

## Joint Synergy

The NutriLinks MD Joint Synergy is a formula that combines nutritional cartilage support with natural inhibitors of COX-2 for optimal joint health. As this formula was born of research on clinical studies of efficacy, we can't make a case for this product as well as the abstracts below.

### Related Abstracts

#### **Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial.**

**Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacobelli G, Henrotin Y, Dacre JE, Gossett C.**

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**BACKGROUND:** Treatment of osteoarthritis is usually limited to short-term symptom control. We assessed the effects of the specific drug glucosamine sulphate on the long-term progression of osteoarthritis joint structure changes and symptoms. **METHODS:** We did a randomised, double-blind placebo controlled trial, in which 212 patients with knee osteoarthritis were randomly assigned 1500 mg sulphate oral glucosamine or placebo once daily for 3 years. Weightbearing, anteroposterior radiographs of each knee in full extension were taken at enrolment and after 1 and 3 years. Mean joint-space width of the medial compartment of the tibiofemoral joint was assessed by digital image analysis, whereas minimum joint-space width--ie, at the narrowest point--was measured by visual inspection with a magnifying lens. Symptoms were scored by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index. **FINDINGS: The 106 patients on placebo had a progressive joint-space narrowing, with a mean joint-space loss after 3 years of -0.31 mm (95% CI -0.48 to -0.13). There was no significant joint-space loss in the 106 patients on glucosamine sulphate: -0.06 mm (-0.22 to 0.09).** Similar results were reported with minimum joint-space narrowing. **As assessed by WOMAC scores, symptoms worsened slightly in patients on placebo compared with the improvement observed after treatment with glucosamine sulphate.** There were no differences in safety or reasons for early withdrawal between the treatment and placebo groups. **INTERPRETATION:** The long-term combined structure-modifying and symptom-modifying effects of glucosamine sulphate suggest that it could be a disease modifying agent in osteoarthritis.

Arch Intern Med. 2002 Oct 14;162(18):2113-23.

#### **Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study.**

**Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacobelli G, Rovati LC.**

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**BACKGROUND:** Conventional symptomatic treatments for osteoarthritis do not favorably affect disease progression. The aim of this randomized, placebo-controlled trial was to determine whether long-term (3-year) treatment with glucosamine sulfate can modify the progression of joint structure and symptom changes in knee osteoarthritis, as previously suggested. **METHODS:** Two hundred two patients with knee osteoarthritis (using American College of Rheumatology criteria) were randomized to receive oral glucosamine sulfate, 1500 mg once a day, or placebo. Changes in radiographic minimum joint space width were measured in the medial compartment of the tibiofemoral joint, and symptoms were assessed using the algo-functional indexes of Lequesne and WOMAC (Western Ontario and McMaster Universities). **RESULTS:** Osteoarthritis was of mild to moderate severity at enrollment, with average joint space widths of slightly less than 4 mm and a Lequesne index score of less than 9 points. **Progressive joint space narrowing with placebo use was -0.19 mm (95% confidence interval, -0.29 to -0.09 mm) after 3 years. Conversely, there was no average change with glucosamine sulfate use (0.04 mm; 95% confidence interval, -0.06 to 0.14 mm), with a significant difference between groups (P =.001). Fewer patients treated with glucosamine sulfate experienced predefined severe narrowings (>0.5 mm): 5% vs 14% (P =.05). Symptoms improved modestly with placebo use but as much as 20% to 25% with glucosamine sulfate use, with significant final differences on the Lequesne index and the WOMAC total index and pain, function, and stiffness subscales. Safety was good and without differences between groups. CONCLUSION:** Long-term treatment with glucosamine sulfate retarded the progression of knee osteoarthritis, possibly determining disease modification.

Osteoarthritis Cartilage. 2004 Apr;12(4):269-76.

### **Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo.**

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**OBJECTIVE:** To investigate the efficacy and tolerability of a 3-month duration, twice a-year, intermittent treatment with oral chondroitin sulfate (CS) in knee osteoarthritis (OA) patients. **DESIGN:** A total of 120 patients with symptomatic knee OA were randomized into two groups receiving either 800mg CS or placebo (PBO) per day for two periods of 3 months during 1 year. Primary efficacy outcome was **Lequesne's algo-functional index (AFI)**; secondary outcome parameters included VAS, walking time, global judgment, and paracetamol consumption. Radiological progression was assessed by automatic measurement of medial femoro-tibial joint space width on weight-bearing X-rays of both knees. Clinical and biological tolerability was assessed. **RESULTS:** One hundred and ten of 120 patients were included in the ITT analysis. **AFI decreased significantly by 36% in the CS group after 1 year as compared to 23% in the PBO group.** Similar results were found for the secondary outcomes parameters. **Radiological progression at month 12 showed significantly decreased joint space width in the PBO group with no change in the CS group.** Tolerability

was good with only minor adverse events identically observed in both groups.

**CONCLUSION: This study provides evidences that oral CS decreased pain and improved knee function.** The 3-month intermittent administration of 800mg/day of oral CS twice a year does support the prolonged effect known with symptom-modifying agents for OA. **The inhibitory effect of CS on the radiological progression of the medial femoro-tibial joint space narrowing could suggest further evidence of its structure-modifying properties in knee OA.**

Drugs Exp Clin Res. 2004;30(1):11-6.

**A two-year study of chondroitin sulfate in erosive osteoarthritis of the hands: behavior of erosions, osteophytes, pain and hand dysfunction.**

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**The aim of this study was to evaluate the effect of 800 mg/die of chondroitin sulfate (CHS) per os plus naproxen versus naproxen over 2 years in patients with erosive osteoarthritis (EOA) of the hands.** Joint count for erosions, Heberden and Bouchard nodes, Dreiser's algofunctional index and physicians' and patients' global assessment of disease activity were studied. A total of 24 consecutive patients (22 women and 2 men, mean age 53.0 +/- 6) suffering from symptomatic OA with radiographic characteristics of EOA were evaluated. The patients were divided into two groups of 12 patients each. The first group took naproxen 500 mg only. The second group was treated with CHS 800 mg orally plus naproxen 500 mg. Joint counts, radiological hand examinations and assessment of disease activity were performed at baseline, at 12 months and at 24 months. **In the second year the treated group showed significant worsening in erosion, Heberden, Bouchard and Dreiser scores was recorded. Physician and patient global assessments of disease activity showed no significant difference from baseline scores. The untreated group showed significant worsening in erosion, Heberden and Bouchard nodes, Dreiser index and physician and patient global assessment scores. This study confirms the partial efficacy of oral CHS in improving some aspects of EOA.**

J Rheumatol. 2001 Jan;28(1):173-81.

**Chondroitin sulfate in osteoarthritis of the knee: a prospective, double blind, placebo controlled multicenter clinical study.**

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**OBJECTIVE: To assess the efficacy and safety of chondroitin sulfate (CS) 1 g/day per os compared to placebo, in a double blind, randomized, parallel group study, with 3 months treatment followed by a 3 month posttreatment period, in patients with femorotibial osteoarthritis (OA).** **METHODS:** The main criterion was the functional handicap assessed by Lequesne's algofunctional index (AFI). Secondary efficacy criteria were: self-assessed pain with activity and at rest, self-assessed impact of OA on daily living, patient and physician assessed overall change in patient state since the previous visit, and daily NSAID and analgesic consumption, all evaluated

monthly. The main analysis was performed on the **intent-to-treat (ITT)** population at treatment endpoint compared to baseline (Day 0). **RESULTS: The ITT efficacy data set comprised 130 patients (63 in CS group and 67 in placebo group). At treatment endpoint, the AFI showed greater but nonsignificant improvement in the CS than in the placebo group. Improvement became significant ( $p = 0.02$ ) in the completer population ( $n = 114$ ). In the ITT population, all variables tended towards greater improvement in the CS than the placebo group. In the completer population, pain at rest also significantly decreased in the CS group compared to the placebo group ( $p = 0.03$ ), and, one month after treatment, CS had a significantly higher persistent effect than placebo on the AFI ( $p = 0.01$ ), pain with activity ( $p = 0.001$ ), physician assessed patient state ( $p = 0.05$ ), and most other efficacy criteria. Adverse event rates did not differ significantly.** **CONCLUSION:** We observed a trend towards efficacy of CS 1 g/day compared to placebo with good tolerability after 3 month treatment, and persistent efficacy one month posttreatment. Further investigations are required to confirm this trend.

Oncogene. 2004 Oct 18 [Epub ahead of print]

### **Nonsteroidal anti-inflammatory agents differ in their ability to suppress NF-kappaB activation, inhibition of expression of cyclooxygenase-2 and cyclin D1, and abrogation of tumor cell proliferation.**

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Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin have been shown to suppress transcription factor NF-kappaB, which controls the expression of genes such as cyclooxygenase (COX)-2 and cyclin D1, leading to inhibition of proliferation of tumor cells. There is no systematic study as to how these drugs differ in their ability to suppress NF-kappaB activation and NF-kappaB-regulated gene expression or cell proliferation. In the present study, **we investigated the effect of almost a dozen different commonly used NSAIDs on tumor necrosis factor (TNF)-induced NF-kappaB activation and NF-kappaB-regulated gene products, and on cell proliferation.** Dexamethasone, an anti-inflammatory steroid, was included for comparison with NSAIDs. As indicated by DNA binding, none of the drugs alone activated NF-kappaB. **All compounds inhibited TNF-induced NF-kappaB activation, but with highly variable efficacy. The 50% inhibitory concentration required was 5.67, 3.49, 3.03, 1.25, 0.94, 0.60, 0.38, 0.084, 0.043, 0.027, 0.024, and 0.010 mM for aspirin, ibuprofen, sulindac, phenylbutazone, naproxen, indomethacin, diclofenac, resveratrol, curcumin, dexamethasone, celecoxib, and tamoxifen, respectively.** All drugs inhibited I $\kappa$ B kinase and suppressed I $\kappa$ B degradation and NF-kappaB-regulated reporter gene expression. They also suppressed NF-kappaB-regulated COX-2 and cyclin D1 protein expression in a dose-dependent manner. **All compounds inhibited the proliferation of tumor cells, with 50% inhibitory concentrations of 6.09, 1.12, 0.65, 0.49, 1.01, 0.19, 0.36, 0.012, 0.016, 0.047, 0.013, and 0.008 mM for aspirin, ibuprofen, sulindac, phenylbutazone, naproxen, indomethacin, diclofenac, resveratrol, curcumin, dexamethasone, celecoxib, and**

**tamoxifen, respectively.** Overall these results indicate that aspirin and ibuprofen are least potent, **while resveratrol, curcumin, celecoxib, and tamoxifen are the most potent anti-inflammatory and antiproliferative agents of those we studied.** Oncogene advance online publication, 18 October 2004; doi:10.1038/sj.onc.1208169.

Biofactors. 2000;13(1-4):225-30.

**Anti-tumor and anti-carcinogenic activities of triterpenoid, beta-boswellic acid.**

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Boswellin (BE), a methanol extract of the gum resin exudate of *Boswellia serrata*, contains naturally occurring triterpenoids, beta-boswellic acid and its structural related derivatives, has been used as a traditional medicine for the treatment of inflammatory and arthritic diseases. **Topical application of BE to the backs of mice markedly inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced increases in skin inflammation, epidermal proliferation, the number of epidermal cell layers, and tumor promotion in 7,12-dimethylbenz[a]anthracene (DMBA)-initiated mice.** Feeding 0.2% of BE in the diet to CF-1 mice for 10-24 weeks reduced the accumulation of parametrial fat pad weight under the abdomen, and inhibited azoxymethane (AOM)-induced formation of aberrant crypt foci (ACF) by 46%. **Addition of pure beta-boswellic acid, 3-O-acetyl-beta-boswellic acid, 11-keto-beta-boswellic acid or 3-O-acetyl-11-keto-beta-boswellic acid to human leukemia HL-60 cell culture inhibited DNA synthesis in HL-60 cells in a dose-dependent manner with IC50 values ranging from 0.6 to 7.1 microM. These results indicate that beta-boswellic acid and its derivatives (the major constituents of Boswellin) have anti-carcinogenic, anti-tumor, and anti-hyperlipidemic activities.**

Phytomedicine. 2003 Jan;10(1):3-7.

**Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee--a randomized double blind placebo controlled trial.**

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Osteoarthritis is a common, chronic, progressive, skeletal, degenerative disorder, which commonly affects the knee joint. *Boswellia serrata* tree is commonly found in India. The therapeutic value of its gum (guggulu) has been known. It possesses good anti-inflammatory, anti-arthritic and analgesic activity. **A randomized double blind placebo controlled crossover study was conducted to assess the efficacy, safety and tolerability of *Boswellia serrata* Extract (BSE) in 30 patients of osteoarthritis of knee, 15 each receiving active drug or placebo for eight weeks.** After the first intervention, washout was given and then the groups were crossed over to receive the opposite intervention for eight weeks. **All patients receiving drug treatment reported**

**decrease in knee pain, increased knee flexion and increased walking distance. The frequency of swelling in the knee joint was decreased. Radiologically there was no change.** The observed differences between drug treated and placebo being statistically significant, are clinically relevant. BSE was well tolerated by the subjects except for minor gastrointestinal ADRs. **BSE is recommended in the patients of osteoarthritis of the knee with possible therapeutic use in other arthritis.**