

Non-Opioid Analgesic Options for Chronic Pain

Rebecca Andrews, MS, MD, FACP
 Director of Ambulatory Education
 Associate Program Director,
 Internal Medicine Residency
 Associate Professor of Medicine

Kevin Chamberlin, PharmD, FASCP
 Interim Associate Dean of Admissions &
 Student Affairs
 Associate Clinical Professor & Assistant
 Department Head, Pharmacy Practice
 PGY1 Pharmacy Residency Program Director



Learning Objectives

- 1) Define the role of non-opioid medications for analgesia in patients with chronic pain.
- 2) List the various categories of non-opioid pain medications.
- 3) Describe non-medication options for the management of chronic pain.



Multimodal Analgesia

| | |
|---|--|
| Interventional Nerve blocks Neuraxial analgesia | Analgesics |
| Cognitive modalities Deep breathing Virtual reality Distraction | Physical modalities RICE *Rest, Ice, Compression, Elevation |

Chou R, et al. J Pain. 2016;17(2):131-57.

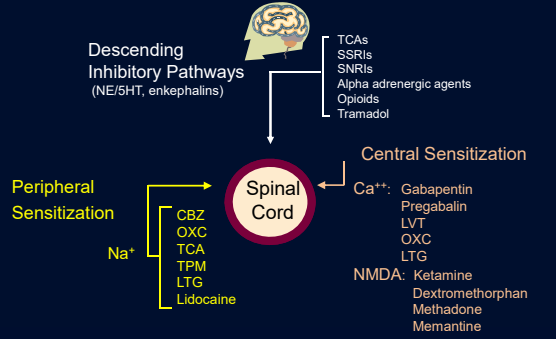


Non-Opioid Medication Options

Treatment appropriateness based on severity of pain



Medications affect pain differently



Descending Inhibitory Pathways
(NE/5HT, enkephalins)

- TCAs
- SSRIs
- SNRIs
- Alpha adrenergic agents
- Opioids
- Tramadol

Central Sensitization

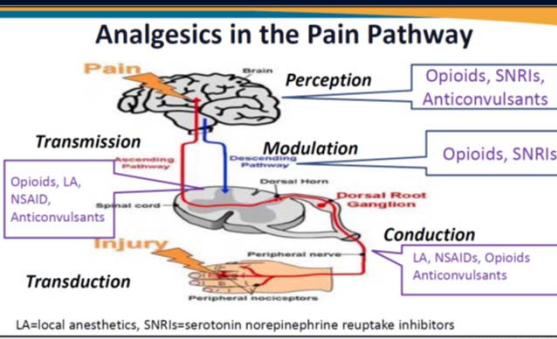
- Ca⁺⁺: Gabapentin, Pregabalin, LVT, OXC, LTG
- NMDA: Ketamine, Dextromethorphan, Methadone, Memantine

Peripheral Sensitization

- Na⁺: CBZ, OXC, TCA, TPM, LTG, Lidocaine

TCA: Tricyclic antidepressant, SSRI: Selective serotonin reuptake inhibitor, SNRI: Serotonin and norepinephrine reuptake inhibitor, CBZ: Carbamazepine, OXC: Oxcarbazepine, TPM: Topiramate, LTG: Lamotrigine, GBP: Gabapentin, LVT: Levitalofam, PREGAB: Pregabalin. Adapted from Brydson A, Backonja M.M. Mechanistic stratification of antineurologic agents. Journal of Pain and Symptom Management, 2003;25:55 (p.527) with permission from the U.S. Cancer Pain Relief Committee.

Analgesics in the Pain Pathway



Transmission: Opioids, LA, NSAID, Anticonvulsants

Modulation: Opioids, SNRIs

Conduction: LA, NSAIDs, Opioids, Anticonvulsants

Transduction: LA, NSAIDs, Opioids, Anticonvulsants

LA=local anesthetics, SNRIs=serotonin norepinephrine reuptake inhibitors

Slide from: Patanwala A, Kral L. Optimizing Acute Pain Management. ASHP 2018.

Range of Low Back Pain Pharmacotherapy

- Beneficial
 - No definitive pharmacotherapy
- Likely beneficial
 - Opioids, antidepressants, NSAIDs, acetaminophen
- Trade-off's
 - SMRs
- Unknown
 - Epidural steroid injections, local injections

Koes, et al. Diagnosis and treatment of low back pain. *BMJ* 2006.
Van Tulder, et al. Low back pain: chronic. *Clinical Evidence* 2006.



Acetaminophen (APAP)

- Inhibits central prostaglandin synthesis without affecting peripheral prostaglandin synthesis
- Additive analgesia with opioids
- IV product has comparable efficacy with oral, more expensive
- Single doses provided 4hrs of at least 50% relief in 37% of patients with post-op pain
 - ↓ opioid consumption by 30% in first 4hrs
 - No reduction in opioid-related adverse effects

Gaskell H, et al. *Coch Data Syst Rev*. 2009;Jul 8(3):CD002763.
McNicol ED, et al. *Br J Anaesth*. 2011;106(6):764-75.



NSAIDs – they aren't all ibuprofen



Comparison Chart: NSAIDs & Other Analgesics Prepared by Lynn Kaplan, Shanna Dossney, The Rx Files, AUG 2008

| Class / Agent | Comments / Products | Usual Dosage Range | Max /day | Cost \times 30 days (comparative dose) |
|----------------------------------|--|---|---|---|
| Salicylates | | | | |
| ASA-Plain | ASPIREN [®] | OTC: 850mg supp; 80,325mg tab; 81,322,606/975mg EC tabs | 325-650mg q4-6h | 650mg po QID \$11 |
| ASA-Enteric Coated | ENTROPHEN [®] | irreversible platelet inhibition | 325-975mg QID | 250mg po BID \$37 |
| Dibenzos | DOLOCHIB [®] | 150,500mg tab | 250-500mg BID | 1.5g 1500mg po BID \$54 |
| Non-acylated Salicylates | low adverse GI reactions; less gastric allergy in NSAID (A/C/S/T) allergic patients available, but not commonly used | | | |
| Salicylate | BISALITIP [®] | 1,900,750mg tab | 1000mg TID | 1500mg po BID \$54 |
| Choline Mg Trisalicylate | TRISALATE [®] | 500mg tab | 1-1.5g BID | 1000mg po BID \$36 |
| Indole Acetic Acids | | | | |
| Indometacin | INDOCID [®] | 25,50mg cap; 50,100mg supp | 25-50mg TID | 200mg 25mg po TID \$17 |
| Sulindac | CLINORIL [®] | 150,200mg tab; PD | 150-200mg BID | 400mg 150mg po BID \$34 |
| Tolmetin | TOLECTIN [®] | 200,600mg tab; 600mg cap | 200-600mg TID-QID | 2g 400mg po TID \$53 |
| Phenylacetic Acids | | | | |
| Diclofenac | VOLTAREN [®] | 25,50mg EC tab; 50,100mg supp; 75,100mg SR tab | 25-50mg BID-TID | 200mg 50mg po TID \$22 |
| Diclofenac + Misoprostol | ARTHRITEC-50 [®] ARTHRITEC-75 [®] | (50mg + 200ug) tab (75mg + 200ug) tab | 1 tab BID-TID 1 tab QD-BID | 200mg 800ug Once tab po BID \$47 \$61 |
| Pyridine Carboxylic Acids | | | | |
| Ketorolac | TORADOL [®] | 60, 10mg tab; 30mg injectable IM formulation available | 10mg po q6h x7d max 10,30mg IM q4-6h | 40mg 10mg po QID [®] \$67 [®] |
| Pyranocarboxylic Acids | | | | |
| Etoricoxib | ULTRADOL [®] | 60% reduction; 200,300mg cap | 200-600mg BID | 1.2g 300mg po BID \$50 |



| | | | | | |
|---|------------------------|--|--------------------------------------|--------------|---|
| Propionic Acids | | | | | |
| NALFON [®] | 300mg cap; 600mg tab | 300-600mg TID-QID | 3,2g | 600mg po TID | \$63 |
| Flurbiprofen | ANSAID [®] | 50-100mg tab | 50-100mg TID-QID | 300mg | 100mg po BID \$32 |
| Ibuprofen | MOTRIN [®] | OTC: 200mg tab; 100mg/5ml susp; Rx: 50,100,400,600mg tab | 200-800mg TID-QID | 3,2g | 400mg po QID \$13 |
| Ketoprofen | ORUDIS [®] | 50,100mg EC; 200mg SR tab; 50mg cap; 25,100mg supp | 25-100mg TID-QID | 300mg | 50mg po TID \$25 |
| Naproxen | NAPROSYN [®] | 125,250,375,500mg SR; 125mg/5ml susp; 500mg supp (EC available non-formulary) | 125-500mg BID | 1.5g | 375mg po BID \$16 |
| Oxaprozin | DAYPRO [®] | 600mg caplet; long 11.2 (506) | 600-1800mg OD | 1.8g | 600mg po OD \$30 |
| Tiaprofenic Acid | SURGAM [®] | 200,300mg tab | 200-300mg BID | 600mg | 200mg po BID \$32 |
| Oxicams | | | | | |
| Piroxicam | FELDENE [®] | 10,20mg cap & supp | 10-20mg OD | 20mg | 20mg po OD \$33 |
| Piroxicam-beta-cyclodextrin | BRIXIDOL [®] | 20mg tab; 20mg po sup; 40mg qd wafer | 20mg OD x 7d max | 20mg | 20mg po OD [®] \$97 [®] |
| Tepoxycam | MOBIFLEX [®] | 20mg tab | 20-40mg OD | 40mg | 20mg po OD \$51 |
| Naphthylalanones | | | | | |
| Nimesulide | RELAFIN [®] | <10% reduction; PD; 500mg tab | 1-2g OD | 2g | 1g po OD \$43 |
| Anthranic Acids | | | | | |
| Etoricoxib | IDARAC [®] | 200,400mg cap | 200-600mg TID-QID | 1,2g | 200mg po QID \$59 |
| Mefenamic Acid | PONSAID [®] | 200mg cap (initially 500mg x1) | 250mg QID x 7d max | 1.5g | 250mg po QID [®] \$37 [®] |
| COX-2 Specific Inhibitors (CSIs) | | | | | |
| Celecoxib | CELLEBREX [®] | 100,200mg cap | 100mg BID (OA) + 200mg BID (RA/\$97) | 400mg | 100mg BID 200mg OD \$52 |
| Rofecoxib | VIROXA [®] | 12.5, 25mg tab; 12.5mg/ml susp; methotrexate BI if for acute pain; 50mg XL, then 25-50mg od (X 5d) | 12.5-25mg OD (OA) | 50mg | 12.5mg OD 25mg OD \$52 |



NSAIDs – they aren't all equal, either

The 2007 Oxford league table of analgesic efficacy

Numbers needed to treat are calculated for the proportion of patients with at least 50% pain relief over 4-6 hours compared with placebo in randomised, double-blind, single-dose studies in patients with moderate to severe pain. Drugs were oral, unless specified, and doses are milligrams. Shaded rows are intramuscular administration

| Analgesic | 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 |
| Valdecoxib 40 | 473 | 73 | 1.6 | 1.4 | 1.8 |
| Dipyrone 1000 | 113 | 79 | 1.6 | 1.3 | 2.2 |
| Ibuprofen 600/800 | 165 | 80 | 1.7 | 1.4 | 2.3 |
| Valdecoxib 20 | 204 | 68 | 1.7 | 1.4 | 2.0 |
| Ketorolac 20 | 69 | 57 | 1.8 | 1.4 | 2.5 |
| Ketorolac 60 (intramuscular) | 116 | 56 | 1.8 | 1.5 | 2.3 |
| Diclofenac 100 | 545 | 69 | 1.8 | 1.6 | 2.1 |
| Piroxicam 40 | 30 | 80 | 1.9 | 1.2 | 4.3 |
| Celecoxib 400 | 298 | 52 | 2.1 | 1.8 | 2.5 |
| Paracetamol 1000 + Codeine 60 | 197 | 57 | 2.2 | 1.7 | 2.9 |
| Oxycodone IR 5 + Paracetamol 500 | 150 | 60 | 2.2 | 1.7 | 3.2 |
| Bromfenac 25 | 370 | 51 | 2.2 | 1.9 | 2.6 |
| Rofecoxib 50 | 675 | 54 | 2.3 | 2.0 | 2.6 |

| | | | | | |
|-----------------------------------|------|----|-----|-----|-----|
| Oxycodone IR 15 | 60 | 73 | 2.3 | 1.5 | 4.9 |
| Aspirin 1200 | 279 | 61 | 2.4 | 1.9 | 3.2 |
| Bromfenac 50 | 247 | 53 | 2.4 | 2.0 | 3.3 |
| Dipyrone 500 | 288 | 73 | 2.4 | 1.9 | 3.2 |
| Ibuprofen 400 | 5456 | 55 | 2.5 | 2.4 | 2.7 |
| Bromfenac 100 | 95 | 62 | 2.6 | 1.8 | 4.9 |
| Oxycodone IR 10 + Paracetamol 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 |
| Paracetamol 650 + tramadol 75 | 679 | 43 | 2.6 | 2.3 | 3.0 |
| Oxycodone IR 10+Paracetamol 1000 | 83 | 67 | 2.7 | 1.7 | 5.6 |
| 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 |
| Dextropropoxyphene 130 | 50 | 40 | 2.8 | 1.8 | 6.5 |
| Paracetamol 650 + tramadol 112 | 201 | 60 | 2.8 | 2.1 | 4.4 |
| Bromfenac 10 | 223 | 39 | 2.9 | 2.3 | 4.0 |

| | | | | | |
|--|------|----|------|------|------|
| 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 |
| Paracetamol 500 | 561 | 61 | 3.5 | 2.2 | 13.3 |
| Celecoxib 200 | 805 | 40 | 3.5 | 2.9 | 4.4 |
| Paracetamol 1500 | 138 | 65 | 3.7 | 2.3 | 9.5 |
| Ibuprofen 100 | 495 | 36 | 3.7 | 2.9 | 4.9 |
| Oxycodone IR 5 + Paracetamol 1000 | 78 | 55 | 3.8 | 2.1 | 20.0 |
| Paracetamol 1000 | 2759 | 46 | 3.8 | 3.4 | 4.4 |
| Paracetamol 600/650 + Codeine 60 | 1123 | 42 | 4.2 | 3.4 | 5.3 |
| Paracetamol 650 + Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) | 963 | 38 | 4.4 | 3.5 | 5.6 |
| Aspirin 600/650 | 5061 | 38 | 4.4 | 4.0 | 4.9 |
| Paracetamol 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 |
| Oxycodone IR 5 + Paracetamol 325 | 149 | 24 | 5.5 | 3.4 | 14.0 |
| Ketorolac 10 (intramuscular) | 142 | 48 | 5.7 | 3.0 | 53.0 |
| Paracetamol 300 + Codeine 30 | 379 | 26 | 5.7 | 4.0 | 9.8 |
| Bromfenac 5 | 138 | 20 | 7.1 | 3.9 | 28.0 |
| Tramadol 50 | 770 | 19 | 8.3 | 6.0 | 13.0 |
| Codeine 60 | 1305 | 15 | 16.7 | 11.0 | 48.0 |

Anticonvulsants

Prototypical Agents:

- **Gabapentin/Pregabalin Carbamazepine, Valproic acid, Topiramate**
- Act by a reduction of neuronal irritability

Indications: Neuropathic pain

- **Gabapentin/ Pregabalin:** Postherpetic Neuralgia, Diabetic Peripheral Neuropathy, fibromyalgia
- **Valproic Acid, Topiramate:** migraine
- **Carbamazepine:** Trigeminal neuralgia

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Gabapentinoids

- Modestly ↓ opioid requirement & pain scores post-op*
- Some data indicates ↓ in chronic post-op pain
 - Gabapentin: 600-1200mg pre-op, 600mg x1+ doses post-op
 - Pregabalin: 150-300mg pre-op, 150-400mg x1+ doses post-op
- Consider using for major surgeries and opioid-tolerant patients
- May cause additive sedation with opioids

Doleman B, et al. Anaesthesia. 2015;70:1186-204.
Chou R, et al. J Pain. 2016;17(2):131-57.

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Gabapentin

- Binds to the $\alpha 2\text{-}\delta$ subunit of presynaptic voltage dependent Ca^{++} channels
- Reduces the release of pain neurotransmitters
- Uses include:
 - Fibromyalgia (off-label)
 - DPN (off-label)
 - PHN (approved)

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Gabapentin

Gabapentin

Dosing: start low, go slow

- Strive for a dose of 1800-3600 mg/day
- Stack doses at nighttime
- Adjust for renal creatinine clearance
- Never stop abruptly

Adverse Effects

- Somnolence!!
- Can cause leukopenia, thrombocytopenia
- **Boxed warning:** increased suicidal thinking

Contraindications

- Renal failure

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Pregabalin

Pregabalin (Schedule V)

- Approved indications:
 - PHN, DPN, fibromyalgia, spinal neuropathic pain
- Better absorption, decreased somnolence (vs. gabapentin)
- Improvement in Non-REM sleep
- 150mg/d in divided doses...up to 600mg/d (maximum dosage dependent upon condition)
- Reduce dose by 50% if Clcr 30-60 mL/min

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Pregabalin

Adverse Effects

- Somnolence, dysphoria, euphoria
- Increased risk of angioedema-caution with ACEI
- Boxed warning:** Increased risk of suicidal ideation

“Pearls”

- Don't stop abruptly
- Don't drink alcohol

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Table 1. Randomized Clinical Trials of Gabapentin vs Placebo for Off-label Treatment of Pain

| Clinical Condition | No. of Participants | Treatment Duration, wk | Difference in Pain Compared With Placebo* | Additional Comments* |
|--|---------------------|------------------------|---|---|
| Diabetic neuropathy ¹¹ | 421 | 12 | No | None |
| Diabetic neuropathy ¹² | 147 | 4 | 1.1 On 0-10 scale, P = .002 | Experimental gabapentin formulation |
| Diabetic neuropathy ¹³ | 165 | 8 | 1.1 On 0-10 scale, P = .001 | None |
| Diabetic neuropathy ¹⁴ | 40 | 6 | No | Crossover trial |
| Diabetic neuropathy ¹⁴ | 80 | 8 | 1.0 On 0-10 scale, P = .01 | None |
| Low back pain/radiculopathy ¹⁵ | 108 | 12 | No | Participants had back pain with or without radiculopathy |
| Low back pain/radiculopathy ¹⁶ | 65 | 8 | No | Participants had back pain after "redneck leg pain" |
| Low back pain/radiculopathy ¹⁷ | 24 | 6 | No | Crossover trial, participants had "lumbar intervertebral ligament pain" |
| Low back pain/radiculopathy ¹⁸ | 43 | 8 | 0.72 On 0-3 scale, P = .01 | Participants had lumbosacral radiculopathy |
| Unspecified neuropathy ¹⁹ | 305 | 8 | 0.5 On 0-10 scale, P = .048 | Enrolled patients with any pain deemed as neuropathic by clinician |
| Spinal cord injury ²⁰ | 20 | 8 | 4.3 On 0-10 scale, P < .001 | Crossover trial |
| Spinal cord injury ²¹ | 7 | 4 | No | Crossover trial |
| Chronic pelvic pain, women ²² | 47 | 26 | No | None |
| Phantom limb pain ²³ | 19 | 6 | 1.4 On 0-10 scale, P = .03 | Crossover trial |
| Phantom limb pain ²⁴ | 24 | 6 | No | Crossover trial |
| Carpal tunnel syndrome ²⁵ | 140 | 8 | No | None |
| Complex regional pain syndrome ²⁶ | 58 | 3 | No | Crossover trial |
| Fibromyalgia ²⁷ | 150 | 12 | 0.9 On 0-10 scale, P = .01 | None |
| HIV neuropathy ²⁸ | 26 | 4 | No | None |
| Mastocytosis ²⁹ | 50 | 12 | Approximately 2.0 on 0-10 scale, P = .04 | None |
| Traumatic nerve injury ³⁰ | 120 | 5 | No | Crossover trial |
| Acute zoster ³¹ | 87 | 4 | No | None |

*No indicates P = .05. Because the most consistently reported primary outcome in these trials was reduction in pain on an 11-point (0-10) pain scale, that outcome is reported here (except for the radiculopathy study¹⁶ that used a 0-3 scale).
*Study is a parallel group trial unless otherwise stated.

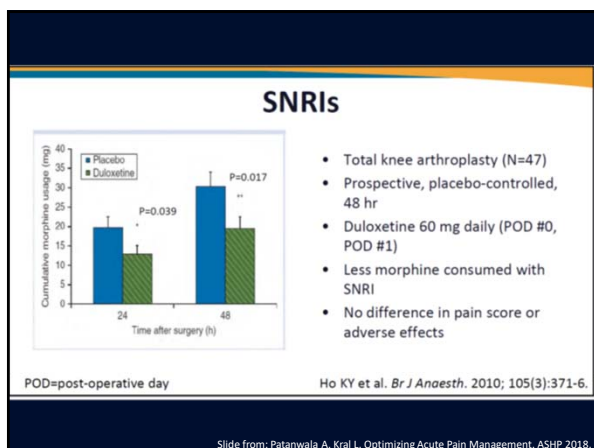
Goodman CW, Brett AS. JAMA Intern Med. 2019; doi:10.1001/jamainternmed.2019.0086

Table 2. Randomized Clinical Trials of Pregabalin vs Placebo for Off-label Treatment of Pain

| Clinical Condition | No. of Participants | Treatment Duration, wk | Difference in Pain Compared With Placebo* | Additional Comments* |
|--|---------------------|------------------------|---|---|
| Central neuropathic pain ³² | 219 | 13 | No | Central poststroke pain |
| Central neuropathic pain ³³ | 40 | 4 | 2.18 On 0-10 scale, P = .01 | Etiology predominantly from stroke and spinal cord lesions (93%) |
| HIV neuropathy ³⁴ | 302 | 14 | No | None |
| HIV neuropathy ³⁵ | 377 | 17 | No | None |
| Acute and chronic sciatica ³⁶ | 209 | 8 | No | 52-wk Follow-up also negative, not beneficial in either acute or chronic |
| Unspecified neuropathy ³⁷ | 73 | 5 | No | Crossover trial |
| Acute zoster ³⁸ | 29 | 3 | No | None |
| Chronic prostatitis/chronic pelvic pain syndrome ³⁹ | 324 | 6 | No | Men only |
| Traumatic nerve injury ⁴⁰ | 367 | 8 | 0.62 On 0-10 scale, P = .01 | 2-wk Placebo run-in phase |
| Chronic pancreatitis ⁴¹ | 64 | 3 | 0.58 On 0-10 scale, P = .02 | None |
| Burn injury ⁴² | 90 | 4 | See comments | 10 End points of different types of pain, 5 favored pregabalin (P < .05), 5 did not |
| Chronic sickle cell pain ⁴³ | 22 | 12 | No | None |

*No indicates P = .05. Because the most consistently reported primary outcome in these trials was reduction in pain on an 11-point (0-10) pain scale, that outcome is reported here.
*Study is a parallel group trial unless otherwise stated.

Goodman CW, Brett AS. JAMA Intern Med. 2019; doi:10.1001/jamainternmed.2019.0086



Slide from: Patanwala A, Kral L. Optimizing Acute Pain Management. ASHP 2018.

Ketamine

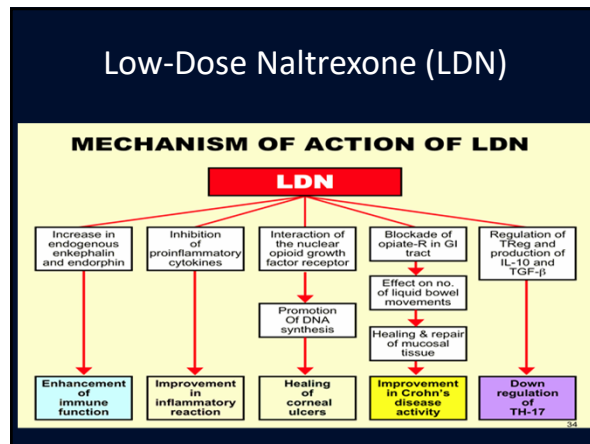
- Adjunct to opioid therapy for:
 - Patients with inadequate relief or ADEs from opioids
 - Patients with opioid tolerance
- 0.5mg/kg IV bolus, then 10mcg/kg/min intraoperatively +/- continuous infusion post-operatively

Chou R, et al. J Pain. 2016;17(2):131-57.

Local Anesthetics

- Infiltration anesthesia
 - Prior to incision and at wound closure
- IV infusions intraoperatively
- IV regional anesthesia
 - Injection of local anesthetic into an extremity with a tourniquet on
- Peripheral nerve blocks
 - Individual nerves or plexus can be blocked
 - Most applicable for extremity surgeries
- Central neuraxial blocks (spinals, epidurals)

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LDN in Chronic Pain

Table 1. Mechanisms of action and clinical use in regard to different doses of naltrexone used.

| Dose Range | Dose Specific Mechanism of Action | Clinical Use |
|----------------------------|--|--|
| Standard (50-100 mg) | Opioid receptor antagonism | Alcohol and opiate abuse |
| Low-dose (1-5 mg) | Toll-like receptor 4 antagonism, opioid growth factor antagonism | Fibromyalgia, multiple sclerosis, Crohn's disease, cancer, Hantley-Hantley disease, complex-regional pain syndrome |
| Very low-dose (0.001-1 mg) | Possibly same as low-dose | Add-on to methadone detoxification taper |
| Ultra low-dose (<0.001 mg) | Binding to high affinity filament-A (FLNA) site and reducing-opioid receptor associated G-coupling | Potentiating opioid analgesia |

Toljan K, Vrooman B. Med Sci. 2018;6:82.

LDN in Chronic Pain

- Complex Regional Pain Syndrome (CRPS)
 - In addition to a standard pain management, “considerably improved symptoms” in patients with LDN
- Fibromyalgia
 - 8 weeks of 4.5mg po LDN
 - 32.5% reduction in symptoms (vs. 2.3% placebo)
 - 20-week study
 - 57% LDN ‘responders’ to 3mg po LDN
- Crohn’s
 - 4 weeks of 0.5mg po LDN
 - 75% response rate for pain free days and symptom relief

Toljan K, Vrooman B. Med Sci. 2018;6:82.

SMR Overview

- Appear to ↓ discomfort & accelerate recovery in acute situations
- Benefit with NSAID in acute situations
- Adverse effects problematic, esp. longer use
- Avoid carisoprodol.
- No good data or consensus on chronic use

PHARMACISTS LETTER

We're getting questions about differences between muscle relaxants. Some are for SPASTICITY due to multiple sclerosis, spinal cord injury, etc. These are not for musculoskeletal problems.

Baclofen (Lioresal) is the mainstay of spasticity treatment. It's effective and inexpensive.

Tizanidine (Zanaflex) works about as well as baclofen and causes less weakness. But tizanidine causes hypotension, has a greater incidence of dry mouth, and costs more than baclofen.

Suggest tizanidine for ambulatory patients if they can tolerate about a 20% drop in systolic blood pressure. Recommend gradual titration...up to about 24 mg/day.

Don't combine it with fluvoxamine, ciprofloxacin, or other CYP1A2 inhibitors such as oral contraceptives. These drugs may drastically increase tizanidine levels and cause more hypotension.

Dantrolene may also be used for spasticity. Recommend it only after other agents due to its rare but serious hepatotoxicity.

The others are for MUSCULOSKELETAL problems such as low back pain. These probably work due to their sedating effects.

Cyclobenzaprine (Flexeril) has been studied the most, but its use may be limited by anticholinergic side effects.

Recommend 5 mg TID. It's as effective as higher doses...causes less side effects...and only costs \$17 a month.

Carisoprodol (Soma) is often effective but can cause more dizziness than cyclobenzaprine.

Keep in mind that **carisoprodol has a higher abuse potential** due to one of its metabolites, meprobamate.

Some patients use it to enhance or prolong the effects of opioids.

Metaxalone (Flexonin) may cause less drowsiness than cyclobenzaprine. But it requires QID dosing and costs twenty times more.

Chlorzoxazone (Parajon Forte)...**orphenadrine (Norflex)**...and **methocarbamol (Robaxin)** require multiple daily doses, are more expensive, or have increased toxicities. Consider these second- or third-line choices.

Diazepam can be used for BOTH spasticity or musculoskeletal problems. But keep in mind that chronic use can lead to dependence.

Get our [Detail Document](#) for a great chart of muscle relaxants that compares their indications, side effects, dosing, and cost. [View Detail Document #21206](#)

Non-NSAID Topical Analgesics

- Lidocaine
 - Multiple concentrations
 - 5% patch approved for PHN; 4% OTC (same effect)
 - Also as ointment, cream and gel
- Camphor, menthol, methyl salicylate (Bengay)
- Capsaicin- may deplete substance P to inhibit transmission of pain signal

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Capsaicin

- Many concentrations: (0.025% to 8%!)
 - Effective for: PHN, DPN, surgical neuropathic pain, osteoarthritis, neck pain
 - Works at the vanilloid (temperature) receptor
 - Chronic distal painful neuropathy

Simpson D, et al. Journal of Pain and Symptom Management. 2008;35

Herbal Medications for Pain

Feverfew: *Tanacetum parthenium*

- Migraine treatment and prophylaxis
- 50-100mg of dried leaves

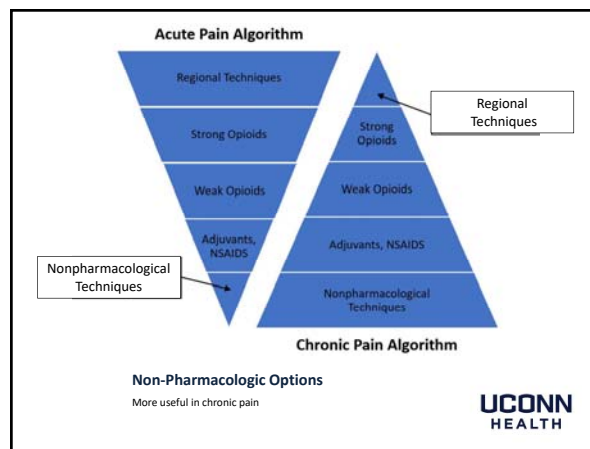
Butterbur: *Petasites hybridis*

- Migraine prophylaxis
- Root extract Petadolex™ 150mg/d

Alpha Lipoic Acid:

- Diabetic peripheral neuropathy, other neuropathy
- 300-600mg daily

Chamberlin KW, Salvo M. "Chapter 10: The Use of Dietary Supplements." In: Touhy: Ebersole & Hess' Toward Healthy Aging. 10e. In press.



Non-Pharmacologic Pain Management

- **Psychosocial Support and Counseling**
 - Cognitive-Behavioral Therapy
- **Physical Therapy**
 - Heat/Cold Therapy
 - Exercise Therapy
 - Massage
 - TENS
- **Spinal Manipulation**
- **Complementary Therapies:**
 - Acupuncture
 - Hypnosis
 - Biofeedback
 - Meditation
 - Progressive Muscle Relaxation
 - Music Therapy
 - Yoga

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Bed Rest

- Not necessary for most
- > 2 days of bed = worse outcomes

Manipulation and Mobilization

- OMT
- Massage: effleurage, petrissage, tapotement, friction
- Graston
- Myofascial release
- Exercise
- TENS
- Electrical stimulation
- Traction (not a stand-alone treatment)
- Cupping

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The Devil Is in the Details

- OMT
 - 2004 review said healthy patients derive more benefit
 - Techniques
 - Soft tissue applies pressure to the muscle area around the spine. It consists of rhythmic stretching, deep pressure, and traction.
 - Muscle energy, the patient is directed to use his or her muscles from a precise position and in a specific direction against a counterforce
 - Thrust uses high velocity forces to restore motion to a joint "cracking"
 - Counterstrain where the patient is moved away from a position where motion is restricted to one of greater comfort

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J Am Osteopath Assoc. 2004;104:193-202

Cryotherapy and Superficial Heat



- ICE = first few days
- HEAT = thereafter
- DON'T use in combo with rubs, i.e.:
 - Bengay® (trolamine salicylate)
 - Flexall 454® (menthol and methyl salicylate)
 - IcyHot® (capsaicin)


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Things You Can Do

- Corrective posture
- Sleeping position
- Weight
- Exercise
- Proper lifting with KNEES, not back
- Stress reduction


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Stretches




PELVIC TILT

-tighten ab muscles and tilt pelvis so curve of back is flat to floor



KNEE RAISE

-lie flat with knees bent up
-bring one knee to chest and hug
-repeat with other knee



PARTIAL PRESS-UP

-lie face-down on carpeted surface
-arms bent alongside, raise upper body enough to lean on elbows
-hold for 30 seconds; ▲ up to 5 min

| | | Low Back Pain | Acute | Subacute or Chronic |
|--------------------------|--|---------------|-----------|---------------------|
| | | Duration | < 4 Weeks | > 4 Weeks |
| Self-care | Advice to remain active | | • | • |
| | Books, handout | | • | • |
| | Application of superficial heat | | • | |
| | Acetaminophen | | • | • |
| | NSAIDs | | • | • |
| Pharmacologic therapy | Skeletal muscle relaxants | | • | |
| | Antidepressants (TCA) | | | • |
| | Benzodiazepines | | • | • |
| | Tramadol, opioids | | • | • |
| | Spinal manipulation | | • | • |
| Nonpharmacologic therapy | Exercise therapy | | | • |
| | Massage | | | • |
| | Acupuncture | | | • |
| | Yoga | | | • |
| | Cognitive-behavioral therapy | | | • |
| | Progressive relaxation | | | • |
| | Intensive interdisciplinary rehabilitation | | | • |

• Interventions supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens). No intervention was supported by grade A evidence (good-quality evidence of substantial benefits).

Chou R. Ann Int Med 2007;147:478.

And the elephant...

- Patients on chronic opioid therapy
- Tolerance, physical dependence
- Compared with opioid-naïve patients:
 - Severity of post-op pain is 3 times higher
 - Use 3 times more opioids post-op
 - Require epidurals for 3 extra days



Un- / Under-treated acute pain → chronic pain

Rapp SE. Pain. 1995;61:195-201.
De Leon-Casasola O. Anesth Analg. 1993;76:302-7.

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Non-Opioid Analgesic Options for Chronic Pain

Rebecca Andrews, MS, MD, FACP
reandrews@uchc.edu

Kevin Chamberlin, PharmD, FASCP
chamberlin@uchc.edu

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