Opioid Management; 6 Building Blocks

Shared Learning Call

Nov 19, 2020

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PRACTICE INNOVATION PROGRAM COLORADO
OPIOID MANAGEMENT

Department of Family Medicine

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Agenda

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PRACTICE INNOVATION PROGRAM COLORADO
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Purpose of Calls:

- An opportunity for the program sites to help one another through implementing improvements to opioid management with chronic non cancer pain.
- A time to share successes and to brainstorm through the real challenges that arise in this difficult work.
- Not a report out of what sites have done, but a sharing of ideas about how to do the work.
- Your entire Opioid Improvement Team should attend the call, if possible.

Department of Family Medicine

Who is in the room?

- Tell us about you and your organization
- What do you expect to get out of today's call?

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Non-Opioid Analgesics

Rachael Rzasa Lynn, M.D.
Associate Professor of Anesthesiology
18 November 2020

Pain Med Safety Precautions

- Start low, go slow
- Begin in the evening with lowest dose
- Increase every 4-7 days if no side effects and ongoing pain
- Stay at goal dose x4 weeks before declaring failure
- If no improvement in function/pain relief after adequate trial, wean down by initial dose every 3 days
  - For opioids, restrict dose reductions to 10-20% of *total daily MED* per day every 4-7 days

Multimodal Pain Control

- Defined as the continuous use of more than one method for controlling pain
- Takes advantage of additive or synergistic effects by combining multiple agents with different mechanisms of action
- Reduced side effects due to lower doses of drugs and differences in SE profiles

Kehlet H, Wilmore DW. Am J Surg. 200;183(6):630-41.
Hartrick CT, Am J Health Syst Pharm. 2004 Apr;61 Suppl 1:S4-10.

Mechanistic Stratification of Medications Used to Treat Neuropathic Pain

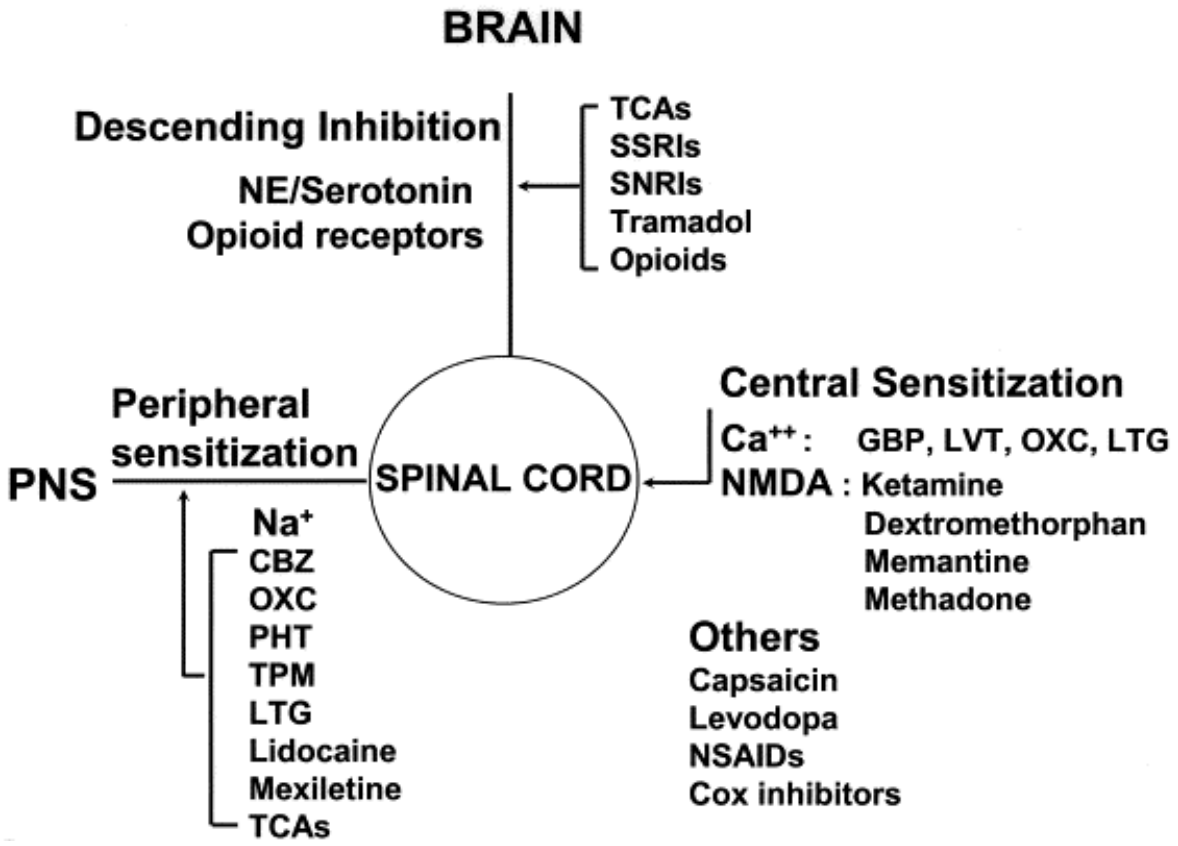

Fig. 4. Mechanistic stratification of antineuralgic agents. PNS = peripheral nervous system; CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; TPM = topiramate; LTG = lamotrigine; TCA = tricyclic antidepressant; NE = norepinephrine; SSRI = selective serotonin re-uptake inhibitor; SNRI = serotonin and norepinephrine re-uptake inhibitor; GBP = gabapentin; LVT = levetiracetam; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug.

Beydouna & Backonja M. *J Pain Symptom Manage.* 2003;25:S18-30

Common Analgesics

- Nonsteroidal anti-inflammatories (NSAID) and Cyclooxygenase-2 (COX2) Inhibitor
- Opioids
- Anticonvulsants
- Antidepressants
- Skeletal Muscle Relaxants
- Local Anesthetics
- Capsaicin
- Corticosteroids
- N-methyl-D-aspartate (NMDA) receptor antagonists
- Alpha-adrenergic agonists

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Analgesic
- Anti-inflammatory
- Antipyretic
- Drugs of choice for orthopedic-related pain
- Opioid sparing

NSAIDs

- Act both **peripherally** and **centrally**
  - In peripheral, afferent pathway: block COX, preventing synthesis of prostaglandins
    - Prevents **sensitization** of pain receptors after injury
  - In central pathways:
    - Block production of PGE2 in the spinal dorsal horn
    - Activate medullary and cortical areas involved in **descending inhibition**

Gupta Curr Pain Headache Rep 2016

NSAIDS

- COX1 and COX2
  - Diclofenac (Voltaren)
    - Accumulates in synovial tissue
  - Diflusinal (Dolobid)
  - Ibuprofen
  - Indomethacin
  - Ketorolac (Toradol)
  - Naproxen (Naprosyn)
  - Piroxicam (Feldene)
  - Sulindac*
  - Nabumetone*
  - ASPIRIN
  - Meloxicam (Mobic)
    - COX2>COX1 at lower dose
- COX2
  - Celebrex (Celecoxib)
- Acetaminophen inhibits central PG synthesis, poor COX inhibition

*prodrug

NSAIDs

- Similar efficacy for nonselective NSAIDs and COX-2 inhibitors
  - Formulation may matter: liquid ibuprofen faster and better analgesia than tablet
- Lower NNT than APAP (3.0 v 3.9)

Gupta Curr Pain Headache Rep 2016. PAIN 107:86-90 (2004)

Analgesic and Dose (mg)	Number of Patients in Comparison	Percent with at Least 50% Pain Relief	NNT	Lower Confidence Interval	Higher Confidence Interval
Etoricoxib 180/240	248	77	1.5	1.3	1.7
Etoricoxib 120	500	70	1.6	1.5	1.8
Diclofenac 100	545	69	1.8	1.6	2.1
Celecoxib 400	298	52	2.1	1.8	2.5
Acetaminophen 1000 + codeine 60	197	57	2.2	1.7	2.9
Rofecoxib 50	675	54	2.3	2.0	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Ibuprofen 400	5456	55	2.5	2.4	2.7
Oxycodone IR 10 + acetaminophen 650	315	66	2.6	2.0	3.5
Diclofenac 25	502	53	2.6	2.2	3.3
Ketorolac 10	790	50	2.6	2.3	3.1
Naproxen 400/440	197	51	2.7	2.1	4.0
Piroxicam 20	280	63	2.7	2.1	3.8
Lumiracoxib 400	370	48	2.7	2.2	3.5
Naproxen 500/550	784	52	2.7	2.3	3.3
Diclofenac 50	1296	57	2.7	2.4	3.1
Ibuprofen 200	3248	48	2.7	2.5	2.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10 (intramuscular)	946	50	2.9	2.6	3.6
Naproxen 200/220	202	45	3.4	2.4	5.8
Ketorolac 30 (intramuscular)	359	53	3.4	2.5	4.9
Acetaminophen 500	561	61	3.5	2.2	13.3
Celecoxib 200	805	40	3.5	2.9	4.4
Ibuprofen 100	495	36	3.7	2.9	4.9
Acetaminophen 1000	2759	46	3.8	3.4	4.4
Acetaminophen 600/650 + codeine 60	1123	42	4.2	3.4	5.3
Aspirin 600/650	5061	38	4.4	4.0	4.9
Acetaminophen 600/650	1886	38	4.6	3.9	5.5
Ibuprofen 50	316	32	4.7	3.3	8.0
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2
Aspirin 650 + codeine 60	598	25	5.3	4.1	7.4
Acetaminophen 300 + codeine 30	379	26	5.7	4.0	9.8
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1305	15	16.7	11.0	48.0
Placebo	>10,000	18	N/A	N/A	N/A

- ***Lowest NNT values were combinations of ibuprofen + paracetamol (NNT values below 2)***
- Analgesics with NNT values close to 2 included
  - -fast acting ibuprofen 200 mg/400 mg,
  - -ibuprofen 200 mg plus caffeine 100 mg
  - -diclofenac potassium 50 mg
- Important finding- low doses of some medicines in fast acting formulations among the best

Fewer side effects for people taking ibuprofen plus paracetamol than those taking placebo. The results for side effects may be different if the painkillers are taken for more than a few days.

Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L./ Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews./Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD010794./ DOI: 10.1002/14651858.CD010794.pub2.

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[Overview of Reviews]

Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews

R Andrew Moore[1], Philip J Wiffen[2], Sheena Derry[3], Terry Maguire[4], Yvonne M Roy[5], Laila Tyrrell[5]

- 21 different OTC analgesic drugs, doses, formulations from 10 Cochrane Reviews
- Postop pain model primarily 3rd molar extraction (industry model for everyday pain)
- Lowest NNT values were combo of ibuprofen + paracetamol (NNT <2)
  - Combinations of ibuprofen plus paracetamol worked in 7 out of 10 people
- Analgesics with NNT values close to 2 included
  - Fast-acting ibuprofen 200mg/400mg
  - Ibuprofen 200mg + caffeine 100mg
  - Diclofenac 50mg
- Important finding: low doses of some medications in fast-acting formulations were best
- Fewer side effects for people taking ibuprofen plus paracetamol than those taking placebo. The results for side effects may be different if the painkillers are taken for more than a few days.

Drug	Dose (mg)	NNT (95% confidence interval)
Aspirin	500	Not better than placebo
Aspirin	600/650	4.2 (3.8 to 4.6)
Aspirin	1000	4.2 (3.8 to 4.6)
Diclofenac potassium	25	2.4 (2.0 to 2.9)
Diclofenac potassium	50	2.1 (1.9 to 2.5)
Dipyrone	500	2.3 (1.9 to 3.1)
Ibuprofen acid	200	2.9 (2.7 to 3.2)
Ibuprofen acid	400	2.5 (2.4 to 2.6)
Ibuprofen fast acting	200	2.1 (1.9 to 2.4) Good ibuprofen dose choice
Ibuprofen fast acting	400	2.1 (1.9 to 2.3)
Ibuprofen + caffeine	200+100	2.1 (1.9 to 3.1)
Ibuprofen + paracetamol	200+500	1.6 (1.5 to 1.8) Best choice
Ibuprofen + paracetamol	400+1000	1.5 (1.4 to 1.7) Higher doses not much better
Naproxen	200/220	3.4 (2.4 to 5.8)
Naproxen	400/440	2.7 (2.2 to 3.5)
Naproxen	500/550	2.7 (2.3 to 3.3)
Paracetamol	500	3.5 (2.7 to 4.8) Good APAP dose choice
Paracetamol	600/650	4.6 (3.9 to 5.5)
Paracetamol	975/1000	3.6 (3.2 to 4.1)

Adapted from- Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L./ Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews./Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD010794./ DOI: 10.1002/14651858.CD010794.pub2.

Clinical studies document greater efficacy and more rapid pain relief with ibuprofen liquid caps when compared to tablets

- Lower doses of faster onset ibuprofen can be as effective as higher doses of standard formulations
- Reduced need for rescue medication
- Rapid onset

Advil Liquid Capsules

Postoperative Dental Pain

Formulation	Dose	NNT
Standard	200	2.9
Fast-acting	200	2.1
Standard	400	2.4
Fast-acting	400	1.8

Adapted from Moore et al., PAIN 155:14, 2014

NSAIDs-Side Effects

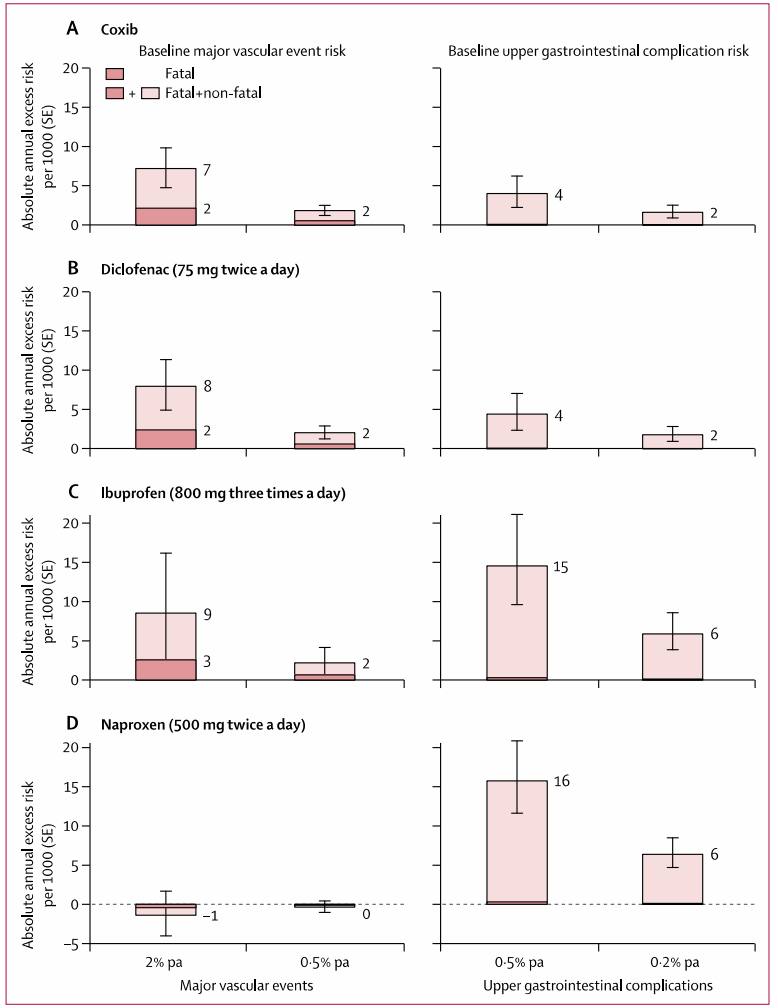
- Increase risk of GI complications 2-4 times.
  - Least to most GI complication (max dose): salsalate (3000 mg), diclofenac (150mg), ibuprofen (3200mg/2400mg chronic use), aspirin (4000 mg), sulindac (400 mg), naproxen (1250mg/1000mg chronic), indomethacin (150 mg), piroxicam (20mg), ketorolac (40 mg)
- Other safety issues: renal, hepatic injury (rarely failure)
  - Avoid COX-2 inhibitors if sulfa allergy ??

NSAID Precautions

- Hepatotoxicity
- Hematologic
- ASA-induced asthma
- Renal
  - Prostaglandins minimally influence RBF or GFR in normal healthy individuals BUT oppose renal vasoconstriction in hypovolemia, CHF, cirrhosis
- Cardiovascular

NSAIDs-Side Effects

- Least to most cardiovascular risk: Naproxen, Diclofenac, COX-2 inhibitors, Ibuprofen
  - Naproxen has most COX-1 inhibition (at high doses similar to ASA)
  - Risk of hospitalization for heart failure doubled by tx with any NSAID
  - COX-2 inhibitors: no platelet effects



Bhala N, et al. *Lancet* 2013; 382: 769–79

Anticonvulsants

Anticonvulsants

- Very useful for burning pain, dysethesias
  - Phenytoin no longer used 2/2 mixed results and ADRs
- Decision on which to use is based on patient specific variables, co-morbidities and side effect profile of the individual drugs
- Therapeutic ranges similar to those used for the treatment of seizures
  - One of the most common reasons for treatment failure is **subtherapeutic dose** and **inadequate trial duration**
    - EXPECTATIONS: slow to achieve maximum effect (up to 8 weeks for gabapentin given titration) → Minimum trial 12 weeks

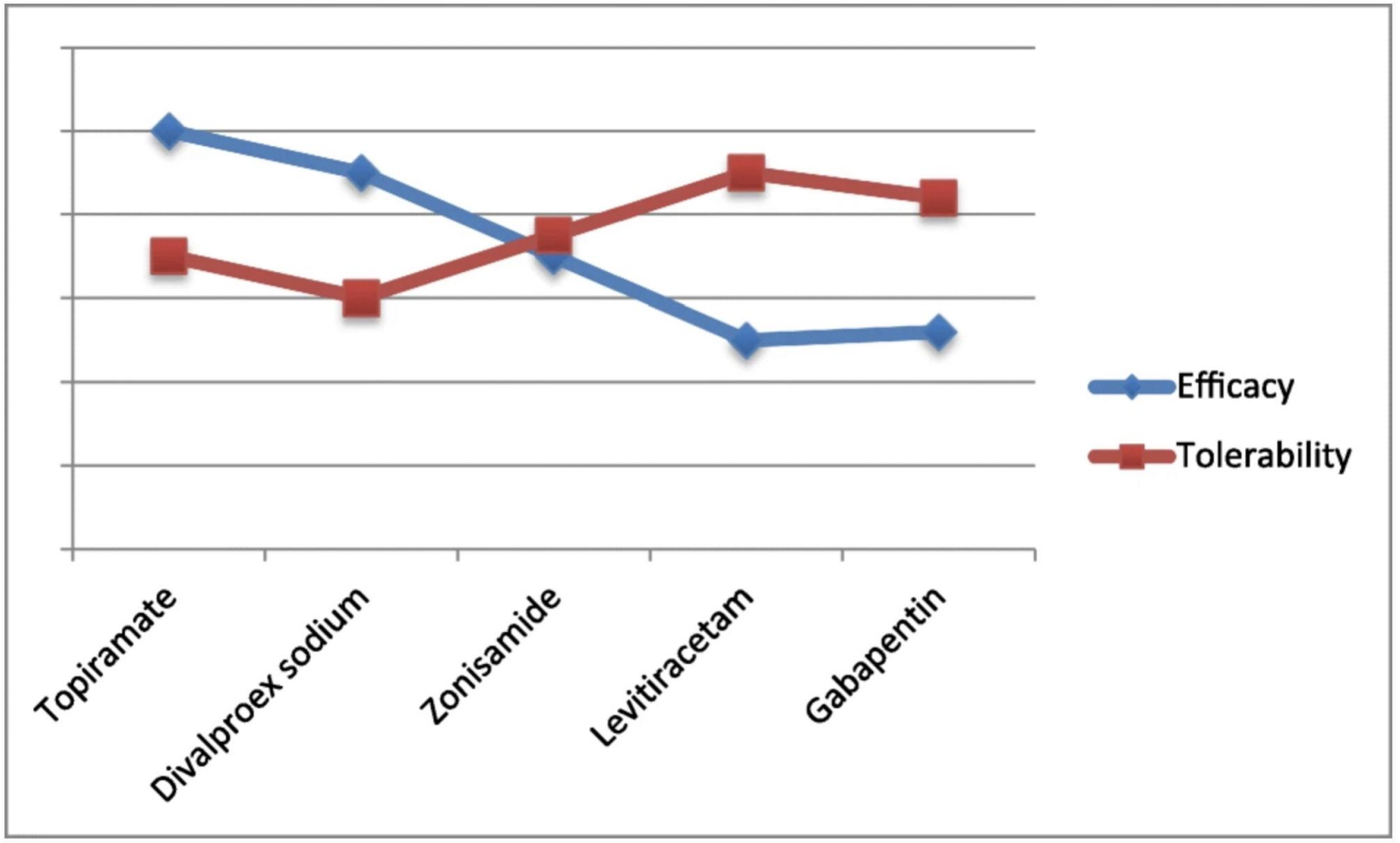
Anticonvulsants

- Mechanisms of Action:
  - Stabilize the nerve membrane
    - Calcium channel blocker (gabapentin, pregabalin)
  - Prevent depolarization
    - Increase synthesis of gamma aminobutyric acid (GABA) (VPA) or its binding to a receptor in the brain (topiramate)
    - Alter voltage-gated sodium channel currents (carbamazepine, oxcarbazepine, zonisamide)
  - Block transmission of pain impulses
    - Glutamate modulation (pregabalin) or NMDA antagonism (topiramate)

Anticonvulsants

- Almost all are slightly soluble, but well absorbed (80-100%) PO
- Not highly bound to plasma protein (EXCEPT: Phenytoin, VPA)
- Primarily cleared via hepatic metabolism, low extraction (thus subject to alterations in CYP)
  - many have active metabolites also cleared by liver
  - Many older antisz are INDUCERS of CYPs
  - Plasma clearance is slow, some t1/2 > 12 hrs

Anticonvulsants for Migraine



Curr Treat Options Neurol **21,** 16 (2019).

Gabapentin

- Good evidence for neuropathic pain
  - 2017 Cochrane Review: 37 studies

Pain Condition	Outcome	Daily Dose	NNT
PHN	30% pain reduction	≥1200mg	4.8 (6.7 for 50%)
DPN	30% pain reduction	≥1200mg	6.6 (same for 50%)

  - NNH an adverse event: 7.5, for study withdrawal: 30
    - Dizziness, somnolence, gait disturbance, peripheral edema
  - No difference in serious adverse events

- Not much evidence for fibromyalgia
  - 2017 Cochrane Review: one study, found 49% achieved 30% pain reduction vs 31% placebo but PGIC "better" achieved by 91% vs 47% placebo

Cochrane Database Syst Rev. 2017 Jun 9;6(6)
Cochrane Database Syst Rev. 2017 Jan 3;1(1)

Pregabalin

- Good evidence for neuropathic pain
  - 2019 Cochrane Review, 45 studies (PDN>>PHN>mixed)
  - No difference serious adverse events but more somnolence, dizziness

Pain Condition	Outcome	Daily Dose	NNTB
PHN	30% pain reduction	300mg/600mg	3.9/2.7
DPN	30% pain reduction	300mg/600mg	22/9.6
DPN	PGIC much/very much improved	300mg	4.9
Mixed NP	30% pain reduction	600mg	8.2 (7.2 for 50%)
Central NP	30% pain reduction	600mg	5.9
HIV neuropathy		600mg	no benefit
back pain, sciatica, NP cancer pain			ltd evidence of benefit

Cochrane Database Syst Rev. 2019 Jan 23;1(1)

Anticonvulsants: Dosing and Additional Benefits

Anticonvulsant	Starting Dose (QHS)	Goal Dose/ Max Daily Dose	Additional Benefits
Gabapentin^^ (Neurontin)	300mg	600mg TID/3600mg	Anxiolysis
Pregabalin^^ (Lyrica)	50-75mg	150mg BID/600mg	Anxiolysis
Topiramate^ (Topamax)	25mg	50mg BID/200mg	Weight loss, nightmares?
Oxcarbazepine^ (Trileptal)	150mg	300mg BID/1200mg	Fewer side effects than carbamazepine
Carbamazepine (Tegretol)	100mg	200mg BID/1200mg	Bipolar *monitor levels
Valproic Acid (Depakote)	125mg	250mg BID/1000mg	Anti-panic, bipolar
Zonisamide (Zonegran)	100mg	200 mg/400 mg/day	Bipolar ↑Dose q2 wk

^=renal impairment: start at ½ and titrate slowly; ^^see package insert for renal dosing

Local Anesthetics

- Block Sodium Channel currents
- IV lidocaine (monitored setting)
- Mexilitine
  - May cause nausea, blurred vision, HA
  - 2019 Cochrane Review for Neuropathic Pain found safe, better than placebo

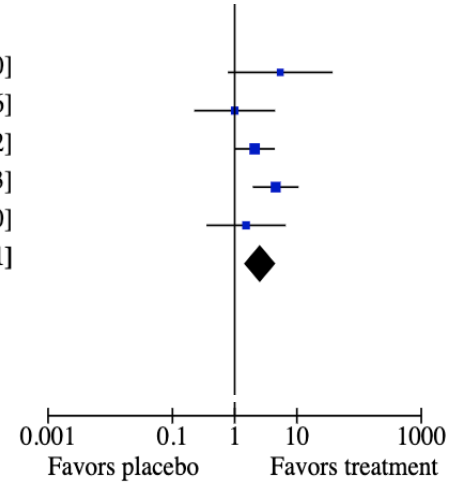
1.2.2 Mexiletine						
Chabal 1992	6	11	2	11	5.3%	5.40 [0.78 , 37.50]
Kemper 1998	5	16	5	16	8.0%	1.00 [0.22 , 4.46]
Matsuoka 1996	40	110	12	56	17.9%	2.10 [0.99 , 4.42]
Matsuoka 1997	29	55	11	56	16.0%	4.56 [1.96 , 10.63]
Wright 1997	8	14	7	15	8.2%	1.52 [0.35 , 6.60]
Subtotal (95% CI)		**206**		**154**	**55.4%**	**2.52 [1.47 , 4.31]**
Total events:	88		37			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 4.64$, df = 4 (P = 0.33); $I^2 = 14\%$

Test for overall effect: Z = 3.38 (P = 0.0007)

Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 17.54$, df = 13 (P = 0.18); $I^2 = 26\%$

Test for overall effect: Z = 4.88 (P < 0.00001)



Cochrane Database Syst Rev . 2019 Oct 7;2019(10)

Antidepressants

Tricyclic Antidepressants

- First line
  - EXPECTATIONS: slow onset (days to weeks) = 8-12 weeks for adequate trial
    - Initiate Amitriptyline 10 - 25 mg QHS; titrate slowly Q5 days
  - Less expensive than gabapentin
- Relieve nerve pain
  - blocking the reuptake of neurotransmitters serotonin and norepinephrine, which are released by the pain modulatory systems that descend from the brain stem to the spinal cord
  - accumulation of serotonin and norepinephrine at the synapse inhibits pain impulse transmission
  - NNT for neuropathic pain approximately 3 (Saarto, 2010)
- additional benefit in reducing anxiety and depression

Pain 132 (2007) 237–251. J Neurol Neurosurg Psychiatry 2010;81:1372e1373. doi:10.1136

Tricyclic Antidepressants

- Limited by side effects
  - Sedation, orthstatic hypotension, anticholinergic effects (dry mouth, obstipation, cardiac arrythmias, urinary retention)
- Most have similar efficacy → Select less anticholinergic
  - Nortriptyline (less hypotension), desipramine a.m. or early p.m. as it may increase insomnia (elderly)
  - Trazodone (Desyrel) not a TCA but has some of the same activity

Drug	Serotonin	Norepinephrine	Dopamine	Sedative	Antimuscarinic
Amitriptyline	+++	+	—	+++	+++
Nortriptyline	+++	++	—	++	++
Desipramine	—	+++	—	+	+
Imipramine	+++	++	—	++	++

Pringsheim T et al. *Can J Neurol Sci*, 2012, 39(2 Suppl 2):S1-59.

Anticholinergic effects: desipramine < nortriptyline < imipramine < doxepin < amitriptyline

Tricyclics

Tricyclic Effects:
- Antihistamine/Sedation (Rx at HS) ✓
- Weight gain ✓
- Cardiotoxicity
- Antipruritic
- Blocks sodium channels
  - Explains efficacy in neuropathic pain
  - Explains cardiotoxicity

Target dose: 150mg daily

½ Life: approx 23h

Tricyclic Effects:
- Activating (Rx in AM) ✓
- Anorexia ✓
- May inc. risk of BRCA
- Orthostasis
- Constipation/urinary retention
- Tachycardia
- Inc. IOP/Worsening glaucoma
- Blocks NE in ascending pain pathways of spinal cord
  - Explains efficacy for neuropathic pain

2nd Generation

Trazadone
- Some NE activity

Venlafaxine (Effexor)
- NE activity only above 150mg
- Some DA reuptake inhibition

Bupropion
- Both NE & DA reuptake inhibition

Duloxetine (Cymbalta)
- NE activity at all doses
- Much less DA reuptake inhibition

Milnacipran (Savella)
- NE activity > 5HT

3rd Generation

SSRI's
- Virtually no analgesia

Mirtazapine (Remeron)
- Weight gain & sedation
- Nightmares

Tricyclic Antidepressants

- Caution: Use with other CNS depressants, serotonergic medications
  - Tramadol, muscle relaxants (cyclobenzaprine), SSRIs, triptans, 5-HT_3 inhibitors, etc.
  - Also caution with CYP450 2D6 inhibitors (cimetidine, diphenhydramine, methylphenidate, fluoxetine, duloxetine, amiodarone)
- Metabolized by liver, excreted in urine and feces

Drug	Usual Start Dose	Average Dose	Maximum Dose
Amitriptyline (Elavil)	10–25 mg qd	75–150 mg qd	300 mg/day
Amoxapine (Asendin)	25 mg bid	75–200 mg bid	600 mg/day
Clomipramine (Anafranil)	25 mg qd	150–250 mg qd	250 mg/day
Desipramine (Norpramin)	10–25 mg qd	75–150 mg qd	300 mg qd
Doxepin (Sinequan)	10–25 mg qd	75–150 mg qd	300 mg qd
Nortriptyline (Pamelor)	10–25 mg qd	75–150 mg qd	200 mg qd
Protriptyline (Vivactil)	5 mg qd	10 mg tid	60 mg/day

Pringsheim T et al. *Can J Neurol Sci*, 2012, 39(2 Suppl 2):S1-59.

Antidepressants – Selective Serotonin Reuptake Inhibitors

- Fewer side effects than tricyclics.
- Not as effective in relieving nerve pain
  - May have some benefit in fibromyalgia if not responsive to other treatments
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
  - duloxetine, milnacipran both well-studied; less data to support the use of venlafaxine, desvenlafaxine
  - Like TCAs, require 8-12 weeks at target dose for adequate trial
  - NNT 6.4, NNH 11.8

Saarto T, Wiffen PJ. J Neurol Neurosurg Psychiatry. 2010;81(12):1372. Finnerup NB, Attal N, Haroutounian S, et al. Lancet Neurol 2015;14(2):162-173.

SNRIs

Medication	Adverse Effects, Contraindications	5HT:NE selectivity
Milnacipran (Savella®)	nausea and vomiting, headache, dizziness, insomnia, and palpitations Avoid if hx serotonin syndrome or NMS, uncontrolled HTN, szs or liver dz	n/a
Duloxetine (Cymbalta®)	Nausea, dry mouth, constipation, loss of appetite, fatigue, drowsiness, sweating	9
Desvenlafaxine (Pristiq®)	↑ By 50mg Q 2-4 wks to 100mg QD	85
Venlafaxine (Effexor XR ®)	Hypertension, also orthostatic hypotension, increased QTc, mydriasis, anxiety, nervousness, insomnia, and weight loss Caution with narrow-angle glaucoma, liver disease, or renal impairment	115-120
Amitriptyline Nortriptyline		8 0.24

Pain 132 (2007) 237–251

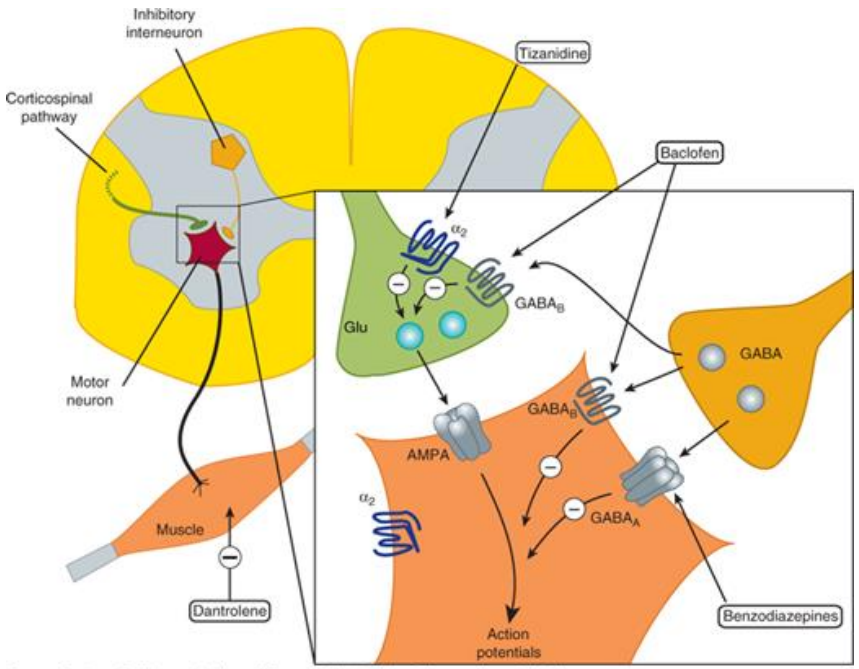
SNRI Dosing

Medication	Starting Dose	Titration & Therapeutic Dose	Maximum dose
Milnacipran (Savella®)	12.5 mg QD	Gradual to 50mg BID by day 7	100mg BID
Duloxetine (Cymbalta®)	30 mg QD	X 2wk then 60mg QD Avoid w/ hepatic impair. Decrease dose in severe renal dz	60mg BID*
Desvenlafaxine (Pristiq®)	50mg	↑ By 50mg Q 2-4 wks to 100mg QD Decrease dose in renal dz	400mg QD
Venlafaxine (Effexor XR ®)	37.5 mg QD	X 1 wk then 75mg; ↑ by 75mg Q1-2 wks to 75mg BID Decrease dose in hepatic or renal dz	375mg total daily

Pain 132 (2007) 237–251

Muscle Relaxants

- Skeletal muscle relaxants
  - Cyclobenzaprine (Flexeril) – 5-10 mg TID/Amrix 15-30 mg daily
  - Tizanidine (Zanaflex) – 4-8 mg TID/QID
  - Metaxalone (Skelaxin) – 800 mg TID/QID
  - Baclofen (Lioresal) 5-20 mg BID/TID
    - lancinating pain, spasticity, HA, trigeminal and postherpetic neuralgia, fibromyalgia
    - Binds to GABA-B receptors
- NOT RECOMMENDED FOR CHRONIC PAIN:
  - Carisoprodol (Soma) - metabolized into barbiturate (meprobamate)
  - Diazepam (Valium) – 2-10 mg PO/IV; BID/TID
  - Methocarbamol (Robaxin) – 1000-1500 mg QID



N-methyl-D-aspartate Receptor Antagonist

- Blocks excitatory receptor in the spinal cord thought to be involved in the development of **central sensitization and the wind-up** phenomenon (due to either persistent nociceptor activation or chronic opioid administration)
- Classic antagonist:
  - Ketamine:
    - Oral: start 25-50 mg TID with meals, titrate to 100 mg tid, max 1000mg daily
    - Topical: 10% ointment to affected area tid-qid

N-methyl-D-aspartate Receptor Antagonist

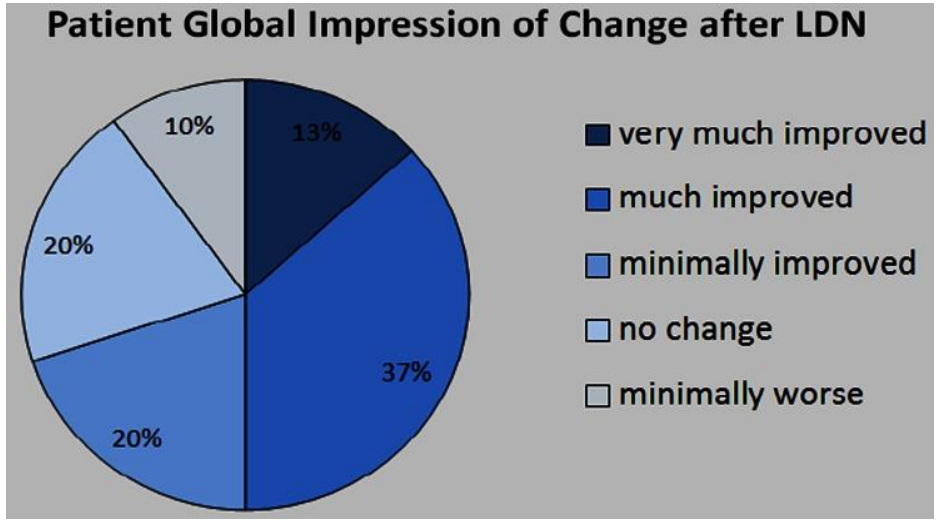
- Blocks excitatory receptor in the spinal cord thought to be involved in the development of **central sensitization and the wind-up** phenomenon (due to either persistent nociceptor activation or chronic opioid administration)
  - Methadone
  - Memantine (Namenda) 5-10 mg bid (max 40 mg bid)
  - Amantadine 400 mg: start 100 mg bid
  - Magnesium: Magnesium citrate 300mg/day
    - some data for IV infusions for perioperative use, 2019 Cochrane review of Mg for sickle cell found 5 RCTs, limited evidence of no difference from placebo, otherwise limited evidence for migraine, etc.

ALPHA-ADRENERGICS

- Receptors found pre and post-synaptically
  - Mechanisms: decrease calcium conductance, increase potassium conductance, reduce sympathetic outflow, increase acetylcholine levels at the dorsal horn
  - Clonidine: 0.1 mg -0.3mg/day patch or 0.1% gel
    - NNTB for 30% reduction in DPN = 8.33 (95% CI 4.3 to 50)
  - Tizanidine: start 2-4 mg qhs, then bid-qid prn up to 36 mg/day

Low-Dose Naltrexone

- Glial-cell modulator
  - May reverse hyperalgesia due to opioid use, other central sensitization
  - Anti-inflammatory: elevated ESR correlates to better treatment response in fibromyalgia
- Dose: 4.5mg QHS
    - Compounded
- Side effects: Nausea, vivid dreams, headache



Younger et al. Clin Rheumatol 2014; 33(4): 451-459

Younger et al. Clin Rheumatol 2014; 33(4): 451-459
Younger J et al. Arthritis Rheum. 2013;65(2):529-38.

Some Bad News…

- AHRQ comparative review 2020 of nonopioid pharmacologic agents for chronic pain
  - Considered pain and function, also QoL, Aes
- Included 185 RCTs and 5 systematic reviews
- Evaluated short term (1-<6 months), intermediate (6 to <12 months), long term (≥12 months)

McDonagh MS, Selph SS, Buckley DI, et al.]. Agency for Healthcare Research and Quality (US); 2020 Apr. (Comparative Effectiveness Review, No. 228.)

- "In the short term, **anticonvulsants** (pregabalin, gabapentin, and oxcarbazepine for **neuropathic** pain, pregabalin/gabapentin for fibromyalgia), **SNRI antidepressants** (duloxetine for **neuropathic pain, fibromyalgia, osteoarthritis, and low back pain**, milnacipran for fibromyalgia), and **NSAIDs** (for **osteoarthritis and inflammatory arthritis**) were associated with mostly small improvements (e.g., 5 to 20 points on a 0 to 100 scale) in pain and function. Function was not found to be improved with duloxetine for low back pain or pregabalin/gabapentin for neuropathic pain."

- “1 RCT showed **memantine** moderately improved pain, function, and quality of life in patients with **fibromyalgia**” in the intermediate term.
- “Other drugs studied, including acetaminophen (osteoarthritis), capsaicin (neuropathic pain), cannabis (neuropathic pain), amitriptyline (fibromyalgia, neuropathic pain), and cyclobenzaprine (fibromyalgia) had **no clear effects**.”
- “Withdrawal from study due to adverse events was significantly increased with nonopioid drugs, with the greatest increase over placebo seen with cannabis.”

PAIN

Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]

- 2018 meta-analysis
- 104 studies identified
  - 47 RCTs (24 parallel, 23 cross-over)
  - 57 observational
  - Total 9,958 participants
  - 48 studied neuropathic pain
  - 7 studied fibromyalgia
  - 48 for other CNCP
  - 1 arthritis

- Nabiximols (Sativex)
  - In the UK, approved for MS spasticity
  - In Canada, also approved for MS neuropathic pain
- Nabilone
  - oral synthetic cannabinoid, mimics THC
    - Schedule II
  - FDA approved for n/v with chemotherapy
- Oral THC
  - Extract
  - Synthetic: dronabinol (Marinol [cap] or Syndros [liquid])
    - Anorexia and weight gain in AIDS
    - Chemo n/v
- Whole flower, inhaled (smoked or vaporized)

https://www.bayer.ca/omr/online/sativex-dhcpl-lapds-04-01-2005-en.pdf
https://www.bayer.ca/omr/online/sativex-pm-en.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/205525Orig1s000Approv.pdf

Cannabis for CNCP: 2018 Meta-analysis

- Overall, cannabinoids were more likely than placebo to produce a 30% reduction in pain or significant reduction in pain intensity

BUT

- Effects were **SMALL**
  - For 30% reduction in pain, OR 1.46 (95% %CI 1.16-1.84)
    - 29.0% achieved this with cannabinoids vs 25.9% with placebo
      - However in observational studies, the pooled prevalence of 30% pain reduction was 72%
  - Change in pain intensity SMD -0.14 vs placebo (95%CI -0.20 to -0.08)

    = reduction of **2.9mm on 100mm VAS**!
  - The longer the intervention, the smaller the effect
    - Single-administration and very short term (<4 weeks) studies remained significant, but longer studies >13 weeks, did not

Cannabis for CNCP: 2018 Meta-analysis

- No significant effect on physical functioning
- No difference in emotional functioning, nor depression or anxiety symptoms specifically
- 2x greater risk of study withdrawal, for any reason, if receiving cannabinoid
  - 3.47x odds of withdrawing due to AE
  - Those receiving placebo were more likely to withdraw due to lack of effects
- 2.33x greater risk of adverse events vs placebo
  - Dizzines (OR 5.52), cognitive or attention disturbance (OR 5.67), confusion and disorientation (OR 5.35)

Cannabis for CNCP: 2018 Meta-analysis

- Number Needed to Benefit: 24
  - 24 patients have to be exposed for 1 to achieve 30% reduction in pain
  - MUCH higher than other analgesics
- Number Needed to Harm: 6
  - 1 out of every 6 patients will experience an AE
    - Similar to opioids

Resource

American Chronic Pain Association (www.theacpa.org)

- They have a combination of provider education, self-education, and tools that providers can use to address pain management concerns/education with patients.

Nonopioid Treatments for Chronic Pain (CDC)

- https://www.cdc.gov/drugoverdose/pdf/nonopioid_treatments-a.pdf

Poll

Overall, how helpful was today's session for you?

a. Very helpful

b. Somewhat helpful

c. Neither helpful nor unhelpful

d. Somewhat unhelpful

e. Very unhelpful

Chat In

What is one thing you will try this week, as a result of this session?

Poll

Overall, how satisfied are you with today's session?

a. Very satisfied

b. Somewhat satisfied

c. Neither satisfied nor dissatisfied

d. Somewhat dissatisfied

e. Very dissatisfied

Chat In

What do you need us to cover in upcoming sessions to help you?

Schedule

Shared Learning Calls will take place every other month

8:00AM – 9:00AM on the 3rd Thursday.

- **2021 Dates**
  - **Jan Thurs 1/21**
  - **Mar Thurs 3/18**

PRACTICE INNOVATION PROGRAM COLORADO
OPIOID MANAGEMENT

Department of Family Medicine