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Review

Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis

S. Brien B.Sc., M.Sc., Ph.D.†*, P. Prescott B.Sc., D.I.C., A.R.C.S.‡, N. Bashir†, H. Lewith† and G. Lewith D.M., F.R.C.P.†

† *Department of Primary Care, University of Southampton, UK*

‡ *School of Mathematics, University of Southampton, UK*

Summary

Objective: Conventional treatment of osteoarthritis (OA) with non-steroidal anti-inflammatory drugs is associated with serious gastrointestinal side effects and in view of the recent withdrawal of some cyclo-oxygenase-2 inhibitors, identifying safer alternative treatment options is needed. The objective of this systematic review is to evaluate the existing evidence from randomised controlled trials of two chemically related nutritional supplements, dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of OA to determine their efficacy and safety profile.

Methods: The electronic databases [Cochrane Library, Medline, Embase, Amed, Cinahl and NeLH (1950 to November 2007)] were searched. The search strategy combined terms: osteoarthritis, degenerative joint disorder, dimethyl sulfoxide, DMSO, methylsulfonylmethane, MSM, clinical trial; double-blind, single blind, RCT, placebo, randomized, comparative study, evaluation study, control. Inclusion and exclusion criteria were applied. Data were extracted and quality was assessed using the JADAD scale.

Results: Six studies were included [evaluating a total of 681 patients with OA of the knee for DMSO ($N = 297$ on active treatment); 168 patients for MSM ($N = 52$ on active treatment)]. Two of the four DMSO trials, and both MSM trials reported significant improvement in pain outcomes in the treatment group compared to comparator treatments, however, methodological issues and concerns over optimal dosage and treatment period, were highlighted.

Conclusion: No definitive conclusion can currently be drawn for either supplement. The findings from all the DMSO studies need to be viewed with caution because of poor methodology including; possible unblinding, and questionable treatment duration and dose. The data from the more rigorous MSM trials provide positive but not definitive evidence that MSM is superior to placebo in the treatment of mild to moderate OA of the knee. Further studies are now required to identify both the optimum dosage and longer-term safety of MSM and DMSO, and definitive efficacy trials.

Key words: Dimethyl sulfoxide, Methylsulfonylmethane, DMSO, MSM, Osteoarthritis, Systematic review.

Introduction

Osteoarthritis (OA) is the most common of all joint disorders and affects over 30 million people in the US and one in10 people aged 35–75 in the UK[1]. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed and although effective are associated with serious gastrointestinal (GI) side effects[2,3]. NSAIDs' users are up to 5.5 times more likely to experience side effects which require hospitalisation than non-users; 12,000 admissions and approximately 2000 deaths are attributed to NSAIDs in the UK every year[4]. Patients with OA look to complementary and alternative medicine (CAM) to gain symptomatic relief and avoid iatrogenic illness with OA being the sixth most common condition treated with CAM[5]. CAM use in patients with OA is substantially greater than that in the general population with a reported prevalence of up to 90%[6,7].

Both dimethyl sulfoxide (DMSO, an organic form of sulphur commercially prepared from lignin) and its oxidised form, methylsulfonylmethane (MSM, occurring in green plants fruits and vegetables) have been used to treat arthritic conditions[8]. Both have similar pharmacological properties and their putative effects and mechanisms have been reviewed previously (MSM[9–11]; DMSO[12–15]; both[16]). Ameye and Chee conducted a systematic review of neutriceuticals in OA and concluded that MSM showed "moderate" evidence of efficacy; they did not evaluate DMSO. MSM and DMSO reduce peripheral pain[17–19], inflammation[20] and arthritis[21], and might inhibit the degenerative changes occurring in OA[22]. These compounds may act through their ability to stabilise cell membranes, slow or stop leakage from injured cells and scavenge hydroxyl free radicals which trigger inflammation[18,20,23–28]. Their sulphur content can rectify dietary deficiencies of sulphur improving cartilage formation[29,30].

*Address correspondence and reprint requests to: Dr Sarah Brien, B.Sc., M.Sc., Ph.D., Primary Medical Care, Aldermoor Health Centre, Aldermoor Close, Southampton, Hampshire SO16 5ST, UK. Tel: 44-7870642667; Fax: 44-2380701125; E-mail: sbb@soton.ac.uk

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DMSO is a topical agent, diluted for therapeutic use [concentrations are expressed %(v/v)] and penetrates the skin; it is also used as a carrier to aid penetration of other medications[19,23,31]. Clinicians are advised to prescribe DMSO for OA for at least 3 months to ensure a clinical effect. However, the optimum dosage for this supplement in OA has not been clearly evaluated as no dose ranging studies have been conducted. Previous empirical reports suggest that the therapeutic concentrations of DMSO are 60–90%[14,32] and that doses of under 10% are clinically inactive[32–34]. There is limited formal safety data and no long-term assessment of DMSO although the toxicity of oral DMSO appears very low (LD50 = 14.5 g/kg body weight). Adverse effects associated with topical DMSO administration have been reported (GI upset, skin irritation, and garlic like taste, breath and body odour)[35,36]. Its garlic odour can compromise blinding in double-blinded trials.

MSM is used orally and topically. Like DMSO, the treatment duration for OA is at least 3 months. The optimum dosage has not been clearly defined as no dose ranging studies have been carried out. The suggested oral therapeutic doses are 4–6 g/d[37,38], although doses of up to 20 g/d have also been used[39]; over the counter preparations are typically 1–5 g daily[40]. There is limited formal safety data and no long-term assessment. However, MSM is rapidly excreted from the body[41,42] and animal toxicity studies of MSM showed only minor adverse events using doses of 1.5 g/kg and 2.0 g/kg of MSM for 90 days. This dose represents a human dose of 30–42 g/d, which is equivalent to 5–7 times the proposed maximum recommended human dose of 6 g/d[43]. A further study confirmed MSM had no toxic effects on either pregnant rats or their foetus[44]. Only minor adverse effects are associated with MSM administration in humans and include allergy, GI upsets and skin rashes[45].

A review assessing the effectiveness and safety of both DMSO and MSM in OA is timely and pertinent because of the withdrawal of some cyclooxygenase (COX)-2 inhibitors[3] as well as the frequent use of nutritional supplements by this patient group[6,7]. The specific objective of this systematic review is to evaluate the existing evidence from randomised controlled trials (RCTs) of DMSO or MSM in the treatment of OA to determine their efficacy and safety profile.

Methods

LITERATURE SEARCH STRATEGY AND STUDY SELECTION

Only randomised or quasi-RCTs comparing DMSO or MSM to other therapies or to no therapy in the treatment of OA were included. Electronic databases [Cochrane Library, Medline, Embase, Amed, Cinahl, and NeLH (Complementary and Alternative Medicine Specialist Library)] were used to identify studies between 1950 and November 2007. Citation tracking was undertaken to identify unpublished trials. As numerous pharmaceutical companies market DMSO, it was impractical to contact each of them for unpublished data. Free text searches were performed on each database with the following keywords: osteoarthritis, degenerative joint disorder, dimethyl sulfoxide, DMSO, methylsulfonylmethane, MSM, clinical trial; double-blind, single blind, RCT, placebo, randomized, comparative study, evaluation study, control.

DATA EXTRACTION

RCTs were included if they were in humans; reported comparison of DMSO or MSM to either placebo, or standard treatment in OA; used validated outcome measures for OA; and did not include patients with other joint pathology. JADAD was used to assess the reporting quality and methodological rigour[46]. The trials were assessed by four of the authors independently; any disagreements were discussed and resolved. The authors reported on other measures of internal validity (dosage, treatment period, and appropriateness of statistical analysis) and external validity (inclusion and exclusion criteria, baseline characteristics, trial setting, and outcome measures). Additional data such as joint location, age of sample population, compliance, statistical evaluation, results and adverse effects were extracted and tabulated.

Results

RESULTS OF SEARCH STRATEGY

Seven RCTs were identified (1971–2006). The NeLH search strategy identified four[31,37,38,47]; Embase identified (1980–2007) five, two of which were additional to those identified by NeLH[48,49]. The searches on the other databases did not identify any additional RCTs [Cochrane (three citations); Medline (1950–2007, three citations); Amed (1985–2007, one citation); and Cinahl (1982–2007, zero citation). Citation tracking identified one further RCT[50]. Five of the RCTs were in English[31,37,38,47,50] and two in German[48,49]. Five were placebo-controlled; the remaining two were comparator trials, one an equivalence trial[48]. However, the trial by Roth[47] was excluded as its aim was not to evaluate the efficacy or effectiveness of DMSO; it assessed the efficacy of Diclofenac (DF) using DMSO as a carrier vehicle to enhance drug uptake. Six RCTs were available for analysis, four assessing DMSO[31,48–50] (in topical form) and two MSM[37,38] (in oral form). Three of the studies were multi-centred[31,37,48]. Detailed descriptions for each of the studies are presented in Tables I(a) (DMSO) and I(b) (MSM) and Tables II(a) (DMSO) and II(b) (MSM), and information on adverse events is reported in Table III.

RCTs OF DMSO

Four double-blind RCTs assessing DMSO have been reported; three placebo-controlled trials (two, two armed[49,50] and a three armed study[31] and a comparator study[48]). The first study in 1971[50] was a single-centred, parallel, placebo-controlled trial of DMSO in OA knee ($N = 100$) (JADAD 2). The study assessed the efficacy of 50% topical DMSO ointment vs placebo. Treatment period was 1 month and the only outcome was patients' subjective assessment of pain (Likert scale). It is unclear if DMSO was used as an adjunctive or sole treatment; the use of rescue medication was not reported. Both groups reported similar increased levels of positive analgesic effects, and no statistical analysis was carried out because of the similarity of treatment response. The dose of DMSO used in this study is just below the suggested optimal 60% concentration and it failed to show any significant statistical or clinical benefit.

Eberhardt *et al.*'s[49] double-blind, placebo-controlled parallel study evaluated 25% DMSO gel (suboptimal dose) ($N = 56$) vs placebo gel ($N = 56$) in OA knee (diagnosed radiographically) who had not received anti-inflammatory drugs for the previous 3 months (Tables I and II provide reporting details JADAD 4). The treatment period was only 3 weeks and DMSO was used as a sole treatment; the use of rescue medication was not reported. The primary outcome measure was pain reduction on resting, on loading and on palpation using visual analogue scales (VASs). DMSO showed significant reduction vs placebo in all primary outcomes (resting pain, $P = 0.015$; loading pain $P = 0.019$; and palpation $P = 0.029$). The dose in this study was below the suggested optimal level of 60% concentration yet significant statistical effects were identified. Neither comparison between group baseline characteristics, nor a power calculation was reported. Drop out rates were low, and only minor adverse events were reported.

Table I(a)
RCTs of DMSO in the treatment of OA

Author	Jaded score	Study design	Joint location	Sample size	Intervention/control	Outcome measures	Main result
Vuopala *et al.*[50]	2 Blinding: 2 Randomisation: 0 Withdrawals: 0	Single-centre, double-blind, placebo-controlled	Knee	100 (50 DMSO; 50 placebo)	1. 50% DMSO ointment 2. Placebo Treatment period: 1 month	*Primary outcomes:* Likert scale of patient assessment of analgesic effect Evaluated at 1 month	No inferential statistical group analysis performed Authors state that DMSO has the same effect as placebo 76% of DMSO and 76% of placebo patient rated treatment good or intermediate Authors reported that no side effects were observed
Eberhardt *et al.*[49]	4 Blinding: 2 Randomisation: 1 Withdrawals: 1	Double-blind, placebo-controlled	Knee	112 (56 DMSO; 56 placebo)	1. 25% DMSO gel 5−8 cm 2. Placebo gel 5−8 cm Dosage: TID Treatment period: 3 weeks	*Primary outcomes:* *change in pain scores for* • Pain under loading VAS • Pain at rest: Likert scale • Pain on palpation: Likert scale *Secondary outcomes:* • Mobility 6-point Likert • Swelling • Patient and physicians global assess of efficacy and tolerability • Adverse events Evaluated at baseline, 7, 14 and 21 days	All primary efficacy criteria significantly better than placebo Statistically significant and clinically relevant reduction in loading pain of mean 42.7 mm (reduction of 64.5%) in DMSO compared to a significant reduction of 30.8 mm in the placebo (reduction of 46.5%). Difference in mean reduction was 11.7 mm (CI −18.35 to −5.1). DMSO significantly better than placebo ($P = 0.019$) Pain at rest is significantly reduced by mean of −1.3 in DMSO compared to −0.9 in placebo, $P = 0.015$ Pain on palpation is significantly reduced by mean of −1.5 in DMSO compared to −1.1 in placebo, $P = 0.029$. NS group differs for mobility and swelling PGA and PhGA better for DMSO than placebo No serious AE 9 AE DMSO: 12 *P*
Bookman *et al.*[31]	5 Blinding: 2 Randomisation: 2 Withdrawal: 1	Double-blind, three arm comparative, multi-centre and placebo-controlled trial	Knee	248 (84 DF; 80 DMSO; 84 placebo)	1. Topical DF + DMSO (45.5% wt/wt) 40 drops 4 times daily 2. Topical (45.5% wt/wt) DMSO 40 drops four times daily 3. Topical placebo-control solution (containing 4.5% wt/wt DMSO) 40 drops four times daily Dosage: four times a day Treatment period: quarter in die (QID) 28 days	*Primary outcomes:* • WOMAC pain subscale *Secondary outcomes:* • Physical and stiffness subscales of (WOMAC) • Weekly PGA • Pain on walking (*post hoc*) • Amount of rescue medication taken	WOMAC pain scores was significant reduced in the DF group [−3.9 (95% (CI) −4.8 to −2.9)] compared to DMSO [−2.5 (CI: −3.3 to −1.7)]; $P = 0.023$ or placebo [−2.5 (CI −3.3 to −1.7)]; $P = 0.016$ DF is significantly greater at reducing pain compared to DMSO and placebo. DMSO was not superior to placebo in pain reduction DF was significantly better than DMSO and placebo for improving physical function, stiffness, pain on walking and PGA NSD for adverse event reporting No therapeutic benefit on efficacy variables for DMSO as vehicle control (45.5%) vs placebo solution (4.5% DMSO)

(*continued on next page*)

Table I(a) (*continued*)

Author	Jaded score	Study design	Joint location	Sample size	Intervention/control	Outcome measures	Main result
Koenen *et al.*[48]	2 Blinding: 0 Randomisation: 1 Withdrawals: 1	Multi-centre, controlled, double-blind equivalence trial	Knee	221 (111 DMSO; 110 DF)	1. 10% DSMO gel 4.0 g 2. DF gel 4.0 g Dosage: four times a day Treatment period: 3 weeks (for use in an acute inflammatory phase)	*Primary outcomes:* • VAS pain during movement *Secondary outcomes:* • VAS pain at rest • Pain functional index, physician assessed • Tolerability of treatment Likert scale • Evaluated at baseline, 7 and 21 days	Mean values of VAS reduced by 28.4 ± 19.9 mm DMSO; 24.1 ± 23.6 mm DF group. These decreases are clinical relevant decrease in both treatment groups No significant group differences reported (CI -3.5 to $+8.6$ mm). The authors claim that both treatments equivalent Secondary outcome (pain at rest) supports primary outcome Clinically relative improvement in pain functional index in each group. Tolerability of DMSO slightly superior to DF

TID: tri-daily (three times a day); MSM (the isoxidised form of DMSO); PGA: patient global assessment; PhGA: physician global assessment; Glu: glucosamine; BID: bi-daily (twice a day); %(v/v).

Bookman *et al.*[31] conducted a three armed randomised, double-blind, multi-centre, three armed trial in OA knee to assess the efficacy of; topical DF in a carrier solution using DMSO (45.5% wt/wt); DMSO as a control (45.5% concentration); placebo, a very low level of DMSO for blinding purposes (JADAD 5). This is the sole study using DMSO in an inactive dose in the placebo to ensure blinding. Patients diagnosed with radiological OA knee for at least 6 months with current moderate or severe pain were included ($N = 248$). The 4 weeks' treatment began after a 1-week washout for all medication; no rescue medication was used, DMSO was the sole treatment. This study was included since it was possible to compare DMSO to placebo; however, the study was not powered to assess this as its primary outcome. Primary outcome was the VAS pain subscale of the Western Ontario and McMaster Universities (WOMAC) OA Index. The mean change in pain scores was significantly greater with topical DF in DMSO carrier treatment [-3.0 (95% confidence interval (CI) -4.9 to -2.9)] than DMSO [-2.5 (CI -3.3 to -1.7)], $P = 0.023$ or placebo [-2.5 (CI -3.3 to -1.7)], $P = 0.016$. DMSO was shown to have the same analgesic effect as placebo. This study compares DMSO with topical DF and does not reflect a comparison with standard conventional treatment since DF is generally taken orally. A power calculation indicated that 40 patients per group would be needed to detect a difference of 3 (out of 20) in WOMAC pain scores; the sample size was doubled, so power was adequate. The clinical effect size is limited; 19.5 mm VAS change for DF in DMSO and 12.5 mm for DMSO difference compared to 28.6 mm oral for COX-2 inhibitors[51]. DMSO was used in this study as a carrier rather than as a therapeutic agent, however, the dosage prescribed, although lower than recommended in normal clinical practice (45.5 vs 60%), it was comparable to other clinical trials. No significant statistical or meaningful clinical effect was observed.

The last DMSO study, a comparator study[48], an equivalence trial, was performed comparing DMSO to standard conventional treatment i.e., DF (JADAD 2). This was a multi-centre phase IV trial which assessed the effect of topical (10%) DMSO vs topical DF in 221 patients ($N = 111$ DMSO; $N = 110$ DF) with radiological confirmed acute inflamed OA knee for 21 days. All medication ceased before entry (steroids for 1 month and analgesics and anti-inflammatory agents for 7 days); the use of rescue medication was not reported. The primary outcome was pain on movement (VAS). A clinically relevant reduction in pain was observed for both treatments (mean VAS reduction: 28.4 ± 19.9 mm DMSO compared to 24.1 ± 23.6 in the DF group) and no significant differences were observed between treatment groups [CI -3.5 to $+8.6$ mm] suggesting equivalence of both treatments. However, no definition of equivalence was given and it is unclear if this study was powered as a formal equivalence trial. A low dose of DMSO was used in this trial (10%) but in spite of this the study reported clinically meaningful and statistical significant benefits. Adverse drug reactions were mild and localised to skin reactions.

RCTs OF MSM

Two double-blind, placebo-controlled trials have assessed MSM[37,38]. Usha and Naidu[37] performed a multi-centred double-blind, parallel and placebo-controlled trial (Tables I and II provide reporting details, JADAD 4) recruiting ($N = 118$) patients with mild to moderate OA knee (Lequesne diagnostic criteria). Patients with current

Table I(b)
RCTs of MSM in the treatment of OA

Author	Jaded score	Study design	Joint location	Sample size	Intervention/control	Outcome measures	Main result
Usha and Naidu[37]	4 Blinding: 2 Randomisation: 1 Withdrawal: 1	Double-blind, parallel, placebo-controlled	Knee	118 (27 Glu; 27 MSM; 28 Glu + MSM; 24 placebo)	1. Glu 500 mg/d and MSM placebo (both capsules) 2. MSM 1500 mg/d and Glu placebo (both capsules) 3. Glu 500 mg/d and MSM 1500 mg/d (capsule) 4. Glu and MSM placebo (both capsules) All treatments were two capsules taken three times daily Dosage: three times a day Treatment period: 12 weeks	*Primary outcomes:* • Responder − i.e., a 3-point decrease in Lequesne index from baseline plus physician overall efficacy assessment of good or fair • Pain intensity VAS • Joint mobility • PGA and PhGA • Lequesne index *Secondary outcomes:* • Physician completed pain and swelling Likert • 15 m walking time • Consumption of rescue medication Efficacy and safety evaluated at baseline 2, 4, 8 and 12 weeks	Significant decrease in mean pain index from 1.74 to 0.65 with Glu ($P < 0.001$) and a significant decrease from 1.53 to 0.74 with MSM Combined Glu and MSM resulted in a significant decrease in mean pain of 1.7−0.36 ($P < 0.001$). Placebo did not show any significant change (1.57−1.16) Combination of Glu and MSM was superior to individual and placebo for number of variables: pain index, swelling index: $P < 0.05$, joint function, walking time, joint mobility index and overall function ability Combination was more effective in reducing pain than individual therapy. MSM was superior to placebo and inferior to Glu in this trial
Kim *et al.*[38]	5 Blinding: 2 Randomisation: 2 Withdrawals: 1	Single-centre, RCT, double-blind, placebo-controlled	Knee	50 (MSM, 25; placebo, 25)	1. Oral MSM, 3 g (DMSO content <0.05%)* 2. Placebo Dosage frequency: BID Treatment period: 12 weeks	*Primary outcomes (at baseline, 2, 4, 8 and 12 weeks):* • Pain, physical function and stiffness and total scores (WOMAC) *Secondary outcomes (at baseline and 12 weeks):* • PGA and PhGA (5-point Likert scale) • Short Form (SF)-36 • Labs (CRP, homocysteine, ESR and MDA) • Use of rescue analgesia weekly by telephone − compliance and AE	*Primary*: MSM significantly improved WOMAC pain (−14.6 vs −7.3, $P = 0.041$) and physical function (−15.7 vs −8.8, $P = 0.045$) compared to placebo. Neither significant difference noted for stiffness (−10.1 vs −6.5, $P = 0.32$) nor total scores −13.4 vs −7.5, $P = 0.054$) compared to placebo *Secondary*: no significant difference in decrease in either patient ($P = 0.549$) or physician (0.447) GA. Significant decreases in MDA ($P = 0.01$) and homocysteine ($P = 0.004$) observed in MSM compared to placebo *AEs* were minor (notably GI, fatigue, and insomnia) and no group difference in levels reported (MSM, $N = 21$; placebo, $N = 19$) Authors reported that significant differences found in MSM were not necessarily clinically relevant when compared to NSAID treatment changes on these measures

*1-week step-up dose from 2 g/d until 6 g/d reached.

Table II(a)
Further methodological details of RCT for DMSO

Author	Sex ratio (M:F)	Mean age of sample group (year) (range)	Inclusion criteria stated	Exclusion criteria stated	Concomitant medications recorded	Consort statement	Compliance assessed	Power calculation performed, statistical analysis	Baseline characteristics	Dropouts	Comment
Vuopala *et al.*[50]	No information	No differentiation between groups' ages. Overall mean age 60	No 1. OA of the knee with continuous pain for several years	No	No information	No	No	No	Not reported	No information	• No details of blinding or randomisation process noted although numbered tubes used in blind manner • Query blinding of medication due to smell? • Short treatment period • Treatment dose not at therapeutic levels • No baseline measures reported • No power calculation or justification of sample size • Objective assessment • No statistical analysis • Paper publication date is prior to stricter methods now introduced
Eberhardt *et al.*[49]	DMSO, 28:28 Placebo, 27:29	DMSO, 62.3 (34–81) Placebo, 63.3 (38–81)	Yes 1. Radiological and clinical diagnosis of OA of the knee in the past 5 years. 2. Only one joint requiring treatment 3. Age 18–80	Yes 1. Treatment needed in greater than 1 joint 2. Other inflammation diseases of the joint 3. Treatment for the joint in the last 3 months 4. Local or systemic treatment in previous 1 day or 7 days, respectively	All anti-rheumatic therapy stopped 3 months, systemic therapy topped 7 days and local therapy stopped 24 h before start of study No mention of rescue medication	No	No	No ITT Primary outcomes: ANOVA, other outcomes: contingency board method and *t* test	No significant group differences at baseline for symptom duration, age, height, weight, length of activation of current symptoms	Total: 4% *DMSO: 3 (5%)* 2 LOE 1 Other *Placebo: 1 (2%)* 1 SE	• Short treatment period • Treatment dose not at therapeutic levels • Use of Likert scale to assess pain at rest and palpation • No power calculation performed • Lower age range unusual for this condition • Patients who were pain free could cease study medication and stop trial before day 21 • Short washout periods for systemic and local
Bookman *et al.*[31]	Total, 91:157 DF, 32:52 DMSO, 26:54 Placebo, 33:51	DF: 62.5 DMSO: 62.1 Placebo: 60.8	Yes 1. Radiological confirmation of primary OA in at least one knee 2. Moderate pain (WOMAC pain subscale) in previous 2 weeks	Yes 1. Secondary arthritis 2. Use of an other topical agent at site 3. Corticosteroid use	Rescue medication allowed except 24 h before baseline and final WOMAC assessments Prohibited medication stopped 1 week before baseline assessment	Yes	Yes by weighing bottles at weekly visit	$N = 40$ per group plus 10 for drop outs, to detect a difference of 3, 4 or 5 units in WOMAC pain 80% power and $\alpha = 0.05$ ITT analysis *Primary outcomes:* ANCOVA	No significant group difference for demographics, baseline knee pain, radiographic status or compliance	Total: 16% *DF: 10 (12%)* AE: 5 LOE: 2 Other: 3 *DMSO: 14 (18%)* AE: 3 LOE: 8 Other: 3 *Placebo: 15 (18%)* AE: 0 LOE: 10 Other: 5	• Aim of the study was not to evaluate the efficacy of DMSO. Is power therefore adequate? • DMSO was used in this study to enhance absorption of DF • Multi-centre trial – high external validity • Compliance did not differ between groups • Drop out rates due to lack of effect was significant lower in DF compared to DMSO and placebo • Only 1-week washout of prohibited medication before baseline assessment • Scale of improvement with DF comparable to that of oral intake of DF • Clinical significance of results not reported by author • Treatment period not long enough to assess AE • DMSO dose not at therapeutic level

Koenen *et al.*[48]	DMSO, 39:72 DF, 30:80	DMSO: 61.5 DF: 63.9 (40–80)	Yes 1. Radiological evidence of knee 2. Aged 40–80	Yes 1. Patients with other form of arthritis or trauma at the knee	All steroids and other analgesic/ anti-inflammation medication stopped 28 or 7 days before start of study, respectively	No	No	No ITT analysis *Primary outcomes:* ANOVA	No significant group differences at baseline demographic data and baseline values for primary efficacy values (i.e., pain at rest and on movement)	Total: 24 (10%) Reasons included: non-compliance, failure to attend, SE (seven cases − 30%), age over 80	• Aim of trial was to show equivalence but no formal definition of equivalence given • Multi-centre trial − high external validity • Dose not therapeutic and inadequate treatment • Short treatment period but the aim of this study was to assess outcome during an acute inflammatory phase • No group difference in baseline characteristics • Over 90% of patient rated tolerability as good or very good • No use of a placebo, a direct comparison trial • No power calculation • Conclusions that both treatments are equivalent are sound • ADR; mild (DMSO 12; DF 2)

M: male; ANOVA: analysis of variance; F: female; ITT: intent to treat; SEs: side effects; LOE: lack of effect.

symptoms (>6 months) were randomised to one of four oral treatments: glucosamine 1500 mg/d; MSM 1500 mg/d; combination of MSM (1500 mg/d) and glucosamine (1500 mg/d) or placebo, for 12 weeks. The dosage used is lower than that recommended for clinical practice. No other treatment was allowed during the trial, but rescue medication was permitted. Treatment began after a 2-week washout. Main outcome measures were pain and swelling indices (4-point scale), VAS pain, joint mobility, patients and physician global assessment and the disease specific Lequesne index. The primary outcome was "responder rate" defined by a >3-point decrease in Lequesne index together with investigator assessment of efficacy; "good" or "fair". The power calculation was based on VAS of pain, and not the responder rate, and identified 120 patients would be required. No definitive evaluation of MSM can be evaluated as the results for the primary outcome was not reported; changes in VAS pain were reported but no statistical results were described. Significant decreases in pain scores were reported for the pain index (secondary outcome), from baseline to end of treatment in the glucosamine ($P < 0.001$), MSM ($P < 0.001$) and in the combination of glucosamine and MSM ($P < 0.05$); all three combinations were superior to placebo. Results are presented as means at baseline and 12 weeks but analysis using analysis of covariance (ANCOVA) at 12 weeks with baseline values as covariates would have been more appropriate to compare the main treatments effects between the four groups utilising the factorial nature of the trial. The main adverse event was diarrhoea which occurred in 5% of the participants in the study.

Kim *et al.*[38] compared oral MSM (2-week step-up dose from 2 g/d to 6 g/d) vs placebo over 12 weeks in a double-blind RCT (JADAD 5). Twenty-five patients with American College of Rheumatology (ACR) mild to moderate knee OA with regular persistent pain over 3 months entered treatment after a 1-week washout period from all other therapies. The primary outcome measure was the disease specific WOMAC. Both treatments resulted in benefit in all measured variables, with significant differences between treatments in favour of MSM for pain ($P = 0.041$) and physical function ($P = 0.045$). Adverse events were minor and mainly GI related. This study used a dose of MSM in upper range of the suggested therapeutic level for a clinically appropriate period. The findings suggest efficacy for MSM but the improvement of 14.6 mm (pain VAS) is a lower effect size than reported in trials using COX-2 inhibitor Celecoxib (28.6 mm)[51]. However, our sensitivity analysis confirms that this study was not sufficiently powered; 50 subjects were recruited, 25 in each of the two arms. The reported power calculation was based on anticipated improvements over baseline rather than on a clinical difference between the two treatment groups. As the observed difference between the improvements in pain from baseline for the two treatments was 7.3 mm (±3.5 mm S.E.M.) greater on active MSM than on placebo, with a significance of $P = 0.04$, this study had a power of 55% to detect such a difference using a 5% level of significance. The positive outcome may be overestimated because baseline recordings were measured after washout, so any deterioration in pain for this washout week may have enhanced the apparent treatment effect.

Discussion

Biological mechanisms of action for DMSO and MSM provide support for their proposed anti-inflammatory[52] and

Table II(b)
Further methodological details of RCT for MSM

Author	Sex ratio (M:F)	Mean age of sample group (year) (range)	Inclusion criteria stated	Exclusion criteria stated	Concomitant medications recorded	Consort statement	Compliance assessed	Power calculation performed, statistical analysis	Baseline characteristics	Dropouts	Comment
Kim *et al.*[38]	MSM, 9:12 Placebo, 6:13	MSM: 56.6 Placebo: 55.6	Yes 1. Knee OA according to ACR criteria functional class 1−3 and radiographic confirmed Kellgren−Lawrence (K−L) grades 2−3 2. Regular arthritic pain for >3 months 3. Appropriate high scores in PGA and VAS 4. Age > 40 years	Yes 1. Severe OA (K−L IV) 2. Other types of arthritis or chronic pain 3. Corticosteroid use in previ ous 3 months	All medication (NSAID, CAM) stopped days prior to baseline Rescue analgesia was permitted	Yes	Yes, weekly telephone calls and pills counted at end of study	Yes ITT analysis Group differences in baseline to week 12 by *t* test	No significant group differences at baseline for sex, age, height, weight and symptom duration, NSAID use, MSM or DMSO use, ACR classification, baseline VAS scores, PGA or PhGA scores, and radiological stage	Total: 10 (20%) *MSM: 4 (16%)* 2 LOE 1 SE 1 Lost to follow-up *Placebo: 6 (24%)* 5 LOE 1 Lost to follow-up	• Dosage and treatment duration appropriate • Demographic information only about patients who finished the trial • Short washout period of only 7 days so may enhance apparent treatment effect • Compliance in both groups was good (MSM −89.5 and placebo −90.5%) • Power calculation based on 25% improvement of WOMAC pain scale at 12 weeks with 80% power, $P = 0.05$ identified $N = 22$ per group and allowed for 10% drop our rate (i.e., $N = 25$). But did not consider differences be tween treatment groups • Authors report no ''major'' difference between treatment groups at baseline • Longitudinal analysis could have been completed • Authors reported that length of trial inadequate, with WOMAC scales de creasing at 12 weeks hence further monitoring would be needed. • Patients recruited were not as severe as other NSAID trials (mainly ACR I and II) • Exclusion criteria included patients with a body mass index (BMI) >45 kg/m^2 • No statistical analysis of adverse events

Usha and Naidu[37]	Glu, 12:18 MSM, 8:22 Both, 10:20 Placebo, 12:16	Glu: 52 MSM: 51 Both: 52 Placebo: 50 (40−70)	Yes 1. Radiological evidence of mild to moderate severity of knee OA 2. Minimum duration of symptoms for 6 months 3. Lequesne score between 8 and 18 4. Age 40−70 years 5. No NSAID in previous 2/52	Yes 1. Severe OA or $<$grade 1 OA 2. Any anti-inflammatory medication 3. Involved in an other clinical trial in last 30 days	All medication stopped 2 weeks prior paracetamol as rescue medication	No	Yes Pill counting	Yes $N = 120$ to detect 20% score on VAS, 80% power and $\alpha = 0.05$ ITT analysis *Primary outcomes:* Analysis Fisher's two-tailed test Other: ANOVA, Mann Whitney or Student's *t* test for other variables	No significant group differences at baseline for age, height, weight and symptom duration, baseline VAS scores, concomitant use of analgesic and radiological stage	Total: 8% *Glu*: 3 (10%) *MSM*: 3 (10%) *Combination*: 2 (7%) *Placebo*: 4 (13%) All lost due to follow-up after 4 weeks therapy	• Aim of study was to assess efficacy of all three treat ments vs placebo • Dosage and treatment du ration appropriate • Results of primary outcome ''responder rates'' were not reported. No clear definition of the primary and secondary outcomes • Compliance good in 80% of patients, no significant group differences • Drug taken as capsules • All participants had to stop OA treatment prior to the study • CI not recorded • No statistical results re ported for various variables e.g., VAS pain, rescue medication, walking time, joint motility • Analysis was based on re sponder rates (even though power was based on differ ence in VAS means) • ANOVA was used for the comparisons of the Lequesne pain and swelling index, the results presented as means at baseline and 12 weeks (with SD at each time period). More appropriate to have carried out an ANCOVA on the scores at 12 weeks with baseline values as covariates and comparisons made between the four groups using the factorial nature of the trial • Longitudinal analysis could have been performed

Table III
Adverse effects

Author	Nutritional supplement	Adverse events noted?	How noted and by whom?	Total no. of adverse events	Total no. of patient experiencing adverse effect	Observed adverse effects
DMSO studies						
Vuopala *et al.*[50]	DMSO	No	No information	No information	No information	No adverse effects noted.
Eberhardt *et al.*[49]	DMSO	Yes	Documentation of adverse events by the patient or questioning by the examiner	DMSO: 5 Placebo: 4	DMSO: 9 (16%) Placebo: 10 (18%)	*DMSO*: slight redness of skin (5), burning sensation (1), taste sensation (2), diarrhoea (1), vomiting (1) *Placebo*: slight redness of skin (7), itching (2), febrile infection (2), cough (1)
Koenen	DMSO	Yes	No information	No information	DMSO: 17 (16%) DF: 5 (5%)	Mild and localised skin reactions
Bookman *et al.*[31]	DMSO	Yes	Patient diaries	DF: 9 DMSO: 10 Placebo: 9	DF: 76 (90%) DMSO: 54 (68%) Placebo: 23 (27%)	Most frequent AE was skin dryness or flakiness at application site and occurred in 36% DF, 15% DMSO and 1% placebo No significant group differences in GI events *DF*: constipation (1), diarrhoea (1), dyspepsia (6), halitosis (4), body odour (2), dry skin (30), paraesthesia (12), rash (11), pruritus (9) *DMSO*: constipation (1), diarrhoea (2), dyspepsia (4), nausea (4), vomiting (1), halitosis (1), dry skin (11), paraesthesia (18), rash (6), pruritus (6) *Placebo*: constipation (1), diarrhoea (3), dyspepsia (5), nausea (1), vomiting (1), dry skin (1), paraesthesia (5), rash (3), pruritus (3)
MSM studies						
Usha and Naidu[37]	MSM	Yes	Reported by the patient or questioning at visit and recording in case report	No information	No information	Authors do not state in which treatment group the adverse effect occurred in. Minor GI discomfort. Main adverse event was diarrhoea, occurred in 5% patients. No patients stopped trial due to adverse drug reactions
Kim *et al.*[38]	MSM	Yes	Questionnaire assessing GI and neurotoxic symptoms at baseline and 12 weeks	No information	MSM: 12 (57%) Placebo: 11 (58%)	All minor symptoms No statistical evaluation of adverse events *MSM*: bloating (14%), constipation (10%), indigestion (5%), fatigue (10%), concentration problems (5%), insomnia (10%) and headaches (5%) *Placebo*: bloating (10%), constipation (10%), indigestion (5%), fatigue (16%), concentration problems (5%), insomnia (5%) and headaches (5%)

AE: adverse event.

analgesic[17–19]action. The history, pharmacology and relevant pre-clinical studies of DMSO/MSM have been reviewed comprehensively elsewhere[15,16]. This review confirms that currently there is no definitive evidence for the efficacy of either DMSO or MSM in OA. The four studies evaluating DMSO trials were conflicting, two (evaluating a total of 333 patients) were positive[48,49] and two (evaluating a total of 348 patients) were negative[31,50]. The two MSM studies[37,38] assessed a total of 168 patients and reported significant effects of MSM over placebo. These results initially are promising but no definitive conclusion can be drawn for the efficacy of MSM in OA knee due the methodological issues highlighted. These include the lack of reporting of primary outcome variables by Usha and Naidu trial[37]; and inadequate power and non-clinically relevant improvements identified for Kim *et al.*[38].

This review has highlighted the need to identify the optimal treatment period and dose of DMSO and MSM in OA. Only two of the six studies (both the MSM trials[37,38]) treated for an apparently clinically relevant time period (more than 3 months). The DMSO trials only medicated for 3–4 weeks which appears to be an insufficient time to adequately evaluate treatment. DMSO was used topically in all trials in doses below 50% suggesting suboptimal treatment according to current recommendations. However, significant positive findings were identified in two studies using low dose concentrations (25%[49] and 10%[48] vs the recommended 60%) taken for inadequate time period. These contradictory findings have also been identified previously in both the early uncontrolled trials of DMSO for OA in humans[14] (some showing beneficial effects[12,54,55] including a multicentre outcome trial[53] while others did not[56]) as well as in animal models[57–59]. This suggests the current guidelines may be incorrect and emphasises the need for a phase II trial. A number of factors may explain these inconsistencies. Although variation in the dosages makes comparison between trials difficult and can contribute to variability in trial outcomes [as observed in the supplementation trials of omega-3 essential fatty acids (EFA)[60]], it is unlikely that this is the case with DMSO given that only low not high dose studies demonstrated an effect. Further trials are needed to clarify and explain these anomalous results.

Five of the six studies clearly evaluated DMSO or MSM as an alternative rather than an adjunctive treatment[31,37,38,48,49]. All the studies identified assessed OA knee with pain as the primary outcome in all the studies with relevant validated outcome measures. Only two studies employed the disease specific WOMAC as a primary outcome[31,38]; with the others reporting either VAS pain[37,48], Likert pain[49] or assessment of pain relief[50] as one of the primary outcomes. All but one study[50] clearly stated the inclusion and exclusion criteria. The studies were pragmatic and generally representative of this condition involving the elderly with appropriate comorbidity thus increasing the external validity. All the studies, except Vuopala *et al.*[50], recruited participants with radiological evidence of OA although only two[37,38] used formal X-ray classification criteria and excluded severe OA which is clinically more difficult to treat. Pain was a selection criterion for three of the six studies ranging from current pain (over 2 weeks)[31] to longer-term pain (3–6 months). Patients were excluded if they had recent conventional treatment[31,37,38,49] or other secondary arthritis or other painful conditions[31,38,48,49].

The methodology quality of the studies was variable. Four of the six studies[31,37,38,49], obtained high JADAD scores (i.e., a score of 4 or 5) with two obtaining the maximum score of 5[31,38]. The remaining two studies received low scores due to lack of description of blinding[48], randomisation and dropouts[50]. In addition, the issue of blinding was questionable in all but one of the DMSO studies[31] as DMSO has a pungent smell.

The quality of adverse event reporting was poor; group differences were assessed in only one study[31] and causality was not reported in any studies consequently it was not possible to identify an adverse reaction from a study event. One study did not report any adverse events[50] and two did not identify which events arose in which treatment group[37,48]. The number of adverse events in the trials ranges from 16[48,50] to 68%[31] in the DMSO studies and 57% for the only MSM study[38] to report it. No serious adverse events were reported, the majority of events were minor and related to localised skin reactions and GI symptoms. DMSO elicited more skin reactions than oral MSM but minor GI complaints were reported for both supplements[31,37,38,49]. Body odour is one of the main adverse effects that are associated with DMSO but only one study[31] noted this adverse effect, suggesting poor reporting. Drop out rates due to adverse events were very low, and coupled with the adverse event data, this suggests that these supplements are only associated with minor and transitory adverse events when taken for short time periods but also that longer-term evaluation is essential. Standard conventional treatment causes 9–39%[3,61–63] of OA patients to experience GI adverse events compared to 4–15% in those taking DMSO. However, the shorter time periods reported do not provide information relevant to longer-term use of these supplements in large populations. Based on these data it is currently difficult to definitively evaluate the safety profile of DMSO or MSM.

This is the first systematic review assessing DMSO, and the first to assess the combination of both DMSO and MSM in the treatment of OA. We have highlighted the necessity for improved design, analysis and reporting in future studies. Despite the plausible biological mechanism for their purported action, further rigorous investigations are need to assess their efficacy as an adjunctive or alternative treatment in OA, as it is currently impossible to arrive at definitive conclusion about their effectiveness. Some of the data shows promise and therefore further studies are warranted as both supplements may have potential as a safe alternative to NSAIDs. The evidence for MSM is stronger suggesting that it may be more beneficial to DMSO. Studies to evaluate their safety and in particular phase II studies to evaluate appropriate dose are essential as current data on safety and dose are limited and constrain the design of further RCTs. Subsequent efficacy studies are also needed with adequately power to detect a significant effect size, an adequate treatment period, use of appropriate outcome measures and appropriate blinding. In addition, a comparator trial of MSM against standard conventional treatment would now seem valuable.

Conflict of interest

None of the authors had any conflict of interest.

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