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

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

Pain Classifications

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
- A δ and C fibers > dorsal horn
- Ascending spinothalamic tracts > Brain
- Insula, amygdala, prefrontal cortex, anterior cingulate cortex, supplemental motor area, hypothalamus.

http://www.changepain-emodules.com/index.php?modulesId=2&languagesId=16

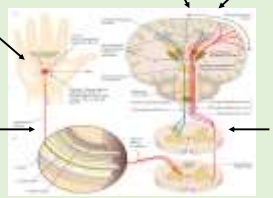
The Pain Pathway

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.

Central Nervous System Mechanisms of Pain Modulation

Site(s) of action of various classes of analgesics



Locally
NSAIDs
Local anesthetic
Capsaicin
Cold/Heat

Peripheral Nervous System/Ascending Pathway
Topical agents
Local anesthetics
Anti-consultants
Anti-depressants
Anti-inflammatories
Cytokine inhibitors
Cannabinoids

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

Brain (CNS)
TCA
SSRI, SNRI
Tramadol
Opiates
NSAIDs

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

GENERIC (BRAND) NAMES	USES IN PAIN	DOSING	CONSIDERATIONS
gabapentin (Neurontin)	Diabetic peripheral neuropathy (DPN), Fibromyalgia (FM), Post-herpetic neuralgia (PHN), neuropathies (central/peripheral), restless leg, headache	600-3600 mg/d, TID dosing	- Sedating, weight gain, peripheral edema, mood instability. - Growing recreational use. - Renal excreted (100% unchanged). - Calcium channel modulator
pregabalin (Lyrica)	Same as gabapentin (less likely in restless leg or headache)	150-600 mg/d, TID dosing	- Similar to gabapentin (schedule V controlled substance, renal excreted 90% unchanged). - Calcium channel modulator
carbamazepine (Tegretol)	Trigeminal neuralgia	200-1200 mg/d, BID dosing	- Serious dermatological reactions (Stevens-Johnson syndrome). - Mood changes, aplastic anemia, thrombocytopenia, monitor -BUN/Cr, CBC w/diff, LFTs. - Sodium channel modulator, GABA receptor agonist, serotonin releasing properties

GENERIC (BRAND) NAMES	USES IN PAIN	DOSING	CONSIDERATIONS
oxcarbazepine (Trileptal)	Neuropathies (central/peripheral), similar to carbamazepine	600-2400 mg/d, BID dosing	- Serious dermatological reactions (Stevens-Johnson syndrome). - Mood changes, aplastic anemia, thrombocytopenia, hypernatremia, monitor -BUN/Cr, CBC w/diff, LFTs. - Sodium channel modulator
topiramate (Topamax)	Migraine	50-200 mg/d, BID dosing	- Weight loss, cognitive dysfunction, renal dosing. - Sodium channel modulator, GABA agonist, glutamate receptor antagonist
lamotrigine (Lamictal)	Neuropathies (central/peripheral)	100-400 mg/d, BID dosing	- Serious dermatological reactions (Stevens-Johnson syndrome), - Caution in liver or renal dysfunction. - Sodium channel modulator, decreases presynaptic glutamate & aspartate release

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

- 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	CLASS	DOSING	CONSIDERATIONS
amitriptyline	Tricyclic antidepressant (TCA) (tertiary amine)	25-150 mg/d Once daily dosing	- Uses: DPN, PHN, FM, migraine. - Anticholinergic symptoms, arrhythmias. - Inhibits serotonin & norepinephrine uptake equally.
nortriptyline (Pamelor)	TCA (secondary amine)	25-150 mg/d Once daily dosing	- Similar to amitriptyline, less sedating. - More potent inhibitor of noradrenaline than of serotonin uptake. - Predictable therapeutic window (60-200 ng/ml).
desipramine (Norpramin)	TCA (secondary amine)	25-300 mg/d Once daily dosing	- Uses & SE profile similar to above, less sedating, more activating. - Less predictable therapeutic window (100-300 ng/ml). - Inhibits reuptake of serotonin & norepinephrine. - Superior efficacy than amitriptyline.

GENERIC (BRAND) NAMES	CLASS	DOSING	CONSIDERATIONS
duloxetine (Cymbalta)	Serotonin norepinephrine reuptake inhibitors (SNRI)	60-120 mg/d Once daily dosing	- Uses: FM, chronic musculoskeletal (MSK) pain. - Renal dosing & hepatic considerations.
milnacipran (Savella)		25-200 mg/d BID dosing	- Similar in terms of efficacy, pharmacodynamics & side effects profile. - Inhibits norepinephrine and serotonin reuptake in CNS.
venlafaxine	SNRIs	75-300 mg/d BID dosing	- Uses: generalized neuropathic pain, Migraine. - Renal & hepatic dosing adjustments.
desvenlafaxine (Pristiq)	venlafaxine is metabolized to desvenlafaxine	50-100 mg/d Once daily dosing	- May effect bleeding time. - Similar in terms of efficacy, pharmacodynamics & side effects profile. - Inhibits norepinephrine, serotonin & dopamine reuptake in CNS.

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).

GENERIC (BRAND) NAMES	CLASSIFICATION	DOSING	CONSIDERATIONS
cyclobenzaprine (Flexeril)	Central Nervous System Depressants	5-10 mg TID, prn	- Structurally similar to a TCA. - Functions primarily at supraspinal levels, not at cord.
carisoprodol (Soma)		250-350 mg TID, prn	- Schedule IV - Active metabolite (meprobamate) – wean to discontinue.
diazepam (Valium)		2-10 mg TID, prn	- Schedule IV - Wean to discontinue
Chlorzoxazone (Parafon Forte DSC)		250-500 mg QID, prn	
metaxalone (Skelaxin)		800 mg QID, prn	Less sedating
methocarbamol (Robaxin)		1000-1500 mg QID, prn	
orphenadrine (Norflex)		100 mg BID, prn	- Sodium channel modulation - Higher anticholinergic side effects.

GENERIC (BRAND) NAMES	CLASSIFICATION	DOSING	CONSIDERATIONS
baclofen	Centrally Acting Antispacisity	20-80 mg/d TID, prn	- Selective GABA-B receptor agonist. - DO NOT abruptly d/c intra-thecal use.
tizanidine (Zanaflex)		2-4 mg tid, prn, Maximum 36 mg/d	Hypotension
dantrolene (Dantrium)	Peripherally Acting Antispacisity	25-100 mg TID-QID, Maximum 400 mg/d	Black Box warning: Rare but serious hepatotoxicity - especially in women and patients >35 years of age.

Muscle Relaxants

- All equally effective for short-term relief of low back pain.
- Not more effective that 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:

- First-line treatments = gabapentinoids TCA & SNRI. Second-line = Tramadol & controlled-release opioid analgesics. Third-line = Cannabinoids.

Cannabinoids/Forms & Preparations

Herb 3-22% THC

Hashish/Hash Oil
40-90% THC

nabiximols (Sativex/Epidiolex)

Synthetic:
dronabinol (Marinol) CIII
nabilone (Cesamet) CII

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

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

Other drugs for Neuropathic & Nociceptive pain

DRUGS/CLASSES	USE IN PAIN	DOSING	CONSIDERATIONS/ COMMENTS
Calcitonin-salmon nasal spray	Bone pain, phantom limb, complex regional pain syndrome (CRPS)	100-200U/d	Inhibits osteoclasts, helps regulate calcium via bone, use with calcium/vit. D. (Lyritis, 2002)
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

DRUGS/CLASSES	USE IN PAIN	DOSING	CONSIDERATIONS/ COMMENTS
clonidine	Sympathetically maintained pain Mild anxiety	TD patch 0.1-0.3mg/d.	Alpha2agonist, efficacy better with epidural/intrathecal/IV delivery. (Kumar, 2014)
NMDA antagonists: 1. memantine (Namenda) 2. dextromethorphan 3. ketamine 4. amantadine	Neuropathic pain Face pain/headache CRPS	 1. 10–30 mg/d. 2. 45–400mg/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)

GENERIC (BRAND) NAMES	USES IN PAIN	DOSING	CONSIDERATIONS
zolpidem tartrate (Ambien)	sleep aid	5-10 mg, 6.25-12 mg CR	Sleep walking, memory loss, tolerance/dependence. Schedule IV
eszopiclone (Lunesta)	sleep aid	1-3 mg	Dizziness and loss of coordination, dependence. Schedule IV
Zaleplon (Sonata)	sleep aid	5-20 mg	Schedule IV

Sleep aids (non-benzodiazepines)

GENERIC (BRAND) NAMES	USES IN PAIN	DOSING	CONSIDERATIONS
Trazodone	Sleep aid	50-200 mg	Inhibits serotonin reuptake, alpha-1 adrenergic receptor antagonist
Doxepin	Sleep aid	10-50 mg	TCA, inhibits serotonin & norepinephrine reuptake
ramelteon (Rozerem)	sleep aid	8 mg	melatonin receptor agonist with high affinity for MT-1 and MT-2 receptors, sleep aid

Tramadol/Tapentadol

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

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

Buprenorphine

- Non-selective, mixed agonist–antagonist opioid receptor modulator, acting as a weak partial agonist of the mu opioid receptor w/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.

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.

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

	CONSIDERATIONS
Knee osteoarthritis: ▪ 300-500mg glucosamine sulfate ▪ 480mg glucosamine hydrochloride three times daily +/- chondroitin 40 mg TID	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.
Low back pain: ▪ 1500mg/d. glucosamine	Glucosamine may also cause insomnia, drowsiness, dry mouth, constipation, Δ liver and kidney studies.
Osteoarthritis (general): ▪ 1000-2000mg/d.	Glucosamine & Chondroitin may increase the risk of bleeding. Glucosamine may ↑ blood pressure & blood glucose (affecting insulin resistance).

Migraine

	CONSIDERATIONS
Riboflavin: 400 mg qd-TID CoQ10: 100 mg TID	Riboflavin/CoQ10 = Regulate mitochondrial dysfunction.
Magnesium: 400-600 mg daily	Mg = Normalize brain neuronal hyperexcitability.
Feverfew (MIG-99): 100-300mg qd-QID [0.2%-0.4% parthenolide]	Anti-inflammatory properties.

Neuropathic Pain		CONSIDERATIONS
Benfotiamine (B1 derivative) 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).		DPN: Balakumar P, et al. Pharmacol Res. 2010 Jun;61(6):482-8. Side Effects = mild GI complaints, "skin allergic reactions"
Alpha Lipoic Acid	600mg/daily	DPN: Mijnhout GS, et al. Neth J Med. 2010 Apr;68(4):158-62. Side Effects = headache, nausea, skin rash.
Gamma-Linolenic Acid	480mg/daily	DPN: Keen H, et al. Diabetes Care. 1993 Jan;16(1):8-15. SE = nausea.
Vitamin C	500mg TID	PHN: Kapoor, S. Korean J Pain. 2012 Jul; 25(3): 200–201.
Vitamin E 400mg & Eve Primrose 500-1000 mg/day.		DPN: Ogbera, AO, et al. Indian J Endocrinol Metab. 2014 Nov-Dec; 18(6): 846–849.

Central Pain (FM, stroke, CRPS)	CONSIDERATIONS
Coenzyme Q10 100mg TID	(see supplements for migraine)
Acetyl L-carnitine 500mg/qd-BID	Impacts mitochondrial function, thought to play a significant role in peripheral nerve injury. Free radical scavenger & T-type calcium channel blocker.
5-HTP 100mg TID	Works in the brain & central nervous system by increasing the production of the chemical serotonin. Serotonin can affect sleep, appetite, temperature, sexual behavior, and pain sensation.
Omega 3 fatty acids	Antioxidant, anti-inflammatory properties.
Vitamin C 500mg TID	Antioxidant, anti-inflammatory properties.
Creatine http://www.mayoclinic.org/drugs-supplements/creatine/dosing/hrb-20059125	Reduces muscle damage by decreasing the inflammatory response and oxidative stress, regulating calcium homeostasis, and activating satellite cells.

Turmeric/Curcumin

Curcumin 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

Turmeric/Curcumin

Studies: J. Med. Chem., 2017, 60 (5), pp 1620–1637

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.

Drug	Originator company	Action	Indication	Clinical trial phase	Comments
AZD-9272	AstraZeneca	Metabotropic glutamate, receptor-1 modulator	Neuropathic pain	Phase I	Glutamate antagonists
EAA-090	Wyeth	NMDA antagonist	Painful diabetic neuropathy	Phase II	Glutamate antagonists
AV-411 (ibudilast)	Avigen	Cytokine inhibitor, glial attenuator, IL-1β and IL-6 inhibitor	Diabetic neuropathy	Phase II	Cytokine inhibitors
Thalidomide	Celgene	TNF antagonist	Complex regional pain syndrome, arachnoiditis	Phase II	Cytokine inhibitors

Drug Action	Originator company	Action	Indication	Clinical trial phase	Comments
AGN-199981	Allergan	α2b-Adrenergic agonist	Neuropathic pain	Phase II	Catecholamine modulators
Desvenlafaxine SR	Wyeth	Serotonin–noradrenaline re-uptake inhibitor	Painful diabetic neuropathy	Phase III	Catecholamine modulators
KDS-2000	Kadmus Pharmaceuticals	Topical cannabinoid agonist	Postherpetic neuralgia	Phase II	Cannabinoid agonists
IP-751	Manhattan Pharmaceuticals	Cannabinoid derivative TNF antagonist, lipoxygenase inhibitor, interleukin antagonist	Neuropathic pain	Phase II	Cannabinoid agonists

Drug Action	Originator company	Action	Indication	Clinical trial phase	Comments
GSK-644784	GlaxoSmithKline	COX-2 inhibitor	Neuropathic pain	Phase II	COX inhibitors
GW-406381	GlaxoSmithKline	COX-2 inhibitor	Neuropathic pain	Phase III	COX inhibitors
LY2951742 Erenumab MK-1602 & MK-8031 TEV-48125 Eptinezumab	Lilly Amgen Allergan Teva Alder	CGRP antagonists	Migraine	Phase II/III	Acute and chronic migraine

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
- Vitamins & Supplements Search http://www.webmd.com/vitamins-supplements/condition-1452-Pain.aspx?query
- An article entitled Herbal Remedies: Adverse Effects and Drug Interactions at http://www.aafp.org/afp/990301ap/1239.html and a patient handout (Herbal Health Products--What You Should Know at http://www.aafp.org/afp/990301ap/990301e.html) on the American Academy of Family Physicians web site.

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