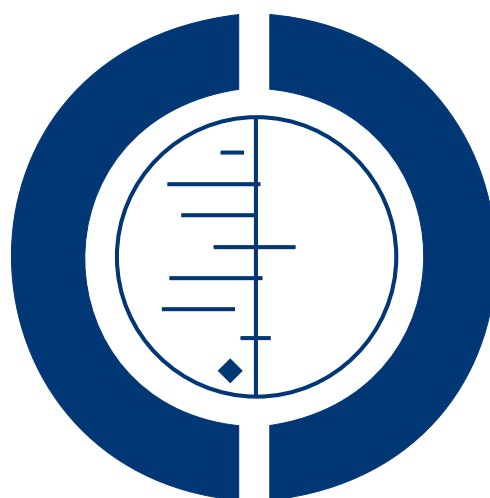


Doxycycline for osteoarthritis of the knee or hip (Review)

Nüesch E, Rutjes AWS, Trelle S, Reichenbach S, Jüni P



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[Intervention Review]

Doxycycline for osteoarthritis of the knee or hip

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Cochrane Database of Systematic Reviews, Issue 4, 2009 (Status in this issue: *New*)

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DOI: 10.1002/14651858.CD007323.pub2

This version first published online: 7 October 2009 in Issue 4, 2009.

Last assessed as up-to-date: 10 January 2009. (Help document - [Dates and Statuses](#) explained)

This record should be cited as: Nüesch E, Rutjes AWS, Trelle S, Reichenbach S, Jüni P. Doxycycline for osteoarthritis of the knee or hip. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD007323. DOI: 10.1002/14651858.CD007323.pub2.

ABSTRACT

Background

Osteoarthritis is a chronic joint disease that involves degeneration of articular cartilage. Pre-clinical data suggest that doxycycline might act as a disease-modifying agent for the treatment of osteoarthritis, with the potential to slow cartilage degeneration.

Objectives

To examine the effects of doxycycline compared with placebo or no intervention on pain and function in patients with osteoarthritis of the hip or knee.

Search strategy

We searched CENTRAL (*The Cochrane Library* 2008, issue 3), MEDLINE, EMBASE and CINAHL up to 28 July 2008, checked conference proceedings, reference lists, and contacted authors.

Selection criteria

We included studies if they were randomised or quasi-randomised controlled trials that compared doxycycline at any dosage and any formulation with placebo or no intervention in patients with osteoarthritis of the knee or hip.

Data collection and analysis

We extracted data in duplicate. We contacted investigators to obtain missing outcome information. We calculated differences in means at follow-up between experimental and control groups for continuous outcomes and risk ratios for binary outcomes.

Main results

We found one randomised controlled trial that compared doxycycline with placebo in 431 obese women. After 30 months of treatment, clinical outcomes were similar between the two treatment groups, with a mean difference of -0.20 cm (95% confidence interval (CI) -0.77 to 0.37 cm) on a visual analogue scale from 0 to 10 cm for pain and -1.10 units (95% CI -3.86 to 1.66) for function on the WOMAC disability subscale, which ranges from 17 to 85. These differences correspond to clinically irrelevant effect sizes of -0.08 and -0.09 standard deviation units for pain and function, respectively. The difference in changes in minimum joint space narrowing was in favour of doxycycline (-0.15 mm, 95% CI -0.28 to -0.02 mm), which corresponds to a small effect size of -0.23 standard deviation

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1

units. More patients withdrew from the doxycycline group compared with placebo due to adverse events (risk ratio 1.69, 95% CI 1.03 to 2.75).

Authors' conclusions

The symptomatic benefit of doxycycline is minimal to non-existent. The small benefit in terms of joint space narrowing is of questionable clinical relevance and outweighed by safety problems. Doxycycline should not be recommended for the treatment of osteoarthritis of the knee or hip.

PLAIN LANGUAGE SUMMARY

Doxycycline for osteoarthritis

This summary of a Cochrane review presents what we know from research about the effect of doxycycline on osteoarthritis.

The review shows that in people with osteoarthritis:

- Doxycycline probably will not improve pain or physical function.
- Doxycycline probably causes side effects. We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects.

What is osteoarthritis and what is doxycycline?

Osteoarthritis (OA) is a disease of the joints, such as your knee or hip. When the joint loses cartilage, the bone grows to try and repair the damage. Instead of making things better, however, the bone grows abnormally and makes things worse. For example, the bone can become misshapen and make the joint painful and unstable. This can affect your physical function or ability to use your knee.

Doxycycline is a type of antibiotic that seems to stop the process of damage to the joints. It is taken in pill form.

Best estimate of what happens to people with osteoarthritis who take doxycycline:

Pain

- People with doxycycline and people with placebo are equally likely to respond to treatment (difference of 0%).
- People who took doxycycline rated their pain to be 2 on a scale of 0 (no pain) to 10 (extreme pain) after 30 months.
- People who took a fake medication (placebo) also rated their pain to be about 2 on a scale of 0 (no pain) to 10 (extreme pain) after 30 months.

Physical function

- People with doxycycline and people with placebo are equally likely to respond to treatment (difference of 0%).
- People who took doxycycline rated their physical function to be about 36 on a scale of 17 (no disability) to 85 (extreme disability) after 30 months.
- People who took a fake medication rated their physical function to be about 37 on a scale of 17 (no disability) to 85 (extreme disability) after 30 months.

Side effects

- 7 more people who took doxycycline withdrew or dropped out from the trial because of side effects (absolute difference of 7%).
- 17 people out of 100 who took doxycycline withdrew or dropped out from the trial because of side effects (17%).
- 10 people out of 100 who used a fake medication withdrew or dropped out from the trial because of side effects (10%).

Serious harms

- There was no difference in the number of people who experienced serious harms (difference of 0%). This could be the result of chance.
- 14 people out of 100 who took doxycycline experienced serious harms (14%)
- 14 people out of 100 who used a fake medication experienced serious harms (14%).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Doxycycline compared with placebo for osteoarthritis of the knee or hip						
Patient or population: Patients with osteoarthritis of the knee or hip Settings: Clinical Research Centres Intervention: Doxycycline Comparison: Placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk ¹	Corresponding risk				
	Placebo	Doxycycline				
Pain 10 cm VAS scale (follow-up: 30 months)	2.2 cm pain on 10 cm VAS	2.0 cm pain (Δ -0.2 cm, -0.8 to +0.4 cm)		307 (1)	++00 low ²	Little evidence of beneficial effect (NNT: not statistically significant)
Function WOMAC function (range 17 to 85) (follow-up: 30 months)	37.4 units on WOMAC (range 17 to 85)	36.3 units on WOMAC (Δ -1.1, -3.9 to +1.7)		307 (1)	++00 low ²	Little evidence of beneficial effect (NNT: not statistically significant)
Minimum joint space width (follow-up: 30 months)	-45 mm change	-30 mm change (Δ 15 mm, 2 to 28 mm)		361 (1)	+++0 moderate ³	No reasonable assumption could be made for the calculation of NNT
Number of patients withdrawn due to adverse events (follow-up: 30 months)	103 per 1000	174 per 1000 (106 to 283)	RR 1.69 (1.03 to 2.75)	431 (1)	+++0 moderate ³	NNH: 14 (95% CI 6 to 324)
Number of patients experiencing any serious adverse event (follow-up: 30 months)	136 per 1000	141 per 1000 (88 to 227)	RR 1.04 (0.65 to 1.67)	431 (1)	++00 low ⁴	Little evidence of harmful effect (NNH: not statistically significant)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio; GRADE: GRADE Working Group grades of evidence (see explanations); NNT: number needed to treat; NNH: number needed to harm

GRADE Working Group grades of evidence

High quality (+ + + +): Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality (+ + + 0): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality (+ + 00): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality (+ 000): We are very uncertain about the estimate.

¹ Scores for efficacy outcomes and risks for safety outcomes from the placebo group in the trial.

² Downgraded (2 levels) because the effect was estimated from a single trial, confidence intervals were wide and crossed no difference, and the analyses were not done according to the intention-to-treat principle.

³ Downgraded (1 level) because the effect was estimated from a single trial.

⁴ Downgraded (2 levels) because the effect was estimated from a single trial, confidence intervals were wide and crossed no difference.

BACKGROUND

Osteoarthritis is a chronic joint disease that involves degeneration of the articular cartilage. Doxycycline is a tetracycline antibiotic which has been shown to induce inhibition of cartilage matrix metallo-proteinases (MMPs) and to slow down the progression of structural damage to the affected joint (Shlopov 1999; Smith 1996). Doxycycline was therefore suggested as a disease-modifying agent for the treatment of osteoarthritis. Treatment with oral doxycycline may slow down the rate of joint space narrowing, which is used as a surrogate measure for cartilage loss of the knee in patients with knee osteoarthritis (Brandt 2005). However, treatment benefits of putative chondro-protective disease-modifying agents are still controversial. Chondroitin and glucosamine are other potentially structure-modifying pharmacological substances that are widely used to reduce the symptoms of osteoarthritis of the hip or knee. Recently published meta-analyses, however, have questioned their effectiveness because of large heterogeneity between studies and biases introduced by industry sponsored, methodologically weak and small trials (Reichenbach 2007; Vlad 2007). As a tetracycline antibiotic, doxycycline interferes with various biological pathways and has effects on tissues other than cartilage (Rubin 2000). Safety concerns about the long-term use of doxycycline have also been expressed, especially in elderly patients with co-morbid conditions (Dieppe 2005).

OBJECTIVES

We set out to compare doxycycline with placebo or no specific intervention in patients with knee or hip osteoarthritis in terms of effects on pain, function and safety outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials with a control group receiving placebo or no intervention.

Types of participants

Studies including at least 75% of patients with clinically and/or radiologically confirmed osteoarthritis of the knee or hip.

Types of interventions

Trials investigating doxycycline at any dosage and in any formulation. Eligible control interventions were placebo or no intervention.

Types of outcome measures

Primary outcomes

Main outcomes were pain and function, as currently recommended for osteoarthritis trials (Altman 1996; Pham 2004). If data on more than one pain scale were provided for a trial, we referred to a previously described hierarchy of pain-related outcomes (Juni 2006; Reichenbach 2007) and extracted data on the pain scale that was highest on this list.

1. Global pain
2. Pain on walking
3. WOMAC osteoarthritis index pain subscore
4. Composite pain scores other than WOMAC
5. Pain on activities other than walking
6. Rest pain or pain during the night
7. WOMAC global algofunctional score
8. Lequesne osteoarthritis index global score
9. Other algofunctional scale
10. Patient's global assessment
11. Physician's global assessment

If data on more than one function scale were provided for a trial, we extracted data according to the hierarchy presented below.

1. Global disability score
2. Walking disability
3. WOMAC disability subscore
4. Composite disability scores other than WOMAC
5. Disability other than walking
6. WOMAC global scale
7. Lequesne osteoarthritis index global score
8. Other algofunctional scale
9. Patient's global assessment
10. Physician's global assessment

If pain or function outcomes were reported at several time points, we extracted the measure at the end of the trial or at a maximum of three months after termination of therapy, whichever came first.

Secondary outcomes

Secondary outcomes were minimum and mean radiographic joint space width, the number of patients experiencing any adverse event, patients who withdrew because of adverse events, and patients experiencing any serious adverse events. We defined serious adverse events as events resulting in in-patient hospitalisation, prolongation of hospitalisation, persistent or significant disability, congenital abnormality/birth defect of offspring, life-threatening events or death.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 3), MEDLINE (1966 to July 2008) and EMBASE (1975 to July 2008) through the Ovid platform (www.ovid.com), and CINAHL (1937 to July 2008) through EBSCOhost, using truncated variations of preparation names, including brand names, combined with truncated

variations of terms related to osteoarthritis, all as text words. We applied a validated methodological filter for controlled clinical trials (Dickersin 1994). The specific search algorithms are displayed in [Appendix 1](#) for MEDLINE, EMBASE and CINAHL, and in [Appendix 2](#) for CENTRAL.

Searching other sources

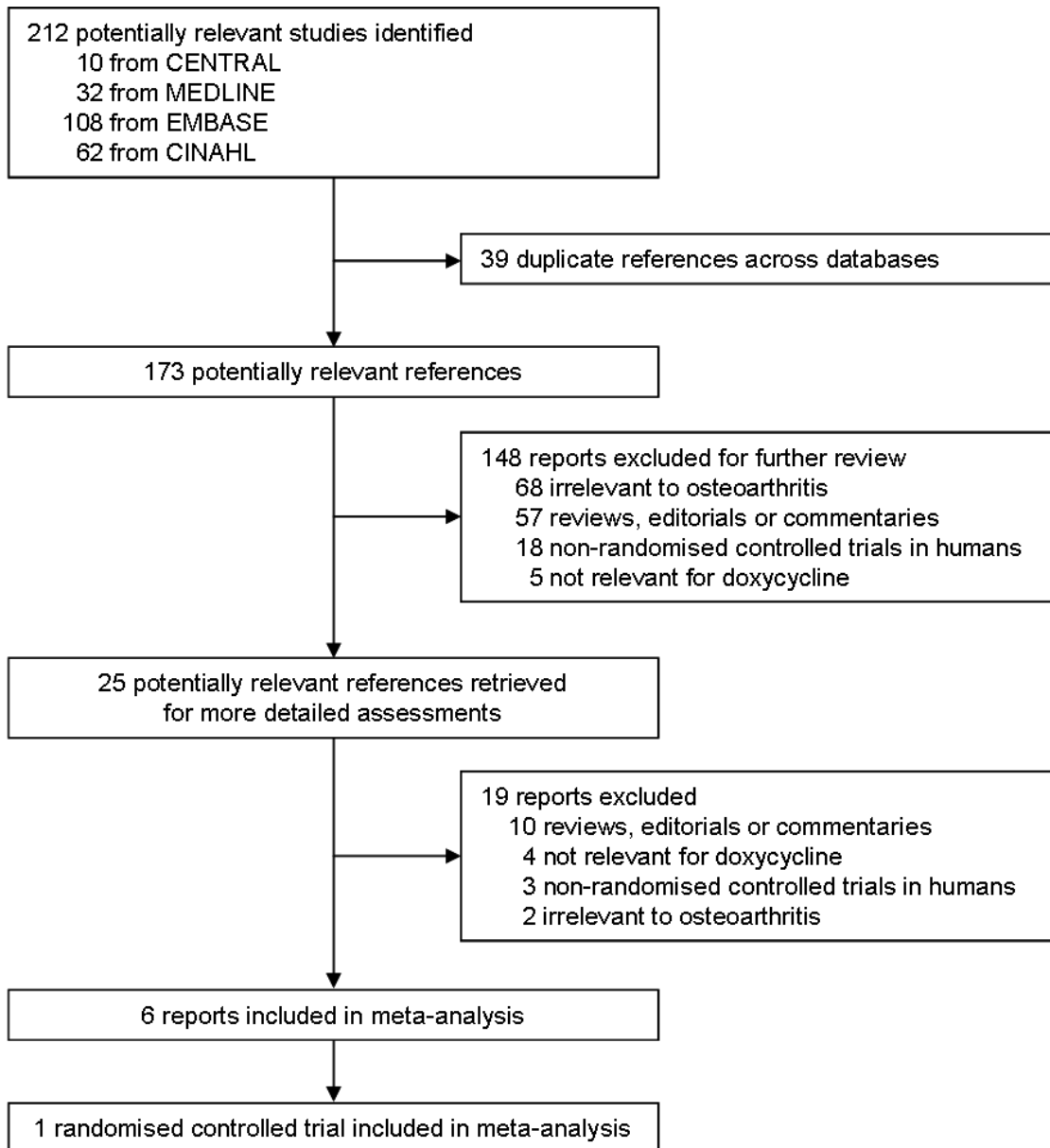
We manually searched conference proceedings, used Science Citation Index to retrieve reports citing relevant articles, contacted content experts and trialists, and screened reference lists of all obtained articles, including related reviews. Finally, we searched several clinical trial registries (www.clinicaltrials.gov, www.controlled-trials.com, www.actr.org.au and www.umin.ac.jp/ctr) to identify ongoing trials. The last update of the search was performed on 28 July 2008.

Data collection and analysis

Selection of studies

Two review authors (EN and AR) independently evaluated all yielded titles and abstracts for eligibility (see [Figure 1](#)). We resolved disagreements by consensus. No language restrictions were applied. In case of multiple reports relating to the same trial, we considered all reports.

Figure 1. Flow chart



Data extraction and management

Two review authors (EN and AR) extracted trial information independently using a standardised, piloted data extraction form accompanied by a codebook. We resolved disagreements by discussion or by involvement of a third review author (SR or PJ). We extracted generic and trade names of the experimental intervention, the type of control used, dosage, frequency and duration of treatment, patient characteristics (average age, gender, mean duration of symptoms, type of joints affected), type of pain- and function-related outcome extracted, trial design, trial size, duration of follow-up, type and source of financial support, and publication status from trial reports. When necessary, we approximated means and measures of dispersion from figures in the reports. For cross-over trials, we extracted data from the first period only because of possible carry-over effects. Whenever possible, we used results from an intention-to-treat analysis. If effect sizes could not be calculated, we contacted the authors for additional data.

Assessment of risk of bias in included studies

Two review authors (EN and AR) independently assessed the adequacy of randomisation, blinding and analyses (Juni 2001). We resolved disagreements by consensus or discussion with a third review author (SR or PJ). We assessed two components of randomisation: generation of allocation sequences and concealment of allocation. We considered generation of sequences adequate if it resulted in an unpredictable allocation schedule; mechanisms considered adequate included random-number tables, computer-generated random numbers, minimisation, coin tossing, shuffling cards and drawing lots. We considered concealment of allocation adequate if the investigators responsible for patient inclusion were unable to suspect before allocation which treatment was next; methods considered adequate include central randomisation, pharmacy controlled randomisation using identical pre-numbered containers, and sequentially numbered, sealed, opaque envelopes. We considered blinding of the patients adequate if experimental and control preparations were explicitly described as indistinguishable or if a double-dummy technique was used. We considered blinding of therapists and outcome assessors adequate if it was explicitly mentioned in the report that they were unaware of the assigned treatment. If pain outcomes were patient-administered, however, we considered patients to be the outcome assessors and rated blinding of outcome assessors adequate if patients were deemed adequately blinded as described above. We considered analyses adequate if all randomised patients were included in the analysis (intention-to-treat principle). Finally, we used GRADE to describe the quality of the overall body of evidence (Guyatt 2008; Higgins 2008), defined as the extent of confidence in the estimated treatment benefits and harms.

Data synthesis

We summarised continuous outcomes using differences in means at the end of treatment across treatment groups. If some of the required data were unavailable, we used approximations as previ-

ously described (Reichenbach 2007). We also expressed continuous outcomes as effect sizes in standard deviation units, with the differences in mean values at the end of follow-up across treatment groups divided by the pooled standard deviation. An effect size of -0.20 standard deviation units can be considered a small difference between experimental and control groups, a SMD of -0.50 a moderate difference, and -0.80 a large difference (Cohen 1988; Juni 2006). We expressed binary outcomes as risk ratios (RR). We performed analyses in RevMan version 5 (RevMan 2008). All P values are two-sided.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

We retrieved 212 potentially relevant reports from our electronic searches (Figure 1). We excluded a randomised placebo-controlled trial of doxycycline in seronegative arthritis (Smieja 2001) and an animal study that assessed the effects of oral doxycycline in dogs (Brandt 1995). Six reports, describing one randomised controlled trial, met our inclusion criteria (Brandt 2005). We did not find any additional completed trials in conference proceedings, nor did we identify relevant ongoing trials in trial registers. The included trial was a multicentre, placebo-controlled trial in 431 obese women with radiologically confirmed osteoarthritis of the knee. After a single-blind placebo run-in of four weeks duration, which was designed to allow the exclusion of patients unlikely to be compliant with trial procedures, patients were randomly allocated to receive 100 mg doxycycline or placebo twice a day for 30 months. Patients were permitted to take any pain medication throughout the trial.

Risk of bias in included studies

An overview of the methodological characteristics of the included trial is presented in Figure 2. The trial was described as randomised in blocks of six, although mechanisms to generate blocks of random sequences and methods used to conceal allocation to treatments were not specified. The trial was reported as double-blind after a single-blind run-in period. We deemed blinding of patients adequate in view of the use of a matching placebo. Patients were explicitly described as blinded, whereas blinding of treating physicians was not explicitly described. Analyses of clinical outcomes, such as pain and function, were based on 307 patients who completed the 30-month treatment period as mandated in the protocol (Brandt 2005). Analyses of radiological outcomes included all 361 patients who returned for their radiographic follow-up irrespective of whether they discontinued the study drug. Safety analyses included all 431 randomised patients according to the intention-to-treat principle. The primary outcome of the trial was joint space

narrowing on the semiflexed AP view in the tibiofemoral joint ([Buckland-Wright 1995](#)). Measurements were done manually, according to the method of Lequesne ([Lequesne 1995](#)), using the points of a screw-adjustable compass and a graduated magnifying lens. Measurements were made by an observer who was blinded to the treatment group assignment of the subject. The intra- and inter-reader reproducibilities of repeated measurements of joint space width in a random sample of 30 radiographs (on which all identifying information was masked) were excellent (intraclass correlation coefficients of 0.99 and 0.96, respectively). Assessors determining the joint space width were not blinded to the sequence of the radiographs. No sample size calculation was described. The trial was supported in part by the National Institute of Health (NIH); no commercial funding was reported. For the effectiveness outcomes, we classified the quality of the evidence ([Guyatt 2008](#)) as low to moderate, because only a single trial was available, estimates were not derived from intention-to-treat analyses, and were imprecise for pain and function (see '[Summary of findings for the main comparison](#)'). For withdrawals due to adverse events and serious adverse event outcomes, we classified the quality of the evidence ([Guyatt 2008](#)) as low to moderate in view of a single available trial and an imprecise estimate for serious adverse events (see '[Summary of findings for the main comparison](#)').

Figure 2. Methodological characteristics and source of funding of the included trial. (+) indicates low risk of bias, (?) unclear and (-) a high risk of bias on a specific item.

	Adequate sequence generation?	Allocation concealment?	Blinding of patients described?	Blinding of physicians?	Blinding of outcome assessors?	Interventions reported as indistinguishable?	Intention-to-treat analysis?	Funding by commercial body avoided?	Funding by non-profit organisation?
Brandt 2005	?	?	+	+	+	+	-	?	+

Effects of interventions

See: [Summary of findings for the main comparison](#)

Data on clinical outcomes at the end of treatment were provided by the investigators in personal communications. Pain in the index knee was measured after a 50-foot walk on a 10 cm visual analogue scale (VAS) (Brandt 2005). The analysis revealed a difference in means between doxycycline and placebo of -0.20 cm (95% CI -0.77 to 0.37 cm, $P = 0.49$, Figure 3). The Likert version of the WOMAC function subscale was used to measure disability after 30 months (range 17 to 85), with a mean difference of -1.10 (95% CI -3.86 to 1.66, $P = 0.44$, Figure 4). These differences correspond to clinically irrelevant effect sizes of -0.08 and -0.09 standard deviation units for pain and function, respectively. The difference in changes in minimum joint space narrowing was in favour of doxycycline (-0.15 mm, 95% CI -0.28 to -0.02 mm, $P = 0.03$, Figure 5), which corresponds to a small effect size of -0.23 standard deviation units.

Figure 3. Forest plot of 1 trial comparing the effects of doxycycline and placebo on knee pain. Values on x-axis denote mean differences in 50-foot walking pain as measured on a 10-cm VAS scale.

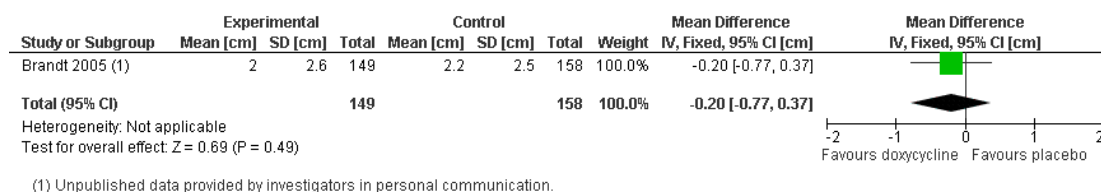


Figure 4. Forest plot of 1 trial comparing the effects of doxycycline and placebo on physical function. Values on x-axis denote mean differences in WOMAC disability scores.

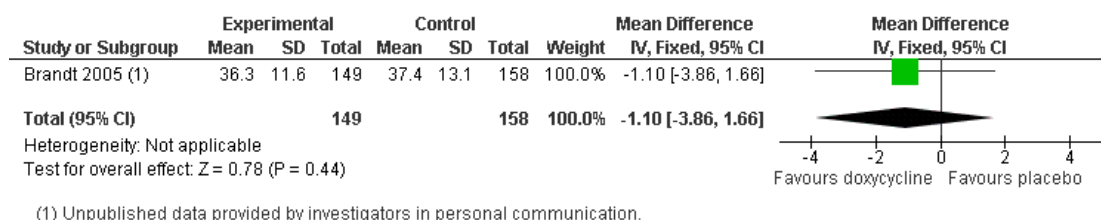
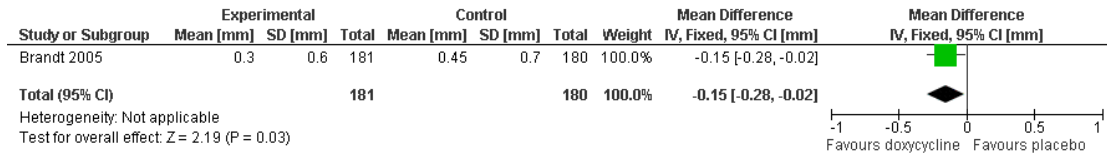


Figure 5. Forest plot of 1 trial comparing the effects of doxycycline and placebo on physical function. Values on x-axis denote mean differences in minimum joint space width in mm.



During the 30 months of treatment, patients were more likely to withdraw due to adverse events in the doxycycline group compared to the placebo group (RR 1.69, 95% CI 1.03 to 2.75, $P = 0.04$, Figure 6). Data on serious adverse events were provided by investigators in personal communications. The authors found 31 patients with serious adverse events in the doxycycline group and 29 in the placebo group (RR 1.04, 95% CI 0.65 to 1.67, $P = 0.86$, Figure 7). None of these events were fatal and none of the serious adverse events were deemed to be related to doxycycline (Brandt 2005).

Figure 6. Forest plot of I trial comparing patients withdrawn or dropped out because of adverse events between doxycycline and placebo. Values on x-axis denote risk ratios.

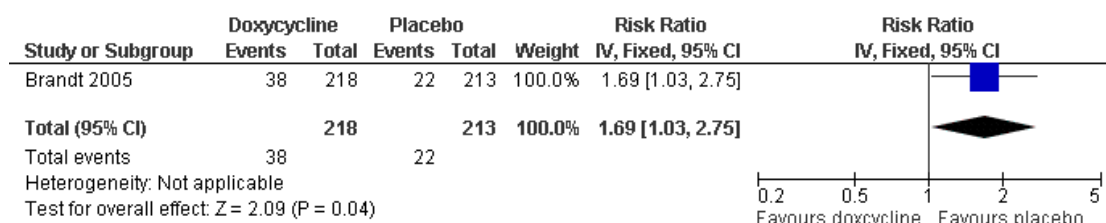
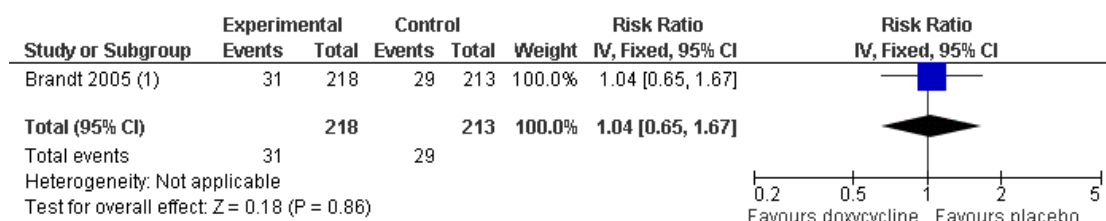


Figure 7. Forest plot of I trial comparing patients experiencing any serious adverse event between doxycycline and placebo. Values on x-axis denote risk ratios.



(1) Unpublished data provided by investigators in personal communication.

DISCUSSION

Summary of main results

Our systematic review indicates that the symptomatic benefit of doxycycline in patients with osteoarthritis of the knee is minimal to non-existent. The small benefit in terms of joint space narrowing is of questionable clinical relevance. The higher risk of drop-outs due to adverse events in the doxycycline group compared to placebo indicates that this benefit is outweighed by safety problems.

Quality of the evidence

The evidence is based on a single available randomised trial including only obese women with mild to moderate osteoarthritis of the knee (Brandt 2005). The trial was designed to detect differences in joint space narrowing rather than differences in clinical outcomes. No threshold for the level of knee pain was used for inclusion and the average level of knee pain was low at baseline, leaving little room for improvement. Radiological and clinical outcomes correlate poorly in patients with osteoarthritis and it is not surprising that effects of doxycycline differ for these outcomes. Joint space width in millimetres evaluated on radiographs is currently considered to be the preferred technique to evaluate structural progression in osteoarthritis, and is required by the regulatory agencies (Helliö 2009). The use of semiflexed radiographs instead of AP views improves detection of tibiofemoral joint space narrowing,

especially in early osteoarthritis (Merle-Vincent 2007). However, there is a debate about how to define relevant radiographic progression, and a recently published OARSI-OMERACT initiative recommends dichotomising the continuous variable of joint space narrowing to distinguish between progressors and non-progressors, based on the absolute change in joint space width over a predefined threshold (Ornetti 2009). Mazzuca et al. reported that doxycycline did not differ from placebo in the frequency of relevant joint space loss using a range of different cut-offs to distinguish between the presence or absence of relevant joint space loss (≥ 0.5 mm, ≥ 1.0 mm, $\geq 20\%$, or $\geq 50\%$ of joint space width at baseline, Mazzuca 2006). No evidence is available for patients representing a broader spectrum of osteoarthritis, including males, patients with hip osteoarthritis and non-obese patients. The available trial is potentially biased: it remains unclear whether sequence generation and allocation concealment were adequate and a high number of patients were excluded from analyses, which may result in overestimation of benefits (Nuesch 2009).

Potential biases in the review process

We based our review on a broad literature search and it seems unlikely that we missed relevant trials (Egger 2003). Two review authors performed selection of trials and data extraction independently to minimise bias and transcription errors (Egger 2001; Göttsche 2007). As with any systematic review, our study is limited by the quality of the available evidence. As indicated above, only one trial was available and this trial suffered from some methodological shortcomings. Therefore, this systematic review is inconclusive (Nuesch 2009a). The observed effects, both beneficial and harmful, would need to be confirmed in at least one independent, methodologically sound trial in a wider spectrum of patients with symptomatic osteoarthritis before definite conclusions can be drawn.

Agreements and disagreements with other studies or reviews

Doxycycline may reduce the progression of cartilage degeneration in canine osteoarthritis through inhibition of cartilage matrix metallo-proteinases (Brandt 1995; Yu 1992). Similar results were ob-

tained in guinea pigs (Greenwald 1994) and rabbits (Golub 1993). In a canine osteoarthritis model, doxycycline reduced disease progression (Yu 1992). This notion supports the observed reduction in joint space narrowing in the randomised trial in humans (Brandt 2005). When studied in patients with chronic seronegative arthritis (Smieja 2001), doxycycline had no effect on pain reduction or function improvement compared to placebo after three months of treatment. The trial included in our review included patients with non-inflammatory symptomatic osteoarthritis and used a longer treatment duration of 30 months, but results were similar (Brandt 2005).

AUTHORS' CONCLUSIONS

Implications for practice

The symptomatic benefit of doxycycline is minimal to non-existent, while the small benefit in terms of joint space narrowing is of questionable clinical relevance and outweighed by safety problems. Doxycycline should therefore not be recommended for the treatment of osteoarthritis of the knee or hip.

Implications for research

The available evidence of the effectiveness of doxycycline is based on a single randomised trial. An additional placebo-controlled trial would be needed before firm conclusions can be drawn. This trial should be appropriately powered, use adequate mechanisms to conceal allocation and include all patients in the analyses according to the intention-to-treat principle. The trial should include a broad spectrum of patients, including males and non-obese individuals.

ACKNOWLEDGEMENTS

We thank the Cochrane Musculoskeletal Group editorial team for valuable comments and Malcolm Sturdy for database support. The authors are grateful to Kenneth Brandt and Steve Mazzuca for providing unpublished data from their trial.

REFERENCES

References to studies included in this review

Brandt 2005 {published and unpublished data}

Brandt KD, Mazzuca SA. Experience with a placebo-controlled randomized clinical trial of a disease-modifying drug for osteoarthritis: the doxycycline trial. *Rheumatic Diseases Clinics of North America* 2006;**32**(1):217-34, xi-xii.

* Brandt KD, Mazzuca SA, Katz BP, Lane KA, Buckwalter KA, Yocum DE, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis and Rheumatism* 2005;**52**(7):2015-25.

Hellio Le Graverand MP, Brandt KD, Mazzuca SA, Katz BP, Buck R, Lane KA, et al. Association between concentrations of urinary type II collagen neopeptide (uTIINE) and joint space narrowing in patients with knee osteoarthritis. *Osteoarthritis Cartilage* 2006;**14**(11):1189-95.

Mazzuca SA, Brandt KD, Katz BP, Lane KA, Bradley JD, Heck LW, et al. Subject retention and adherence in a randomized placebo-controlled trial of a disease-modifying osteoarthritis drug. *Arthritis and Rheumatism* 2004;**51**(6):933-40.

Mazzuca SA, Brandt KD, Katz BP, Lane KA, Buckwalter KA. Comparison of quantitative and semiquantitative indicators of joint space narrowing in subjects with knee osteoarthritis. *Annals of the Rheumatic Diseases* 2006;**65**(1):64-8.

Mazzuca SA, Brandt KD, Schauwecker DS, Katz BP, Meyer JM, Lane KA, et al. Severity of joint pain and Kellgren-Lawrence grade at baseline are better predictors of joint space narrowing than bone scintigraphy in obese women with knee osteoarthritis. *Journal of Rheumatology* 2005;**32**(8):1540-6.

References to studies excluded from this review

Brandt 1995 {published data only}

Brandt KD. Modification by oral doxycycline administration of articular cartilage breakdown in osteoarthritis. *Journal of Rheumatology* 1995;**22**(SUPPL. 43):149-51.

Smieja 2001 {published data only}

Smieja M, MacPherson DW, Kean W, Schmuck ML, Goldsmith CH, Buchanan W, et al. Randomised, blinded, placebo controlled trial of doxycycline for chronic seronegative arthritis. *Annals of the Rheumatic Diseases* 2001;**60**(12):1088-94.

Additional references

Altman 1996

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**(4):217-43.

Buckland-Wright 1995

Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. *Annals of the Rheumatic Diseases* 1995;**54**(11):872-80.

Cohen 1988

Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd Edition. Hillsdale, NJ: Lawrence Earlbaum Associates, 1988.

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964):1286-91.

Dieppe 2005

Dieppe P. Disease modification in osteoarthritis: are drugs the answer?. *Arthritis and Rheumatism* 2005;**52**(7):1956-9.

Egger 2001

Egger M, Smith GD. Principles of and procedures for systematic reviews. In: Egger M, Smith GD, Altman DG editor(s). *Systematic Reviews in Health Care: Meta-Analysis in Context*. London: BMJ Books, 2001:23-42.

Egger 2003

Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health technology assessment (Winchester, England)* 2003;**7**(1):1-76.

Golub 1993

Golub LM, Ramamurthy NS, McNamara TF, et al. Method to reduce connective tissue destruction. US Patent 5 258 371 November 3, 1993.

Greenwald 1994

Greenwald RA. Treatment of destructive arthritis disorders with MMP inhibitors. *Annals of the New York Academy of Sciences* 1994;**731**:181-98.

Guyatt 2008

Guyatt G, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Schunemann HJ. GRADE: what is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**:995-8.

Gøtzsche 2007

Gøtzsche PC, Hróbjartsson A, Maric K, Tendal B. Data extraction errors in meta-analyses that use standardized mean differences. *JAMA* 2007;**298**(4):430-7.

Hellio 2009

Hellio Le Graverand-Gastineau MP. OA clinical trials: current targets and trials for OA. Choosing molecular targets: what have we learned and where we are headed?. *Osteoarthritis Cartilage* 2009;**in press**.

Higgins 2008

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org. The Cochrane Collaboration.

Juni 2001

Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;**323**(7303):42-6.

Juni 2006

Juni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the individual. *Best Practice and Research. Clinical Rheumatology* 2006;**20**(4):721-40.

Lequesne 1995

Lequesne M. Quantitative measurements of joint space during progression of osteoarthritis: chondrometry. In: Kuettner K, Goldberg V editor(s). *Osteoarthritic disorders*. Rosemont (IL): American Academy of Orthopaedic Surgeons, 1995:427–44.

Mazzuca 2006

Mazzuca SA, Brandt KD, Katz BP, Lane KA, Buckwalter KA. Comparison of quantitative and semiquantitative indicators of joint space narrowing in subjects with knee osteoarthritis. *Annals of the Rheumatic Diseases* 2006;**65**(1):64–8.

Merle-Vincent 2007

Merle-Vincent F, Vignon E, Brandt K, Piperno M, Coury-Lucas F, Conrozier T, et al. Superiority of the Lyon schuss view over the standing anteroposterior view for detecting joint space narrowing, especially in the lateral tibiofemoral compartment, in early knee osteoarthritis. *Annals of the Rheumatic Diseases* 2007;**66**(6):747–53.

Nuesch 2009

Nuesch E, Trelle S, Reichenbach S, Rutjes AWS, Burgi E, Scherer M, Altman DG, Juni P. The effects of the exclusion of patients from the analysis in randomised controlled trials: meta-epidemiological study. *BMJ* (in press).

Nuesch 2009a

Nuesch E, Juni P. Commentary: which meta-analyses are conclusive?. *International Journal of Epidemiology* 2009;**38**(1):298–303.

Ornetti 2009

Ornetti P, Brandt K, Hellio-Le Graverand MP, Hochberg M, Hunter DJ, Kloppenburg M, et al. OARSI-OMERACT definition of relevant radiological progression in hip/knee osteoarthritis. *Osteoarthritis Cartilage* 2009;**17**(7):842–9.

Pham 2004

Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004;**12**(5):389–99.

Reichenbach 2007

Reichenbach S, Sterchi R, Scherer M, Trelle S, Burgi E, Burgi U, et al. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Annals of Internal Medicine* 2007;**146**(8):580–90.

RevMan 2008

The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2008.

Rubin 2000

Rubin BK, Tamaoki J. Macrolide antibiotics as biological response modifiers. *Current Opinion in Investigational Drugs* 2000;**1**(2):169–72.

Shlopov 1999

Shlopov BV, Smith GN Jr, Cole AA, Hasty KA. Differential patterns of response to doxycycline and transforming growth factor beta1 in the down-regulation of collagenases in osteoarthritic and normal human chondrocytes. *Arthritis and Rheumatism* 1999;**42**(4):719–27.

Smith 1996

Smith GN Jr, Brandt KD, Hasty KA. Activation of recombinant human neutrophil procollagenase in the presence of doxycycline results in fragmentation of the enzyme and loss of enzyme activity. *Arthritis and Rheumatism* 1996;**39**(2):235–44.

Vlad 2007

Vlad SC, LaValley MP, McAlindon TE, Felson DT. Glucosamine for pain in osteoarthritis: why do trial results differ?. *Arthritis and Rheumatism* 2007;**56**(7):2267–77.

Yu 1992

Yu LP Jr, Smith GN Jr, Brandt KD, Myers SL, O'Connor BL, Brandt DA. Reduction of the severity of canine osteoarthritis by prophylactic treatment with oral doxycycline. *Arthritis and Rheumatism* 1992;**35**(10):1150–9.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brandt 2005

Methods	Randomised controlled trial with 2 parallel groups Randomisation stratified by centre Trial duration: 30 months Multicentre trial including 6 centres No power calculation reported
Participants	431 patients with radiologically confirmed knee osteoarthritis were randomised Number of females: 431 (100%) Average age: 54.9 years Average BMI: 36.7 kg/m ² Severity of knee osteoarthritis: 59% with Kellgren/Lawrence grade 2 and 41% with Kellgren/Lawrence grade 3
Interventions	Experimental intervention: doxycycline, 100 mg twice daily Control intervention: placebo, twice daily Treatment duration: 30 months Analgesics other than study drugs allowed and intake was similar between groups
Outcomes	Extracted pain outcome: 50-foot walking pain after 30 months Extracted function outcome: WOMAC disability subscore after 30 months Primary outcome: joint space narrowing in the tibiofemoral compartment
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Subjects (...) were randomly assigned" Comment: no mention of the mechanism used for sequence generation
Allocation concealment?	Unclear	Quote: "Patients were allocated randomly to treatment groups in blocks of 6" Comment: no mention of concealment of allocation
Blinding of patients described?	Yes	Comment: indistinguishable interventions and the description of a double-blind phase implies blinding of patients
Blinding of physicians?	Yes	Comment: clearly distinguished between single blind run-in period and double-blind phase. Blinding of physicians probable

Brandt 2005 (Continued)

Blinding of outcome assessors?	Yes	Comment: depending on the outcome, patients or physicians were the assessors, both of which were blinded
Interventions reported as indistinguishable?	Yes	Quote: “matched placebo”
Intention-to-treat analysis? All outcomes	No	69 of 218 patients (32%) excluded in experimental group and 55 of 213 patients (26%) excluded in control group
Funding by commercial body avoided?	Unclear	No information provided
Funding by non-profit organisation?	Yes	Quote: “Supported by the NIH (grants R01-AR-43348, P60-AR-20582, and R01-AR-44370)”

BMI = body mass index

Characteristics of excluded studies [ordered by year of study]

Brandt 1995	Animal study
Smieja 2001	No patients in osteoarthritis

DATA AND ANALYSES

Comparison 1. Doxycycline versus placebo

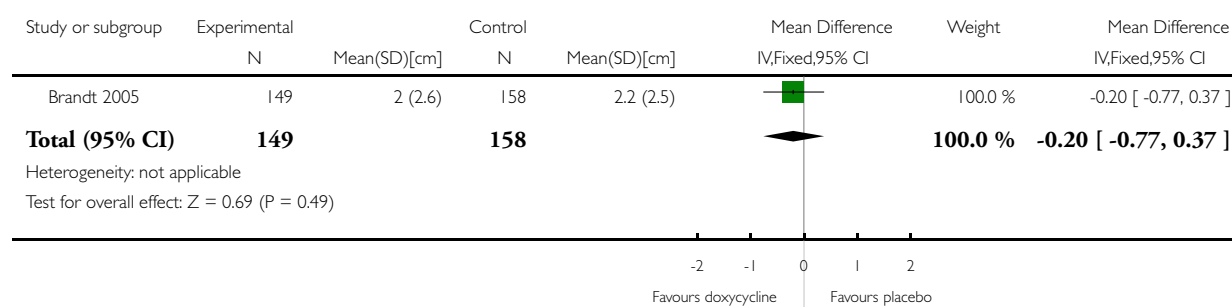
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	1	307	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.77, 0.37]
2 Physical function	1	307	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-3.86, 1.66]
3 Minimum joint space width	1	361	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.28, -0.02]
4 Number of patients withdrawn due to adverse events	1	431	Risk Ratio (IV, Fixed, 95% CI)	1.69 [1.03, 2.75]
5 Number of patients experiencing any serious adverse events	1	431	Risk Ratio (IV, Fixed, 95% CI)	1.04 [0.65, 1.67]

Analysis 1.1. Comparison 1 Doxycycline versus placebo, Outcome 1 Pain.

Review: Doxycycline for osteoarthritis of the knee or hip

Comparison: 1 Doxycycline versus placebo

Outcome: 1 Pain

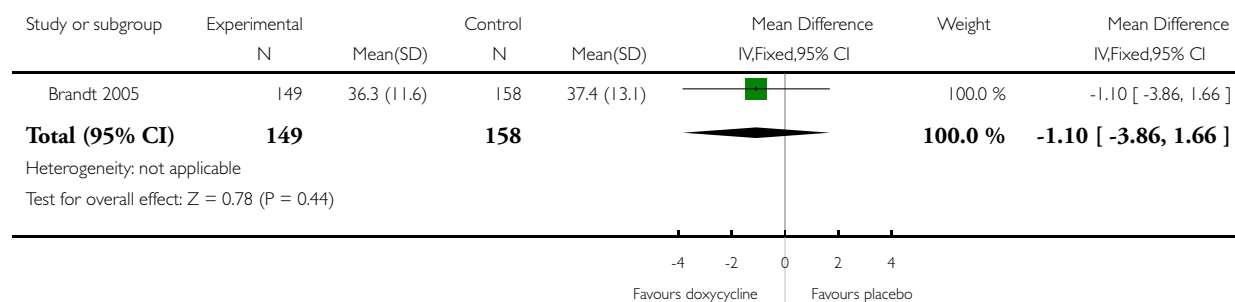


Analysis 1.2. Comparison 1 Doxycycline versus placebo, Outcome 2 Physical function.

Review: Doxycycline for osteoarthritis of the knee or hip

Comparison: 1 Doxycycline versus placebo

Outcome: 2 Physical function

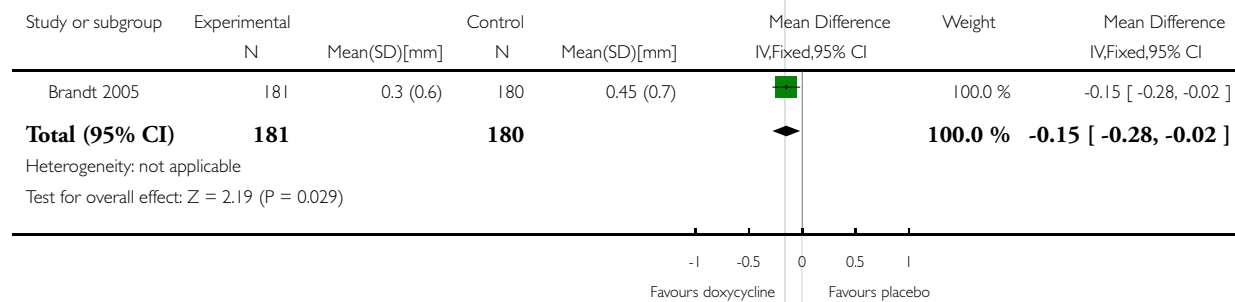


Analysis 1.3. Comparison 1 Doxycycline versus placebo, Outcome 3 Minimum joint space width.

Review: Doxycycline for osteoarthritis of the knee or hip

Comparison: 1 Doxycycline versus placebo

Outcome: 3 Minimum joint space width

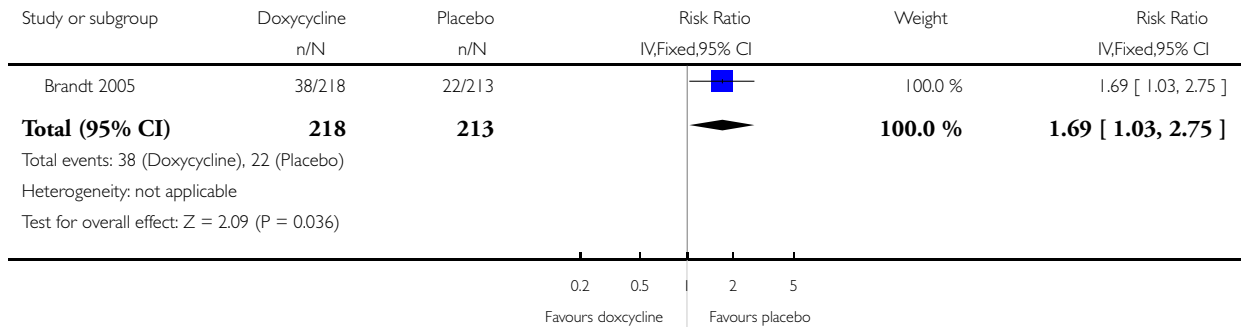


Analysis 1.4. Comparison 1 Doxycycline versus placebo, Outcome 4 Number of patients withdrawn due to adverse events.

Review: Doxycycline for osteoarthritis of the knee or hip

Comparison: 1 Doxycycline versus placebo

Outcome: 4 Number of patients withdrawn due to adverse events

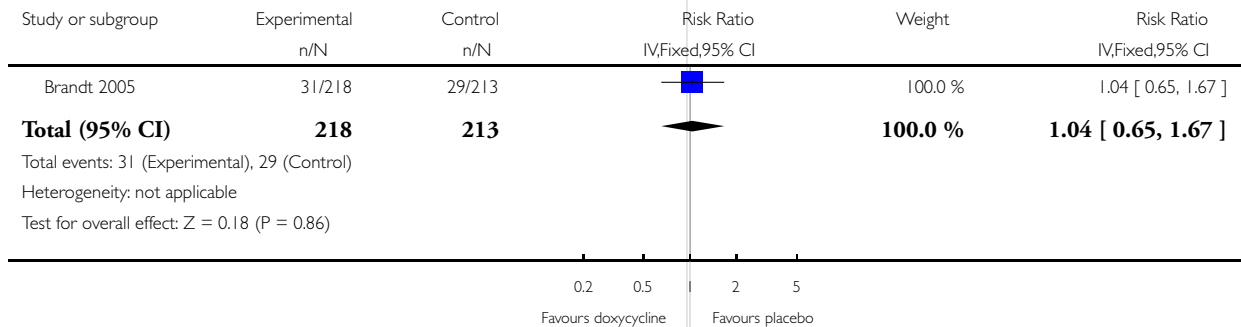


Analysis 1.5. Comparison 1 Doxycycline versus placebo, Outcome 5 Number of patients experiencing any serious adverse events.

Review: Doxycycline for osteoarthritis of the knee or hip

Comparison: 1 Doxycycline versus placebo

Outcome: 5 Number of patients experiencing any serious adverse events



APPENDICES

Appendix I. MEDLINE, EMBASE and CINAHL search strategy

OID MEDLINE	OID EMBASE	CINAHL through EBSCOhost
<p><i>Search terms for design</i></p> <ol style="list-style-type: none"> 1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized controlled trial.sh. 4. random allocation.sh. 5. double blind method.sh. 6. single blind method.sh. 7. clinical trial.pt. 8. exp clinical trial/ 9. (clin\$ adj25 trial\$).ti,ab. 10. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. 11. placebos.sh. 12. placebo\$.ti,ab. 13. random\$.ti,ab. 14. research design.sh. 15. comparative study.sh. 16. exp evaluation studies/ 17. follow up studies.sh. 18. prospective studies.sh. 19. (control\$ or prospectiv\$ or volunteer\$).ti,ab. 	<p><i>Search terms for design</i></p> <ol style="list-style-type: none"> 1. randomized controlled trial.sh. 2. randomization.sh. 3. double blind procedure.sh. 4. single blind procedure.sh. 5. exp clinical trials/ 6. (clin\$ adj25 trial\$).ti,ab. 7. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. 8. placebo.sh. 9. placebo\$.ti,ab. 10. random\$.ti,ab. 11. methodology.sh. 12. comparative study.sh. 13. exp evaluation studies/ 14. follow up.sh. 15. prospective study.sh. 16. (control\$ or prospectiv\$ or volunteer\$).ti,ab. 	<p><i>Search terms for design</i></p> <ol style="list-style-type: none"> 1. (MH "Clinical Trials+") 2. (MH "Random Assignment") 3. (MH "Double-Blind Studies") or (MH "Single-Blind Studies") 4. TX (clin\$ n25 trial\$) 5. TX (sing\$ n25 blind\$) 6. TX (sing\$ n25 mask\$) 7. TX (doubl\$ n25 blind\$) 8. TX (doubl\$ n25 mask\$) 9. TX (trebl\$ n25 blind\$) 10. TX (trebl\$ n25 mask\$) 11. TX (tripl\$ n25 blind\$) 12. TX (tripl\$ n25 mask\$) 13. (MH "Placebos") 14. TX placebo\$ 15. TX random\$ 16. (MH "Study Design+") 17. (MH "Comparative Studies") 18. (MH "Evaluation Research") 19. (MH "Prospective Studies+") 20. TX (control\$ or prospectiv\$ or volunteer\$) 21. S1 or S2 or (.....) or S20
<p><i>Search terms for Osteoarthritis</i></p> <ol style="list-style-type: none"> 20. exp osteoarthritis/ 21. osteoarthritis\$.ti,ab,sh. 22. osteoarthro\$.ti,ab,sh. 23. gonarthriti\$.ti,ab,sh. 24. gonarthro\$.ti,ab,sh. 25. coxarthriti\$.ti,ab,sh. 26. coxarthro\$.ti,ab,sh. 27. arthros\$.ti,ab. 28. arthrot\$.ti,ab. 29. ((knee\$ or hip\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ti,ab. 30. ((knee\$ or hip\$ or joint\$) adj3 stiff\$).ti,ab. 	<p><i>Search terms for Osteoarthritis</i></p> <ol style="list-style-type: none"> 17. exp osteoarthritis/ 18. osteoarthritis\$.ti,ab,sh. 19. osteoarthro\$.ti,ab,sh. 20. gonarthriti\$.ti,ab,sh. 21. gonarthro\$.ti,ab,sh. 22. coxarthriti\$.ti,ab,sh. 23. coxarthro\$.ti,ab,sh. 24. arthros\$.ti,ab. 25. arthrot\$.ti,ab. 26. ((knee\$ or hip\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ti,ab. 27. ((knee\$ or hip\$ or joint\$) adj3 stiff\$).ti,ab. 	<p><i>Search terms for Osteoarthritis</i></p> <ol style="list-style-type: none"> 22. osteoarthritis\$ 23. (MH "Osteoarthritis") 24. TX osteoarthro\$ 25. TX gonarthriti\$ 26. TX gonarthro\$ 27. TX coxarthriti\$ 28. TX coxarthro\$ 29. TX arthros\$ 30. TX arthrot\$ 31. TX knee\$ n3 pain\$ 32. TX hip\$ n3 pain\$ 33. TX joint\$ n3 pain\$ 34. TX knee\$ n3 ach\$ 35. TX hip\$ n3 ach\$ 36. TX joint\$ n3 ach\$

(Continued)

		<p>37. TX knee\$ n3 discomfort\$ 38. TX hip\$ n3 discomfort\$ 39. TX joint\$ n3 discomfort\$ 40. TX knee\$ n3 stiff\$ 41. TX hip\$ n3 stiff\$ 42. TX joint\$ n3 stiff\$ 43. S22 or S23 or S24....or S42</p>
<p><i>Search terms for Doxycycline</i> 31. exp doxycycline/ 32. doxycycline.tw. 33. deoxyxytetracycline.tw. 34. hydramycin.tw. 35. vibramycin.tw. 36. vibravenos.tw. 37. oracea.tw. 38. adoxa.tw. 39. doryx.tw. 40. doxy\$.tw. 41. monodox\$.tw. 42. periostat.tw. 43. atridox.tw. 44. vibrox\$.tw.</p>	<p><i>Search terms for Doxycycline</i> 28. exp doxycycline/ 29. doxycycline.tw. 30. deoxyxytetracycline.tw. 31. hydramycin.tw. 32. vibramycin.tw. 33. vibravenos.tw. 34. oracea.tw. 35. adoxa.tw. 36. doryx.tw. 37. doxy\$.tw. 38. monodox\$.tw. 39. periostat.tw. 40. atridox.tw. 41. vibrox\$.tw.</p>	<p><i>Search terms for Doxycycline</i> 44. (MH " Doxycycline ") 45. TX doxycycline 46. TX deoxyxytetracycline 47. TX hydramycin 48. TX vibramycin 49. TX vibravenos 50. TX oracea 51. TX adoxa 52. TX doryx 53. TX doxy\$ 54. TX monodox\$ 55. TX periostat 56. TX atridox 57. TX vibrox\$ 58. S44 or S45 or S57</p>
<p><i>Combining terms</i> 45. or/1-19 46. or/20-30 47. or/31-44 48. and/45-47 49. animal/ 50. animal/ and human/ 51. 49 not 50 52. 48 not 51 53. remove duplicates from 52</p>	<p><i>Combining terms</i> 42. or/1-16 43. or/17-27 44. or/28-41 45. and/42-44 46. animal/ 47. animal/ and human/ 48. 46 not 47 49. 45 not 48 50. remove duplicates from 49</p>	<p><i>Combining terms</i> 59. S21 and S43 and S58</p>

Appendix 2. CENTRAL search strategy

CENTRAL

Search terms for osteoarthritis

- #1. MeSH descriptor Osteoarthritis explode all trees
- #2. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot* OR ((knee* OR hip* OR joint*) near/3 (pain* OR ach* OR discomfort*)) OR ((knee* OR hip* OR joint*) near/3 stiff*)) in Clinical Trials

Search terms for doxycycline

- #3. MeSH descriptor Doxycycline explode all trees
- #4. doxycycline in Clinical Trials
- #5. deoxyxytetracycline in Clinical Trials
- #6. hydramycin in Clinical Trials
- #7. vibramycin in Clinical Trials
- #8. vibravenos in Clinical Trials
- #9. oracea in Clinical Trials
- #10. adoxa in Clinical Trials
- #11. doryx in Clinical Trials
- #12. doxy* in Clinical Trials
- #13. monodox* in Clinical Trials
- #14. periostat in Clinical Trials
- #15. atridox in Clinical Trials
- #16. vibrox* in Clinical Trials

Combining terms

- #17. (#1 OR #2)
- #18. (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
- #19. (#17 AND #18) in Clinical Trials

WHAT'S NEW

Last assessed as up-to-date: 10 January 2009.

1 May 2008	Amended	MSG ID C118-R
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HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

Protocol completion: Nüesch, Rutjes, Trelle, Reichenbach, Jüni

Acquisition of data: Nüesch, Rutjes

Analysis and interpretation of data: Nüesch, Rutjes, Trelle, Reichenbach, Jüni

Manuscript preparation: Nüesch, Rutjes, Trelle, Reichenbach, Jüni

Statistical analysis: Nüesch, Rutjes

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Institute of Social and Preventive Medicine, University of Bern, Switzerland.
Intramural grants

External sources

- Swiss National Science Foundation, Switzerland.
National Research Program 53 on musculoskeletal health (grant numbers 4053-40-104762/3 and 3200-066378)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Because only one study was included in our review, we used inverse variance fixed-effect model instead of the random-effects model of meta-analysis, and we did not perform the stratified analyses. Differences between experimental and control groups were expressed as mean differences instead of standardised mean differences due to better interpretability of the results. We could not perform stratified analyses or funnel plot evaluation to investigate whether potential variation between trials could be explained by biases affecting individual trials or by publication bias.