PAINWEEK®

A Garden of Earthly Delights: Evaluating OTC Options for Pain Management

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Disclosures

- Stephanie Abel
  - Nothing to disclose
- Annabelle Hood
  - Nothing to disclose
- Tanya Uritsky
  - Consulting Fee (e.g., Advisory Board): AcelRx

Learning Objectives

- Describe the literature surrounding the use of over the counter (OTC) and nutraceuticals in the treatment of osteoarthritis
- Discuss OTC and herbal analgesics commonly used for osteoarthritis
- Select a safe and effective OTC/herbal regimen for a patient presenting with osteoarthritis

Meet Agent Jerry

- Jerry is a 53 year old male that comes to your pharmacy seeking help for pain in his knees. He tells you that he has been diagnosed with osteoarthritis in both knees. He mentions that he would like “to avoid narcotics” because of concerns with his job as a federal agent.
- His current medications include:
  - Albuterol sulfate inhalation aerosol 90 mcg per actuation, sig. 2 inhalations every 4 to 6 hours as needed for shortness of breath
  - Pravastatin 20 mg tablet, sig. 1 tablet daily for hyperlipidemia

What Are the Available Options?

- Over the counter (OTC) medications
  - Systemic Analgesics
  - Topical Agents
- Herbals
- Prescription medications
- Interventional procedures
- Physical approaches
- Psychosocial approaches
- Mind-body approaches

The OTC Aisle…

PaiNweek.

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Acetaminophen

- Mechanism is unknown
  - Inhibits prostaglandin synthesis through cyclooxygenase (COX) pathway in CNS
  - Stimulates serotonergic pathways in CNS
  - Endocannabinoid system activation
- Has analgesic and antipyretic properties, but lacks anti -inflammatory properties
- 325 to 650 mg every 4 to 6 hours as needed or 1 gram every 6 hours as needed
  - Maximum daily dosage varies, however 3 grams/day generally recommended
- OTC formulations disintegrating tablets, chewable tablets, capsules, tablets, liquid, powder packet, suppositories

Acetaminophen Considerations

Contraindications	Severe hepatic impairment
Adverse Effects	Gastrointestinal (GI) upset, hepatotoxicity
Drug Interactions	Alcohol Fosphenytoin/Phenytoin Isoniazid Vitamin K Antagonists (Ex. warfarin)

Zhang Q, et al. European Journal of Clinical Pharmacology. 2011;67(3):309-14.v

Nonsteroidal Anti -Inflammatory Drugs (NSAIDs)

- Mechanism of action
  - Inhibits COX-1 and COX-2 enzymes, which results in decreased prostaglandin synthesis
- Has antipyretic, analgesic, and anti-inflammatory properties
- Onset of action within a few hours
- Inter-patient variability in the response
- Degree of selectivity for COX-1 versus COX-2 affects activity and toxicity
- Adverse effects: GI upset, GI ulcer, bleeding, renal impairment, cardiovascular (CV) events

NSAIDs Cyclooxygenase Enzyme Selectivity

>5-Fold COX-2 Selective	5-50-Fold COX-2 Selective	>50-Fold COX-2 Selective
Aspirin Ibuprofen Fenoprofen Indomethacin Ketorolac Ketoprofen Naproxen Piroxicam	Celecoxib Diclofenac Etodolac Meloxicam Sulindac	Etoricoxib Lumiracoxib

Timpe Behnen EM. Practical Pain Management. 2014;13(7).

Over-the-Counter NSAIDs for Osteoarthritis

Ibuprofen

- "Non-selective"
- Propionic acid
- Dosing:
  - 400 to 800 mg three times daily (max 3,200 mg/day)
- Available as tablet, capsule, chewable tablet, and suspension
- May diminish cardioprotective effect of aspirin
  - Ibuprofen should be administered at least 8 hours before or 2-4 hours after aspirin

Naproxen

- "Non-selective"
- Propionic acid
- Dosing:
  - IR: 250 to 500 mg every 8 to 12 hours
  - XR: 750 mg to 1 gram once daily
  - Max 1,500 mg/day
- Available as tablet, capsule, suspension
- Questionable inhibition of aspirin efficacy

NSAIDs Adverse Effects: GI Complications

- Associated with GI upset, dyspepsia, abdominal pain, GI bleeding and GI ulcers
  - Combine with a proton pump inhibitor (PPI)
  - Avoid NSAIDs in patients with history of NSAID associated upper GI tract bleeding
- Risk factors of GI bleeding
  - Older age (>60 years of age)
  - History of dyspepsia or peptic ulcer bleeding
  - High-dose NSAID therapy
  - Medications:
    - Corticosteroids
    - Antiplatelets/Anticoagulants (Ex. warfarin)
    - Serotonergic drugs (Ex. SSRI, SNRI)

Gwee KA., et al. Journal of Pain Research;2018;11:361–374.
Freedberg DE., et al. Gastroenterology. 2017;152(4):706-715.

NSAIDs Adverse Effects: GI Complications Cont…

NSAID	Rate Ratio (95% CI)	P-value
Coxibs	1.81 (1.17-2.81)	0.0070
Diclofenac	1.89 (1.16-3.09)	0.0106
Ibuprofen	3.97 (2.22-7.10)	<0.0001
Naproxen	4.22 (2.71-6.56)	<0.0001

Coxib and traditional NSAID Trialists' (CNT) Collaboration., et al. Lancet 2013;382:769–79.

NSAIDs Adverse Effects: Cardiovascular (CV) Effects

- Associated with increased risk of CV events in patient with and without CV disease
  - Myocardial infarction (MI)
  - Stroke
  - CV death
  - Worsening hypertension
  - New or worsening heart failure
- To minimize risk for adverse CV events, NSAIDs should be recommended at the lowest effective dose for the shortest duration possible
- NSAIDS should be used cautiously in patients with unstable CV disease

Nissen SE., et al. New England Journal of Medicine. 2016; 375(26):2519.
Trelle S., et al. BMJ. 2011;342:c7086
Coxib and traditional NSAID Trialists' (CNT) Collaboration., et al. Lancet. 2013; 382: 769–79.

Topical NSAID: Diclofenac 1% gel

- Indicated for osteoarthritis of lower extremity (Ex. knee) and upper extremity (Ex. hand)
  - Questionable efficacy in hip osteoarthritis
- OTC Dosing:
  - Lower extremity: 4 grams to each area up to 4 times daily (max dose per joint: 16 grams/day)
  - Upper extremity: 2 grams to each area up to 4 times daily (max dose per joint: 8 grams/day)
  - Maximum total body dose (all combined joints): 32 grams/day
- Requires proper application using dosing card to avoid systemic toxicity

Kolasinski S., et al. 2019 American College of Rheumatology 2020. 72(2): 220-233.
Voltaren® gel (diclofenac sodium topical gel), 1%.. Package insert. Novartis Consumer Health 2014.

Comparison of Voltaren® 1% Gel to Oral Diclofenac Sodium Tablets

Treatment	C_{max} (ng/mL) % of Oral (CI)
Voltaren® gel 4 x 4 g per day (=160 mg diclofenac sodium per day)	15 +/- 7.3 0.6% (0.5-0.7)
Voltaren® gel 4 x 12 g per day (=480 mg diclofenac sodium per day)	53.8 +/- 32 2.2% (1.9-2.6)
Diclofenac sodium tablets, orally 3 x 50 mg per day (=150 mg diclofenac sodium per day)	2270 +/- 778 100%

Voltaren® gel (diclofenac sodium topical gel), 1%.. Package insert. Novartis Consumer Health 2014.

Back to Agent Jerry

Which of the following over-the-counter medication(s) could help manage Jerry's osteoarthritis pain?

a. Ibuprofen
b. Diclofenac Gel
c. Celecoxib
d. Answers A & B

Back to the OTC Aisle…

Capsaicin

- Derived from the chili pepper, depletes substance P
- Meta-analysis of 3 double-blind, placebo-controlled RCTs
  - –Capsaicin >placebo (OR 4.36 (95% CI = 2.77, 6.88; RD = 0.29 (95% CI = 0.2, 0.37)
- Double-blind RCT (Altman, et al)- 0.25% cream 4x/day x12 weeks
  - –Significant decrease in pain severity, improved tenderness on passive range of motion/palpation vs placebo
  - –No difference on morning stiffness or modified health assessment
- Cost – $4.50-$12/oz
- Adverse Effects (A/E)– mild/mod burning/stinging (44%)

L. Long et al. Rheumatology 2001;40:779-793.

Glucosamine

- Endogenous amino sugar required for synthesis of glycoproteins and glycosaminoglycans - found in synovial fluid, ligaments, joint structures
- Has anti-inflammatory effects, thought to stimulate metabolism of chondrocytes
- Dose: Up to 1500 mg daily , once daily or in divided doses
- Rare adverse effects
- Cost - $9-35/month

Gregory PJ, et al. Am Fam Physician. 2008;77(2):177-184

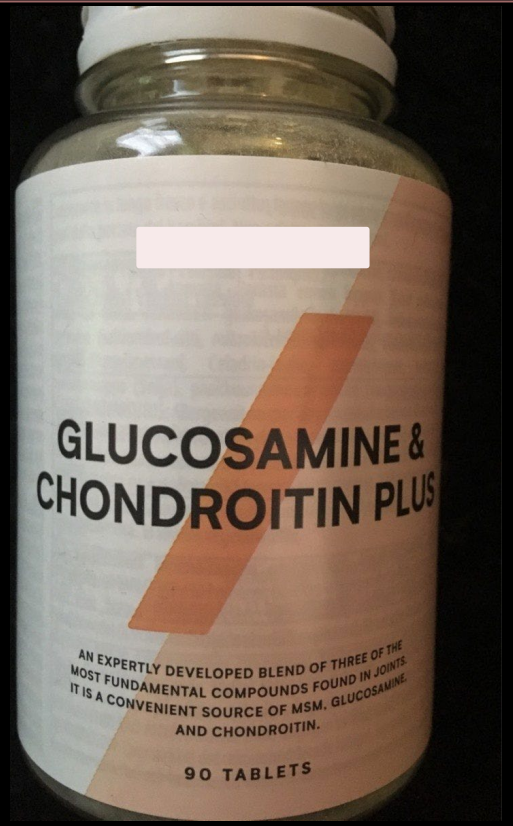
Glucosamine

- > 20 RCTs of >2500 patients looking at OA patients, mostly hip/knee
- May reduce symptoms, possibly slow progression in knee OA
  - –Consistently associated with a reduction in pain
  - –Improvement with specific glucosamine sulfate (*Dona)*
  - –Glucosamine chloride only associated with efficacy when combined with chondroitin for severe symptoms
    - Significant placebo response (20%)
- Compared with acetaminophen, ibuprofen, piroxicam – glucosamine effective for decreasing pain and improving function
- Significantly reduces knee-joint-space narrowing over 3 years

Gregory PJ, et al. Am Fam Physician. 2008;77(2):177-184

Chondroitin

- Endogenous glycosamino-glycan, building block for the joint matrix
- Improved efficacy for conventional analgesics in combination
- May slow joint-space narrowing
- Combination with glucosamine HCl and manganese (Cosamin-DS)
  - Reduced pain in knee OA; not compared with glucosamine sulfate alone
- Cochrane review (2015) – some efficacy (8/100 points) and low risk
- Well tolerated – case report of interaction with warfarin
- Dose: 200-400 mg BID-TID
- Cost - $10-25 per month



Gregory PJ, et al. Am Fam Physician. 2008;77(2):177-184

MSM

- Methylsulfonylmethane – combination with glucosamine/ chondroitin
- Naturally occurring in some green plants, fruits, vegetables, and human adrenal glands
- May decrease degenerative processes in joints
- Modestly reduces joint pain and swelling, but not joint stiffness
- Well tolerated
- No data on long-term safety beyond 12 weeks
- Dose: 500 mg TID – 3 grams BID
- Cost - $5-35 per month

Gregory PJ, et al. Am Fam Physician. 2008;77(2):177-184

SAMe

- S-adenosylmethionine – produced in the liver from methionine
- Increases chondrocytes and cartilage thickness, may decrease cytokine-induced chondrocyte damage
- AHRQ Meta-Analysis and RCTs
  - Efficacy >> placebo, comparable to NSAIDs in reducing pain
  - SAMEe 1200 mg daily = celecoxib 200 mg daily
- A/E - anxiety, HA, insomnia; drug interactions; mania/hypomania
  - Unstable compound, unclear shelf-life - Butanedisulfonate salt
- Dose: 200 mg TID
- Cost - $60-120 per month

Gregory PJ, et al. Am Fam Physician. 2008;77(2):177-184

Devil's Claw

- Harpagophytum Procumbens, medicinal plant native to Africa
- Active ingredient - iridoid glycosides (IG), harpagoside
- Antiinflammatory due to inhibition of COX -2 and lipoxygenase
- RCTs demonstrate when taken together with NSAIDs or alone significantly decrease OA pain
- Dose – 2.4-2.6 mg daily standardized extract
- Cost - $15-40 per month
- A/E – nausea, diarrhea, pruritus, skin reactions; case of warfarin interaction
- No long-term safety data

L. Long et al. Rheumatology 2001;40:779-793.
Gregory PJ, et al. Am Fam Physician. 2008;77(2):177-184

Peppermint/Menthol

- Mentha piperita – hybrid between water mint and spearmint
- Menthol and methly salicylate are active ingredients, also has calcium channel blocker effects
- Regulates pain sensation through TRPM8 receptor
- Moderate efficacy in IBS, dyspepsia, skin irritation, migraine, tension HA, carpal tunnel syndrome
- Reduced pain in knee OA
- A/E– heartburn , nausea, vomiting, flushing, HA

Malone M, Tsai G. J Fam Practice, 2018;67(1):10-16.

Ginger

- Zingiber oficinale
- May inhibit COX and lipoxygenase, affect TNF, decrease PG
- Modest to no relief after 3 -6 weeks in standing/walking
  - –2 separate trials
- Adverse Effects – bad taste, case report of warfarin interaction
- Dose – 510 mg standard extract daily
- Cost - $2-3 per month

L. Long et al. Rheumatology 2001;40:779-793.

Turmeric

- Curcuma longa – active ingredient curcumin
- Anti-inflammatory properties via COX-2 inhibition, prostaglandins, and leukotrienes
- Preliminary clinical research suggests may improve symptoms of rheumatoid arthritis
- Safe, well-tolerated
- Cost - $8-23 per month (one tablet daily)

Gregory PJ, et al. Am Fam Physician. 2008;77(2):177-184

Collagen

- Enzymatically hydrolysed collagen peptide
- Principle component of articular cartilage, with proteoglycans and accessory proteins -- > Loss in OA inflicts damage on cartilage
- Effective dose seems to be 10 gm daily
  - –RCT in knee OA - significant decrease in WOMAC, VAS, and QOL scores from baseline to 13 weeks
  - –Compared to glucosamine sulfate 1.5 gm/day
    - Reduction in WOMAC/VAS 80% versus 46.6% of population
- Generally well-tolerated
- Cost ~$30 for 30 day supply

Kumar S, et al. J Sci Food Agric. 2014; DOI 10.1002/jsfa.6752

Arnica

- Arnica Montana, family Asteraceae
- Anti-inflammatory; synergy of phenolic & flavonoid compounds
- Open multicenter trial alleviated symptoms, improved function, well -tolerated in knee OA
- DB study of 204 patients versus topical ibuprofen in hand OA found arnica gel non-inferior and no difference in adverse effects
  - –Acknowledged in Cochrane Review
- Dose – 50 mg tincture/100 gm gel, apply 4 cm 3 times daily
- Cost - $6-12/month

Widrig, R, et al. Rheumatology International, 2007; 27(6):585-591.
Dragos D, et al. Nutrients ,2017; 9, 70: doi:10.3390/nu9010070

Fish Oil/Omega 3s

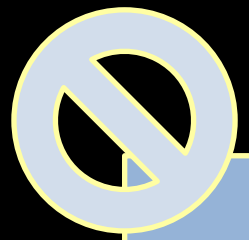
- Docosahexaenoic acid (DHA)/ Eicosapentaenoic acid (EPA) are used In production of lipid mediators involved in regulation of inflammation
- Recent meta-analysis – found only 5 trials in OA, too low grade to assess effect
  - More research needed in OA as well as specific DHA:EPA ratio needed (EPA:DHA > 1.5)
- Cost – depends on product, $0.06 - $0.40/capsule

Senftleber NK, et al. Nutrients. 2017;9(42): doi:10.3390/nu9010042

Musculoskeletal Disorders and Dietary Ingredients

- Capsaicin
- Curcuma*
- Melatonin
- pCGS
- ASU
- Vitamin D
- PUFA

- Ginger*
- Rose Hip
- SAMe
- Boswellia**



- Collagen
- Devil's Claw
- L-carnitine
- Creatine
- Vitamin E
- MSM
- Willow bark extract
- Pycnogenol

ASU = avocado soybean unsaponifiables; PUFA = polyunsaturated fatty acids; pCGS = crystalline glucosamine

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Crawford C, et al. Pain Med. 2019: 20(6):1236-1247.

What would you recommend to Jerry for his OA?

- A. SAMe
- B. Collagen
- C. Ginger
- D. Capsaicin
- E. Turmeric


Risky Business

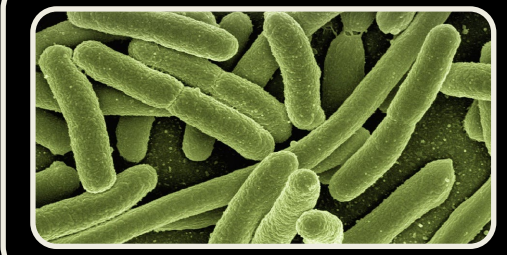
Back to Jerry

- Requesting advice on CBD
- Vaping recommended by a friend

Background

- Dietary supplement regulation
  - 1994 Dietary Supplement Health and Education Act (DSHEA)
    - Put dietary supplements under the general umbrella of “foods”
    - Pre-market testing not required
  - FDA
    - Reviews safety data on “new ingredients”
    - Adulterated or misbranded products
    - Health and Structure / Function claims
    - Legal action against unsafe products

Dangers of Dietary Supplements



Microbial contamination

- Many have fungal / bacterial levels above USP* thresholds

Heavy metals

- Arsenic, lead, cadmium, aluminum, mercury

Image from: https://commons.wikimedia.org/wiki/File:Galena_(Frontenac_Draper_Lake_Lead_Mine,_Ontario,_Canada).jpg

Adulteration

- Unapproved pharmaceutical ingredients

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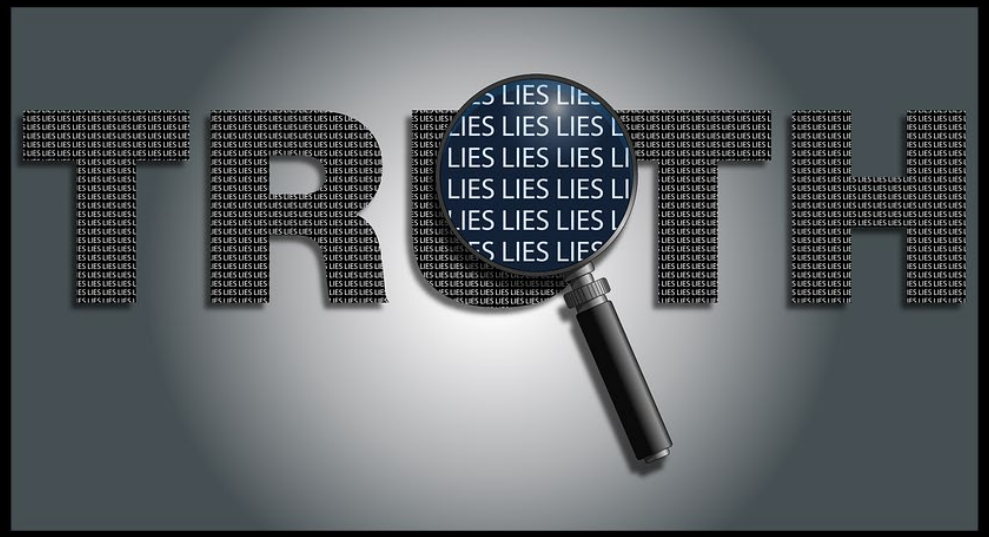
*United States Pharmacopeia

Dangers of Dietary Supplements



- Substitution or enrichment
  - What you see is NOT what you get
- Fraudulent ingredients
  - May contain little to no herbal content
  - Undisclosed herbal material

Tips for Supplement Selection

- Encourage patients to talk to you first
- Evaluate the data / source
- Third-party testing
- Buy from a reputable source
- Evaluate % daily value (DV) and Tolerable Upper Intake Level
- Read the ingredient label
- Avoid products or testimonials that make fraudulent statements / false claims


Pain Supplements to Give Pause
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Kratom

- Tree in the coffee family
- Known active compounds
  - Mitragynine
  - 7-hydroxymitragynine
- Dose-dependent effects
- Data
- Current U.S. regulatory status

Tianeptine

- Atypical antidepressant – not approved in the U.S.
  - Modulates glutamatergic system
  - Agonist of mu & delta opioid receptors
- Available online and many stores as a "dietary supplement"
  - Advertising often claims to treat OUD, pain, and/or anxiety
- Abuse on the rise

Image from: https://cspinet.org/news/fda-urged-protect-consumers-illegal-sales-tianeptine-20200825

Cannabidiol (CBD)

- Non-psychoactive cannabinoid in Cannabis sativa
- FDA approved drug for certain seizure disorders (Epidiolex®)
- Regulatory status in the U.S.
- Evidence for arthritis pain
- Concern for contamination

Key Takeaways

- OTC medications are limited in dosing are not without risk
- OTC supplements are not regulated by the FDA and are increasingly popular
- Patients may not readily reveal the alternative medications they are using
- Quality studies are lacking to provide significant evidence for clinical decision support
- Use drug interactions, other health conditions, and potential adverse effects to guide decision making
- “Risky” medications require extra scrutiny and careful patient and agent selection

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Questions