Pharmacological Treatment of Pain in Multiple Sclerosis

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Friedhelm Sandbrink MD

Clinical Associate Professor of Neurology
Uniformed Services University, Bethesda MD

Assistant Professor of Neurology
Georgetown University, Washington DC

Department of Neurology
Chronic Pain Clinic
Washington DC VAMC

Disclosures

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Friedhelm Sandbrink MD

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
Central neuropathic pain
- Chronic/steady (fluct/remitting)
  - Dysesthetic extremity pain 26%
  - Thalamic pain
- Intermittent (paroxysmal)
  - Trigeminal neuralgia 4%
  - Glossopharyngeal neuralgia
  - Lhermitte 16%
  - Paroxysmal limb pain

Mixed
- Headache 43%
  - Migraine
  - Tension type
  - Unclassified
- Muscle spasm and spasticity
  - Spasticity pain
  - Painful tonic spasms 15%
  - Paroxysmal dystonia with painful muscle spasms

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

Visceral pain

Treatment of Neuropathic Pain

General considerations
- Medication therapy should be in the context of non-pharmacological treatment incl. coping methods (CBT), stress reduction, sleep hygiene, PT, and interventional procedures
- MS pts with pain/sensory symptoms: TENS as effective as nortriptyline
- Discuss realistic expectations, set measurable functional goals
- Individual variation in the response to medications is substantial
- Overall approach: stepwise process to identify the medications that provide the greatest relief with fewest adverse effects.
  - If medication is not effective or causes intolerable side effects, d/c it
  - If medication provides partial relief and is well tolerated, add on second agent with different mechanism of action.
- “Rationale polypharmacy”:
  - use agents with different mechanism of action
  - potential for additive analgesic benefits with less ADEs
  - combine agent with rapid benefit with one that requires weeks
  - but: consider added cost, lower compliance, drug interactions etc.

O’Connor et al. 2008, Pain 137: 96-111
Truini et al. 2013, J Neurol 260:351-367
Foley et al. 2013, Pain 154: 632-642

--> pooled data of 17 studies, 5319 subjects. Overall pain prevalence in MS pts was 63%
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**
  - Topical: Capsaicin, Lidocaine 5%, Diclofenac 1% gel, Methylsalicylate
  - NSAID, Cox-2, aspirin, acetaminophen - only minor effectiveness
  - Antispasticity agents: baclofen, tizanidine
  - Muscle relaxants
  - Clonidine
  - Benzodiazepines - use only with caution, avoid combination with opioids
  - Botulinumtoxin injections
- **Local anesthetics**: Mexiletine
- **Naltrexone**
- **NMDA-receptor antagonists**: Dextromethorphan, Memantine, Ketamine

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## Treatment of Chronic Neuropathic Pain

How do I decide what agent to use?

- What works for the underlying disorder?
- What works for the patient’s pain symptoms?
  - Chronic/steady dysesthesia vs. intermittent, neuralgia-like (TN)
- What are the co-existing symptoms?
  - depression, anxiety, sleep disturbance
- What are the co-morbidities?
  - Medical issues: cardiac, renal, hepatic ds, 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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### Pain Types in MS

<table>
<thead>
<tr>
<th>Optic neuritis</th>
<th>Central neuropathic pain</th>
<th>Mixed</th>
<th>Treatment induced pain</th>
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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 types of MS, and lowest in the relapsing–remitting type
- Pts are more disabled than those without pain
- Pathophysiology is poorly understood
  → Demyelinating lesions in areas involved in pain perception (?)

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

Dysesthetic Extremity Pain (cont’d)

Hypothesis: arises from lesions in the spinal cord nociceptive pathways

- Bilateral and relatively distal (legs) distribution is presumably explained by
  - length of the spinal thalamocortical system to the lower extremities
  - somatotopic location in the spinal cord (more superficial) and brain (periventricular)

Recent study (13 pts with, 10 w/o pain) did not show any correlation between lesion location and pain in MS (Svendsen 2011)

Truini A et al 2013; J Neurol 260(2):351-6
Guideline for Neuropathic Pain (IASP)

For Neuropathic Pain in general, in adults
• Excludes trigeminal neuralgia
• Excludes conditions w/o lesions of the somatosensory neural pathways (FM)

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


Rating of Recommendations

Rating of recommendations:
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, or based on physiology/bench research

Rating of strength of evidence:
A: “Established” - consistent level 1 studies
B: “Probable”- consistent level 2 or 3 studies, or extrapolations from level 1 studies
C: “Possible” - level 4 studies, or extrapolations of level 2 or 3 studies
D or U: “Uncertain” - level 5 evidence, inconsistent of inconclusive studies

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

Antidepressants: TCAs

**Amitriptyline**
- classic TCA in pain treatment
- metabolized to nortriptyline

**Nortriptyline**

**Desipramine**
- More selective for NE re-uptake inhibition
- less anticholinergic and less sedation

**Imipramine**
- > 10 placebo controlled 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:**
  - limited direct evidence, no class 1 studies
  - First line (level A) for chronic dysesthetic pain
  - 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 (Quinidine like)
  – 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 (independently of antidepressive effect)
  – CI: alcohol abuse, renal ds, liver ds (black box); monitor LFTs
  – Begin 30 mg, target 60 mg QD (for pain) after one week possible, maximum 60 mg bid (depression)

Venlafaxine, Desvenlafaxine
  – FDA approval for depression. Use for pain is “off-label”
  – Low dose like SSRI, higher dosage NE reuptake inhibition (>150-225 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 (2009), 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
  - Increased BP (esp. in venlafaxine)
  - Sexual dysfunction (decreased libido, anorgasmia)
  - Mydriasis
  - Withdrawal syndrome: Dizziness, nausea, headache
- **CI**: MAOI, uncontrolled narrow-angle glaucoma

Duloxetine: liver disease, renal insufficiency

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**AEDs for Common Neuropathic Pain Ds**

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

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

*FDA approval

**HIV-associated neuropathy**
- Gabapentin/Pregabalin
- Lamotrigine

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

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


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
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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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 SE1


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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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Back pain 20%
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Visceral pain

Pain Types in MS

Treatment induced pain

Optic neuritis associated pain

Mixed

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?

Visceral pain

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

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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
(Cruecu 2009)

49 y/o with TN as initial sx of MS

Recommendations for TN: Classic TN

- **Carbamazepine** * Level A recommendation
  FDA approved indication
  NNT = 1.8¹ ; NNT 1.7²
- **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, clonazepam, valproic acid, pregabalin, gabapentin,
intranasal lidocaine, misoprostol

- * Attal et al. 2006¹, Sindrup and Jensen 2002²
  Pöllmann and Feneberg 2008, Backonja 2002,
  O’Connor AB et al. 2008
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 the triggering of damaged neurons
  - Reduces firing in polysynaptic neurons within the CNS that process nociceptive signals
- Indication:
  - Effective especially in paroxysmal, sharp, lancinating, electric-shock and lightning-like pain
- MS patients with Trigeminal Neuralgia:
  - Case series (Class IV): 27 pts, 10 pain free, 10 impr; 4/27 d/c due to Ses
- Possible advantage: mood stabilizing benefit (anger outbursts)

AEDs: Carbamazepine

Carbamazepine

- Dosage:
  - Starting dose 100 mg BID to TID
  - Increase gradually (weekly intervals) as tolerated
  - Target therapeutic daily dose of 600 - 900 mg, max. 1200 mg or higher (200 - 400 mg TID)
  - Slow-release carbamazepine allows BID dosing
  - Blood level to monitor treatment and compliance: 4 - 10 μg/ml
- Time course:
  - Relief often within 1 - 2 weeks of therapeutic dosage
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
- 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

AEDs: Oxcarbazepine

**Oxcarbazepine**
- Similar to Carbamazepine
- 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)

Pöllman and Feneberg, CNS Drugs 2008; 22:291-324
AEDs: Lamotrigine

Lamotrigine

- Blocks voltage-sensitive sodium channels, inhibits presynaptic release of glutamate; GABA agonist
- MS: Level B for painful dysesthesias, level C for TN
  - Class IV studies for TN: 16/18 pain free1, 5/5 pain free2
  - Add on therapy 2/15 good improvement, 6/15 partial3
  - 2007 pilot trial in 12 pts of MS with central pain: no difference to placebo (Breuer et al. 2007, Clin Ther 29:9:2022)
- 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)

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 studies for TN: 6/6 pain free, 1 improved1; 4/4 improved4 on fairly low dosage
- 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

1Leandn et al 2000, 2Leandn et al 1997, 3Cianchetti et al 1999

Pöllman and Feneberg, CNS Drugs 2008; 22:291-324
AEDs: Levetiracetam

**Levetiracetam**
- Ca++ channel blocker; binding to the SV2A prot. on presynaptic vesicles
- Indication: neuropathic pain? – not helpful in peripheral neuropathies
- **MS:** central neuropathic pain:
  - 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 and w/o touch evoked pain
- **MS:** trigeminal neuralgia: case study of 10 pts with MS and TN some improvement
- Positive effect on spasticity (phasic, not tonic)?
- **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

\(^1\)Rossi et al, Eur J Neurol 2009
\(^2\)Falah et al, Eur J Pain 2012
\(^3\)Jorn et al, Eur J Neurol 2009

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AEDs: Comparison Study of Side Effects

3-yr study, descriptive analysis of treatment

**Carbamazepine**
- 36 pts, adverse effects in 20. In 12 pts, neurological side effects mimicking a relapse with increase in EDSS (cerebellar > pyramidal); 15 remained on Rx

**Gabapentin**
- 94 pts, adverse effects in 16, incl. nausea (6), dizziness (4), asthenia (2); mimicking relapse in 1 (cerebellar); 78 w/o side effects, 66 remained on Rx

**Lamotrigine**
- 22 pts, adverse effects in 4, incl. rash (2), worsening of gait (2). 18 w/o side effects, 14 remained on Rx

Medications for Chronic Neuropathic Pain

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

Opioids in Chronic Pain

Opioid Analgesics: Overview

- Mechanism of action: Binding to μ, κ and δ opioid-receptors
- “Central” analgesics: Action in CNS > PNS
- Effectiveness of all opioids is similar in equianalgesic dosages
- No ceiling effect to analgesia in general
- Side effects are similar in all opioids
- RCTs are short duration <4 months with small sample sizes <300 pts
- Pain relief modest: meta-analysis decrease by 14 of 100 point scale
  Little evidence of benefit in Central Neuropathic Pain
- Limited or no functional improvement
- >180 mg/d morphine equivalent have not been established in double blind trials for neuropathic pain
- Chronic opioid therapy for non-cancer pain with > 100 mg/d morphine equivalent is of particular concern for risks > benefits
There is no long-term benefit from opioids in chronic non-cancer pain, even in compliant pts
• Pain reduction is usually short-term only
  – “take the edge off” (30% reduction)
• 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
• Increasing concern about “opioid-induced hyperalgesia”

Morphine responsiveness in a group of well-defined multiple sclerosis patients: a study with i.v. morphine
• 14 opioid-free pts with constant, chronic pain caused by MS
• Single blind and placebo controlled.
• Only 4 patients were opioid responders
  minimal effect by placebo, >50% pain reduction after morphine and >25% pain increase after naloxone given i.v. after morphine
• Response required high doses of morphine (mean 41 mg)
• 10 patients non-responders (< 50% pain reduction)
• Conclusion: Only a minority of the patients with central pain due to MS responded to morphine and only at high doses. Neuropathic pain is poorly responsive to opioids. Routine use of strong opioids in MS patients with CP was not recommended.  Kalman et al; Eur J Pain. 2002;6(1)

Rowbotham et al, 2003 NEJM, 348 (13), 1223:
- 81 pts with neuropathic pain (incl. 8 MS pts) treated with high/low dose levorphanol
- Central pain less responsive than peripheral neuropathic pain
- 36% reduction in pain at high dose levorphanol

“ Clearly, insufficient evidence exists for the use of morphine for neuropathic pain in MS.” Solaro et al; Curr Neurol Neurosci Rep. 2013

CMSC 2014
**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

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

Vital Signs: Overdoses of Prescription Opioid Pain Relievers (OPR)
**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

**For VHA:**

For all VA pts treated in FY 2004-5, there were 750 opioid deaths (by 2008)
Frequency of fatal overdose 0.04%; risk directly related to the dosage.

**For chronic pain pts: hazard ratio of 7.18 with ≥100 mg/d versus 1-20 mg/d**

**Abuse and/or addiction rates in chronic pain populations 3-19% — Predictors:**

- Past cocaine use, h/o alcohol or cannabis use
- Lifetime history of substance use disorder
- Family history of substance abuse, a history of legal problems and drug and alcohol abuse
- Heavy tobacco use
- History of severe depression or anxiety

**Opioid Risk Tool**

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history (parents and siblings):</strong></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Personal history:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>(3)</td>
<td>(3)</td>
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<tr>
<td>Illegal drug use</td>
<td>(4)</td>
<td>(4)</td>
</tr>
<tr>
<td>Prescription drug abuse</td>
<td>(5)</td>
<td>(5)</td>
</tr>
<tr>
<td><strong>Mental health:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of ADD, OCD, bipolar, schizophrenia</td>
<td>(2)</td>
<td>(2)</td>
</tr>
<tr>
<td>Diagnosis of depression</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td><strong>Other:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 16-45 years</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>History of pre-adolescent sexual abuse</td>
<td>(0)</td>
<td>(3)</td>
</tr>
</tbody>
</table>

**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

Webster, LR and Webster, RM, Pain Med: 2005; 6:432-442
Opioids for Chronic Pain Patients

If opioids are used ...

• Opioids as only one component of a long-term rehabilitation plan
• Realistic expectations: only short-term benefit of opioids
• Avoid chronic opioid therapy (COT) for long-term use; use opioids only for time-limited (temporary) intervention, as a “trial” with exit strategy
• In high risk pts, avoid all opioids (due to psychiatric/medical comorbidites)
• Keep dosage low; avoid co-prescribing with benzos or other CNS depressants
• Measure pain control and functioning (social, physical, emotional)
  - Specific, measurable, action-oriented, realistic and time-dependent goals “SMART”
• Safety is primary concern
  a) Patient Risk: medication misuse/abuse/death  b) Public risk: diversion
• “Universal precautions”: Opioid Agreement / Informed Consent and random Urine Drug Screens are expected. No early refills. Do Pill (patch) counts.
• Individual risk analysis, tailored monitoring (ORT, structure therapy to match perceived risk incl. visits/quantities, access PDMP, single pharmacy, etc)
• Aberrant behaviors require intervention
• Psychosocial instability is a CI for COT, and requires mental health care
• Document !!! (Analgesia, Activities, Adverse effects, Aberrant behav., etc.)

Opioids for Chronic Pain Patients

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

• If patient transfers to you on opioid medication, establish goal of coming off right from the beginning, before taking the patient on
• Educate all patients about the risks/benefits of opioids (document!)
• Keep dosage below 100 mg of Morphine equivalent daily dosage (MEDD)
• Avoid co-prescribing with benzodiazepines. If on benzo, require MH input
• Monitor and document aberrant behavior
• Document the 4 As: Analgesia, Activities, Adverse effects, Aberrant behav., etc.

Risk assessment:
• Assess psychosocial factors and medical co-morbidities to determine risk
• High risk are pts with active substance abuse, psychiatric instability, sleep apnea, pulmonary ds, cognitive impairment, etc.
• Assess risk of misuse using an established tool such as ORT
• Evaluate carefully the risk of continued opioid therapy vs opioid dosage reduction
Opioids for Chronic Pain Patients

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

High risk patients
• If high risk for overdose: naloxone rescue kit (autoinjector FDA-approved, or off label kits for i.m. or intranasal use)
• Reduce opioid rapidly over 1-2 weeks under close monitoring, rarely stop abruptly (diversion, acute risk for overdose)

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

Treatment of Chronic Neuropathic Pain

How do I decide what agent to use?

– What works for the underlying disorder?
– What works for the patient’s pain symptoms?
  – Chronic/steady dysesthesia vs. intermittent, neuralgia-like (TN)
– What are the co-existing symptoms?
  – depression, anxiety, sleep disturbance
– What are the co-morbidities?
  – Medical issues: cardiac, renal, hepatic ds, 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
- Dysesthetic extremity pain 26%
- Thalamic pain

Chronic/steady (fluct/remitting)
- Gabapentin/Pregabalin
- TCAs
- SNRIs (Duloxetine)

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

Musculoskeletal or Nociceptive pain
- Muscle spasm and spasticity
  - Spasticity pain
  - Painful tonic spasms 15%
  - Paroxysmal dystonia with painful muscle spasms

Musculoskeletal or Nociceptive pain
- Back pain 20%
- Musculoskeletal pain due to postural abnormalities

Optic neuritis associated pain

Pain Types in MS

Headache 43%
- Migraine
- Tension type
- Unclassified

Muscle spasm and spasticity
- Paroxysmal dystonia with painful muscle spasms

Treatment induced pain
- Visceral pain

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

... has medical co-morbidities, many meds?
lamotrigine

... has bipolar disorder, is hypomanic?
TCA: nortriptyline
topiramate

... has headache and depression?
carbamazepine/oxcarb.
gabapentin/pregabalin

... has migraines and is overweight?
prn tramadol

... also has trigeminal neuralgia?
prn oxycodone

... also has TN and many medical issues?

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

... severe flare ups and is on high dose SSRI?
The Biopsychosocial Model of Chronic Pain

Mind and body relationship...
Pain defined as...
Assessment goal...
Diagnostic strategy...

Treatment goal...
Time span...
Treatment modalities...

Provider role...
Patient role...
More appropriate for...

Biomedical Model
Separate
Symptom
Identify cause
High technology

Cure
Short term – pain relief
Analgesics/procedures

Expert
Passive/helpless
Acute pain

Biopsychosocial Model
Holistic – “Total Person”
Complex problem
Identify effects
Comprehensive psychosocial
Restoring function
Long term – reactivation
“Collaborative self-management”
Teach/coach
Active/responsible
Chronic Pain

Thank you
Opioids: Opioid Agreement / Informed Consent

- Educational and informational purpose: rationale and risks of opioid therapy
  - Side effects (short and long term)
  - Opioid induced hyperalgesia/central sensitization ("may worsen pain control over time")
  - Physical dependence, tolerance
  - Risk of drug interactions or combinations (respiratory depression)
  - Risk of unintentional or intentional misuse (abuse, addiction, death)
  - Hold for any sedation
  - Legal responsibilities (disposing, sharing, selling)
- Documentation of "informed consent", to protect patient and provider
- Outlines the expectations: setting the limits
- Articulates monitoring procedures (urine tox screen, pill counts, etc) and action plans for aberrant behavior
- Takes "pressure" off provider (Our clinic policy is...)

LIMITATIONS:
- Not a legal contract
- While opioid agreement cannot always be mandated, an informed consent can be mandated (and is required now in VHA for all patients on opioids > 90 days, except cancer/hospice patients).


Opioids: Urine Drug Screens

STANDARD OF CARE, at least every 6 (-12) mo in all pats
- Know limitations of test and your lab
  Opiates: Morphine, codeine - always positive
  Semisynthetic: Oxycodone/hydromorphone - pos. or neg.
  Methadone and fentanyl - always negative
- Be careful of false negatives and positives
- Consider send out for specific confirmation with GC/MS
- Ask: “If I check your urine right now will I find anything?”
- Ask: “When did you take your last medication?”
- Any unexpected result, requires action/comment
- Random versus scheduled
- ? Supervised, temperature strips, check Crea/Sp grav
- Not a legal “Chain-of-custody”

http://www.bu.edu/aodhealth/presc_drug.html - Alford, Liebschutz, Jackson and Siegel