | (3)  | (3)    |
| Illegal drug use                       | (4)  | (4)    |
| Prescription drug abuse                | (5)  | (5)    |

| Mental health:                         |      |        |
| Diagnosis of ADD, OCD, bipolar, schizophrenia | (2)  | (2)    |
| Diagnosis of depression                | (1)  | (1)    |

| Other:                                  |      |        |
| Age 16-45 years                         | (1)  | (1)    |
| History of pre-adolescent sexual abuse  | (0)  | (3)    |

### Scoring:
- 0-3  low risk: 6% chance of developing problematic behaviors
- 4-7  moderate risk: 28% chance of developing problematic behaviors
- >= 8  high risk: >90% chance of developing problematic behavior

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### Opioids for Chronic Pain Patients

**Dosage reduction in patients on chronic opioid therapy (COT):**

**Higher risk patients**

- Evaluate the risks of continued opioid therapy vs risks associated with opioid dosage reduction
- Rarely abrupt opioid cessation is required (diversion, acute risk for overdose)

- Consider rapid opioid dosage reduction (over 1-2 weeks under) vs. slow opioid tapering regimen (months)

- If high risk for overdose:
  - Naloxone rescue kit (autoinjector FDA-approved, or off label kits for i.m. or intranasal use)

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"Give it to me straight, Doc. How long do I have to ignore your advice?"

http://www.newyorker.com/online/blogs/culture/2013/10/turning-life-into-cartoons.html
Opioids for Chronic Pain Patients

Dosage reduction in patients on chronic opioid therapy (COT):

Low risk patients
- Low risk pts on COT should be gradually reduced to off, if possible
- Work with the patient towards “better” pain care:
  - Educate the pt with every refill and establish the goal of coming off
  - Get your treatment team members on board to speak “in one voice”
  - Maximize non-opioid medications and non-pharmacological measures
  - Consider dosage reduction by 10-20% every month (or at each refill)
  - Usually taper the long-acting medication first
  - If slow reduction, symptomatic Rx of withdrawal sx is usually not necessary.
  - Be available for support and anticipate complications

Medications for Chronic Pain

How do I decide what agent to use?
- What works for the underlying disorder?
  - Musculoskeletal/nociceptive vs. neuropathic pain
- What works for the patient’s pain symptoms?
  - Sharp stabbing vs. electrical vs. burning vs. aching pain
- What are the co-existing symptoms?
  - depression, anxiety, sleep disturbance
- What are the co-morbidities?
  - Medical: cardiac, renal, hepatic, bladder/bowel fct
  - Psychiatric co-morbidities, substance abuse
- What is the patient’s level of functioning?
  - Occupation? Walking ability? Sexual fct?
- What are the characteristics of my potential drugs?
  - Side effects (adverse or beneficial), interactions, ease of use, cost, abuse potential, risk of overdose, etc.
Central neuropathic pain

Chronic/steady (fluct/remitting)
- Dysesthetic extremity pain 26%
- Thalamic pain

Gabapentin/Pregabalin
TCAs
SNRIs (Duloxetine)
Topiramate?
Levetiracetam?
Lamotrigine?

Intermittent (paroxysmal)
- Trigeminal neuralgia 4%
- Lhermitte 16%
- Paroxysmal limb pain

Carbamazepine/Oxcarb
Baclofen
Gabapentin/Pregabalin
Lamotrigine
Misoprostol

Musculoskeletal pain

Mixed

Headache 43%
- Migraine
- Tension type
- Unclassified

Muscle spasm and spasticity
- Spasticity pain
- Painful tonic spasms 15%

Back pain 20%
- Musculoskeletal pain due to postural abnormalities

NSAID
Acetaminophen
Tramadol

Summary of Treatment Suggestions

What do YOU want to use?

32 y/o f with MS and severe dysesthesia pain in legs that...

... appears depressed and c/o poor sleep?
TCA: nortriptyline

... is severely depressed and overweight?
SNRI: duloxetine/venlaf.
gabapentin/pregabalin

... wants “something as safe as possible”?
gabapentin/pregabalin
topiramate, lamotrigine

... has medical co-morbidities, many meds?
TCA: nortriptyline

topiramate

carbamazepine/oxcarb.
gabapentin/pregabalin
prn tramadol

... has headache and depression?
prn oxycodone

... has migraines and is overweight?

... also has trigeminal neuralgia?

... also has TN and many medical issues?

... has severe flare-ups lasting for days?

... severe flare ups and is on high dose SSRI?
Thank you.
Questions?

Think
It's what to do
when you don't know what to do

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