Auranofin versus placebo in rheumatoid arthritis (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

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[Intervention Review]

Auranofin versus placebo in rheumatoid arthritis

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Editorial group: Cochrane Musculoskeletal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.
Review content assessed as up-to-date: 21 February 2000.

Citation: Suarez-Almazor ME, Spooner C, Belseck E, Shea B. Auranofin versus placebo in rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2000, Issue 2. Art. No.: CD002048. DOI: 10.1002/14651858.CD002048.

ABSTRACT

Background

Auranofin is an oral gold compound used for the treatment of rheumatoid arthritis (RA). The use of auranofin has declined in the past few years, perhaps due in part to conflicting results from different studies.

Objectives

To estimate the short-term efficacy and toxicity of auranofin for the treatment of (RA)

Search methods

An electronic literature search was conducted using MEDLINE and EMBASE, followed by hand searches of the reference lists of the trials retrieved from the electronic search.

Selection criteria

All randomized controlled trials (RCTs) and controlled clinical trials (CCTs) comparing auranofin against placebo in patients with RA

Data collection and analysis

The methodological quality of the trials was assessed using Jadad's score. Rheumatoid arthritis outcome measures were extracted from the publications for the 6-month endpoint. The pooled analysis was performed using standardized mean differences (SMDs) for joint counts, pain and global assessments. The weighted mean difference (WMD) was used for ESR. Toxicity was evaluated with pooled odds ratios for withdrawals and adverse reactions. A chi-square test was used to assess heterogeneity among trials. Fixed effects models were used throughout.

Main results

A statistically significant benefit was observed for auranofin when compared to placebo for tender joint scores, pain, patient and physician global assessments and ESR. The standardized weighted mean difference between treatment and placebo was -0.39 (95% CI -0.54, -0.25) for tender joint scores, -0.08 (95% CI -0.22, -0.07) for swollen joint scores, and the weighed mean difference was -4.68 (95% CI -6.59, -2.77) for pain scores. The WMD for ESR was -9.85mm (95% CI -16.46, -3.25). Withdrawals from adverse reactions were 1.5 times higher in the auranofin group OR = 1.52 (95% CI 0.94, 2.46) but this result was not statistically significant. Patients receiving placebo were four times more likely to discontinue treatment because of lack of efficacy than patients receiving auranofin OR=0.29 (95% CI: 0.19, 0.43).

Authors' conclusions

Auranofin appears to have a small clinically and statistically significant benefit on the disease activity of patients with RA. The beneficial effects appear to be modest compared to drugs such as methotrexate or parenteral gold. Its effects on long term health status and radiological progression are not clear at this time.

PLAIN LANGUAGE SUMMARY

Auranofin for the treatment of rheumatoid arthritis

The objective of this review was to evaluate the short-term efficacy of auranofin for the treatment of rheumatoid arthritis when compared to placebo. Our results show that auranofin appears to be efficacious in the short-term treatment of patients with RA (6 months), and has a small but clinically and statistically significant benefit on the disease activity of these patients. Its effects on overall health status and radiological progression are not clear at this time, but would appear to be modest. Auranofin may be most appropriate for those patients with early and mild disease who are more likely to respond to less potent (and less toxic) therapies.

BACKGROUND

A number of disease-modifying antirheumatic drugs (DMARDs) can be used to treat patients with rheumatoid arthritis (RA). These drugs have a more profound effect than anti-inflammatory agents. Although most patients with RA will have increased articular damage over the years, DMARDs are believed to limit or retard this disease progression, compared to anti-inflammatory drugs which only have a symptomatic effect alleviating the pain and stiffness. Auranofin is an oral gold compound which has been used for the treatment of RA since the early 1980's. Auranofin was developed as an alternative to parenteral gold compounds. Parenteral gold is an effective treatment for RA but its use is limited by its toxicity which can be serious. Furthermore, parenteral gold salts are administered weekly by intramuscular injection, which is less convenient for patients than oral administration. Auranofin is more frequently used in some areas of the world such as some European countries compared to Canada or the United States. A number of studies have evaluated auranofin in comparison to placebo, but the results have not been consistent. Some of the variation in use may relate to the differences in the reported magnitude of clinical benefits across trials.

OBJECTIVES

The objective of this study was to evaluate the short-term efficacy of auranofin in comparison to placebo for the treatment of RA.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and controlled clinical trials (CCT), with a minimum duration of 6 months.

Types of participants

Patients with a diagnosis of RA (as stated in the publication).
Age >16 years old.
Patients receiving no DMARDs other than auranofin.

Types of interventions

Intervention group: auranofin, minimum dosage 6 mg/day, oral administration
Control group: placebo

Types of outcome measures

Outcome endpoints included measures of efficacy and toxicity.
1. Efficacy
All the outcome measures in OMERACT (OMERACT 1993) and the American College of Rheumatology (ACR) (Felson 1995) were included for potential analysis, although only some were consistently reported across trials.
OMERACT measures for efficacy include:
a) Number of tender joints
b) Number of swollen joints

c) Pain
d) Physician global assessment
e) Patient global assessment
f) Functional status
g) Acute phase reactants (e.g. erythrocyte sedimentation rate, ESR)
h) Radiological damage
2. Withdrawals and dropouts - these were analyzed as:
a) Total number of withdrawals and dropouts
b) Number of withdrawals from lack of efficacy
c) Number of withdrawals due to concurrent illness
d) Number of withdrawals due to adverse reactions
e) Number of withdrawals due to system-specific adverse reactions (e.g. gastrointestinal, renal, etc.)
3. Adverse reactions (ADRs) not causing withdrawal were analysed by system:
a) Gastrointestinal - all signs and symptoms plus diarrhea only
b) Mucosal / cutaneous
c) Renal
d) Liver
e) Hematological
f) Neurological (headache, dizziness, tingling)
g) Miscellaneous adverse reactions

Search methods for identification of studies

1. Electronic searches
A comprehensive MEDLINE search was performed using the strategy developed by Dickersin et al (Dickersin 1994) from 1966 to December 1998.
EMBASE was searched from 1988 to December 1998, with a strategy similar to the one used for MEDLINE
2. Hand searches
Reference lists of all the trials selected through the electronic search were manually searched to identify additional trials.
3. The Controlled Clinical Trials Register (CCTR) was also searched.

Data collection and analysis

Data extracted from the publications included study characteristics and outcome measures of efficacy and toxicity. Data was extracted by one reviewer and cross checked by a second.
1. Efficacy
The results on efficacy were analysed for the 6-month endpoint. Although some trials had longer duration, this endpoint was chosen because it was reported in most of the trials and was thought to be the minimum required time to adequately assess the efficacy of auranofin.
Nine trials were included in the review. Each study reported at least one OMERACT outcome measure and could be included in the meta-analysis. The most consistently reported measures were joint and pain scores. Three different measures of function were reported by at least one trial. The three functional measures were not pooled, and were analyzed separately in a subgroup analysis.
The analysis compares end of trial results. When the standard deviation (SD) was not reported, we used either the baseline SD or imputed a SD from the weighted average coefficient of variation (CV) calculated from the other trials. (CV = SD/mean) If trials reported medians and ranges, the median was entered as the mean, the range was divided by 3 to estimate the SD. (Interquartile ranges were divided by 2 to estimate a SD.) Change from baseline scores were converted to end of trial results when baseline values were available. When imputing a SD we elected to be as conservative as possible. We thought these procedures would introduce less bias than excluding the trial altogether.
End-of-trial results were pooled as standardized weighted mean differences for joint scores, and global assessments. This was necessary because of the variation in the outcome measures included in each study (e.g. number of tender joints, tender joint index). All trials that reported pain scores had used a VAS scale therefore pain results were pooled using a weighted mean difference. ESR results were also pooled using a weighted mean difference.
Trial results were entered in RevMan using the same direction to enable the pooling of results where the lowest value was improvement and the highest value was worsening. Negative values in standardized weighted means indicate a benefit of the active drug over placebo.
2. Withdrawals and dropouts
Adverse reactions (ADRs) were generally reported as overall results at the end of the trial. We therefore pooled withdrawals and dropouts at the end of the study, although in some cases follow-ups exceeded 6 months. Toxicity was analysed using a pooled odds ratio for total withdrawals from adverse reactions, and withdrawals for system-specific side-effects.
The heterogeneity of the trials for each pooled analysis was estimated using a chi-square test. Fixed effects models were used throughout. Random effects models were only used for outcomes showing statistically significant heterogeneity.
All studies reported global reasons for withdrawal or dropout but not all reported ADRs by system.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Nine parallel design RCTs met the criteria for inclusion. Three trials were conducted in North America, five in the UK and Europe, one in New Zealand, all between the years 1982 and 1997.

All trials included patients with active RA. Glennas 1997 accepted only those with elderly onset (i.e. > 60 yr), while Davies 1982 and Johnsen 1989 accepted only those with early disease (i.e. < 3 and 2 years respectively).

Auranofin was administered orally at a dose of 6 mg/day in all trials. The duration of trials ranged from 21 weeks to 2 years.

No single measure was reported by all nine trials. Tender joint indices, pain scores and ESR were adequately reported to allow pooling in seven studies, swollen joints in six, patient global assessment in four and physician global in three. One of the studies (Lewis 1984) reported the results for a disease activity index which combined several measures, and p values for each single measure; only ESR could be pooled with results from other trials.

Four studies included one or more functional scales. Bombardier 1986 included a number of functional measures and quality of life instruments. The purpose of this study was to examine changes in overall health with a number of instruments. We chose three of these measures for comparative purposes in this review including the Health Assessment Questionnaire, Keitel Assessment and 15m walk time. We felt that of all of the measures reported these were the most commonly used in patients with RA. The other two studies reported changes in Health Assessment Questionnaire and walk time. An additional trial (Ward 1983) reported functional class. This is a 4-point scale which is not considered to be as discriminative as the other measures in this study and was not included in the review.

Three studies reported radiological progression (Prouse 1982, Johnsen 1989, Glennas 1997). The results were reported in a similar fashion and were not pooled, but are summarized in the text of the review. Another two trials (Ward 1983; Wenger 1983) reported that they performed x-rays but the results were not included in any of the publications identified for this review. Three studies (Davies 1982, Lewis 1984, Ward 1983) included a third arm involving gold sodium thiomalate (GSTM). The results related to parenteral gold are not included in the present review.

Risk of bias in included studies

The methodological quality of the studies was assessed by two of the investigators using a quality scale validated and published by Jadad 1996. This scale includes an assessment of randomization, double-blinding procedures and description of withdrawals. The possible range of scores is 0 (worst) to 5 (best). Two studies had a score of 5, five a score of 4, and two a score of 3. (See table of included studies). Concealment of allocation was considered adequate in four studies, and unclear in five. Disagreements were resolved by consensus.

Effects of interventions

A total of 539 people received auranofin while 510 received placebo.

Efficacy

Data for all the outcome measures was not reported by all the studies. The number of trials included for each analysis ranged from one to seven.

Statistically significant improvements favouring auranofin were noted for tender joint scores, pain scores, global patient and physician assessments and ESR. For tender joint scores the SMD was -0.39 (95% CI -0.54, -0.25), and for patient assessments the SMD was -0.20 (95% CI -0.38, -0.03) . There was demonstrated heterogeneity in the pooled result for physician assessments, therefore this result is reported using random effects. The SMD for physician global assessment was -0.38 (95% CI -0.73, -0.02). The WMD between auranofin and placebo scores for pain was -4.68 (95% CI -6.59, -2.77) and for ESR values was -9.85 (95% CI -16.46, -3.25). The pooled ERS results also showed heterogeneity so random effects estimates are reported. The heterogeneity was due to the Johnsen study which included only patients with RA of less than two years duration. No significant differences were observed between auranofin and placebo groups in swollen joint scores; these trials were also heterogeneous, but no major differences were observed between fixed and random effects. The heterogeneity was due to the results reported in Glennas 1997. Removing this trial corrected the heterogeneity but did not change substantially the results which remained insignificant.

No significant differences were observed in the measures that examined function (Health Assessment Questionnaire, Keitel Assessment or 50 ft. walk times) or in global assessment measures by physician or patients.

Lewis 1984 reported a disease activity index which combined six clinical variables (duration of morning stiffness, pain, grip strength, articular index, hemoglobin and ESR). Only p values were reported for most single measures and therefore only the ESR results could be pooled with those from other trials. At 24 weeks, the auranofin group showed significant improvement in pain, disease activity index and ESR.

Withdrawals from lack of efficacy were less frequent in the auranofin group (OR: 0.31, 95% CI: 0.21-0.44).

Three studies reported radiological outcomes (Prouse 1982, Johnsen 1989, Glennas 1997). Prouse 1982 stated that at three months, xray changes generally showed progression in those not responding clinically to gold therapy and amongst placebo group. Changes in those responding to therapy was variable. At 12 months only one patient on active therapy was thought to have progression. The actual aggregated data were not reported so no statistical inferences could be made. The results from Johnsen 1989 were reported at two years (Borg 1991) and showed that the placebo group had significantly more progression than the auranofin group measured by Larsen scores. These results were based on an intent to treat analysis. In Glennas 1997 results from 49 of 65 (75%) of patients showed no statistically significant intergroup differences

or changes in the Larsen-Dale index over 24 months.

Two studies had a longer duration, two years. One of them (Johnsen 1989) reported 2-year outcomes in a subsequent publication (Borg 1991): 53% (35) of the patients on auranofin and 37% (24) on placebo remained on trial drugs for the two years. There were improved effects noted especially in ESR, Ritchie index and number of swollen joints in those who remained on auranofin. A larger proportion of these patients could reduce (31 vs 17%) or stop (23 vs 4%) treatment with NSAIDS than those on placebo. Those on auranofin required fewer local steroid injections than those on placebo (37 vs 58%).

In the other study (Glennas 1997) 55% patients on auranofin completed the two year trial compared to 18% receiving placebo.

Toxicity

Analysis of withdrawals and dropouts was available for all trials. Overall, patients on auranofin were significantly less likely to withdraw than those receiving placebo: OR = 0.62 (95%CI: 0.46, 0.83). Patients on auranofin were significantly less likely to withdraw from lack of efficacy OR = 0.31 (95%CI: 0.21, 0.44) but were 1.5 times more likely to withdraw due to adverse reactions OR = 1.52 (95% CI 0.94, 2.46) however this difference was not statistically significant.

Patients taking auranofin demonstrated significantly higher withdrawal rates in only two system specific areas: 1) gastrointestinal symptoms in general OR = 2.98 (95% CI 1.36, 6.52), particularly diarrhea OR = 3.02 (95% CI 1.29, 7.06) and 2) mucosal or cutaneous reactions OR = 1.56 (95% CI 0.75, 3.23). Overall, 3.7%, and 3.5% of patients taking auranofin experienced gastrointestinal symptoms or muco/cutaneous reactions severe enough to cause withdrawal or change in therapy. This same trend was observed in pooled OR results reporting frequency of ADR (with or without withdrawal). Withdrawals due to hematological or renal effects were rare (1% each). Glennas and Bombardier (1986) reported ADRs as total number of events of a specific ADR reported per group rather than events per person thus are not included in the pooled OR with the other trials. Glennas reported a rate of 8.5 ADR events per person in the auranofin group vs 7.6 events per person in the placebo group; 142 gastrointestinal ADRs (51 were diarrhea) were reported in 31 persons taking auranofin compared to 152 GI complaints (85 were diarrhea) in 34 persons taking placebo. Muco-cutaneous, renal and liver ADRs were more frequent in the placebo group, and headaches and general complaints in the auranofin group. Over the course of the study 10 % vs 41% withdrew due to ADRs respectively. Bombardier reported a rate of 1.92 ADR events per person in the auranofin group vs 1.02 events per person in the placebo group. ADRs numbering 174 related to gastrointestinal events (93 were diarrhea) were reported in 157 persons taking auranofin compared to 82 complaints (29 were diarrhea) in 152 persons taking placebo. Most frequent gastrointestinal complaint was loose stools or diarrhea which generally occurred early and often resolved itself while cutaneous reactions occurred throughout. Muco-cutaneous ADRs were more common in the auranofin group, 74 events in 157 auranofin patients vs 59 events in 152 patients. All ADRs were reversible.

DISCUSSION

Gold salts were the first DMARD used for the treatment of RA. The most commonly used compounds are sodium aurothiomalate and aurothioglucose. These salts are administered weekly as intramuscular injections. The efficacy of parenteral gold salts has been well established (Clark 1999). However, its toxicity is frequent and can be serious. Mucocutaneous manifestations, in particular rash are very common. Hematological effects include leucopenia, thrombocytopenia, and in rare cases aplatic anemia. Renal effects such as proteinuria are also frequent and result in discontinuation of the drug. These drawbacks led to the search for gold compounds which could be administered orally, and had lower toxicity profiles. Auranofin was developed in the 1970's and the reports of the first RCTs were published in the 1980's. Despite the initial enthusiasm subsequent studies showed that auranofin was not as potent as parenteral gold (Felson 1990, Berkey 1996) although it had a safer toxicity profile.

The objective of this study was to conduct a systematic review of placebo-controlled trials of auranofin for the treatment of RA. We have conducted a number of systematic reviews for other DMARDS using the same methods which allow us to compare the efficacy of a DMARD in relation to other drugs. The results of the review show that auranofin is efficacious in reducing disease activity in patients with RA over a 6 month period. Statistically significant results favouring auranofin were observed for number of tender joints, pain scores, physician and patient global assessments and ESR. The magnitude of the differences between placebo and auranofin was nevertheless small. The effect size for tender joints was 0.39, the difference in pain 5mm on a 0 to 100mm scale, and the difference in ESR 10mm/hr. No significant differences were observed for functional status These results suggest that auranofin has a small beneficial effect on the disease activity of patients with RA. When the efficacy of auranofin is compared to the results obtained in meta-analyses of other DMARDs, auranofin appears to be less potent than some of the other drugs including parenteral gold, methotrexate, sulfasalazine and cyclosporine (Felson 1990, Suarez-Almazor 1999a, Suarez-Almazor 1999b, Suarez-Almazor 1999c, Wells 1999). However, the confidence limits of the estimated effects overlap for most measures so the differences cannot be considered to be statistically significant . For these other DMARDS, the effect sizes in the meta-analyses of placebo-controlled trials were approximately 0.5 to 0.6. For auranofin the effect sizes ranged between 0.20 and 0.40. Effect sizes of 0.30 and higher can be considered clinically significant (Kazis 1989). The efficacy of auranofin appears to be very comparable to that of antimalarials, with similar effect sizes for both drugs when compared

with placebo (Suarez-Almazor 1999d). However, in the systematic review of antimalarials, the improvement in swollen joints was statistically significant, but no differences were observed for auranofin in the current review.

The effect of auranofin on the radiological progression of RA remains inconclusive. Unfortunately, some of the trials which measured radiological damage did not report the results. The two trials reporting quantitative results had conflicting findings with one study finding a significant difference (Johnsen 1989) but not the other (Glennas 1997).

No serious adverse reactions occurred with auranofin. Although patients receiving the drug were 1.5 times more likely to discontinue treatment because of toxicity, but the differences were not statistically significant. Most of the toxicity withdrawals were related to loose stools or diarrhoea and mucocutaneous events. The toxicity observed with auranofin was less frequent and serious than the findings reported with parenteral salts in previous studies were leucopenia and proteinuria are common events. Other DMARDS which may be more effective than auranofin such as methotrexate or cyclosporin have the potential for more serious effects than auranofin. Antimalarials also have a low toxicity profile in the short term, but have a small but definite risk of retinopathy with longer treatments. A meta-analysis by Felson which included placebo-controlled as well as drug-to-drug comparisons concluded that auranofin was one of the least toxic DMARDS as measured by the number of discontinuations. When choosing one drug over another risk-benefit ratios have to be considered in relation to the severity of the disease, and patient preferences.

In this review, some of the studies only included patients with early disease. Because auranofin may be somewhat weaker than other DMARDS its most appropriate use may be for those patients with early, mild disease who are more likely to respond to any therapy.

The role of auranofin in combination with other drugs has not been adequately assessed so far. Combination therapy with two or more DMARDS is increasingly being used to treat patients with RA, most frequently those who fail treatment with a single drug.. One study compared methotrexate, auranofin and the combination of both and found no clear advantage in using the combined therapies (Williams 1992).

AUTHORS' CONCLUSIONS

Implications for practice

Auranofin appears to be efficacious in the short-term treatment of patients with RA (6 months), and has a small but clinically and statistically significant benefit on the disease activity of these patients. Its effects on overall health status and radiological progression are not clear at this time, but would appear to be modest. Auranofin may be most appropriate for those patients with early and mild disease who are more likely to respond to less potent (and less toxic) therapies.

Implications for research

The role of auranofin in combination with other DMARDS deserves further study.

Many of the studies did not report (or reported inadequately) outcomes of interest which made it impossible to pool results for all measures across trials. This reinforces the need to use systematic methods or guidelines when designing, conducting and publishing clinical trials (Begg 1996).

REFERENCES

References to studies included in this review

Bombardier 1986 ***{published data only}***
Bombardier C, Ware J, Russell IJ, Larson M, Chalmers A, Read JL. Auranfin therapy and quality of life in patients with rheumatoid arthritis. *Am J Med* 1986;**81**:565–578. Thompson MS, Read JL, Hutchings HC, Paterson M, Harris ED Jr. The cost effectiveness of auranofin: Results of a randomised clinical trial. 35–42.

Davies 1982 ***{published data only}***
Davies J, Bacon PA, Hall ND, Ring EFJ. Placebo-controlled comparison of auranofin with myocrisin in patients with rheumatoid arthritis. In: Capell HA, Cole DS, Manghani KK & Morris RW. (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium. *Exerpta Medica, Netherlands (Amsterdam)* 1983:Capell HA, Cole DS, Manghani KK & Morris RW. (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium . Exerpta Medica, Netherlands (Amsterdam) 1983;194-200. Davies J, Bacon PA, Hall ND, Ring EFJ. Placebo-controlled comparison of oral gold with injectable gold in early rheumatoid arthritis. *Clin Rheumatol* 1984;**3**:553–4.

Glennas 1997 ***{published data only}***
Glennas A, Kvien TK, Andrup O, Clarke-Jenssen, Karstensen B, Brodin U. Auranofin is safe and superior to placebo in elderly-onset rheumatoid arthritis. *British Journal of Rheumatology* 1997;**36**(8):870–877.

Johnsen 1989 ***{published data only}***
Borg G, Allander E, Lund B, Berg E, Brodin U, Pettersson H, Trang L. Auranofin improves outcome in early rheumatoid arthritis. Results from a 2-year, double blind, placebo controlled study. *J Rheumatol* 1988;**15**:1747–1754. Johnsen V, Borg G, Trang LE, Berg E, Brodin U. Auranofin (SK&F) in early rheumatoid arthritis: Results from a 24-

month double blind, placebo-controlled trial. *Scand J Rheumatol* 1989;**18**:251–260.

Lewis 1984 ***{published data only}***

Lewis D, Capell HA. Is auranofin preferable to gold sodium thiomalate in the management of rheumatoid arthritis. In: Capell HA, Cole DS, Manghani KK & Morris RW (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium. *Exerpta Medica, Netherlands (Amsterdam)* 1983:Capell HA, Cole DS, Manghani KK & Morris RW (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium. Exerpta Medica, Netherlands (Amsterdam) 1983;147-155.

Lewis D, Capell HA. Oral gold: A comparison with placebo and intramuscular sodium aurothiomalate. *Clin Rheumatol* 1984;**Supp 1**:83–96.

Palmer 1982 ***{published data only}***

Palmer DG, Highton J, MacKinnon M, Myers DB, Sharma R. A double-blind parallel trial of auranofin and placebo in rheumatoid arthritis with evidence for compatibility with certain non-steroidal anti-inflammatory drugs. In: Capell HA, Cole DS, Manghani KK & Morris RW. (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium. *Exerpta Medica, Netherlands (Amsterdam)* 1983:Capell HA, Cole DS, Manghani KK & Morris RW. (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium. Exerpta Medica, Netherlands (Amsterdam) 1983;313-324.

Prouse 1982 ***{published data only}***

Prouse PJ, Gumpel JM. Placebo-controlled comparison of auranofin with gold sodium thiomalate. In: Capell HA, Cole DS, Manghani KK & Morris RW. (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium. *Exerpta Medica, Netherlands (Amsterdam)* 1983:Capell HA, Cole DS, Manghani KK & Morris RW. (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium. Exerpta Medica, Netherlands (Amsterdam) 1983;303-312.

Ward 1983 ***{published data only}***

Ward JR, Williams HJ, Boyce E, Egger MJ, Reading JC, Samuelson CO. Comparison of auranofin, gold sodium thiomalate and placebo in the treatment of rheumatoid arthritis. *Am J Med* 1983;**133-137**.

Ward JR, Williams HJ, Egger MJ, Reading JC, Boyce E, Altz-Smith M, et al.Comparison of auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis: A controlled clinical trial. *Arthritis Rheum* 1983; **26**(11):1303–1315.

Ward JR, Williams HJ, Egger MJ, Reading JC, Boyce E, Samuelson Jr CO, et al.Comparison of auranofin, gold sodium thiomalate and placebo in the treatment of rheumatoid arthritis: Response by treatment duration. In: Capell HA, Cole DS, Manghani KK & Morris RW. (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium ..Exerpta Medica, Netherlands (Amsterdam). 1983:Capell HA, Cole DS, Manghani KK & Morris RW. (eds). Auranofin, Proceedings of a Smith Kline & French International Symposium ..Exerpta Medica, Netherlands (Amsterdam). 1983;115-132.

Williams HJ, Ward JR. Comparison of oral and parenteral gold therapy and placebo in the treatment of rheumatoid arthritis. *Scand J of Rheum* 1983;**Supp**(51):92–99.

Wenger 1983 ***{published data only}***

Gofton JP, O'Brien WM, Hurley JN, Scheffler BJ. Radiographic evaluation of erosion in rheumatoid arthritis: Double blind study of auranofin vs placebo. *J Rheumatol* 1984;**11**(6):768–771.

Katz WA, Alexander S, Bland JH, Blechman W, Bluhm GB, Bonebrake RA, Falbo A, et al.The efficacy of Auranofin compared to placebo in rheumatoid arthritis. *J of Rheumatol Supplement* 1982;**8**:173–78.

Wenger ME, Alexander S, Bland JH, Blechman W, Auranofin vs placebo in the treatment of rheumatoid arthritis. *Am J of Med* 1983;**123-127**.

References to studies excluded from this review

Baldassare 1985 ***{published data only}***

* * Baldassare AR, Weiss TD, Arthur RE, Osborn TG, Moore TL, Zuckner J. Auranofin in the treatment of rheumatoid arthritis: A two year study. *Missouri Medicine* 1985;**82**(11):711–15.

Borg 1991 ***{published data only}***

Borg G, Allander E, Berg E, Brodin U, From A, Trang L. Auranofin treatment in early rheumatoid arthritis may postpone early retirement. Results from a 2-year double blind trial. *J Rheum* 1991;**18**(7):1015–20.

Champion 1982 ***{published data only}***

Champion DG, Bieri D, Browne CD, Cohen ML, Day RO, Graham GG, Haavisto TM, Sambrook PN, Vallance JB. Auranofin in rheumatoid arthritis. *J Rheum Supplement* 1982;**8**:137–45.

Champion 1988 ***{published data only}***

Champion DG, Cairns DR, Bieri D, Adena MA, Browne CD, Cohen ML, et al.Dose response studies and longterm evaluation of auranofin in rheumatoid arthritis. *J Rheumatol* 1988;**15**:28–34.

Egsmose 1995 ***{published data only}***

Egsmose C, Lund B, Borg G, Pettersson H, Berg E, Brodin U, Trang L. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. *J Rheum* 1995;**22** (12):2208–13.

Jajic 1990 ***{published data only}***

Jajic I, Jajic Z, Kos-Golja M. Klinicka djelotvornost i podnosljivost auranofina u lijecenju reumatoidnog artritisa [Clinical efficacy and safety of auranofin in the treatment of rheumatoid arthritis]. *Rad Med Fak Zagrebu* 1990;**31**(5): 299–304.

Lundberg 1988 ***{published data only}***

Lundberg MS, Cannon GW, Ward JR. Peripheral lymphocyte depletion in gold sodium thiomalate-treated rheumatoid arthritis patients. *Arthritis Rheum* 1988;**31**(7): 909–13.

Additional references

Begg 1996

Begg C, Cho M, Eastwood S, et al.Improving the quality of randomized controlled trials: the CONSORT statement. *JAMA* 1996;**276**:637–9.

Berkey 1996

Berkey CS, Anderson JJ, Hoaglin DC. Multiple outcome meta-analysis of clinical trials. *Stat Med* 1996;**15**:537–557.

Clark 1999

Clark P, Tugwell P, Bennet K, et al.Meta-analysis of injectable gold in rheumatoid arthritis.. *In: Tugwell P, Brooks P, Wells G, de Bie R, Bosi-Ferraz M, Gillespie W, eds. Musculoskeletal module of The Cochrane Database of Systematic Reviews. In: The Cochrane Library, Oxford: Update Software* 1999.

Dickersin 1994

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

Felson 1993

Felson DT, Anderson JJ, Boers M, et al.The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;**36**:729–40.

Felson 1995

Felson DT, Anderson JJ, Boers M, et al.American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35.

Jadad 1996

Jadad A, Moore A, Carrol D, et al.Assessing the quality of reports of randomized trials: is blinding necessary?. *Control Clin Trial* 1996;**17**:1–12.

Kazis 1989

Kazis LEE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Medical Care* 1989;**27** (S3):S178–89.

OMERACT 1993

OMERACT. Conference on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *J Rheumatol* 1993;**20**: 526–91.

Suarez-Almazor 1999a

Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Rheumatoid arthritis (RA): methotrexate versus placebo.. *In: Tugwell P, Brooks P, Wells G, de Bie R, Bosi-Ferraz M, Gillespie W, eds. Musculoskeletal module of The Cochrane Database of Systematic Reviews. In: The Cochrane Library, Oxford: Update Software* 1999.

Suarez-Almazor 1999b

Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Rheumatoid arthritis (RA): sulfasalazine vs. placebo.. *In: Tugwell P, Brooks P, Wells G, de Bie R, Bosi-Ferraz M, Gillespie W, eds. Musculoskeletal module of The Cochrane Database of Systematic Reviews. In: The Cochrane Library, Oxford: Update Software* 1999.

Suarez-Almazor 1999c

Suarez-Almazor ME, Belseck E, Shea B, Homik J, Wells G, Tugwell P. Rheumatoid arthritis (RA): antimalarials vs. placebo. *In: Tugwell P, Brooks P, Wells G, de Bie R, Bosi-Ferraz M, Gillespie W, eds. Musculoskeletal module of The Cochrane Database of Systematic Reviews. In: The Cochrane Library, Oxford: Update Software.* 1999.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bombardier 1986

Methods	Allocation: randomized in blocks of 8 stratified for steroid use. Blinding: double blind Design: parallel study Sample size at entry: 311 Analysis: completers, 97% follow-up; auranofin 154; placebo 149
Participants	Country: Canada & US, Multicentre tial (K=14) Patients with active RA Age: mean 50.5 yr (SD 11.08) Duration of disease: mean 8.05 yr (SD 8.0) Females: 73% RF: 74% Concomitant use of steroids: oral 23.5% Concomitant use of other DMARDS: none Previous use of DMARDS: not in previous 6 mo.
Interventions	Auranofin 6 (could increase to 9) mg /day vs identical placebo Treatment duration: 6 months
Outcomes	Tender joint count Swollen joint count Pain: 3 scales. Included only 10 cm pain line, 10=severe Function: 4 scales. Included 2: Health Assessment Questionnaire (0 to 3, 3=worse) and Keitel function test (0-98, 98=worse) Patient assessment: 4 scales. Included only 10 cm line, 10 = perfect Physician assessment: 3 scales. Included only 10 cm line, 10 = perfect 50 ft walk time in seconds (results in text only) Quality of life: quality of wellbeing scale (results in text only) ESR
Notes	Quality score: 4 Allocation concealment: adequate Reported: baseline & SE, mean change scores & SE Calculated baseline SD values & imputed them to end-of-trial results

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Davies 1982

Methods	Allocation: randomised Blinding: double blind Design: parallel study Sample size at entry: Auranofin 10; GSTM 11, placebo 11 Analysis: completers 85.7% (auranofin 10, placebo 8)
Participants	Country: UK Patients with active RA (early, mild disease) Age: mean 53.3 yr Duration of disease: mean 3.02 yr Females: 72% RF: not reported Concomitant use of steroids or other DMARD: none Previous use of DMARDS or steroids: none
Interventions	Auranofin 6m g/day, GSTM IM 50 mg/wk or placebo Treatment duration: 12 mo, 9 m data reported
Outcomes	Tender joints: Ritchie index Pain VAS
Notes	Quality score: 4 Allocation concealment: unclear Group using GSTM not included in analysis Reported: baseline & end of trial values. Imputed 12 mo SD to 9 mo data for Ritchie index Withdrawals at six mo. reported ADR results reported at 9 months.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Glennas 1997

Methods	Allocation: randomized, blocks of 4, stratified for RH and myalgias Blinding: double blind Design: parallel study Sample size at entry 65: auranofin 31; placebo 34 Analysis: Intention to treat 78.5% follow-up
Participants	Country: Norway Patients with active RA: onset age >60 yr. 4 pts in auranofin gr had oligoarthritis with PMR or myalgias. Age: median 71 y (SD 8) Duration of disease: median auranofin 16 wk (SD 172); placebo 25wk (SD 259) Females: 68% RF: auranofin 32%, placebo 35% Concomitant use of steroids: oral & intra-articular allowed

Glennas 1997 (*Continued*)

	Concomitant use of other DMARDS: none Previous use of DMARDS: 16%, no previous gold Tx
Interventions	Auranofin 6 mg/day vs identical placebo Treatment duration: 2 yrs
Outcomes	Swollen joints Pain: 100mm VAS Function: HAQ Xray: baseline vs 2 yr: Larsen-Dale (range 0-150)
Notes	Quality score: 5 Allocation concealment: adequate Reported: baseline medians & ranges. 6 mo results & SDs estimated from box & whisker plots. Median = mean; SD = IQ range/2 Reasons for withdrawal reported at 24 months ADRs reported by # of events/group not per person, therefore not included in ORs for ADRs not requiring withdrawal

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Johnsen 1989

Methods	Allocation: randomized (blocks of 4 within each centre, size of block unknown to investigator) Blinding: double blind Design: parallel study Sample size at entry: 132. auranofin 67; placebo 65 Analysis: Completers, 81.8% follow-up (auranofin 57, placebo 51)
Participants	Country: 5 Nordic countries (K=11) Patients with active RA (early disease, < 2 yr) Age: mean 57 yr. (SD 9.5) Duration of disease: mean 11 mo. (SD 6) Females: 63% RF: 66% Concomitant use of steroids: Intra-articular steroids allowed Concomitant use of other DMARDS: none Previous use of DMARDS: no gold salts, penicillamine, or levamisole. No antimalarials in past 1 mo. All patients on NSAIDs
Interventions	Auranofin 6 mg/day vs indentical placebo Treatment duration: 24 months.

Johnsen 1989 (*Continued*)

Outcomes	Tender joints: Ritchie index Swollen joint count Pain: 100 mm VAS, 100=worst possible pain Function: Stanford Health Assessment Questionnaire & Keitel function test Patient assessment: 100 mm VAS, 100=perfect health Physician assessment: 100 mm VAS, 100=worst possible deterioration ESR X-ray: Larsen index, 32 joints, 6 point scale, 5=mutilating changes
Notes	Johnsen 1989 reports 3, 6, 12 & 18 mo results from Borg et al 1988 2 yr. trial. Quality score: 4 Allocation concealment: unclear Report: baseline medians with 1st-3rd quartiles. Results reported as % change from baseline median values and quartiles. End of trial results calculated. Medians were imputed as means. End of trial SD = baseline (1st - 3rd quartile)/2 6 mo.withdrawal data estimated from graphs ADR data reported at 24 months only.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lewis 1984

Methods	Allocation: randomized Blinding: double blind for tablet therapy but not injections. Blind assessments. Design: parallel study, 3 groups Sample size at entry 90: Auranofin 30; placebo 30, GSTM 30. Analysis: completers
Participants	Country: UK Patients with active RA Age: median 52.17 yrs (sd 16.7) Duration of disease: median 5 yrs (sd 13.00) Females: 69% RF: 88.9% Concomitant use of steriods: none Concomitant use of DMARDS: none Previous of DMARDS: not in past 6 mo.
Interventions	Auranofin 6mg/day or matching placebo or GSTM 50 mg IM/wk Treatment duration: 6 mos
Outcomes	ESR Disease activity index (combining other measures)

Lewis 1984 (*Continued*)

Notes	Quality score: 4 Allocation concealment: unclear Except for ESR no OMERACT end of trial results reported Six outcome measures were combined to derive a disease activity index. Reported ESR changes, imputed baseline SD to end of trial Withdrawals and dropouts reported @ 24 wks. ADRs not requiring withdrawal not reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Palmer 1982

Methods	Allocation: randomised Blinding: double blind Design: parallel study Sample size at entry 20: auranofin 10; placebo 10 Analysis: Completers (50% followup)
Participants	Country: New Zealand Patients with active RA Age: mean 52.25 y Disease duration: not reported Females: 75% RF: not reported Concomitant use of steriods: Intra-articular steroids allowed Concomitant use of DMARDs: none Previous use of DMARDS: none
Interventions	Auranofin 6 mg/day vs identical placebo Treatment duration: 6 mo.
Outcomes	Tender joints: Ritchie index Swollen joints Pain Patient's assessment score (4 pt scale, 0=nil, 3=excellent) Time to walk 5 M ESR
Notes	Quality score: 4 Allocation concealment: adequate Results estimated from graphs by two reviewers and averaged. No SDs reported. Withdrawals & ADRs reported at 2 yrs

Risk of bias

Palmer 1982 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Prouse 1982

Methods	Allocation: randomised Blinding: double blind first 6 mo. for auranofin & placebo only Design: parallel study, 3 arms (auranofin, GSTM, placebo) Sample size at entry 30: auranofin 10; placebo 10, GSTM 10. Analysis: Completers 100% follow-up (auranofin 10; placebo 10)
Participants	Country: UK Patients with active RA Age: mean auranofin 57.8 y (SD 11.4) Duration of disease: mean auranofin 8.6y (SD 8.1) Females: 85% RH: not reported Concomitant use of steroids: none Concomitant use of other DMARDs: none Previous use of DMARDs: not reported
Interventions	Auranofin 6 mg/day or matching placebo or open GSTM IM 50 mg/wk Treatment duration: 6 mo. then reallocated as necessary
Outcomes	Articular index (modified Landsbury) Pain ESR
Notes	Quality score: 3 Allocation concealment: unclear Data for six mo. abstracted from bar graphs SDs imputed from weighted average of CV of other studies. ADRs reported at 12 mo

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ward 1983

Methods	Allocation: randomized Blinding: double blind Design: parallel study, 3 arms Sample size at entry 193: auranofin 72; placebo 46, GSTM 75. Analysis: completers 90.7% (auranofin 64; placebo 43)
Participants	Country: USA, multicentre (K=11) Patients with active RA Age: mean 50.5 y (SD 18) Females: 71.5% Duration of disease: mean 70 mo. (SD 120) RF: 83% Concomitant use of steroids: 15% Concomitant use of other DMARDS: none Previous use of DMARDS: not in previous 3 mo. No previous gold
Interventions	Auranofin 6 mg/day plus placebo injection 1/wk or placebo tablets with GSTM, or placebo tablets and placebo injections. Duration of treatment: 21 wks
Outcomes	Tender joints: 68 jnts. 4 pt scale: 0=npne, 3=withdrawal Swollen joints: 66 jts. 4 pt scale:0=none, 3=bulging Pain Patient assessment: 5 pt scale, 5 = worse Physician assessment:5 pt scale, 5=worse Functional class ESR
Notes	Quality score: 5 Allocation concealment: adequate Reported: Baseline means & SD, end of trial, change scores and SD. Results reported at 20 wks

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Wenger 1983

Methods	Allocation: randomized Blinding: First phase double blind, 2nd open label Design: parallel study Sample size at entry 304: auranofin 152; placebo 152 Analysis: completers, 60.5% follow-up (auranofin 106, placebo 78)
Participants	Country: USA, multicentre (K=14) Patients with active RA on NSAIDs Age: median 53 yrs

Wenger 1983 (*Continued*)

	Duration of disease: median 4 yrs Females: 69% RF: not reported Concomitant use of steroids: 13.5% Concomitant use of other DMARDS: none Previous use of DMARDS: none
Interventions	Auranofin 6 mg/day vs identical placebo Treatment duration: 26 wk.
Outcomes	Tender joint count Swollen joint count Physician global efficacy: 4 pt scale 4=worse ESR Xray results reported in text of review
Notes	Wenger 1983 reports final analysis of data from Katz et al 1982 Wenger results included Quality score: 3 Allocation concealment: unclear Only blinded phase included Reported: end of trial results. No SDs included Converted global efficacy to 4 point scale and combined groups = worse with therapeutic failure. Mean & SD calculated. Numbers of ADRs not requiring withdrawal not reported except for diarrhea

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baldassare 1985	Dose comparison. No placebo group
Borg 1991	Followup of Borg 1989. No OMERACT outcomes reported in this article
Champion 1982	Dose comparison, no placebo group.
Champion 1988	Dose comparison, no placebo group
Egsmose 1995	Long term followup of Borg 1989.
Jajic 1990	No placebo group

(*Continued*)

Lundberg 1988	Followup of Ward 1983. No OMERACT outcomes reported in this article

DATA AND ANALYSES

Comparison 1. Auranofin vs. placebo - Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tender joint scores	7	750	Mean Difference (IV, Fixed, 95% CI)	-3.76 [-5.06, -2.45]
2 Swollen joint scores	6	767	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-1.49, 0.90]
3 Pain scores	7	805	Mean Difference (IV, Fixed, 95% CI)	-4.68 [-6.59, -2.77]
3.1 Pain scores	7	805	Mean Difference (IV, Fixed, 95% CI)	-4.68 [-6.59, -2.77]
4 Physician global assessment	3	670	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.52, -0.21]
5 Patient Global assessment	4	528	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.65, -0.17]
6 Global Assessment of function	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Functional status: Health Assessment Questionnaire	2	368	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.27, 0.01]
6.2 Functional status: Keitel Assessment	1	303	Mean Difference (IV, Fixed, 95% CI)	-3.20 [-7.58, 1.18]
6.3 Functional status: 50 ft/15 m walk time	2	313	Mean Difference (IV, Fixed, 95% CI)	-1.42 [-3.07, 0.23]
7 ESR	7	736	Mean Difference (IV, Fixed, 95% CI)	-9.04 [-12.16, -5.92]

Comparison 2. Auranofin vs. placebo - Withdrawals and dropouts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals: Global reasons	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Withdrawals: total	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.46, 0.83]
1.2 Withdrawals: lack of effect	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.31 [0.21, 0.44]
1.3 Withdrawals: concurrent illness	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.74 [0.86, 8.69]
1.4 Withdrawals: adverse reactions	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.94, 2.46]
2 Withdrawals: System specific adverse reactions	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Withdrawals: gastrointestinal -all signs and symptoms	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.98 [1.36, 6.52]
2.2 Withdrawals: diarrhea	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.02 [1.29, 7.06]
2.3 Withdrawals: mucosal / cutaneous adverse reactions	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [0.75, 3.23]
2.4 Withdrawals: renal adverse reactions	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.53, 7.27]
2.5 Withdrawals: liver adverse reactions	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

2.6 Withdrawals: hematology adverse reactions	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.73 [0.84, 16.65]
2.7 Withdrawals: neurological adverse reactions (headache, dizziness, tingling)	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.10, 2.59]
2.8 Withdrawals: cardiovascular adverse reactions	8	984	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.16 [0.14, 360.90]
2.9 Withdrawals: miscellaneous adverse reactions	9	1049	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.20 [0.45, 115.73]

Comparison 3. Adverse reactions not requiring withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse reactions: System specific	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Adverse reaction: gastrointestinal	5	595	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.11 [2.09, 4.65]
1.2 Adverse reaction: diarrhea	5	595	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.95 [1.95, 4.47]
1.3 Adverse reaction: mucosal / cutaneous	4	291	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [1.13, 3.81]
1.4 Adverse reaction: renal	5	293	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.23, 4.03]
1.5 Adverse reaction: liver	4	291	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.6 Adverse reaction: hematology	4	291	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.7 Adverse reaction: neurological	4	291	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.8 Adverse reaction: miscellaneous	4	291	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [0.83, 3.13]

Analysis 1.1. Comparison 1 Auranofin vs. placebo - Efficacy, Outcome 1 Tender joint scores.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 1 Auranofin vs. placebo - Efficacy

Outcome: 1 Tender joint scores

Study or subgroup	Auranofin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bombardier 1986	154	17.7 (11.17)	149	21.5 (10.99)		27.3 %	-3.80 [-6.30, -1.30]
Davies 1982	10	12.6 (6.4)	8	9.5 (10.1)		2.6 %	3.10 [-4.94, 11.14]
Johnsen 1989	57	5.76 (6.5)	51	11.1 (6)		30.6 %	-5.34 [-7.70, -2.98]
Palmer 1982	5	8.8 (6.52)	5	18.25 (9.83)		1.6 %	-9.45 [-19.79, 0.89]
Prouse 1982	10	137.5 (101.85)	10	156 (84.01)		0.0 %	-18.50 [-100.33, 63.33]
Ward 1983	64	23 (16)	43	30 (16)		4.5 %	-7.00 [-13.18, -0.82]
Wenger 1983	106	11.3 (8.37)	78	13.4 (7.22)		33.3 %	-2.10 [-4.36, 0.16]
Total (95% CI)	**406**		**344**			**100.0 %**	**-3.76 [-5.06, -2.45]**

Heterogeneity: $Chi^2 = 8.94$, df = 6 (P = 0.18); $I^2 = 33\%$

Test for overall effect: Z = 5.65 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Auranofin vs. placebo - Efficacy, Outcome 2 Swollen joint scores.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 1 Auranofin vs. placebo - Efficacy

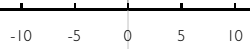
Outcome: 2 Swollen joint scores

Study or subgroup	Auranofin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bombardier 1986	154	15.5 (9.93)	149	18.4 (9.77)		28.9 %	-2.90 [-5.12, -0.68]
Glennas 1997	21	10 (6.33)	34	5.7 (6.8)		11.3 %	4.30 [0.76, 7.84]
Johnsen 1989	57	6.82 (6.5)	51	5.68 (5.5)		27.7 %	1.14 [-1.12, 3.40]
Palmer 1982	5	7.2 (5.13)	5	8.6 (5.92)		3.0 %	-1.40 [-8.27, 5.47]
Ward 1983	64	20 (14)	43	18 (9)		7.5 %	2.00 [-2.36, 6.36]
Wenger 1983	106	11.6 (8.27)	78	13.3 (9.15)		21.5 %	-1.70 [-4.27, 0.87]
Total (95% CI)	**407**		**360**			**100.0 %**	**-0.29 [-1.49, 0.90]**

Heterogeneity: Chi^2 = 15.61, df = 5 (P = 0.01); I^2 =68%

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Auranofin vs. placebo - Efficacy, Outcome 3 Pain scores.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 1 Auranofin vs. placebo - Efficacy

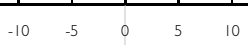
Outcome: 3 Pain scores

Study or subgroup	Auranofin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Pain scores							
Bombardier 1986	154	38.6 (12.4)	149	43.9 (12.2)		47.4 %	-5.30 [-8.07, -2.53]
Davies 1982	10	46.8 (22.24)	8	50.8 (17.62)		1.1 %	-4.00 [-22.41, 14.41]
Glennas 1997	31	50 (14.5)	34	50 (11.4)		8.9 %	0.0 [-6.38, 6.38]
Johnsen 1989	57	35.42 (18)	51	41.82 (17.5)		8.1 %	-6.40 [-13.10, 0.30]
Prouse 1982	10	38 (18.06)	10	47 (16.3)		1.6 %	-9.00 [-24.08, 6.08]
Ward 1983	64	32 (29)	43	42 (25)		3.4 %	-10.00 [-20.31, 0.31]
Wenger 1983	106	27.9 (13.3)	78	31.7 (11)		29.4 %	-3.80 [-7.32, -0.28]
Total (95% CI)	**432**		**373**			**100.0 %**	**-4.68 [-6.59, -2.77]**

Heterogeneity: Chi^2 = 4.09, df = 6 (P = 0.66); I^2 =0.0%

Test for overall effect: Z = 4.81 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Auranofin vs. placebo - Efficacy, Outcome 4 Physician global assessment.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 1 Auranofin vs. placebo - Efficacy

Outcome: 4 Physician global assessment

Study or subgroup	Auranofin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bombardier 1986	154	-6.78 (1.24)	149	-6.66 (1.22)		32.2 %	-0.12 [-0.40, 0.16]
Ward 1983	62	2.48 (0.54)	43	2.74 (0.69)		40.8 %	-0.26 [-0.51, -0.01]
Wenger 1983	130	1.99 (1.24)	132	2.8 (1.26)		27.0 %	-0.81 [-1.11, -0.51]
Total (95% CI)	**346**		**324**			**100.0 %**	**-0.36 [-0.52, -0.21]**

Heterogeneity: Chi² = 12.00, df = 2 (P = 0.002); I² =83%

Test for overall effect: Z = 4.53 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Auranofin vs. placebo - Efficacy, Outcome 5 Patient Global assessment.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 1 Auranofin vs. placebo - Efficacy

Outcome: 5 Patient Global assessment

Study or subgroup	Auranofin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bombardier 1986	154	-6.39 (2.48)	149	-6.11 (2.44)		18.5 %	-0.28 [-0.83, 0.27]
Johnsen 1989	57	-61.6 (16)	51	-59.78 (16.5)		0.2 %	-1.82 [-7.96, 4.32]
Palmer 1982	5	-2.05 (0.75)	5	-1.03 (0.36)		10.7 %	-1.02 [-1.75, -0.29]
Ward 1983	64	2.42 (0.66)	43	2.77 (0.78)		70.6 %	-0.35 [-0.63, -0.07]
Total (95% CI)	**280**		**248**			**100.0 %**	**-0.41 [-0.65, -0.17]**

Heterogeneity: Chi² = 3.27, df = 3 (P = 0.35); I² =8%

Test for overall effect: Z = 3.38 (P = 0.00073)

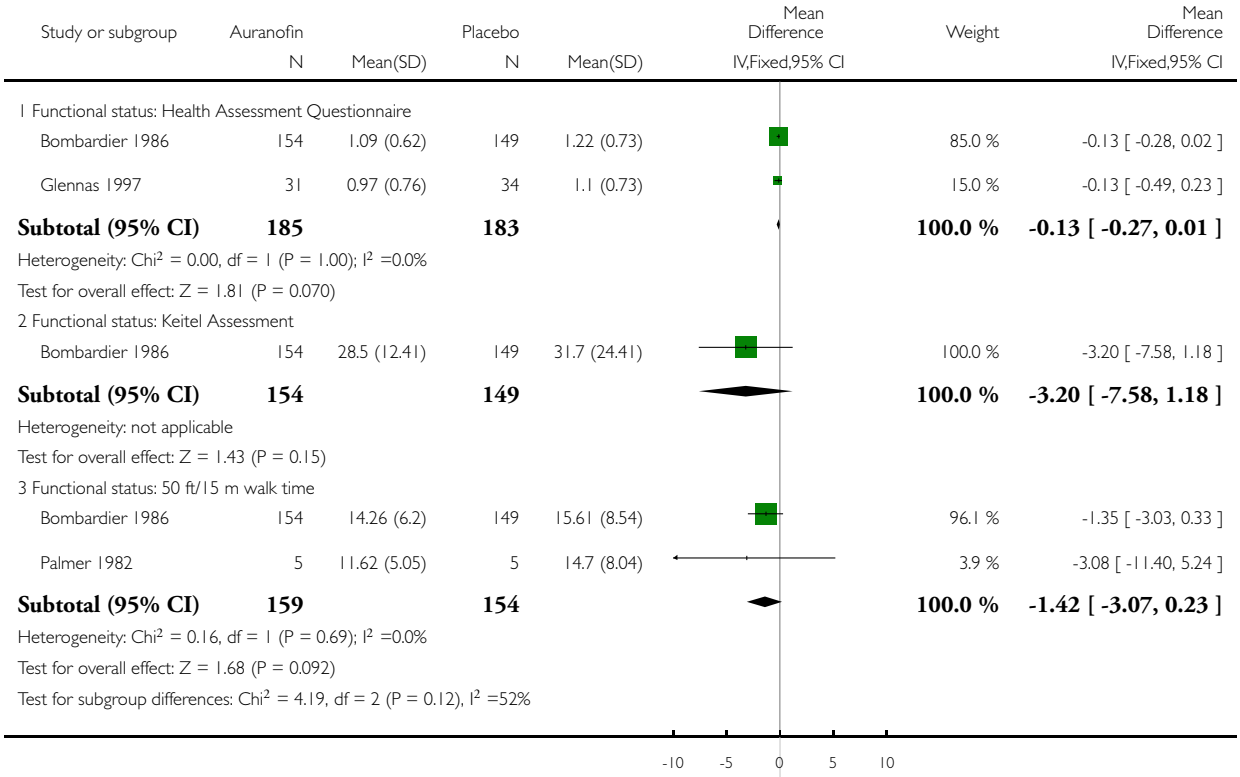
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Auranofin vs. placebo - Efficacy, Outcome 6 Global Assessment of function.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 1 Auranofin vs. placebo - Efficacy

Outcome: 6 Global Assessment of function



Analysis 1.7. Comparison 1 Auranofin vs. placebo - Efficacy, Outcome 7 ESR.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 1 Auranofin vs. placebo - Efficacy

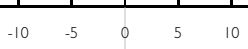
Outcome: 7 ESR

Study or subgroup	Auranofin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bombardier 1986	154	35.69 (24.82)	149	40.57 (24.41)		31.7 %	-4.88 [-10.42, 0.66]
Johnsen 1989	57	18.36 (17)	51	36.63 (13.5)		29.3 %	-18.27 [-24.03, -12.51]
Lewis 1984	30	36.72 (39.67)	30	56 (35.67)		2.7 %	-19.28 [-38.37, -0.19]
Palmer 1982	5	23.25 (17.81)	5	41.5 (20.36)		1.7 %	-18.25 [-41.96, 5.46]
Prouse 1982	10	44.25 (33.9)	10	49.25 (24.17)		1.5 %	-5.00 [-30.80, 20.80]
Ward 1983	35	42 (23)	35	51 (26)		7.4 %	-9.00 [-20.50, 2.50]
Wenger 1983	96	31.2 (23.9)	69	33.4 (16.39)		25.8 %	-2.20 [-8.35, 3.95]
Total (95% CI)	**387**		**349**			**100.0 %**	**-9.04 [-12.16, -5.92]**

Heterogeneity: Chi^2 = 18.55, df = 6 (P = 0.005); I^2 =68%

Test for overall effect: Z = 5.68 (P < 0.00001)

Test for subgroup differences: Not applicable

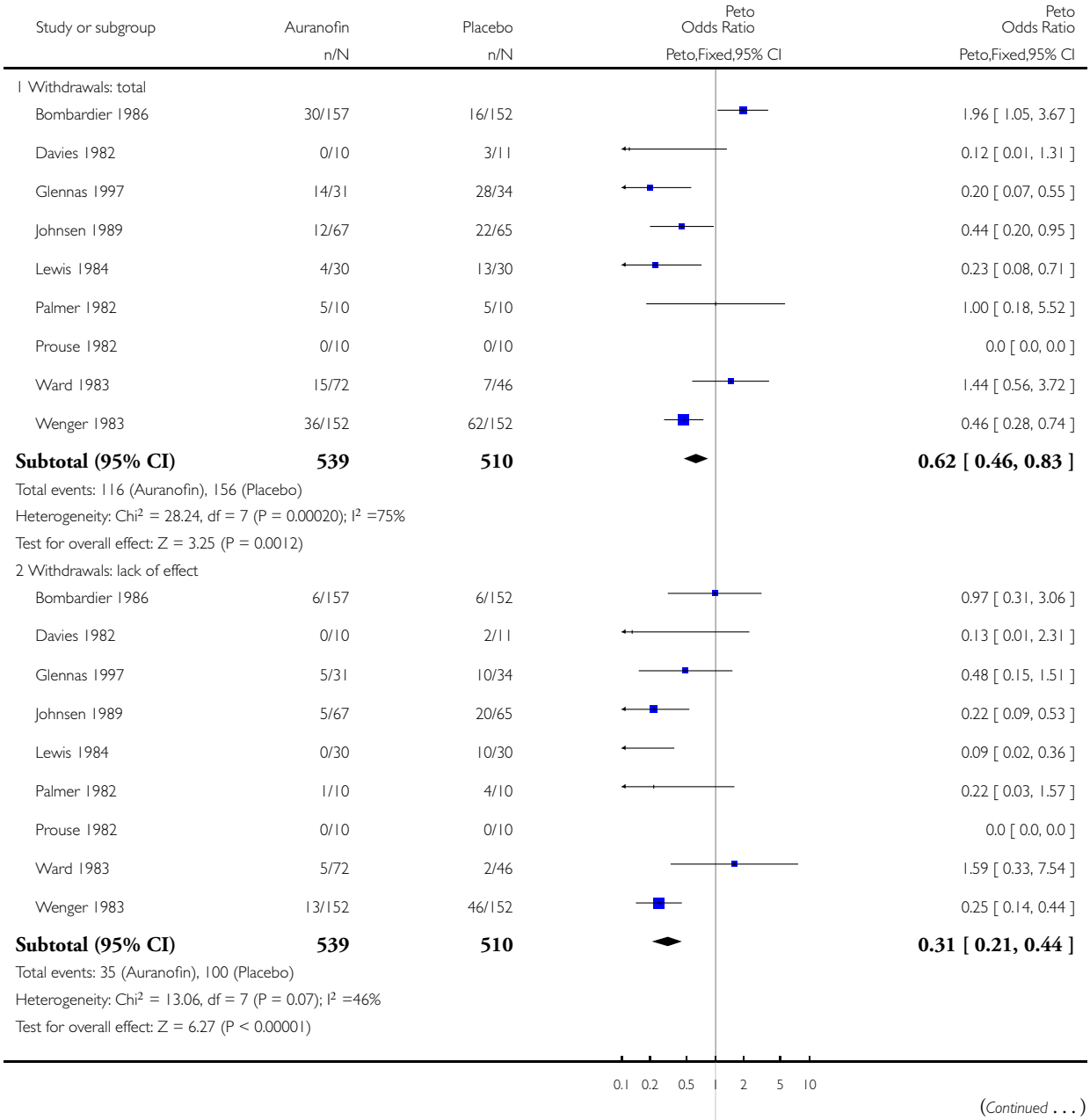


Analysis 2.1. Comparison 2 Auranofin vs. placebo - Withdrawals and dropouts, Outcome 1 Withdrawals: Global reasons.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 2 Auranofin vs. placebo - Withdrawals and dropouts

Outcome: 1 Withdrawals: Global reasons



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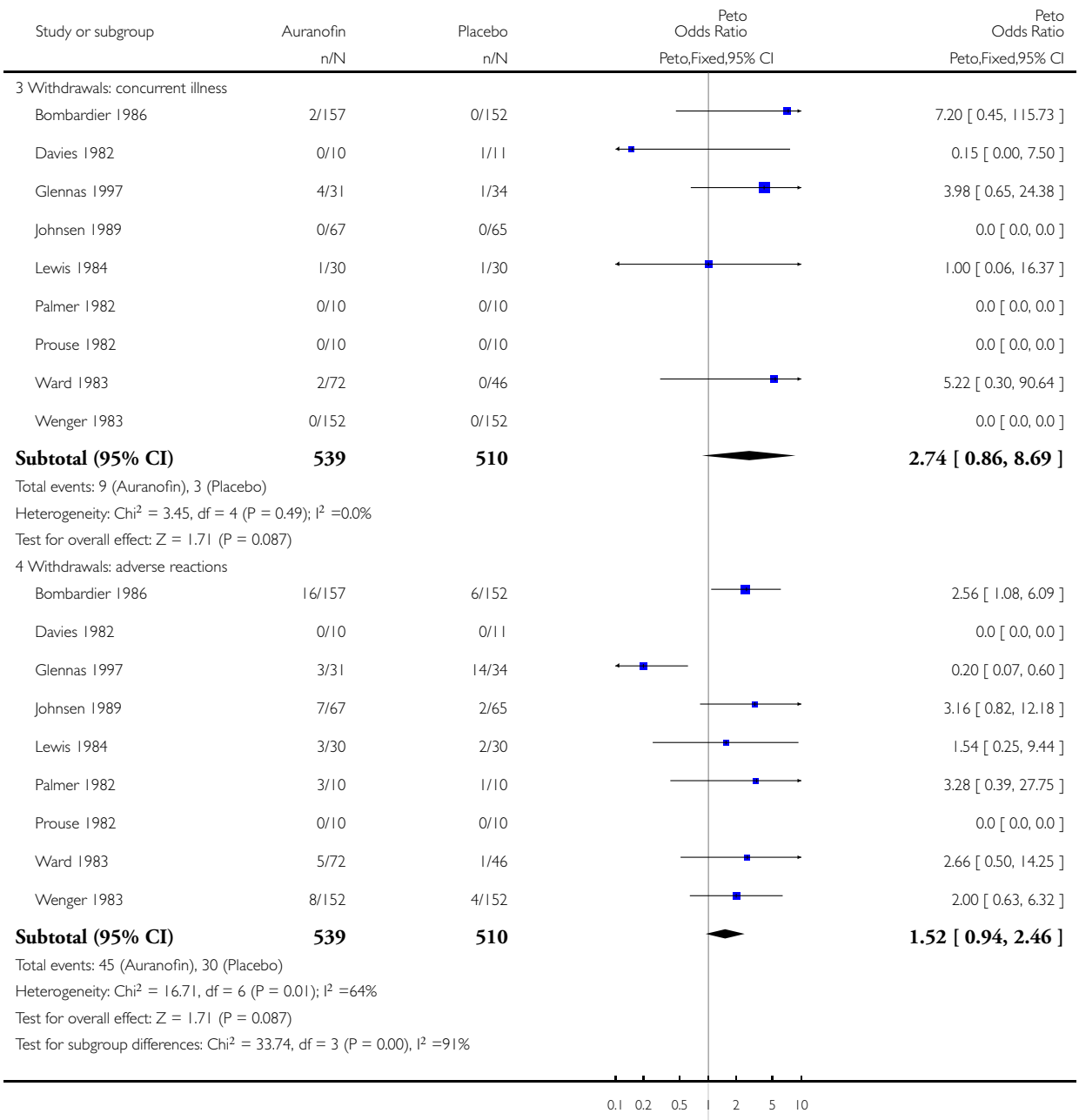
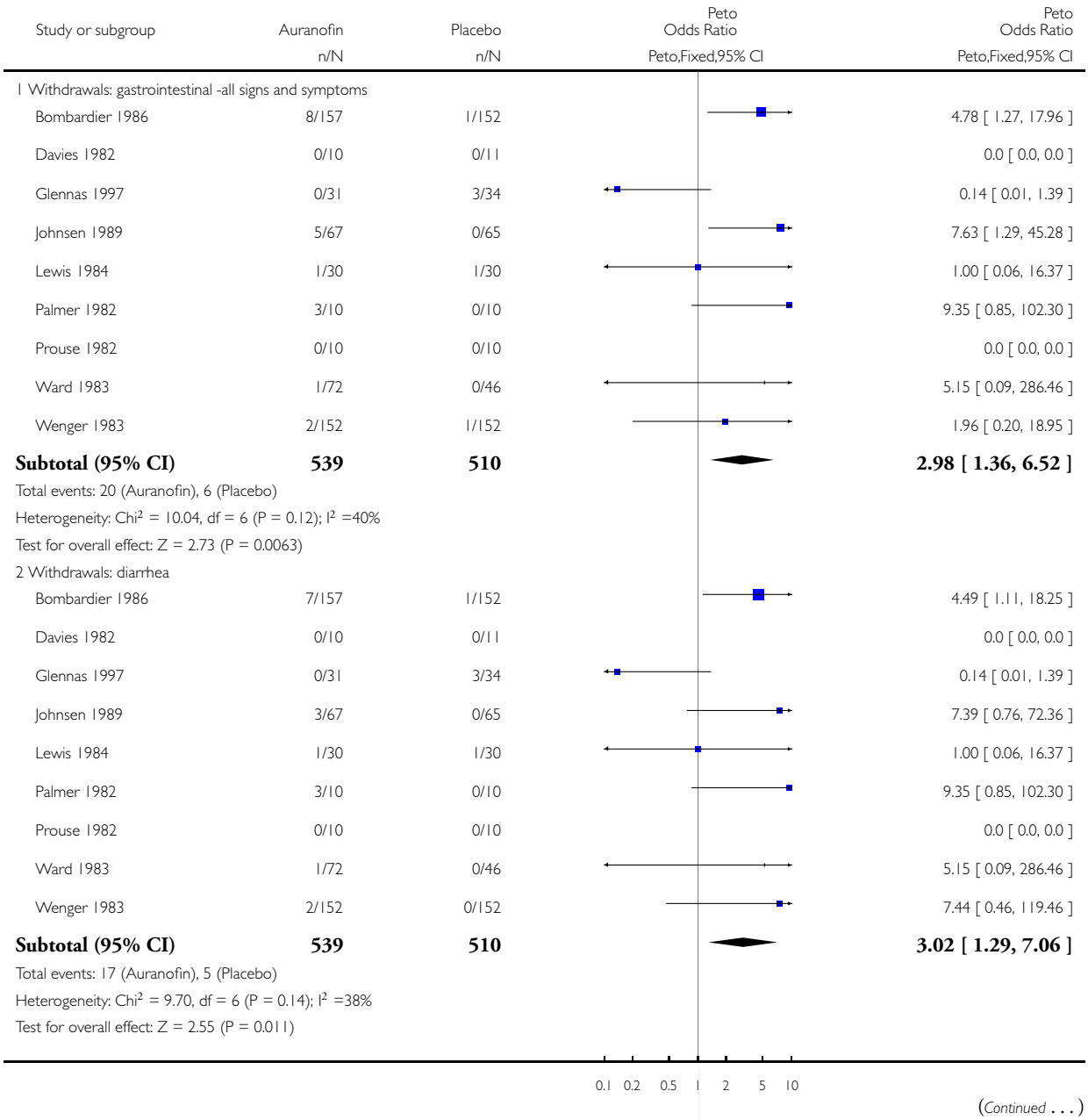


Analysis 2.2. Comparison 2 Auranofin vs. placebo - Withdrawals and dropouts, Outcome 2 Withdrawals: System specific adverse reactions.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 2 Auranofin vs. placebo - Withdrawals and dropouts

Outcome: 2 Withdrawals: System specific adverse reactions



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Study or subgroup	Auranofin n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
3 Withdrawals: mucosal / cutaneous adverse reactions				
Bombardier 1986	2/157	3/152		0.65 [0.11, 3.77]
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]
Glennas 1997	2/31	6/34		0.36 [0.08, 1.57]
Johnsen 1989	9/67	1/65		5.40 [1.49, 19.50]
Lewis 1984	0/30	0/30		0.0 [0.0, 0.0]
Palmer 1982	1/10	0/10		7.39 [0.15, 372.38]
Prouse 1982	0/10	0/10		0.0 [0.0, 0.0]
Ward 1983	2/72	1/46		1.27 [0.12, 13.22]
Wenger 1983	3/152	1/152		2.75 [0.38, 19.68]
Subtotal (95% CI)	**539**	**510**		**1.56 [0.75, 3.23]**
Total events: 19 (Auranofin), 12 (Placebo)				
Heterogeneity: Chi^2 = 9.32, df = 5 (P = 0.10); I^2 =46%				
Test for overall effect: Z = 1.20 (P = 0.23)				
4 Withdrawals: renal adverse reactions				
Bombardier 1986	1/157	0/152		7.16 [0.14, 360.90]
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]
Glennas 1997	0/31	1/34		0.15 [0.00, 7.48]
Johnsen 1989	2/67	0/65		7.28 [0.45, 117.69]
Lewis 1984	1/30	1/30		1.00 [0.06, 16.37]
Palmer 1982	0/10	0/10		0.0 [0.0, 0.0]
Prouse 1982	0/10	0/10		0.0 [0.0, 0.0]
Ward 1983	0/72	0/46		0.0 [0.0, 0.0]
Wenger 1983	2/152	1/152		1.96 [0.20, 18.95]
Subtotal (95% CI)	**539**	**510**		**1.96 [0.53, 7.27]**
Total events: 6 (Auranofin), 3 (Placebo)				
Heterogeneity: Chi^2 = 3.16, df = 4 (P = 0.53); I^2 =0.0%				
Test for overall effect: Z = 1.00 (P = 0.32)				
5 Withdrawals: liver adverse reactions				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Auranofin), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
6 Withdrawals: hematology adverse reactions				
Bombardier 1986	2/157	0/152		7.20 [0.45, 115.73]
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]
Glennas 1997	0/31	0/34		0.0 [0.0, 0.0]

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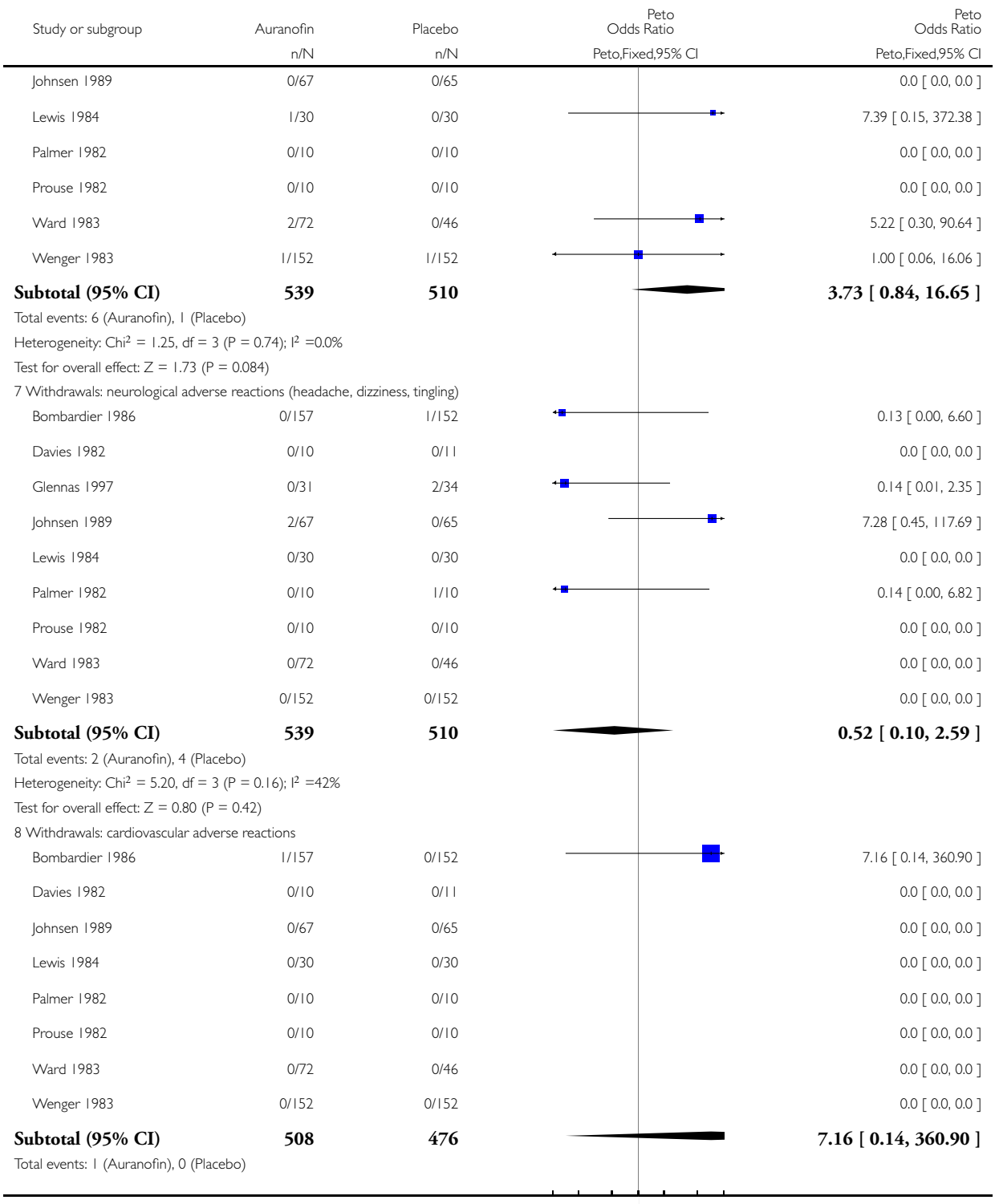

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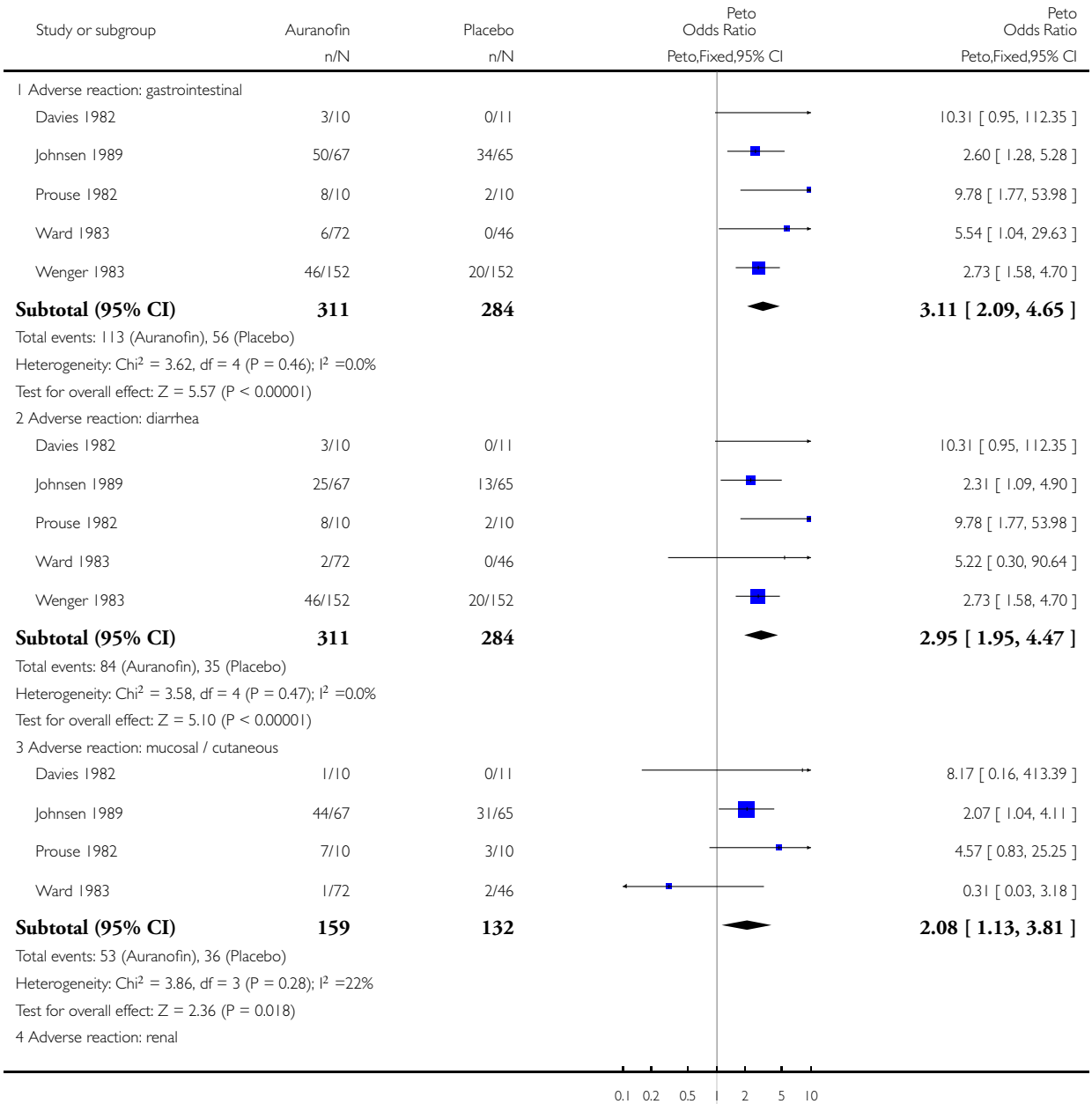
Study or subgroup	Auranofin n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.98 (P = 0.33)				
9 Withdrawals: miscellaneous adverse reactions				
Bombardier 1986	2/157	0/152		7.20 [0.45, 115.73]
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]
Glennas 1997	0/31	0/34		0.0 [0.0, 0.0]
Johnsen 1989	0/67	0/65		0.0 [0.0, 0.0]
Lewis 1984	0/30	0/30		0.0 [0.0, 0.0]
Palmer 1982	0/10	0/10		0.0 [0.0, 0.0]
Prouse 1982	0/10	0/10		0.0 [0.0, 0.0]
Ward 1983	0/72	0/46		0.0 [0.0, 0.0]
Wenger 1983	0/152	0/152		0.0 [0.0, 0.0]
Subtotal (95% CI)	**539**	**510**		**7.20 [0.45, 115.73]**
Total events: 2 (Auranofin), 0 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.39 (P = 0.16)				
Test for subgroup differences: Chi² = 6.63, df = 7 (P = 0.47), I² =0.0%				

Analysis 3.1. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 1 Adverse reactions: System specific.

Review: Auranofin versus placebo in rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 1 Adverse reactions: System specific



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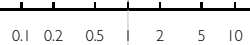
Study or subgroup	Auranofin n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Bombardier 1986	0/1	0/1		0.0 [0.0, 0.0]
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]
Johnsen 1989	4/67	4/65		0.97 [0.23, 4.03]
Prouse 1982	0/10	0/10		0.0 [0.0, 0.0]
Ward 1983	0/72	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**160**	**133**		**0.97 [0.23, 4.03]**
Total events: 4 (Auranofin), 4 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.04 (P = 0.96)				
5 Adverse reaction: liver				
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]
Johnsen 1989	0/67	0/65		0.0 [0.0, 0.0]
Prouse 1982	0/10	0/10		0.0 [0.0, 0.0]
Ward 1983	0/72	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**159**	**132**		**0.0 [0.0, 0.0]**
Total events: 0 (Auranofin), 0 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
6 Adverse reaction: hematology				
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]
Johnsen 1989	0/67	0/65		0.0 [0.0, 0.0]
Prouse 1982	0/10	0/10		0.0 [0.0, 0.0]
Ward 1983	0/72	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**159**	**132**		**0.0 [0.0, 0.0]**
Total events: 0 (Auranofin), 0 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
7 Adverse reaction: neurological				
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]
Johnsen 1989	0/67	0/65		0.0 [0.0, 0.0]
Prouse 1982	0/10	0/10		0.0 [0.0, 0.0]
Ward 1983	0/72	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**159**	**132**		**0.0 [0.0, 0.0]**
Total events: 0 (Auranofin), 0 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
8 Adverse reaction: miscellaneous				
Davies 1982	0/10	0/11		0.0 [0.0, 0.0]



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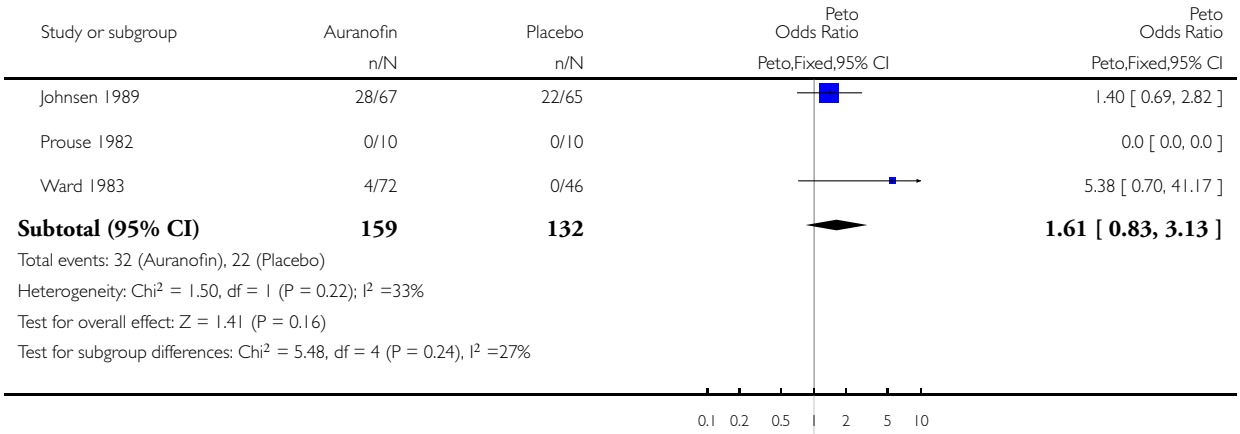

WHAT'S NEW

Last assessed as up-to-date: 21 February 2000.

Date	Event	Description
22 September 2008	Amended	Converted to new review format. C101-R

HISTORY

Review first published: Issue 2, 2000

CONTRIBUTIONS OF AUTHORS

All the authors participated in the development of the protocol and searches. CH Spooner and E Belseck appraised the publications and extracted the data from the trials.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Alberta Hospitals Foundation, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Auranofin [*therapeutic use]

MeSH check words

Humans