

It's natural, so it must be safe and effective: Complementary and alternative medicine for osteoarthritis

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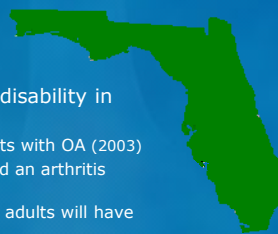


Objectives

- Discuss epidemiology and pathophysiology surrounding osteoarthritis (OA)
- Identify commonly used complementary and alternative medicine (CAM) in the management of OA
- Describe the safety and efficacy of commonly used CAM in the management of OA
- Summarize clinical recommendations for CAM in the management of OA

Epidemiology

- Most common cause of disability in the U.S.
 - Estimated 27 million adults with OA (2003)
 - 50% age \geq 65 yr reported an arthritis diagnosis (2005)
 - Continues to rise, ~ 25% adults will have arthritis by 2030
- Florida - Total costs in 2003 attributable to arthritis \$7.6 billion



CDC. Arthritis: Data and statistics. Accessed Dec 2009.
Hootman JM et al. *MMWR*. 2006;55(40):1089-1092.
Hootman JM et al. *Arthritis Rheum*. 2006;54(1):205-223.
Image from www.localtender.info/banks/florida-banks/count...

Pathophysiology

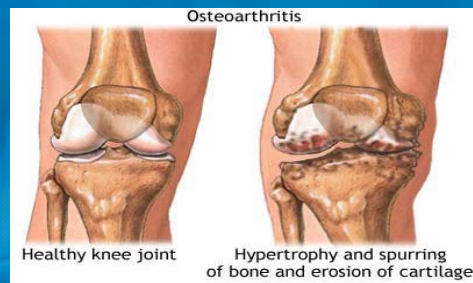


Image from www.nlm.nih.gov/

Management Options

- Nonpharmacologic, surgical & pharmacologic
- Commonly used CAM
 - Glucosamine
 - Chondroitin
 - Methylsulfonylmethane (MSM)
 - S-adenosylmethionine (SAME)
 - Willow bark
 - Devil's claw
 - Cat's claw



Altman RD et al. *Arthritis and Rheumatism*. 2000;43(9):1905-1915.
Image from www.aafp.org

Glucosamine

- Endogenous amino sugar found in synovial fluid, ligaments & other joint structures
 - Required for synthesis of glycoproteins & glycosaminoglycans
- Synthetically produced or naturally derived from marine exoskeletons
- Several salt forms exist, sulfate most effective
- Proposed MOA
 - Stimulate chondrocyte metabolism
 - Incorporation of sulfur into cartilage
 - Protection against degradative processes

Gregory PJ et al. *Am Fam Physician*. 2008;77(2):177-184.
Dahmer S et al. *American Family Physician*. 2008;78(4):471-476.

Glucosamine: Safety



- ADE
 - GI upset, allergic reactions & shortness of breath
- Interactions
 - ↑ effect of warfarin
 - Theoretically ↓ effects of antimitotic chemotherapy & hypoglycemics

Gregory PJ et al. *Am Fam Physician*. 2008;77(2):177-184.
Dahmer S et al. *American Family Physician*. 2008;78(4):471-476.
Image from www.just-servers.co.uk/links.htm

Glucosamine: Efficacy

- Two large placebo-controlled trials in Europe
 - Glucosamine sulfate vs. placebo
 - Three year follow-up showed statistically significant modest pain ↓ and joint space narrowing
- Clegg DO et al. 2006 [GAIT] (n = 1583)
 - Compared glucosamine, chondroitin, glucosamine/chondroitin, celecoxib & placebo
 - Six month period showed no significant ↓ symptoms
 - Limitations - Hydrochloride salt used, 60% placebo response rate & data analysis
- Bottom line = Inconsistent results

Reginster JY et al. *Lancet*. 2001;357(9252):251-256.
Pavelka K et al. *Arch Intern Med*. 2002;162(18):2117-2123.

Chondroitin Sulfate



- Endogenous glycosaminoglycan incorporated into joint matrix
 - "Heparinoid structure"
- Synthetically produced or naturally derived from animal sources
- Proposed MOA
 - Stimulate chondrocyte metabolism
 - Synthesize collagens & proteoglycans
 - Production of hyaluronic acid by synovial cells

Gregory PJ et al. *Am Fam Physician*. 2008;77(2):177-184.
Image from www.fulwood.org

Chondroitin: Safety



- ADE
 - GI upset & asthma exacerbation
 - Theoretically may cause bovine spongiform encephalitis & ↑ risk of prostate cancer
- Interactions
 - ↑ effects of warfarin when taken in significantly higher than recommended doses

Gregory PJ et al. *Am Fam Physician*. 2008;77(2):177-184.
Goldman EL. *MD Consult News*. Dec 15, 2009.
Image from www.yankeepotroast.org

Chondroitin: Efficacy

- Reichenbach S et al. 2007 (20 trials)
 - Meta-analysis 1966-2006
 - Little to no symptomatic benefit shown
- Clegg DO et al. 2006 [GAIT] (n = 1583)
 - No significant difference in ↓ symptoms, but was shown to significantly ↓ joint swelling
- Kahan A et al. 2009 [STOPP] (n = 622)
 - Two yr, randomized double-blind placebo controlled
 - 800 mg/day vs. placebo
 - Primary endpoint: Loss in minimum joint space width
 - Statistically significant ↓ in the primary endpoint & achieved pain relief faster up to 9 months
- Bottom line: Inconsistent results



After the 1999 Oscars, actor James Coburn credited a regimen of deep tissue massage, electromagnetic treatment, and MSM with "curing" his arthritis

Images from www.mirror.co.uk and www.fsmh.com

MSM

- Organic sulfur found in green plants, fruits/veggies & human adrenal glands; commercially produced synthetically
- Proposed anti-inflammatory & ↓ degenerative processes
- Safety: Insufficient data, as safe as placebo
- Efficacy: Insufficient^{1,2}
 - Two randomized double-blind, placebo-controlled trials looking at ↓ pain & physical function over 12 week period
 - Significantly ↓ pain & ↑ physical function
 - Combo w/ glucosamine more effective at ↓ pain, swelling & physical function

Gregory PJ et al. *Am Fam Physician*. 2008;77(2):177-184.
1. Usha PR et al. *Clin Drug Invest*. 2004;24:353-363.
2. Kim LS et al. *Osteoarthritis Cartilage*. 2006;14(3):286-294.

SAMe

- Produced in the liver by methionine; Methyl group donor
- Synthetically produced
 - Unstable compound, concerns w/ product quality despite choosing a reputable company
 - Butanedisulfonate salt preferred for best stability/bioavailability
- Proposed MOA involves chondrocyte metabolism, cartilage thickness & ↓ degenerative processes

Safety

- ADE - GI upset, HA, anxiety, insomnia & mania
- Interactions
 - ↑ effect of hypoglycemic agents
 - Serotonin syndrome w/ concomitant serotonergic agents

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

SAMe: Efficacy

- Studied extensively, consistently positive results
- Agency for Healthcare Research and Quality, 2002
 - Meta-analysis & review
 - Shown to be more effective than placebo & comparable to NSAIDS in ↓ pain after two months of use
 - Limitations - Scoring systems used not validated
- Najm WI et al. 2004 (n = 56)
 - 1200 mg vs. celecoxib 200 mg for 2 months
 - Comparable to celecoxib in ↓ pain after two months of use

Agency for Healthcare Research and Quality, 2002.
Najm WI et al. *BMC Musculoskelet Disord*. 2004;5:6.

Willow Bark (*Salix* spp.)



- Activity attributed to salicin, precursor to aspirin
 - 240 mg salicin ~ 381 mg aspirin
- Proposed inhibition of COX enzymes & cytokines
- Safety [Similar to salicylates]
 - ADE - GI, allergic rxn, bleeding, tinnitus & renal failure
 - Interactions - Warfarin, NSAIDS
- Efficacy [No reliable studies]
 - 240 mg salicin vs. placebo for 14 days showed significantly ↓ pain

Image from blog.luckyvitamin.com
Schmid B et al. *Phytother Res*. 2001;15(4):344-350.

Devil's Claw (*Harpagophytum procumbens*)

- African plant - tuber root used for medicinal purposes
 - Activity attributed to harpagosides
- Inhibits Cox-2 & suppresses protease production
- Safety
 - ADE - GI upset, bradycardia & allergic reactions
 - Interaction - Warfarin (purpura)
- Efficacy [No reliable studies]
 - 2.4-2.6 g/day STD extract for 8-12 wk
 - Short-term benefits in ↓ pain when taken alone or with NSAIDS



Image from www.terraforums.com
Wegener T et al. *Phytother Res*. 2003;17(10):1165-1172.

Cat's Claw (*Uncaria tomentosa*, *Uncaria guianensis*)



- South American vine, activity attributed to alkaloids
- May ↓ cytokine/inflammatory markers and ↑ growth factors
- Safety
 - Texan grown plant - Potentially toxic when commercially substituted for cat's claw
 - Contamination w/ other *Uncaria* spp: ↓ HR/BP & neuroinhibition
 - ADE - Allergic reaction, interstitial nephritis & immunostimulation
 - Interactions - CYP 3A4 substrates, warfarin, antiplatelets & antihypertensives
- Efficacy [No reliable studies] - May ↓ pain

Image from www.latinatc.com/english/e-catsclaw.html
Long L et al. *Rheumatology*. 2001;40:779-793.
Ameye LG et al. *Arthritis Research & Therapy*. 2006;8:R127.

Recommendations

Agent	Glucosamine Sulfate	Chondroitin Sulfate
Efficacy	<ul style="list-style-type: none"> Inconsistent results May modestly ↓ symptoms & slow disease progression Sulfate salt = + results 	<ul style="list-style-type: none"> Inconsistent results; STOPP trial may influence current rec. May modestly ↓ symptoms May ↓ joint space narrowing thus slowing disease progression
Dosing	<ul style="list-style-type: none"> 1500 mg/d Response may take ≥4 wk 	<ul style="list-style-type: none"> 800-1500 mg/d Pain: Effective up to 9 mo Disease modifying: ≥2 yr
Safety	<ul style="list-style-type: none"> Caution w/ shellfish allergy, asthma, warfarin Not rec. in pregnancy 	<ul style="list-style-type: none"> Caution w/ warfarin Harvested from animal sources Not rec. in pregnancy
Other	<ul style="list-style-type: none"> Monthly cost ~ \$9 Patients may need additional pain relief 	<ul style="list-style-type: none"> Monthly cost ~ \$18 Often combined w/ other agents

Recommendations

Agent	MSM	Combination Products (glucosamine/chondroitin +/- MSM)
Efficacy	<ul style="list-style-type: none"> May modestly ↓ pain Not rec. due to insufficient evidence 	<ul style="list-style-type: none"> Lack of clinical trials May modestly ↓ symptoms & slow disease progression
Dosing	<ul style="list-style-type: none"> 1500-6000 mg/d Studied for only 12 wk 	<ul style="list-style-type: none"> See individual products for rec. optimal doses
Safety	<ul style="list-style-type: none"> Well tolerated, no interactions known 	<ul style="list-style-type: none"> See individual products
Other	<ul style="list-style-type: none"> Monthly cost ~ \$5 Usually found in combo w/ glucosamine/chondroitin 	<ul style="list-style-type: none"> Monthly cost ~ \$13-\$18

Recommendations

Agent	SAME	Willow Bark
Efficacy	<ul style="list-style-type: none"> Consistent results in ↓ pain Not rec. due to product quality & high cost 	<ul style="list-style-type: none"> Lack of clinical trials May provide mild-mod relief of symptoms
Dosing	<ul style="list-style-type: none"> 1200 mg/d Response may take ≥2 mo 	<ul style="list-style-type: none"> 1360-2160 mg/d extract Use products w/ 240 mg salicin STD 15%
Safety	<ul style="list-style-type: none"> Caution in patients w/ psychological disorders, or on serotonergic agents 	<ul style="list-style-type: none"> CI: Aspirin allergy Caution: Similar to other salicylates
Other	<ul style="list-style-type: none"> Monthly cost ~ \$90 If patients are interested, rec. butanedisulfonate salt 	<ul style="list-style-type: none"> Monthly cost ~ \$7-\$15 Caution when choosing products, may not contain warning labels

Recommendations

Agent	Devil's Claw	Cat's Claw
Efficacy	<ul style="list-style-type: none"> May ↓ pain & allow dose red. of NSAIDs Insufficient evidence; Not rec. 	<ul style="list-style-type: none"> May ↓ pain Insufficient evidence; Not rec.
Dosing	<ul style="list-style-type: none"> 2.4-2.6 g/d STD extract Use products STD ≥1% harpagosides 	<ul style="list-style-type: none"> 100 mg dried aqueous extract Use products STD ≥3% alkaloids
Safety	<ul style="list-style-type: none"> Caution w/ warfarin May ↓ BP/HR Pregnancy: Not rec. 	<ul style="list-style-type: none"> May ↓ BP, caution w/ warfarin, CYP3A4 substrates Pregnancy: Not rec. has been used for preventing/aborting
Other	<ul style="list-style-type: none"> Monthly cost ~ \$14 Caution in product selection 	<ul style="list-style-type: none"> Monthly cost ~ \$15 Caution in product selection

True/False Questions

- Glucosamine sulfate is effective in modestly reducing osteoarthritis symptoms
- Patients with an aspirin allergy can safely take willow bark
- Devil's claw, cat's claw and chondroitin may interact with warfarin, potentiating bleeding risks

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