OsteoArthritis and Cartilage (2006) **14,** 286–294

doi:10.1016/j.joca.2005.10.003

Osteoarthritis and Cartilage | ICRS International Cartilage Repair Society | OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial[1,2]

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Summary

Objective: Osteoarthritis (OA) is the most common form of arthritis and the second most common cause of long-term disability among middle-aged and older adults in the United States. Methylsulfonylmethane (MSM) is a popular dietary supplement used as a single agent and in combination with other nutrients, and purported to be beneficial for arthritis. However, there is paucity of evidence to support the use of MSM.

Methods: A randomized, double-blind, placebo-controlled trial was conducted. Fifty men and women, 40–76 years of age with knee OA pain were enrolled in an outpatient medical center. Intervention was MSM 3 g or placebo twice a day for 12 weeks (6 g/day total). Outcomes included the Western Ontario and McMaster University Osteoarthritis Index visual analogue scale (WOMAC), patient and physician global assessments (disease status, response to therapy), and SF-36 (overall health-related quality of life).

Results: Compared to placebo, MSM produced significant decreases in WOMAC pain and physical function impairment ($P < 0.05$). No notable changes were found in WOMAC stiffness and aggregated total symptoms scores. MSM also produced improvement in performing activities of daily living when compared to placebo on the SF-36 evaluation ($P < 0.05$).

Conclusion: MSM (3 g twice a day) improved symptoms of pain and physical function during the short intervention without major adverse events. The benefits and safety of MSM in managing OA and long-term use cannot be confirmed from this pilot trial, but its potential clinical application is examined. Underlying mechanisms of action and need for further investigation of MSM are discussed.

Key words: Osteoarthritis, Knee arthritis, Arthritis pain, Methylsulfonylmethane, Randomized controlled trial.

Introduction

Osteoarthritis (OA) is the leading cause of disability, limiting everyday activities of more than 7 million Americans[1], and is associated with restrictions on quality of life[2]. The demand for arthritis pain control has resulted in the widespread use of palliative drugs, e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and cyclooxygenase-2 (COX-2) inhibitors[3,4], surgical interventions[5], and in recent years, the use of complementary and alternative medicine (CAM)[6]. Additional treatment options are being actively sought out by patients as discontinuation of COX-2 drugs rises due to concerns of safety.

A dietary supplement with increasing use is methylsulfonylmethane (MSM) often in combination with glucosamine and chondroitin sulfate, which as opposed to MSM has numerous efficacy trials supporting its use in OA[7–9]. MSM is popularly used for arthritic and rheumatic pain; in 2003, the retail sales of MSM as a single ingredient were $115 million[10]. MSM is a naturally occurring organosulfur molecule and a putative methyl donor. MSM is the first oxidized metabolite of dimethylsulfoxide (DMSO). In the troposphere, DMSO is a byproduct of phytoplankton and algae decay. In commercial production, MSM is synthesized by reacting DMSO and hydrogen peroxide, which yields

[1] *Sources of support*: Financial support from Southwest College of Naturopathic Medicine & Health Sciences and grant sponsorship and products provided by Cardinal Nutrition.

[2] *Conflict of interests*: There is no conflict of interests in the preparation of this manuscript. None of the authors are employed by nor has any direct financial relationship with the project sponsor.

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Received 2 May 2005; revision accepted 8 October 2005.

MSM and water. In the body, approximately 15% of orally ingested DMSO is metabolized into MSM[11]. A recent study showed that MSM was found in human cerebrospinal fluid and plasma at 0–25 μmol/l concentrations[12]. Because of MSM's sulfur content, it is used by the body to maintain normal connective tissues. MSM may have anti-inflammatory activities, chemopreventive properties, prostacyclin (PGI_2) synthesis inhibition, anti-atherosclerotic action, salutary effect on eicosanoid metabolism, and free radical scavenging activity[13–15]. In murine models, MSM was shown to effect inflammatory conditions such as rheumatoid arthritis and lupus[16,17]. One randomized controlled trial of MSM and OA has been published[18]. In Usha and Naidu's[18] 12-week trial ($n = 118$), patients with knee OA received either 1.5 g MSM, 1.5 g glucosamine sulfate, 1.5 g MSM plus glucosamine sulfate, or placebo; significant decreases in the Lequesne Index were reported with MSM, glucosamine sulfate, and their combination ($P < 0.05$). The authors reported a 33% decrease in pain in the MSM group; joint mobility, swelling, global evaluation, and walking time also improved.

MSM safety and toxicity clinical studies have not been published. Acute and subchronic animal toxicity studies using single dose of 2 g/kg and daily doses of 1.5 g/kg MSM for 90 days showed no adverse events, organ pathology or mortality[19]. These doses are considered five to seven times the maximum dose used in humans. MSM is generally considered safe, and listed on *The Arthritis Foundation's Guide to Alternative Therapies* for OA with a cautionary note on lack of research[20]. There have been unconfirmed reports of mild adverse effects from oral use of MSM including gastrointestinal (GI) symptoms, headaches, amplified effects of blood thinning drugs resulting in easy bruising and blood in stool, increased blood pressure, increased hepatic enzymes, and insomnia if taken at bedtime[21]. However, there are no clinical studies on adverse effects, changes in blood chemistry, safety monitoring data or possible subclinical neurotoxicity symptoms of MSM. MSM is currently sold in over 52 different products as a single agent in capsule, caplet, lotion and cream forms, and in more than 30 different products in combination with other dietary supplements (glucosamine and chondroitin sulfate being the most common). MSM is readily available at health food stores and on the Internet with alarmingly little guidance on safety and how to take the supplement. Investigation is needed on MSM efficacy and safety in the dosages commonly used by practitioners and consumers alike to treat OA, which are higher than the dosage used in Usha's study. Equally significant is the public service provided by testing a highly prevalent dietary supplement to contribute to the scientific repertoire of this new supplement that is not regulated by the Food and Drug Administration (FDA). Considering the popularity of MSM and purported improvements in OA pain, additional efficacy and safety trial of MSM will thus be valuable in advising practitioners and patients in the appropriate use, if any, of MSM for arthritis pain management. Although a murine model reported decreasing joint degeneration[22], due to the preliminary design and short intervention period, treatment responses were limited to OA symptoms, and did not include radiographic changes of the joints following intervention.

Methods

PARTICIPANTS

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at Southwest College of Naturopathic Medicine. Written consents were obtained prior to enrollment. Knee OA was selected as opposed to hip or hands to evaluate a single joint for a preliminary efficacy clinical trial. Study inclusion criteria included men and women >40 years diagnosed with knee OA according to modified criteria of the American College of Rheumatology (ACR)[23,24]; ACR functional class I, II or III[25]; radiographic confirmed Kellgren–Lawrence grades 2–3 (mild to moderate osteophytes and joint space narrowing, previous 3 years)[26]; regular arthritis pain (arthritis pain in most days) for 3 months or more; >40 mm arthritis pain rating of target knee (100 mm visual analogue scale (VAS)); and >2 rating on patient global assessment (GA) of overall arthritis disease status (five-point Likert scale). Patients were not required to be asymptomatic in the other joints. Study exclusion criteria included any other type of arthritis; rheumatoid or inflammatory arthritis; fibromyalgia or other chronic pain syndrome; arthroscopy or intra-articular corticosteroids/hyaluronic acid injections in the previous 3 months; concurrent anti-coagulant/anti-platelet drugs, corticosteroids or narcotic pain killers use; history of epilepsy or bleeding disorders; gastric ulcers; renal or hepatic disease; uncontrolled hypertension, or body mass index (BMI) >45 kg/m^2. A washout period of 7 days was required for NSAIDs users. Discontinuing the use of common CAM therapies for arthritis (e.g., glucosamine, chondroitin sulfate, bromelain, DMSO, acupuncture) was required for 7 days prior to enrollment.

ENROLLMENT AND RANDOMIZATION PROCEDURES

Patients were recruited from the Phoenix metropolitan area using newspaper advertisements, flyers at local clinics, and press releases. Initial screening was conducted over the phone or in person. Qualified patients ($n = 50$) were assigned to MSM ($n = 25$) or placebo ($n = 25$) in a 12-week randomized, double-blind, placebo-controlled trial using computer-generated random numbers (Fig. 1). The generation of numbers and assignments were provided by different research staff not involved with patient contacts or data collection. Rescue analgesic, 325 mg acetaminophen tablets (100 tablets), was provided with instructions for use with intolerable pain and to not exceed taking 2.6 g/day. To monitor compliance and adverse events, weekly and biweekly phone calls to patients were made during the 12 weeks by the research staff.

MSM DOSAGE AND PREPARATION

A dosage of 6 g/day was selected based on common clinical and over-the-counter uses of MSM. A 1-week, stepwise approach to the full dose was undertaken. Week 1, started with 2 g/day in two divided doses for 3 days, and then increased to 4 g/day for 4 days. Week 2, increased to 6 g/day. Patients were instructed to take with food, and to avoid taking them at bedtime. Distilled MSM microprill (OptiMSM®, Cardinal Nutrition, Vancouver, WA) in 1 g caps was used. Purity of MSM was confirmed to be 99.9% by high-resolution gas chromatography. DMSO content was <0.05%. The placebo consisted of inert ingredients and was indistinguishable in color, size and taste compared to the MSM. Test materials were certified to be free of microbiological contamination. Heavy metal analysis by graphite furnace atomic absorption spectrophotometry and cold vapor analysis verified no quantifiable lead, arsenic, cadmium, aluminum, or mercury. The analytical tests were validated for

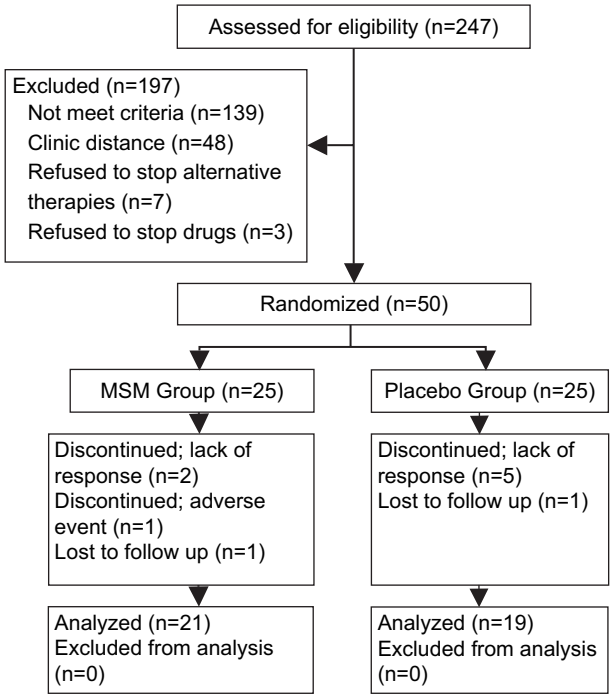

Fig. 1. Patient enrollment and follow-up diagram.

the sample matrix and reported on a signed certificate of analysis from the manufacturer. These assays were performed by an independent, third-party laboratory as part of the standard quality control in the manufacture of the raw ingredient MSM.

EFFICACY EVALUATIONS

The knee with the worst arthritis pain (target joint) at screening was the joint evaluated for efficacy. Primary endpoints were the composite subscales in the Western Ontario and McMaster University Osteoarthritis Index VAS (WOMAC version 3.1) on pain (five questions), stiffness (two questions), physical function (17 questions), and aggregated total symptoms (24 questions)[27,28]. The WOMAC was scored from 0 mm to 100 mm (0 = no pain, 100 = worst pain), and collected at baseline (following the washout period of 7 days), 2, 4, 8 and 12 weeks. Secondary endpoints were the patient GA, physician GA, and SF-36 (version 2) for the overall health-related quality of life, collected at baseline and 12 weeks. The patient GA and physician GA were scored on a five-point Likert scale for overall arthritis disease status (0 = very well, 1 = well, 2 = moderate, 3 = poor, 4 = very poor) and response to therapy (0 = excellent response, 1 = good response, 2 = moderate response, 3 = slight response, 4 = no response). SF-36 was chosen for its previous application in a variety of diseases including OA efficacy studies[29–31]. Responses to the 36 items are categorized into nine domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health, and reported health transition. Scores ranged from 0 to 100 with higher scores indicating better state of health and quality of life.

To investigate MSM's potential activity, although not commonly evaluated in OA studies, serum homocysteine, high sensitive C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and urine malondialdehyde (MDA) were measured at baseline and 12 weeks. Hyperhomocysteinemia is associated with ischemic cardiovascular conditions; and reducing homocysteine with micronutrients has been demonstrated to decrease heart disease[32]. Homocysteine is metabolized by a remethylation pathway (transfer of methyl by methylcobalamin or betaine [trimethylglycine]) generating methionine, and a transsulfuration pathway which degrades homocysteine into cysteine and then taurine[33]. Since MSM is a putative methyl donor, its activity as a co-factor in reducing homocysteine levels was tested. To monitor any anti-inflammatory activities of MSM, as suggested from empirical and published literature, CRP and ESR were tested. The MDA was measured to examine the possible antioxidant effect of MSM, which has also been suggested[15]. Thus, these lab tests were included in the pilot clinical trial to explore MSM's mechanisms of action. Other endpoints included the use of rescue analgesics and compliance with MSM regimen.

ADVERSE EVENTS EVALUATIONS

Laboratory tests, questionnaires, blood pressure, weight, BMI, and other vitals were collected at baseline and 12 weeks. The laboratory tests included hematology (complete blood counts and differential white blood cells), clinical chemistry (renal and hepatic functions), fasting lipid profile, urinalysis, and stool occult blood test. The questionnaires included the standard GI symptoms and modified neurotoxic symptoms using a four-point Likert scale ranging from 0 to 3 (0 = no, 1 = mild, 2 = moderate, 3 = severe). Questions related to changes in blood clotting were also included. Modifications were made on neurotoxicity questionnaires used in drug trials for application in our study[34–36]: cognitive function (fatigue, concentration, slowing, memory, motor coordination and language), peripheral neurological symptoms (sensory disturbance and muscle weakness), and other symptoms (insomnia, headache and blurred vision).

STATISTICAL ANALYSIS

The intent-to-treat analysis was performed using SPSS (version 11.0) software. The changes from baseline to 12 weeks between treatment and placebo groups were considered significant for Student's t test P values < 0.05 at the 95% confidence level. Estimated sample size was calculated using 80% power with a two-sided (tailed) test, alpha of 0.05 to detect a 25% improvement in VAS arthritis pain score from baseline to 12 weeks in the MSM treated group, indicating that 22 patients were required[37,38]. The estimated variance and power calculation were based on previous knee OA pilot trial publications[39,40]. With an anticipated 10% attrition rate, 25 patients per group were adequate to meet the sample size requirement.

Results

DEMOGRAPHIC PROFILE

About 90% of patients were in the ACR classes I and II, and 5% in class III (Table I). Average arthritis duration was about 6 years. The mean pain level was 55 mm in the placebo group and 58 mm in the MSM group. Thirty-seven percent and 38% of patients in the placebo group and MSM group, respectively, used some type of NSAIDs,

Table I
Demographic profile of patients and arthritis characteristics

	MSM ($n=21$)	Placebo ($n=19$)
Sex (%)		
Men	42.9	31.6
Women	57.1	68.4
Age, mean (years)	56.6 (SD = 8.6)	55.6 (SD = 8.7)
Ethnicity (%)		
White/non-Hispanic	100	89.5
Asian/Pacific islander	0	10.5
NSAID use (%)	38.1	36.8
MSM use (%)	28.6	26.3
DMSO use (%)	9.5	5.3
Glucosamine plus chondroitin sulfate use (%)	4.8	10.5
ACR functional capacity classification (%)		
I	23.8	26.3
II	71.4	68.4
III	4.8	5.3
Kellgren–Lawrence grade (%)		
2	61.9	57.9
3	38.1	42.1
Arthritis duration, mean (years)	5.8 (SD = 5.5)	5.9 (SD = 5.2)
Pain VAS, mean ± S.E.M. (0–100 mm, VAS)	58.0 ± 5.5	55.1 ± 5.8
Patient GA of disease status, mean ± S.E.M. (0–4, Likert)	3.0 ± 0.1	2.8 ± 0.2
Physician GA of disease status, mean ± S.E.M. (0–4, Likert)	2.8 ± 0.2	2.5 ± 0.1

and 26% and 29%, respectively, may have used MSM-containing products. The patients with history of MSM intake used less than 1 g/day, were inconsistent in daily use and /or used MSM predominantly in the form of combination dietary supplement products rather than as monotherapy, and the quality of MSM was not determined. Also, one patient in the MSM group and two patients in the placebo group were using glucosamine plus chondroitin sulfate prior to study enrollment. Expectation bias and confounding variables of participating in a study testing MSM were therefore likely to be minimal (patients could not have discerned the individual effects of MSM when taken in products containing many other active ingredients, e.g., glucosamine, chondroitin sulfate, herbs, vitamins, and minerals). No major differences in the arthritis disease status and other characteristics were found between the MSM and placebo groups at enrollment. The baseline patient profiles suggest that any changes in response to the intervention were not due to variability of patients in the two groups. Compliance with pill taking and other study instructions were obtained from the majority of patients. In the MSM group 89.5% and in the placebo group 90.5% took at least five pills a day. The study bottles were returned at the end of treatment, and the number of pills remaining was counted.

EFFICACY RESULTS

The results of WOMAC are listed in Table II. The primary endpoint pain changes at 12 weeks in the MSM group were significantly greater than in the placebo group, $P=0.041$. The changes in the physical function in the MSM group were also greater than in the placebo group at 12 weeks, $P=0.045$. The pain and physical function mean decreases from baseline to 4, 8 and 12 weeks in the MSM group were greater compared to the placebo group (Figs. 2 and 3). The changes in stiffness and aggregated total symptoms after 12 weeks of treatment were not significant between the two groups, $P>0.05$. There were changes found in the placebo group. The differences between the MSM and placebo groups were relatively small in the WOMAC subscales. In the MSM group pain decreased by 14.6 mm (25.1%), and in placebo it decreased by 7.3 mm (13.2%) at 12 weeks. The difference in pain improvement was 7.3 mm (12%) between the MSM and placebo groups. For physical function, stiffness and total symptoms, the decreases in MSM group were 15.7 mm (30.4%), 10.1 mm (19.7%), and 13.4 mm (25.1%) and the decreases in placebo group 8.8 mm (16.7%), 6.5 mm (11.7%), and 7.5 mm (13.8%), respectively. The differences between the groups were 6.8 mm (13.7%), 3.6 mm (8.0%), and 5.9 mm (11.3%) at 12 weeks, respectively. The patient GA and physician GA of overall arthritis disease status changes at 12 weeks in the MSM group and placebo group were not significant, $P>0.05$ (Table II). However, the changes in disease status suggest a trend toward improvement in the treatment group. The patient GA and physician GA of response to therapy also showed no major differences. In the SF-36 quality of life results, of the nine domains, only the role physical domain at 12 weeks in the MSM group was significant with a mean change of 16.45 (SD = 20.84), $P=0.021$. While in the placebo group, a mean change of 12.48 (SD = 23.17) was observed on the role physical domain, $P=0.175$. No notable changes were found in the other eight domains, $P>0.05$. There were no appreciable differences in the use of rescue analgesics; the mean use was 37.9 (SD = 25.7) tablets over 12 weeks in the placebo group compared to 27.4 tablets (SD = 21.2) in the MSM group.

LAB MONITORING

Hematology, clinical chemistry and urinalysis did not have any abnormal changes from baseline to 12 weeks. There were no major changes in the complete blood counts, differential white blood cell counts, hepatic and renal functions, lipid profiles, BMI, vitals, stool occult test, swelling or tenderness of the target knee joints. Three patients did have positive hemoccult tests at 12 weeks, two in the placebo group and one in the MSM group. The hemoccult was repeated 2 weeks later; the results were negative. Homocysteine ($P=0.004$) and urine MDA ($P=0.010$) were the only two laboratory markers with significant differences at 12 weeks between the MSM and placebo groups (Table III).

ADVERSE EVENTS

The incidences of GI and other side effects included bloating, constipation, indigestion, fatigue, concentration issues, insomnia, and headache (Table IV). These symptoms were minor, without complications, and did not interfere with daily activity or require treatment. Patients in the MSM and placebo groups reported the symptoms in comparable frequency. Of the 50 patients enrolled, 40 completed the study: 21 (84%) in the MSM group and 19 (76%) in the placebo group. The majority of patient withdrawals were reportedly due to lack of perceived response to therapy, two in the

Table II
WOMAC, patient and physician GAs

	MSM ($n=21$)			Placebo ($n=19$)			Between group difference at 12 weeks *P* values
	Baseline mean ± S.E.M.	12 weeks mean ± S.E.M.	Change ± S.E.M.	Baseline mean ± S.E.M.	12 weeks mean ± S.E.M.	Change ± S.E.M.	
WOMAC (0–100 mm, VAS)							
Pain	58.0 ± 5.5	43.4 ± 4.6	−14.6 ± 1.3	55.1 ± 5.8	47.9 ± 4.8	−7.3 ± 3.3	0.041*
Stiffness	51.2 ± 5.4	41.1 ± 4.8	−10.1 ± 2.6	55.2 ± 6.2	48.7 ± 6.8	−6.5 ± 2.4	0.320
Physical function	51.5 ± 4.5	35.8 ± 3.2	−15.7 ± 2.0	52.9 ± 5.9	44.1 ± 5.1	−8.8 ± 2.7	0.045*
Total symptoms	53.6 ± 4.9	40.1 ± 3.9	−13.4 ± 1.7	54.4 ± 5.6	46.9 ± 5.2	−7.5 ± 2.5	0.054
Patient GA (0–4, Likert)							
Disease status	3.0 ± 0.1	2.5 ± 0.2	−0.5 ± 0.2	2.8 ± 0.2	2.5 ± 0.2	−0.3 ± 0.2	0.549
Physician GA (0–4, Likert)							
Disease status	2.8 ± 0.2	2.5 ± 0.1	−0.3 ± 0.1	2.5 ± 0.1	2.3 ± 0.2	−0.2 ± 0.2	0.447

*Between group differences in the MSM and placebo evaluated using the Student's *t* test. The changes were considered significant for $P < 0.05$. The changes in the primary endpoints WOMAC pain and physical function at 12 weeks were significant between the MSM and placebo groups.

MSM group and five in the placebo. One patient dropped out in each group due to loss to study follow-up. One patient in the MSM group discontinued prematurely due to an adverse event in the first 2 weeks. The patient reported having neck and back pain that were similar in symptoms to a previous kidney infection. Clinical examination and lab tests of the patient showed that there was no infection or other major health problems. The patient also reported worsening of arthritis pain and joint swelling.

Discussion

In this trial, MSM at 3 g twice a day for 12 weeks produced improvement in two of the three WOMAC subscales, pain and physical function, $P < 0.05$. Comparable efficacy results have been reported in the literature but for different MSM dosages. The dosage we used was four times the dosage of Usha's study, but in our study arthritis pain decreased by 25.1% compared to 33% decrease seen in Usha's study[18]. The small sample size with variations in arthritis pain and other patient characteristics confounding the data may have contributed to the smaller decrease observed in our study compared to Usha's study. An unpublished trial ($n = 16$) of MSM for arthritis pain, 2.25 g, also reported some improvement[41]. The changes in WOMAC subscales, pain, physical function, stiffness, and total symptoms in the placebo group by 7.3 mm (13.2%), 8.8 mm (16.7%), 6.5 mm (11.7%), and 7.5 mm (13.8%), respectively, at 12 weeks are worthy of discussion. The changes in the placebo group and the small differences between the two groups indicate that the effect of MSM was modest. Thus, while improvements in pain and physical function were shown to be statistically significant, the clinical significance of these symptoms improvements remains uncertain. The overall trend in WOMAC subset decreases does show benefits of MSM, and further evaluation for practical application is justified. Another noteworthy finding is that the WOMAC subsets continued to decline at 12 weeks, suggesting that the full effects of MSM were not captured during the relatively short intervention; a longer study is needed to determine if and when the effects of MSM would plateau. The patient GA and physician GA trends correlated with those observed with the WOMAC in the MSM group. However, efficacy changes in previously published COX-2 drug trials are greater, e.g., celecoxib decreased WOMAC pain,

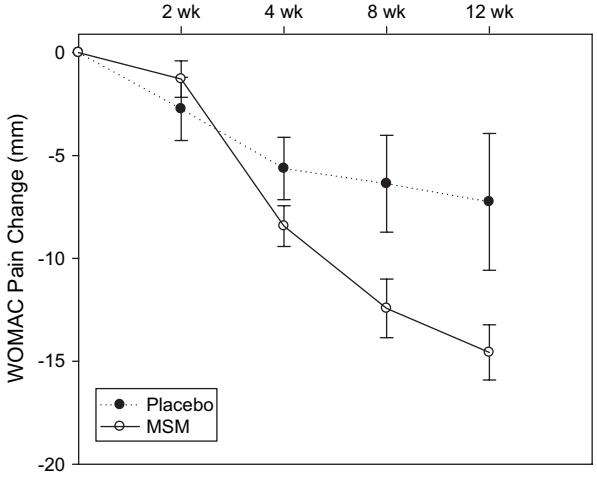

Fig. 2. WOMAC pain changes from baseline to 2, 4, 8 and 12 weeks.

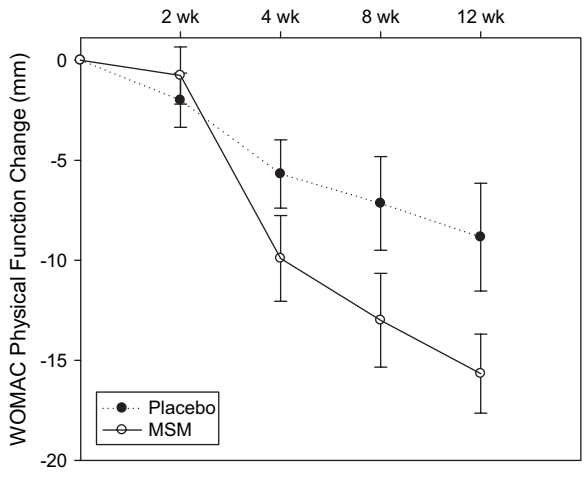

Fig. 3. WOMAC physical function changes from baseline to 2, 4, 8 and 12 weeks.

Table III
Lab markers: total cholesterol, homocysteine, CRP, ESR and urine MDA

	MSM ($n=21$)			Placebo ($n=19$)			Between group difference at 12 weeks *P* values
	Baseline mean ± S.E.M.	12 weeks mean ± S.E.M.	Change ± S.E.M.	Baseline mean ± S.E.M.	12 weeks mean ± S.E.M.	Change ± S.E.M.	
Total cholesterol (mg/dL)	213.5 ± 10.4	203.5 ± 8.5	−10.0 ± 3.2	201.5 ± 9.8	193.7 ± 9.9	−7.8 ± 2.7	0.607
Homocysteine (μmol/L)	8.0 ± 0.4	7.2 ± 0.4	−0.8 ± 0.2	8.3 ± 0.4	8.6 ± 0.5	0.4 ± 0.3	0.004*
CRP (mg/L)	1.6 ± 0.3	1.5 ± 0.2	−0.1 ± 0.2	2.3 ± 0.4	2.3 ± 0.4	0.1 ± 0.2	0.540
ESR (mm/h)	6.4 ± 1.2	5.8 ± 0.9	−0.6 ± 0.7	5.7 ± 1.3	6.2 ± 1.1	0.4 ± 0.6	0.324
Urine MDA (μmol/L)	16.7 ± 1.0	14.3 ± 0.8	−2.4 ± 0.9	15.0 ± 1.0	16.3 ± 0.9	1.3 ± 1.0	0.010*

*Between group differences in the MSM and placebo evaluated using the Student's *t* test. The changes were considered significant for $P < 0.05$. The changes in homocysteine and urine MDA at 12 weeks were significant between the MSM and placebo groups.

stiffness and physical function by 28.6 mm, 27.9 mm, and 24.9 mm, respectively[3], and etoricoxib decreased by 22.29 mm, 19.01 mm, and 22.87 mm[4], compared to our MSM trial, which decreased by 14.6 mm, 10.1 mm, and 15.7 mm, respectively. The differences in OA disease characteristics should be noted for these COX-2 studies, where the patients typically had more severe arthritis compared to the patients enrolled in our study. Symptoms improved in WOMAC subsets, particularly pain from 58.0 mm to 43.3 mm at 12 weeks, these values indicate that the patients were experiencing pain.

MSM has been shown to reduce seasonal allergic rhinitis symptoms[42]. MSM's anti-inflammatory activities were sought by testing CRP and ESR. These markers are used to predict chronic conditions such as cardiovascular disease (CVD) and to monitor inflammatory disease processes[43,44]. In our study, the high sensitive CRP and ESR showed no changes. The Centers for Disease Control and the American Heart Association guidelines on CRP levels define three categories of CVD risks: low risk <1.0 mg/L, average risk 1.0−3.0 mg/L, and high risk >3.0 mg/L[44]. The baseline mean CRP was 1.6 mg/L in the MSM group and 2.3 mg/L in the placebo group, indicating average risks for CVD and no acute inflammation. The difference in CRP values between the two groups at baseline was not statistically significant ($P > 0.05$). However, there were observational clinical differences in the baseline values between the two groups. This may be due to the small sample size. Baseline mean ESR was 6.4 mm/h in the MSM group and 5.7 mm/h in the placebo group, indicating no acute inflammation since ESR < 30 mm/h is considered normal for our patient age group[45]. Thus, the effects of MSM as an anti-inflammatory agent were not determined.

Table IV
Incidence of patients reporting adverse events based on the GI and modified neurotoxic symptoms questionnaires

	Number (%)	
	MSM ($n=21$)	Placebo ($n=19$)
GI symptoms		
Bloating	3 (25)	2 (18)
Constipation	2 (17)	2 (18)
Indigestion	1 (8)	1 (9)
Loose stool	0	0
Gas	0	0
Diarrhea	0	0
Stomach pain	0	0
Acid reflux	0	0
Heartburn	0	0
Vomiting	0	0
Nausea	0	0
Blood clotting		
Bruise easily	0	0
Nose bleeding	0	0
Bleeding (clotting) time longer	0	0
Modified neurotoxic symptoms		
Cognitive function		
Fatigue	2 (17)	3 (27)
Concentration	1 (8)	1 (9)
Slowing	0	0
Memory	0	0
Motor coordination	0	0
Language	0	0
Peripheral neurological symptoms		
Sensory disturbance	0	0
Muscle weakness	0	0
Others		
Insomnia	2 (17)	1 (9)
Headache	1 (8)	1 (9)
Blurred vision	0	0

Reduction of lipid peroxidation signified by MDA levels has been suggested to be beneficial in patients with long-term inflammatory conditions[46]. MDA has been evaluated for mutagenic activity and lipid peroxidation-linked DNA damages, carcinogenicity and genotoxicity[47]. The decrease in urine MDA levels in the MSM group was significantly different from placebo, suggesting changes in oxidative stress with MSM. Although the baseline homocysteine levels were not elevated, the levels did decrease significantly in the MSM group. The decrease in homocysteine may be due to the donation of MSM's two methyl groups. Folic acid and B vitamins are known to reduce hyperhomocysteinemia through similar mechanisms[48]. The decreases in homocysteine and MDA suggest potential role of MSM in supporting metabolic processes requiring methylation, such as antioxidant capacities. The high total cholesterol observed in our study population (Table III) is not uncommon in OA patients[49,50], and hypercholesterolemia and increased homocysteine concentrations have been reported in chronic diseases such as CVD[51,52]. The correlation between oxidative damage and cartilage degeneration in OA has recently been demonstrated[53]. Pro-coagulant factors have been shown to compromise subchondral vasculature, and may thus accelerate joint damage[54]. MSM's effect on homocysteine and MDA could potentially exert favorable effects on hypercoagulation and articular inflammation. The role of oxidative stress, hypercholesterolemia and other dyslipidemia in contributing to joint degeneration and pain control should be explored, and this may provide new treatment possibilities to hasten progression of cartilage degeneration and other articular deformities and develop new palliative

treatment options in an integrative approach to OA. For oxidative damage, cellular damage and low-grade inflammation found in chronic conditions such as OA and increasingly evident as we age, diets that are low in simple carbohydrates, sugar, dairy, and saturated fats shown to be effective in reducing metabolic syndrome and CVD may also be helpful in joint protection and pain control in OA[55]. Such integrative method of reducing oxidative damage and inflammation, improving antioxidative capacity and metabolic markers specific for OA (e.g., hyperlipidemia, elevated inflammatory markers, and compromised vasculature), effective palliative controls, and diet modifications could address the underlying complex pathophysiology of OA.

Considering the risks associated with COX-2 inhibitor drugs[56,57] and the prevalence of coronary risk factors often found in patients with OA (e.g., hypercholesterolemia, dyslipidemia, postmenopausal women, and older age population), providing safe treatment options without life threatening CV events should receive serious consideration. Preparing guidelines for clinical application of MSM at this time is difficult, and to make suggestions that MSM, after only 12 weeks of intervention, is safer than COX-2 drugs would be inappropriate. However, in lieu of controversies surrounding the drugs for OA, and the low incidence of major adverse events and some improvements in pain reported, the possible use of MSM in managing OA symptoms warrants discussion.

Our trial did not find adverse events such as high blood pressure, changes in blood chemistry, increased bruising, or bleeding time. However, since patients taking concurrent anti-coagulant/anti-platelet drugs were excluded from our study, the effects of MSM interfering with these medications need further testing. Our study weaknesses include small sample size and short duration of treatment (12 weeks) resulting in limitations in extrapolating to the target population. Because of the single enrollment site, majority of participants were those nearby the clinic which may have further decreased patient pool size and external validity. Prior history of MSM intake of unknown MSM quality and dosing regimen by patients in both the MSM and placebo groups should be noted in interpreting the outcomes of this preliminary trial for possible influence of such prior use. Other factors to consider are narrowed interpretation of toxicity and adverse events, e.g., inclusion of patients with high blood pressure and heart disease, which are typically found in the age group with OA, may have resulted in more incidences of side effects. Also the adverse events reported by few of the patients including the one patient who prematurely discontinued with worsening of joint pain and swelling, call for further safety studies to identify possible at risk patient populations contraindicated to take MSM. Our study findings are only preliminary, and no dose–response guidance can be determined, e.g., the positive changes at varying daily dosages, 1.5–6 g, need clarification for optimum dosage appropriate for symptoms control in OA. Based on our results and previous studies, future research direction for MSM must include long-term treatments, dose–response trials, larger sample sizes, study design with greater extrinsic value, and preclinical and clinical studies to elucidate bioactivities of MSM to better understand mechanisms of action. Equally critical are MSM-drug interaction studies for safety and toxicity, since the group benefiting most from OA palliative drugs is the elderly with co-morbid conditions taking many different drugs. Future research should also consider MSM's possible antioxidant activity (like folic acid and B vitamins) which may be actually beneficial in this population who has high cholesterol and other CVD risks.

Another possibility to explore is combination treatments for palliative control in arthritis pain, such as recent practice of NSAID plus acetaminophen[58]. MSM appears to be less effective than COX-2 drugs, but its use as an adjuvant with other treatments for OA could be considered. Critical appraisal of MSM is complicated by the fact that the standard drug discovery, safety and efficacy studies from preclinical to phase I, II and III clinical trials are not being followed for MSM. This is commonly the case for CAM therapies currently in the U.S. Without first conducting human safety, pharmacokinetic and pharmacodynamics studies, dietary supplements typically undergo phase II efficacy clinical trials because biological agents under CAM do not require FDA's Investigational New Drug Application or the New Drug Application. Since MSM is generally regarded as safe with no reported serious risks, the animal toxicity study[19], previously published randomized trial[18], one unpublished trial[41], and other publications combined with findings of our trial are encouraging for MSM indication in OA. Our results support short-term intervention with MSM when NSAIDs and COX-2 drugs are contraindicated or when other treatments are ineffective. An approach based on the literature is to start at 1.5 g/day, then to increase up to 6 g/day in divided doses, and to discontinue use if no improvements in arthritis pain are noted in 4 weeks. Thus, while large, long-term, dose–response studies in a more diverse patient population are warranted, MSM should be considered in certain OA patient populations.

Acknowledgment

Special thanks to the Phoenix VA Medical Center for assisting on the project. The manuscript was prepared independently by the authors without restrictions or limitations from the sponsors.

References

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, *et al*. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778–99.
2. Ethgen O, Vanparijs P, Delhalle S, Rosant S, Bruyere O, Reginster JY. Social support and health-related quality of life in hip and knee osteoarthritis. Qual Life Res 2004;13:321–30.
3. Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. JAMA 2002;287:64–71.
4. Gottesdiener K, Schnitzer T, Fisher C, Bockow B, Markenson J, Ko A, *et al*. Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. Rheumatology (Oxford) 2002;41:1052–61.
5. Dieppe P, Basler HD, Chard J, Croft P, Dixon J, Hurley M, *et al*. Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. Rheumatology (Oxford) 1999;38:73–83.
6. Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, *et al*. Osteoarthritis: new insights. Part 2: treatment approaches. Ann Intern Med 2000;133:726–37.

7. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA 2000;283:1469–75.
8. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162:2113–23.
9. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, *et al*. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001;357:251–6.
10. New Business Journal. Top Specialty Supplement Sales Chart 11. San Diego: Penton Media Inc 2004.
11. Hucker HB, Miller JK, Hochberg A, Brobyn RD, Riordan FH, Calesnick B. Studies on the absorption, excretion and metabolism of dimethylsulfoxide (DMSO) in man. J Pharmacol Exp Ther 1967;155: 309–17.
12. Engelke UF, Tangerman A, Willemsen MA, Moskau D, Loss S, Mudd SH, *et al*. Dimethyl sulfone in human cerebrospinal fluid and blood plasma confirmed by one-dimensional (1)H and two-dimensional (1)H-(13)C NMR. NMR Biomed 2005;18:331–6.
13. Ebisuzaki K. Aspirin and methylsulfonylmethane (MSM): a search for common mechanisms, with implications for cancer prevention. Anticancer Res 2003; 23:453–8.
14. Alam SS, Layman DL. Dimethyl sulfoxide inhibition of prostacyclin production in cultured aortic endothelial cells. Ann N Y Acad Sci 1983;411:318–20.
15. Beilke MA, Collins-Lech C, Sohnle PG. Effects of dimethyl sulfoxide on the oxidative function of human neutrophils. J Lab Clin Med 1987;110:91–6.
16. Morton J, Moore R. Lupus nephritis and deaths are diminished in B/W mice drinking 3% water solutions of dimethyl sulfoxide (DMSO) or dimethyl sulfone ($DMSO_2$). J Leukoc Biol 1986;40:322.
17. Hasegawa T. Suppressive effect of methylsulfonylmethane (MSM) on type II collagen-induced arthritis in DBA/1J mice. Jpn Pharmacol Ther 2004;32:421–7.
18. Usha P, Naidu M. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. Clin Drug Invest 2004;24:353–63.
19. Horvath K, Noker PE, Somfai-Relle S, Glavits R, Financsek I, Schauss AG. Toxicity of methylsulfonylmethane in rats. Food Chem Toxicol 2002;40: 1459–62.
20. Horstman J, Arnold W. The Arthritis Foundation's Guide to Alternative Therapies. Atlanta: Arthritis Foundation 1999.
21. Jacob S, Appleton J. MSM—The Definitive Guide. Topanga: Freedom Press 2003.
22. Murav'ev Iu V, Venikova MS, Pleskovskaia GN, Riazantseva TA, Sigidin Ia A. Effect of dimethyl sulfoxide and dimethyl sulfone on a destructive process in the joints of mice with spontaneous arthritis. Patol Fiziol Eksp Ter 1991;37–9.
23. Bellamy N, Klestov A, Muirden K, Kuhnert P, Do KA, O'Gorman L, *et al*. Perceptual variation in categorizing individuals according to American College of Rheumatology classification criteria for hand, knee, and hip osteoarthritis (OA): observations based on an Australian Twin Registry study of OA. J Rheumatol 1999;26: 2654–8.
24. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039–49.
25. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992;35:498–502.
26. Menkes CJ. Radiographic criteria for classification of osteoarthritis. J Rheumatol Suppl 1991;27:13–5.
27. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
28. Davies GM, Watson DJ, Bellamy N. Comparison of the responsiveness and relative effect size of the western Ontario and McMaster Universities Osteoarthritis Index and the short-form Medical Outcomes Study Survey in a randomized, clinical trial of osteoarthritis patients. Arthritis Care Res 1999;12:172–9.
29. Hauser W, Zimmer C, Schiedermaier P, Grandt D. Biopsychosocial predictors of health-related quality of life in patients with chronic hepatitis C. Psychosom Med 2004;66:954–8.
30. Katz JN, Larson MG, Phillips CB, Fossel AH, Liang MH. Comparative measurement sensitivity of short and longer health status instruments. Med Care 1992;30: 917–25.
31. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford) 2002;41:1240–8.
32. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002;325:1202.
33. Selhub J. Homocysteine metabolism. Annu Rev Nutr 1999;19:217–46.
34. Pace A, Bove L, Aloe A, Nardi M, Pietrangeli A, Calabresi F, *et al*. Paclitaxel neurotoxicity: clinical and neurophysiological study of 23 patients. Ital J Neurol Sci 1997;18:73–9.
35. Aldenkamp AP, Baker G, Pieters MS, Schoemaker HC, Cohen AF, Schwabe S. The Neurotoxicity Scale: the validity of a patient-based scale, assessing neurotoxicity. Epilepsy Res 1995;20:229–39.
36. Aldenkamp AP, Baker GA. The Neurotoxicity Scale—II. Results of a patient-based scale assessing neurotoxicity in patients with epilepsy. Epilepsy Res 1997;27: 165–73.
37. Altman DG. Practical Statistics for Medical Research. Boca Raton: CRC Press 1999.
38. Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, *et al*. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. Osteoarthritis Cartilage 1996;4:217–43.
39. Bellamy N, Buchanan WW, Chalmers A, Ford PM, Kean WF, Kraag GR, *et al*. A multicenter study of tenoxicam and diclofenac in patients with osteoarthritis of the knee. J Rheumatol 1993;20:999–1004.

40. Ehrich EW, Schnitzer TJ, McIlwain H, Levy R, Wolfe F, Weisman M, *et al*. Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group. J Rheumatol 1999;26: 2438–47.
41. Lawrence R. Methylsulfonylmethane (MSM): a double-blind study of its use in degenerative arthritis (Abstract). Int J Anti Aging Med 1998;1:50.
42. Barrager E, Veltmann JR Jr, Schauss AG, Schiller RN. A multicentered, open-label trial on the safety and efficacy of methylsulfonylmethane in the treatment of seasonal allergic rhinitis. J Altern Complement Med 2002;8:167–73.
43. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, *et al*. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004; 350:1387–97.
44. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon 3rd RO, Criqui M, *et al*. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
45. Bottiger LE, Svedberg CA. Normal erythrocyte sedimentation rate and age. Br Med J 1967;2:85–7.
46. Dhanakoti SN, Draper HH. Response of urinary malondialdehyde to factors that stimulate lipid peroxidation *in vivo*. Lipids 1987;22:643–6.
47. Niedernhofer LJ, Daniels JS, Rouzer CA, Greene RE, Marnett LJ. Malondialdehyde, a product of lipid peroxidation, is mutagenic in human cells. J Biol Chem 2003;278:31426–33.
48. McKinley MC, McNulty H, McPartlin J, Strain JJ, Pentieva K, Ward M, *et al*. Low-dose vitamin B-6 effectively lowers fasting plasma homocysteine in healthy elderly persons who are folate and riboflavin replete. Am J Clin Nutr 2001;73:759–64.
49. Cheras PA, Whitaker AN, Blackwell EA, Sinton TJ, Chapman MD, Peacock KA. Hypercoagulability and hypofibrinolysis in primary osteoarthritis. Clin Orthop 1997;57–67.
50. Sturmer T, Sun Y, Sauerland S, Zeissig I, Gunther KP, Puhl W, *et al*. Serum cholesterol and osteoarthritis. The baseline examination of the Ulm Osteoarthritis Study. J Rheumatol 1998;25:1827–32.
51. Dinavahi R, Falkner B. Relationship of homocysteine with cardiovascular disease and blood pressure. J Clin Hypertens (Greenwich) 2004;6:494–8.
52. Sacco RL, Anand K, Lee HS, Boden-Albala B, Stabler S, Allen R, *et al*. Homocysteine and the risk of ischemic stroke in a triethnic cohort: the Northern Manhattan Study. Stroke 2004;35:2263–9.
53. Yudoh K, Nguyen T, Nakamura H, Hongo-Masuko K, Kato T, Nishioka K. Potential involvement of oxidative stress in cartilage senescence and development of osteoarthritis: oxidative stress induces chondrocyte telomere instability and downregulation of chondrocyte function. Arthritis Res Ther 2005;7:R380–91.
54. Ghosh P, Cheras PA. Vascular mechanisms in osteoarthritis. Best Pract Res Clin Rheumatol 2001;15: 693–709.
55. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, *et al*. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004;292:1440–6.
56. Day R, Morrison B, Luza A, Castaneda O, Strusberg A, Nahir M, *et al*. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Rofecoxib/Ibuprofen Comparator Study Group. Arch Intern Med 2000;160: 1781–7.
57. Watson DJ, Harper SE, Zhao PL, Quan H, Bolognese JA, Simon TJ. Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch Intern Med 2000;160:2998–3003.
58. Buescher JS, Meadows S, Saseen J. Clinical inquiries. Does acetaminophen and NSAID combined relieve osteoarthritis pain better than either alone? J Fam Pract 2004;53:501–3.