Non-Opioid Pharmacology for Pain Management
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Disclosures
- Speakers Bureau: Allergan, Pernix
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed.

Objectives
- Explore clinical indications, contraindications & dosing for common non-opioid analgesics.
- Describe where analgesics act in the pain pathway.
- Examine nutrition supplements for pain.
### Pain Characteristics

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| **Acute**             | - Short duration  
                        - Recent onset  
                        - Transient  
                        - Protective  
                        - Known causality |
| **Chronic/Persistent**| - Duration >3 months  
                        - Persistent or recurrent  
                        - Outlasts protective benefit/detrimental  
                        - Unknown causality |
| **Breakthrough/flare**| - Unpredictable  
                        - Fear association  
                        - Multi-causality |

### Pain Classifications

#### Nociceptive Pain

- Normal processing of stimuli that damages normal tissues  
  - Responds to opioids

- **Somatic**  
  - Pain arises from bone, joint, muscle, skin or connective tissue  
    - Aching, throbbing  
    - Localized

- **Visceral**  
  - Organs  
  - Deep  
  - Not well localized

#### Neuropathic Pain

- Abnormal processing of sensory input by PNS or CNS  
  - Less responsive to opioids

- **Centrally generated**  
  - Deafferentation pain: injury to PNS or CNS (e.g. phantom limb)  
  - Sympathetically maintained pain: dysregulation of autonomic nervous system (e.g. CRPS)

- **Peripherally generated**  
  - Polyneuropathies (e.g. diabetic neuropathy)  
  - Mononeuropathies (e.g. nerve root compression)
The Pain Pathway

Ascending Pain Pathway
• Injury in periphery > Nociceptors
• Aδ and C fibers > dorsal horn
• Ascending spinothalamic tracts > Brain
• Insula, amygdala, prefrontal cortex, anterior cingulate cortex, supplemental motor area, hypothalamus.


The Pain Pathway

Descending Pain Pathway
• Activation of first somatosensory area > ventroposterior lateral nucleus > periaqueductal gray & raphe nucleus.
• Activation of opiate receptors @spinal cord > results in the inhibition of firing and the release of substance P, thereby blocking pain transmission.
• Neurotransmitters implicated in descending pain control – serotonin, noradrenaline, endogenous opioids, GABA.
Site(s) of action of various classes of analgesics

Locally
- NSAIDs
- Local anesthetic
- Capsaicin
- Cold/Heat

Descending Pathway
- Anti-depressants (TCA, SNRI)
- Opioids
- Muscle relaxants
- Cannabinoids

Brain (CNS)
- TCA
- SNRI
- Tramadol
- Opiates
- NSAIDs

Spinal Cord (CNS)
- Anti-convulsant
- Opioids
- α2 adrenergic agonists
- NMDA antagonists
- Nerve growth factor inhibitors
- Muscle relaxants
- Cannabinoids

Non-opioid Analgesics

- Anticonvulsants
- Antidepressants
- Muscle relaxants
- Topical analgesics/anesthetics
- Acetaminophen/NSAIDs
- Other adjuvants - sleep aids, benzodiazepines
- Cannabinoids
- Other - Opioid agonist/antagonists - Tramadol, Buprenorphine, low-dose naltrexone (LDN)
- Other – supplements/nutraceuticals

Anticonvulsants

- First-line therapy in neuropathic/central pain syndromes.
- The peripheral hyper-excitability is due to a series of molecular changes at the level of the peripheral nociceptor, in dorsal root ganglia, in the dorsal horn of the spinal cord, and in the brain.

- These changes include:
  - Abnormal expression of sodium & calcium channels
  - Increased activity at glutamate receptor sites
  - Changes in gamma-aminobutyric acid inhibition (GABA-ergic)
<table>
<thead>
<tr>
<th>GENERIC (BRAND) NAMES</th>
<th>USES IN PAIN</th>
<th>DOSING</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>gabapentin (Neurontin)</td>
<td>Diabetic peripheral neuropathy (DPN), Fibromyalgia (FM), Post-herpetic neuralgia (PHN), Neuropathies (central/peripheral), restless leg, headache</td>
<td>600-3000 mg/d, TID dosing</td>
<td>Sedation, weight gain, peripheral edema, mood instability. Smoking recreational use. Renal excreted (100% unchanged). Calcium channel modulator.</td>
</tr>
<tr>
<td>pregabalin (Lyrica)</td>
<td>Same as gabapentin (less likely in restless leg or headache)</td>
<td>150-600 mg/d, TID dosing</td>
<td>Similar to gabapentin (schedule V controlled substance, renal excreted 90% unchanged). Calcium channel modulator.</td>
</tr>
<tr>
<td>carbamazepine (Tegretol)</td>
<td>Trigeminal neuralgia</td>
<td>200-1200 mg/d, BID dosing</td>
<td>Serious dermatological reactions (Stevens-Johnson syndrome). Mood changes, aplastic anemia, thrombocytopenia, monitor BUN/Cr, CBC with LFTs. Calcium channel modulator, GABA receptor agonist, serotonin-releasing properties.</td>
</tr>
<tr>
<td>oxcarbazepine (Trileptal)</td>
<td>Neuropathies (central/peripheral), similar to carbamazepine</td>
<td>600-2400 mg/d, BID dosing</td>
<td>Serious dermatological reactions (Stevens-Johnson syndrome). Mood changes, aplastic anemia, thrombocytopenia, monitor BUN/Cr, CBC with LFTs. Sodium channel modulator.</td>
</tr>
<tr>
<td>topiramate (Topamax)</td>
<td>Migraine</td>
<td>50-200 mg/d, BID dosing</td>
<td>Weight loss, cognitive dysfunction, renal dysfunction. Sodium channel modulator, GABA agonist, glutamate receptor antagonist.</td>
</tr>
<tr>
<td>lamotrigine (Lamictal)</td>
<td>Neuropathies (central/peripheral)</td>
<td>100-400 mg/d, BID dosing</td>
<td>Serious dermatological reactions (Stevens-Johnson syndrome). Caution in liver or renal dysfunction. Sodium channel modulator, decreases presynaptic glutamate &amp; aspartate release.</td>
</tr>
</tbody>
</table>

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**Anticonvulsants**

- Studied double-blinded, placebo controlled trials.
- **Suicidality**
  - FDA analysis of data from 199 clinical trials of 11 anticonvulsants showed a risk of suicidal thoughts or behaviors.
- **Dermatologic**
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, 90% of cases occur within first 60 days, dose dependent, HLA B*1502 testing recommended (Asian ancestry).
Anticonvulsants

- Neurocognitive
  - All anticonvulsants appear to have some neurocognitive effects.
  - Psychomotor reaction time, word finding, memory.

- Bone disease
  - Increased risk of bone fracture remains unclear, r/t ↑catabolism of Vit. D & ↑PTH, intestinal Ca absorption inhibition, osteoclastic bone resorption stimulation.
  - General risk factors – Female, post-menopausal, Caucasian & Asian, old age, tobacco use, low BMI, low Ca and Vit. D intake.
  - AED related risk factors – High dose, multiple drug regimens, duration of therapy, chronic illnesses, metabolic acidosis.

- Pearls: Baseline CBC, CMP, EKG, drug specifics, start low-go slow, wean off, patient education.

Antidepressants

- Co-analgesics in neuropathic/central pain syndromes.

- The explicit way in which antidepressants are effective in pain management remains unknown, suspected to be multifactorial.

- Most popular theory is that antidepressants exert their effects on serotonin & norepinephrine, particularly along the descending spinal pain pathways.

- Antidepressants may also exert adjunctive therapeutic influences through histamine receptors as well as modulation of sodium channels.

- Modulate mood and pain perception.

### GENERIC (BRAND) NAMES

<table>
<thead>
<tr>
<th>GENERIC (BRAND) NAMES</th>
<th>CLASS</th>
<th>DOSING</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>TCA</td>
<td>25-150 mg/d</td>
<td>Uses: DPN, PHN, FM, migraine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once daily dosing</td>
<td>Anticholinergic symptoms, arrhythmias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits serotonin &amp; norepinephrine uptake equally.</td>
</tr>
<tr>
<td>nortriptyline (Pamelor)</td>
<td>TCA</td>
<td>25-150 mg/d</td>
<td>Similar to amitriptyline, less sedating.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once daily dosing</td>
<td>More potent inhibitor of norepinephrine than of serotonin uptake.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Predictable therapeutic window (60-200 ng/ml).</td>
</tr>
<tr>
<td>desipramine (Norpramin)</td>
<td>TCA</td>
<td>25-300 mg/d</td>
<td>Uses &amp; SE profile similar to above, less sedating, more activating.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once daily dosing</td>
<td>Less predictable therapeutic window (100-300 ng/ml).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits reuptake of serotonin &amp; norepinephrine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Superior efficacy than amitriptyline.</td>
</tr>
<tr>
<td>duloxetine (Cymbalta)</td>
<td>SNRIs</td>
<td>60-120 mg/d</td>
<td>Uses: FM, chronic musculoskeletal (MKS) pain.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once daily dosing</td>
<td>Renal dosing &amp; hepatic considerations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Similar in terms of efficacy, pharmacodynamics &amp; side effects profile.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits norepinephrine and serotonin reuptake in CNS.</td>
</tr>
<tr>
<td>milnacipran (Savella)</td>
<td>SNRIs</td>
<td>25-200 mg/d</td>
<td>Uses: FM.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BID dosing</td>
<td>More activating.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Similar in terms of efficacy, pharmacodynamics &amp; side effects profile.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits norepinephrine reuptake in CNS.</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>SNRIs</td>
<td>75-300 mg/d</td>
<td>Uses: generalized neuropathic pain, Migraine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BID dosing</td>
<td>Renal &amp; hepatic dosing adjustments.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May effect bleeding time.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Similar in terms of efficacy, pharmacodynamics &amp; side effects profile.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits norepinephrine, serotonin &amp; dopamine reuptake in CNS.</td>
</tr>
<tr>
<td>desvenlafaxine (Pristiq)</td>
<td>SNRIs</td>
<td>50-100 mg/d</td>
<td>Uses: generalized neuropathic pain, Migraine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once daily dosing</td>
<td>Renal &amp; hepatic dosing adjustments.</td>
</tr>
<tr>
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<td>May effect bleeding time.</td>
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<td>Inhibits norepinephrine, serotonin &amp; dopamine reuptake in CNS.</td>
</tr>
</tbody>
</table>

### Antidepressants

- **Studied double-blinded, placebo controlled trials**
  - duloxetine – Fibromyalgia (FM)/DPN/chronic MSK
  - milnacipran – FM
  - venlafaxine – Migraine
  - amitriptyline – Migraine/PHN/FM

- **Side Effects**
  - Serotonin reuptake inhibition include: nausea/insomnia/tremor/sexual dysfunction.
  - Norepinephrine reuptake inhibition include: hypertension/sweating/dry mouth/constipation.
Antidepressants

- **Cardiovascular Risk:** Greater with TCAs
  - Tachycardia
  - Orthostasis
  - QTc monitoring – EKG
  - Elderly

- **Behavioral Health Risks**
  - Abrupt discontinuation: w/d symptoms = malaise/chills/myalgia’s/mood destabilization.
  - Increased suicidality: Black boxed warnings, monitoring.

Antidepressants

- **Serotonin Syndrome:** Risk generally is low

  - Know the signs/symptoms:
    - Hunter Criteria (serotonergic agent PLUS one of the following)
      - spontaneous clonus
      - inducible clonus & agitation or diaphoresis
      - ocular clonus & agitation or diaphoresis
      - tremor & hyperreflexia
      - hypertonia
      - body temperature above 38°C (100.4°F)

  - Education to patient is IMPORTANT

Antidepressants

- **Bleeding Risk/SNRIs:** Controversial data suggests

  - de-amplification of platelet aggregation
  - minimal risk of upper GI bleed as monotherapy
  - increased risk in combination with NSAIDs
  - acid suppression therapy decreases risk

- **Pearls**

  - Baseline CBC, CMP, EKG, drug specifics, start low-go slow, wean off, patient education.

  - Complaints of parasomnias (vivid dreams, racing thoughts, etc.): r/t anticholinergic effects of antidepressants, reduced by low-dose beta blocker.
Muscle Relaxants

Active the descending inhibitory pain pathways.

- **Antispasmodics**: Used for muscular pain & spasm acting at the level of the spinal cord or supraspinal level.
  - benzodiazepines (diazepam)
  - non-benzodiazepines (cyclobenzaprine)

- **Antispasticity agents**: Used to reduce hypertonicity associated with upper motor neuron disorders (multiple sclerosis).

<table>
<thead>
<tr>
<th>GENERIC (BRAND) NAMES</th>
<th>CLASSIFICATION</th>
<th>DOSING</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclobenzaprine (Fleet)</td>
<td>Central Nervous System Depressants</td>
<td>5-10 mg TID, prn</td>
<td>- Structurally similar to a TCA. - Functions primarily at supraspinal levels, not at cord.</td>
</tr>
<tr>
<td>carisoprodol (Soma)</td>
<td></td>
<td>250-350 mg TID, prn</td>
<td>- Schedule IV - Active metabolite (meprobamate) - Wean to discontinue</td>
</tr>
<tr>
<td>diazepam (Valium)</td>
<td>Central Nervous System Depressants</td>
<td>2-5 mg TID, prn</td>
<td>- Schedule IV - Wean to discontinue</td>
</tr>
<tr>
<td>Chlorzoxazone (Parafon Forte DSC)</td>
<td></td>
<td>250-300 mg QID, prn</td>
<td></td>
</tr>
<tr>
<td>metaxalone (Skelaxin)</td>
<td></td>
<td>800 mg QID, prn</td>
<td>Less sedating</td>
</tr>
<tr>
<td>methocarbamol (Robaxin)</td>
<td></td>
<td>1000-1500 mg QID, prn</td>
<td></td>
</tr>
<tr>
<td>orphenadrine (Norflex)</td>
<td></td>
<td>100 mg BID, prn</td>
<td>- Sodium channel modulation - Higher anticholinergic side effects</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Centrally Acting Antispasticity</td>
<td>20-80 mg/d TID, prn</td>
<td>- Selective GABA-B receptor agonist. - DO NOT abruptly discontinue use.</td>
</tr>
<tr>
<td>tizanidine (Zanaflex)</td>
<td></td>
<td>2-4 mg tid, prn, Maximum 36 mg/d</td>
<td>Hypotension</td>
</tr>
<tr>
<td>dantrolene (Dantrium)</td>
<td>Peripherally Acting Antispasticity</td>
<td>25-100 mg TID-QID, Maximum 800 mg/d</td>
<td>Black box warning: Rare but serious hepatotoxicity - especially in women and patients &gt;35 years of age.</td>
</tr>
</tbody>
</table>
Muscle Relaxants

- All equally effective for short-term relief of low back pain.
- Not more effective than NSAIDs for acute low back pain.
- All recommended for 2-3 weeks at a time, attempt to avoid on-going chronic use.
- All sedating, hepatic & renal considerations, some degree of anticholinergic side effects.

Acetaminophen

- First synthesized in 1878, and introduced for medical use in 1883. Comes in many preparations both OTC (oral, rectal, topical), as well as in prescription formulations generally combined with opioids and as a branded intravenous preparation (Ofirmev®).
- Elevation of the pain threshold through central activation of descending serotonergic pathways.
- Recommended maximum daily dose is no more than 4,000 milligrams (mg) from all sources. Caution in liver disease.

Non-steroidal Anti-inflammatories (NSAIDS)

- Non-specific analgesics, but greater effectiveness likely in inflammatory pains.
- Marked individual variation in response to different drugs.
- Drug to drug variability in toxicities only partly determined by COX I/COX II selectivity.
- Significant CV history, CHF, renal insufficiency are strong relative contraindications.
- Can counter act the ASA protection in CV disease and stroke.
- Use lowest effective dose, consider PPI for gastro-protective therapy.
- Comes in OTC & RX strengths; oral, topical, rectal.
Topical analgesics/anesthetics

**Advantages**
- Controlled absorption & more uniform plasma drug concentrations.
- Bioavailability is improved by avoiding first-pass hepatic metabolism.
- Options with poor or no oral intake.
- Increased flexibility in terminating drug administration by patch removal. Patient compliance is improved as patches are simple, non-invasive, and convenient.

**Limitations**
- Local irritation or sensitization of the skin at the site of patch application.
- Possibility of unreliable absorption (too much/too little subcutaneous fat, poor peripheral blood flow, body temperature).
- Cost.

Menthol/Salicylate

**OTC (BenGay, Icy Hot, Salonpas, etc.)**

**Arthritis, low back pain, strains & sprains.**

**Menthol** – stimulates TRPM8 receptors, producing cold sensation/counter irritation.

**Salicylates** – Inhibits COX-1/COX-2, blocks prostaglandin production, inflammatory/pain pathway.

NSAIDS

**Diclofenac**
- 1.3% patch (Flector), 1 patch bid
- 1.5-2% solution/spray (Pennsaid), 2 sprays BID
- 1% gel (Voltaren Gel), 2-4 g QID/Max. 32 g/d

**Black Box Warnings:** Cardiovascular Risk & GI Risk.

**Numerous studies shown lower GI side effects & superior analgesic benefit with dose equivalent topical to oral NSAIDs.**
Capsaicin

- Available in OTC preparations (0.025-0.075% cream) & RX 8%
- Neuropathic pain, arthritis
- Initially stimulates, then desensitizes & degenerates cutaneous nociceptors.
- Down regulates Substance P.
- Avoid touching eyes, mucous membranes.
- Capsaicin 8% patch (Qutenza)
  - FDA approved PHN
  - 1-4 patches per application, no more frequently than q3mo.
  - Pre-treat with topical anesthetic.

Lidocaine

- Class 1b anti-arrhythmic, topical & local anesthetic
- Sodium Channel Modulation
- Available in OTC (0.5-4%) & RX (5%)
- Minimal detectable serum levels with prescribed use
- Lidocaine 5% patch
  - FDA approved PHN
  - No more than 3 patches concurrently
  - 12hrs on/12hrs off
- IV Lidocaine 1mg/kg/hr for acute neuropathic pain.

Cannabinoids

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:
- Treatment for chronic pain in adults (cannabis)
- Improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

There is moderate evidence that cannabis or cannabinoids are effective:
- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols)

Canadian Pain Society:
Cannabinoids/Forms & Preparations

Herb 3-22% THC
Hashish/Hash Oil 40-90% THC
nabiximols (Sativex/Epidiolex)

Synthetic:
dronabinol (Marinol) CIII	nabidol: 1 mg

- Nausea/vomiting, chemo-related
- 1-2 mg oral BID

Synthetic:
dronabinol (Marinol) CIII	nabidol: 1 mg

- Nausea/vomiting, chemo-related
- 5 mg oral q2-4hr x4-6 doses/day
- Anorexia, AIDS-associated
- 2.5-10 mg oral BID

Other drugs for Neuropathic & Nociceptive pain

<table>
<thead>
<tr>
<th>DRUG/CLASSES</th>
<th>USE IN PAIN</th>
<th>DOSING</th>
<th>CONSIDERATIONS/ COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin - salmon nasal spray</td>
<td>Bone pain, phantom limb, complex regional pain syndrome (CRPS)</td>
<td>100-2000U/d</td>
<td>Inhibits osteoclasts, helps regulate calcium via bone, use with calcium/vit D (Lyritis, 2002)</td>
</tr>
</tbody>
</table>

Bisphosphonates:
1. clodronate
2. alendronate

- Bone pain, phantom limb, CRPS
- 1. 300 mg intravenously daily for 10 days.
- 2. 7.5 mg intravenously daily for 3 days.
  - 40 mg orally daily for 8 weeks.
- Efficacy better with intravenous (IV) delivery, esophageal issues, osteonecrosis jaw. (Mackey, 2007)

Other drugs for Neuropathic & Nociceptive pain

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</tr>
</thead>
<tbody>
<tr>
<td>clonidine</td>
<td>Sympathetically maintained pain, Mild anxiety</td>
<td>TID patch 0.1-0.3mg/d</td>
<td>Alpha2 agonist, efficacy better with epidural/intrathecal/IV delivery. (Kumar, 2014)</td>
</tr>
</tbody>
</table>

NMDA antagonists:
1. memantine (Namenda)
2. dextromethorphan
3. ketamine
4. amantadine

- Neuropathic pain
- Face pain/headache
- CRPS
- 1. 10-50 mg/d
- 2. 45-480mg/d
- 3. 20-30mg/2hr
- 4. 100-200mg/d.

- NMDA plays a role in pain amplification.
- CNS side effects including hallucinations, serotonin syndrome.
- Best efficacy for ketamine infusion.
### Sleep aids (non-benzodiazepines)

<table>
<thead>
<tr>
<th>GENERIC [BRAND]</th>
<th>USES IN PAIN</th>
<th>DOSING</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zolpidem tartrate (Ambien)</strong></td>
<td>Sleep aid</td>
<td>5-10 mg, 6.25-12 mg CR</td>
<td>Sleep walking, memory loss, tolerance/dependence. Schedule IV</td>
</tr>
<tr>
<td><strong>Eszopiclone (Lunesta)</strong></td>
<td>Sleep aid</td>
<td>1-3 mg</td>
<td>Dizziness and loss of coordination, dependence. Schedule IV</td>
</tr>
<tr>
<td><strong>Zaleplon (Sonata)</strong></td>
<td>Sleep aid</td>
<td>5-20 mg</td>
<td>Schedule IV</td>
</tr>
</tbody>
</table>

### Sleep aids (non-benzodiazepines)

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</tr>
</thead>
<tbody>
<tr>
<td><strong>Trazodone</strong></td>
<td>Sleep aid</td>
<td>50-200 mg</td>
<td>Inhibits serotonin reuptake, alpha-1 adrenergic receptor antagonist</td>
</tr>
<tr>
<td><strong>Doxepin</strong></td>
<td>Sleep aid</td>
<td>10-50 mg</td>
<td>TCA, inhibits serotonin &amp; norepinephrine reuptake</td>
</tr>
<tr>
<td><strong>Ramelteon (Rozerem)</strong></td>
<td>Sleep aid</td>
<td>8 mg</td>
<td>melatonin receptor agonist with high affinity for MT-1 and MT-2 receptors, sleep aid</td>
</tr>
</tbody>
</table>

### Tramadol/Tapentadol

Synthetic opioid pain medications used to treat moderate to severe pain, in adults.

- **Tramadol C-IV & Tapentadol C-II**
- **Bind to the μ-opioid receptor**
- **Tramadol - Inhibits the reuptake of serotonin and norepinephrine**
- **Tapentadol – Inhibits the reuptake of norepinephrine**
**Buprenorphine**

- Non-selective, mixed agonist-antagonist opioid receptor modulator, acting as a weak partial agonist of the mu opioid receptor with strong binding affinity.
- Behaves differently than other opioids in this respect, as it shows a ceiling effect for respiratory depression.
- Blocks voltage-gated sodium channels via the local anesthetic binding site.
- Slow onset, mild effect, and is very long acting with a half-life of 24-60 hours.

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**Low-dose naltrexone (LDN)**

Opioid antagonist and has been shown effective for treating some central pain states (multiple sclerosis, fibromyalgia, CRPS, migraine, etc.)

- The best evidence for pain treatment shows that at low doses (4.5mg) naltrexone effectively reduces pain. [LDN is used off-label in the treatment of pain, requires compounding.]
- Immune modulation at the microglia cells within the central nervous system (brief blockade of opioid receptors).
- Reduction of pro-inflammatory cytokines as well as neurotoxic super-oxides.

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**Supplements/Nutraceuticals/Nutrition**

**General Rules of Nutrition**

- Nutrition underlies illness & underlie healing, supports wellness
- Correction of deficiencies
- Supporting to skeleton & soft issues (skin, cartilage, bone)
- Low-allergenic
- Low-inflammatory
- Certification symbols, such as a United States Pharmacopeia (USP) symbol, verifies that the product contains the ingredients in stated amounts and strength, is pure, meets limits for contaminants, and disintegrates quickly.

http://www.consumerlab.com/
**Supplements/Nutraceuticals/Nutrition**

**Inflammation & Pain**
- Saturated fatty acids activate skeletal muscle cells to release inflammatory mediators that trigger macrophages.
- Pro-inflammatory cytokines induce genes in dorsal root ganglion neurons and increase pain.
- Ingestion of dietary supplements of n-3 fatty acids has been consistently shown to reduce both the number of tender joints on physical examination and the amount of morning stiffness in patients with rheumatoid arthritis.

Disclaimer: Suggestions from existing research, any prescribing should be done understanding the unique patient medical history/intolerances/medications/allergies.

**Musculoskeletal Pain**

**Knee osteoarthritis:**
- 300-500mg glucosamine sulfate
- 480mg glucosamine hydrochloride three times daily +/ chondroitin 40 mg TID

**Low back pain:**
- 1500mg/d glucosamine

Glucosamine is likely safe when taken by mouth in studied doses, for a short time by healthy adults.
- 500 milligrams three times daily up to 90 days.
- 1,500 milligrams once daily up to six month.

Glucosamine may also cause insomnia, drowsiness, dry mouth, constipation, liver and kidney studies.

Glucosamine & Chondroitin may increase the risk of bleeding.

Glucosamine may ↑ blood pressure & blood glucose (affecting insulin resistance).

**Osteoarthritis (general):**
- 1000-2000mg/d.

**Migraine**

**Riboflavin:** 400 mg qd-TID

**CoQ10:** 100 mg TID

**Magnesium:** 400-600 mg daily

**Feverfew (MIG-99):** 100-300mg qd-QID (0.2%-0.4% parthenolide)

Riboflavin/CoQ10 = Regulate mitochondrial dysfunction.

Mg = Normalize brain neuronal hyperexcitability.

Riboflavin/CoQ10/Fe = Anti-inflammatory properties.
### Neuropathic Pain

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Dosage</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benfotiamine (B1 derivative)</td>
<td>300-600mg/day</td>
<td>Taken at the oral dose of 300-600mg over the course of the day, usually in two divided doses with meals (150mg or 300mg twice daily). Side Effects = mild GI complaints, “skin allergic reactions.”</td>
</tr>
</tbody>
</table>

### Central Pain (FM, stroke, CRPS)

<table>
<thead>
<tr>
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<th>CONSIDERATIONS</th>
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<tr>
<td>Coenzyme Q10 100mg TID</td>
<td></td>
<td>(see supplements for migraine)</td>
</tr>
<tr>
<td>Acetyl-L-carnitine 500mg/qd-BID</td>
<td></td>
<td>Impacts mitochondrial function, thought to play a significant role in peripheral nerve injury. Free radical scavenger &amp; T-type calcium channel blocker.</td>
</tr>
<tr>
<td>5-HTP 100mg TID</td>
<td></td>
<td>Works in the brain &amp; central nervous system by increasing the production of the chemical serotonin. Serotonin can affect sleep, appetite, temperature, sexual behavior, and pain sensation.</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td></td>
<td>Antioxidant, anti-inflammatory properties.</td>
</tr>
<tr>
<td>Vitamin C 500mg TID</td>
<td></td>
<td>Antioxidant, anti-inflammatory properties.</td>
</tr>
</tbody>
</table>

### Turmeric/Curcumin

Turmeric is a key chemical in turmeric. Claims: Reduces pain, inflammation and stiffness related to rheumatoid arthritis (RA) and osteoarthritis (OA); treats bursitis.

**Dosing:** For osteoarthritis: 500 mg of a non-commercial turmeric product four times daily for 4-6 weeks has been used. 500 mg of a specific turmeric extract (Turmacin, Natural Remedies Pvt. Ltd.) has been used twice daily for 6 weeks. 500 mg of a specific turmeric extract (Meriva, Indena) containing turmeric and phosphatidylcholine has been used twice daily for 2-3 months.

**Safety:** Anticoagulation, iron absorption, effect testosterone and estrogen levels, Gastrointestinal effects, not advised during pregnancy.
Curcumin Resource Database (CRDB) that seeks to support the preclinical development of curcuminoids by putting over 1000 analogues and their alleged molecular target(24) at the fingertips of researchers via a Web interface. The CRDB coverage of over 9000 publications and 500 patents demonstrates the magnitude of both the scientific interest and vast amount of dormant information that is awaiting a more global, medicinal chemistry interpretation.

No double-blinded, placebo controlled clinical trial of curcumin has met statistical end points.

Poor pharmacokinetic properties, unstable, reactive, nonbioavailable compound and, therefore, a highly improbable lead.
<table>
<thead>
<tr>
<th>Drug Action</th>
<th>Originator company</th>
<th>Action</th>
<th>Indication</th>
<th>Clinical trial phase</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGN-199981</td>
<td>Allergan</td>
<td>α2-Adrenergic agonist</td>
<td>Neuropathic pain</td>
<td>Phase II</td>
<td>Catecholamine modulations</td>
</tr>
<tr>
<td>Desvenlafaxine SR</td>
<td>Wyeth</td>
<td>Serotonin–norepinephrine re-uptake inhibitor</td>
<td>Painful diabetic neuropathy</td>
<td>Phase III</td>
<td>Catecholamine modulations</td>
</tr>
<tr>
<td>KDS-2000</td>
<td>Kadmus Pharmaceuticals</td>
<td>Topical cannabinoid agonist</td>
<td>Postherpetic neuralgia</td>
<td>Phase II</td>
<td>Cannabinoid agonists</td>
</tr>
<tr>
<td>L-751</td>
<td>Manhattan Pharmaceuticals</td>
<td>Cannabinoid derivative TNF antagonist, lipase inhibitor, interleukin antagonist</td>
<td>Neuropathic pain</td>
<td>Phase II</td>
<td>Cannabinoid agonists</td>
</tr>
<tr>
<td>GSK-644784</td>
<td>GlaxoSmithKline</td>
<td>COX-2 inhibitor</td>
<td>Neuropathic pain</td>
<td>Phase II</td>
<td>COX inhibitors</td>
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<td>Phase III</td>
<td>COX inhibitors</td>
</tr>
<tr>
<td>LY2951742</td>
<td>Lilly, Amgen, Allergan, Teva, Alder</td>
<td>CGRP antagonists</td>
<td>Migraine</td>
<td>Phase II/III</td>
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Thank You
Resources

• http://www.rxlist.com/script/main/hp.asp
• http://www.theacpa.org/Consumer-Guide

WebMD has a Vitamins and Supplements Lifestyle Guide which can be found at http://www.webmd.com/vitamins-and-supplements/lifestyle-guide-11/chronic-pain-relief?page=1

Selected References


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