# Penicillamine for treating rheumatoid arthritis (Review)

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[Intervention Review]

# Penicillamine for treating rheumatoid arthritis

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## ABSTRACT

### Background

D-penicillamine is a penicillin derived compound originally used to treat patients with rheumatoid arthritis (RA) in the 1950's. Although frequently used in the past, its use has declined with the increasing use of other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate.

### Objectives

To estimate the short-term effects of D-penicillamine for the treatment of rheumatoid arthritis (RA).

### Search methods

We searched the Cochrane Musculoskeletal Group's trials register, the Cochrane Controlled Trials Register (issue 3, 2000) and Medline up to and including August 2000 and Embase from 1988-2000. We also carried out a handsearch of the reference lists of the trials retrieved from the electronic search.

### Selection criteria

All randomized controlled trials and controlled clinical trials comparing D-penicillamine against placebo in patients with rheumatoid arthritis.

### Data collection and analysis

The methodological quality of the trials was assessed independently by two reviewers (CS, EB) and checked by a third (MS) using a validated quality assessment tool (Jadad 1996). Rheumatoid arthritis outcome measures were extracted from the publications for the six-month endpoint and stratified according to D-penicillamine dosages: low (<500mg/day), moderate (500 to <1000mg/day) and high (1000 mg/day or greater). Data was abstracted by one reviewer and checked by a second (CS, MS). The pooled analysis was performed using the standardized mean difference for joint counts, pain and global assessments. The weighted mean difference was used for erythrocyte sedimentation rate (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, since no statistical heterogeneity was found.

**Main results**

Six trials were identified, with 425 patients randomized to D-penicillamine and 258 to placebo. A statistically significant benefit was observed for D-penicillamine when compared to placebo for all three-dose ranges and for most outcome measures including: tender joint counts, pain, physician's global assessments and ESR. The standardized weighted mean differences between treatment and placebo in moderate doses were -0.51 [95% CI -0.88, -0.14] for tender joint counts, -0.56 (95% CI -0.87, -0.26) for pain and -0.97 (95% CI -1.25, -0.70) for global assessment. The difference for ESR was -10.6 mm/hr. Similar results were observed for the higher dose group. Total withdrawals were significantly higher in the moderate and high dosage D-penicillamine groups (OR=1.63 and 2.13 respectively), mostly due to increased adverse reactions (OR = 2.60 and 4.95 respectively), including renal and hematological abnormalities.

**Authors' conclusions**

D-penicillamine appears to have a clinically and statistically significant benefit on the disease activity of patients with rheumatoid arthritis. Its efficacy appears to be similar to that of other disease modifying anti-rheumatic drugs (DMARDs), but with a significantly higher toxicity. Its effects on long-term functional status and radiological progression are not clear from this review.

## PLAIN LANGUAGE SUMMARY

**Penicillamine for treating rheumatoid arthritis**

Penicillamine is a penicillin derived compound. Studies showed that this could be used to treat rheumatoid arthritis originally in 1950. It was frequently used in the past, but its use has declined with the increasing use of other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate. The purpose of this summary was to find out if penicillamine is helpful in the treatment of rheumatoid arthritis.

Penicillamine was seen to be beneficial for all ranges of dosages for disease activity on tender joint pain, physician global assessment and sed rate. No major differences were observed between placebo and low dose penicillamine (<500 mg/day). For higher dosages, patients on penicillamine were twice as likely to withdraw than those receiving placebo 500 to <1000 mg/day. D-penicillamine appears be have a clinical and statistical benefit on the disease activity of patients with rheumatoid arthritis. Its benefit is similar to that of other such drugs, such as disease modifying anti-rheumatic drugs (DMARDs). More adverse reactions are seen in patients being treated with D-penicillamine.

## BACKGROUND

D-penicillamine is a penicillin derived compound, originally used for the treatment of Wison's disease and cystinuria. In vitro studies showed that D-penicillamine could dissociate macroglobulins such as rheumatoid factor (RF). The drug was originally used to treat patients with rheumatoid arthritis (RA) in the 1950's. Since then, several clinical trials examining its efficacy have been published. Although frequently used in the past, its use has declined with the increasing use of other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate.

## OBJECTIVES

To evaluate the short-term efficacy and toxicity of d-penicillamine for the treatment of RA, by conducting a systematic review of randomized controlled trials (RCTs) and controlled clinical trials (CCTs) comparing d-penicillamine and placebo.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials and controlled clinical trials, with a minimum duration of 3 months.

### Types of participants

Patients with a diagnosis of RA (as stated in the publication).

### Types of interventions

Intervention group: d-penicillamine, minimum dosage 125 mg/day, oral administration
Control group: placebo

### Types of outcome measures

Efficacy
All the outcome measures in OMERACT (Outcome Measures for Rheumatoid Arthritis Clinical Trials 1993) were included for potential analysis, although only some were consistently reported across trials.
OMERACT measures for efficacy include:
a) Number of tender joints per patient
b) Number of swollen joints per patient
c) Pain
d) Physician global assessment
e) Patient global assessment
f) Functional status
g) Acute phase reactants
h) Radiological damage
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 adverse reactions
d) Number of withdrawals due to concurrent illness
e) Number of withdrawals due to system-specific adverse reactions (e.g. gastrointestinal, renal, etc.)
Adverse effects not causing withdrawal were analysed as system-specific adverse reactions:
a) Gastrointestinal
b) Mucosal / cutaneous
c) Renal
d) Liver
e) Haematological
f) Neurological (headache, dizziness, tingling)
g) Impaired / loss of taste
h) Miscellaneous adverse reactions

## Search methods for identification of studies

We searched the Cochrane Musculoskeletal Group's trials register, the Cochrane Controlled Trials Register (issue 3, 2000) and Medline up to and including August 2000 and Embase from 1988-2000. We also carried out a handsearch of the reference lists of the trials retrieved from the electronic search.

## 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 (CS) and checked by a second (MS).
Efficacy
The results on efficacy were analysed for the 6-month endpoint when these data were available. 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 D-penicillamine. A 4-month duration trial (Mery 1976) was included in the review and the results pooled with the other studies.
To determine if the effect of d-penicillamine depended on dose, outcomes on efficacy, withdrawals and adverse reactions were analyzed into the following dose categories: 125 to less than 500 mg/day, 500 to less than 1000 mg/day, 1000 or more mg/day.
The analysis compares end of trial results. When the standard deviation for results was not available, we imputed the baseline standard deviation (SD) or an estimated value using the coefficient of variation (CV=SD/mean) from the other trials. In the case of ESR results this was 0.70. If trials reported means and ranges, the range was divided by three to estimate the SD. Trials that reported change from baseline scores with no SD were not combined with trials that reported end of trial results. When imputing a SD, we elected to be as conservative as possible. Sensitivity analyses were performed when 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 (SMD) for joint scores, pain, and global assessments. This was necessary because of the variation in the way outcome measures were scored and reported in each study (e.g. different number of tender joints, tender joint index). Trial results were entered into RevMan 3.1.1 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 SMD indicate a benefit of the active drug over placebo. ESR results were pooled using a weighted mean difference (WMD). For the lower dose trial ESR results were reported as change scores (Williams 1983). Because no other trials were pooled in this comparison, results are shown in MetaView as reported in the paper (change scores).
Withdrawals and dropouts
Adverse reactions 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-up exceeded six months. Toxicity was analysed using a pooled odds ratio for total withdrawals from adverse reactions and withdrawals for system-specific side effects.
Adverse reactions
Adverse reactions were analysed using a pooled odds ratio for system-specific reactions that may have necessitated a dose adjustment in treatment but not withdrawal from the trial.
The heterogeneity of the trials for each pooled analysis was estimated using a chi-square test. No significant heterogeneity was

observed so fixed effects models were used throughout.

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Six trials met the criteria for inclusion, five randomized trials (Andrews 1973, Dixon 1975, Mery 1976, Shiokawa 1977, Williams 1983) and one controlled trial (Huskisson 1976). The duration of studies ranged from four months to one year; they were conducted in the UK (3), France (1), Japan (1), and the USA (1), all prior to 1983.

D-penicillamine was administered orally at doses ranging from 125 mg/day to 1500 mg/day. These were stratified as described previously: low dose < 500 mg/day, (Williams 1983), moderate dose 500 to < 1000 mg/day, (Dixon 1975, Mery 1976, Shiokawa 1977, Williams 1983), high dose 1000 or more mg/day (Andrews 1973, Dixon 1975, Huskisson 1976, Mery 1976). Cumulatively, 425 patients received d-penicillamine and 258 placebo at the start of these trials.

Trials reported varying numbers of the OMERACT outcome measures, therefore, different numbers of trials are included in each comparison. The most consistently reported measures were joint scores, pain and ESR.

Two studies analyzed the results on the basis of intention to treat. The other four only reported final data on patients who completed the trial.

## Risk of bias in included studies

The methodological quality of the studies was assessed independently by two of the investigators (MS, EB) using a quality scale validated and published by Jadad (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 five (best). One study had a score of five, three studies a score of four, and one each a score of three and two (see table of included studies). Disagreements were resolved by consensus. Concealment of allocation was considered adequate in two studies, unclear in three, and inadequate in the sixth study.

## Effects of interventions

Five of the six trials could be evaluated for efficacy by meta-analysis. Huskisson reported change scores with no measure of dispersion and no baseline data. Other trials reporting change scores also provided baseline data, which was used to compute end of trial results. Whenever possible these calculations were performed and included. The only efficacy measures adequately reported for pooling were tender joints (three RCTs), pain (three RCTs), physician global assessment (three RCTs) and ESR (three RCTs). Williams was the only study to evaluate a low dose. The results from this study are reported in the tables for comparison but, of course, could not be pooled.

The origins of imputed standard deviations are described in the Table of Included Studies in the Notes section.

In the four-pooled analyses of clinical benefits that were possible, D-penicillamine provided a statistically significant benefit. There were no significant differences in effect size among dosage groups and the suggestion of a dose trend was not evident in these few trials, though the lower dosage showed somewhat smaller effect size that the moderate and high group (only one trial was included in the lower dose range). There was an equal reduction in tender joint scores in the moderate and high dose strata corresponding to an effect size of -0.51 [95% CI -0.88, -0.14] and -0.51 [95% CI -0.93, -0.08], respectively. Pain scores were reduced by an effect size of a similar magnitude SMD -0.56 [95% CI -0.87, -0.26] and -0.65 [95% CI -0.97, -0.32] for moderate and high doses. A statistically significant reduction was also observed for ESR in moderate and high dose groups of -10.65mm [95% CI -20.89, -0.41] and -14.39mm [95% CI -23.21, -5.58] respectively. Three studies reported a global physician score but only two, Williams and Shiokawa, both studying moderate doses, could be pooled. In this analysis d-penicillamine was judged to be superior to placebo with an effect size of -0.97 [95%CI -1.25, -0.70].

Shiokawa grouped outcome measures on ESR, number of active joints, duration of morning stiffness and grip strength into a Rheumatoid Activity Index. The difference was statistically significant in favour of D-penicillamine [placebo: mean index score = 53 (SD 34.2), D-penicillamine = 36 (SD 23.2)].

As mentioned above, the efficacy data of the trial by Huskisson could not be pooled with the other studies. The results at six months showed a significant difference favouring d-penicillamine over placebo for pain, articular index and ESR. This study also included a third group treated with levamisole with results similar to those observed for d-penicillamine.

Three studies evaluated radiological changes (Andrews 1973, Dixon 1975, and Shiokawa 1977). In Andrews all patients had advanced disease with severe erosive changes. Radiographs did not show any striking changes though most deteriorated. No significant differences in the number or severity of erosions were observed in Dixon's trial, and there was no evidence of a trend in either direction. In Shiokawa's study the radiographs were rated by two groups of assessors and the results were not pooled, only independently reported. The orthopedics group concluded there was no difference in response between treatment and placebo groups; however, the internist group concluded that erosive changes were less frequent in the D-penicillamine group.

Withdrawals and dropouts were available for all trials. No major differences were observed between placebo and low dose D-penicillamine (< 500 mg/day). For higher dosages, patients on D-penicillamine were twice as likely to withdraw than those receiving placebo: 500 to < 1000 mg/day OR = 1.63 [95%CI 1.05, 2.53], 1000 mg/day or more OR = 2.13 [95% CI 1.12, 4.06]. Though patients on d-penicillamine were less likely to withdraw because of lack of efficacy: 500mg < 1000 mg/day OR = 0.41 [95% CI: 0.13, 1.29], 1000mg/day or more OR = 0.12 [95% CI 0.03, 0.56] they were three to five times more likely to dropout due to adverse reactions: 500mg < 1000 mg/day OR = 2.60 [95% CI 1.51, 4.47], 1000mg/day or more OR = 4.95 [95% CI 2.38, 10.30].
Withdrawals due to adverse reactions did increase along with the dose of D-penicillamine (moderate dose 21%, high dose 25%) but this difference did not reach statistical significance.
Data from studies that reported specific reasons for withdrawal indicated no statistically significant differences between active treatment and placebo groups, mostly because of small numbers within each group of adverse events. The most frequent adverse effects responsible for D-penicillamine discontinuation were (all doses combined) hematological 6.6%, mucosal/cutaneous 4.9%, impaired/loss taste 4.7%, renal 4.1% or gastrointestinal 2.3%.
Adverse effects not requiring withdrawal occurred in both treatment and placebo groups. Statistically significant differences were only observed for impaired/loss of taste in the moderate dose group, OR = 3.74 [95% CI 1.61, 8.67] and the high dose group, OR = 3.07 [95% CI 1.57, 5.99].

## DISCUSSION

D-penicillamine has been used for the treatment of RA for several decades. Its use nevertheless has markedly declined in the past few years, mostly because of concerns over its safety. The purpose of this systematic review was to evaluate the effects of D-penicillamine for the treatment of patients with RA, when compared to placebo.

We only included in this review placebo-controlled trials, reporting results at approximately six months. Most of the trials included in this review are over 20 years old. The dosages evaluated ranged from 125 mg/day to 1,500 mg/day. Although some of the major outcome measures in the trials were sufficiently homogeneous to allow pooling, there was some lack of standardization of the outcome measurements (e.g. different joint count measures) and even complete omission of some outcomes. All these studies were published before the publication of OMERACT and the American College of Rheumatology (ACR) core set of measures for RA (OMERACT 1993, Felson 1993). We also encountered some difficulties in the data extraction given the lack of standardization in the data reported. Some trials reported results as changes from baseline, others as end-of-trial results. Standard deviations of the change or end-of-trial result were often not reported. We estimated missing data with approximate values derived from the trial per se (e.g. range as a measure of dispersion) or from results from the other trials (e.g. coefficient of variation to estimate standard deviations relative to the mean). Although these procedures may have created some bias, because they were similarly applied to both groups (treatment and control), their overall impact on the estimation of differences between groups is probably small. Our preference was to estimate some of these parameters as opposed to completely excluding some trials.

Statistically significant differences between placebo and D-penicillamine were observed for various measures of disease activity, including tender and swollen joint scores, pain global assessments and ESR. When using standardized mean differences, the effect sizes comparing D-penicillamine with placebo were generally about 0.5. This is considered to be a clinically relevant effect (Kazis 1989) of moderate magnitude. None of the studies examined functional outcomes with comprehensive functional scales or health status measurements and therefore, these outcomes could not be adequately assessed. Three studies examined radiological progression; no clear trends favouring D-penicillamine were observed.

No significant differences in efficacy were observed between low, moderate and high dosages (only one trial evaluated a low dose). Nevertheless, withdrawals were significantly increased in the D-penicillamine group, mostly from toxicity, following a dose response pattern. The odds ratio for withdrawals due to adverse reactions was 2.6 in the moderate dose group and close to five in the higher dose group. These results suggest that on average, there is no advantage from using dosages higher than 500mg/d.

A few studies have compared the efficacy of D-penicillamine with that of other DMARDs, including gold, azathioprine and antimalarials (Huskisson 1974, Berry 1976, Bunch 1984, Gibson 1987, Scott 1990, Jessop 1998). No consistent differences have been reported although some studies suggested better results with D-penicillamine when compared to antimalarials. Yet, treatment with penicillamine is associated with much higher adverse event rates. No major differences can be found when comparing the effect sizes in this meta-analysis with the results reported in the other Cochrane systematic reviews evaluating various DMARDs (Clark 1997, Suarez-Almazor 1998, Wells 1998). Given the high toxicity observed with D-penicillamine and the lack of evidence supporting a stronger beneficial effect, we would recommend the use of this drug only when treatment with some of the other less toxic DMARDs, such as methotrexate, sulphasalazine or antimalarials, has failed.

Most of the trials in this review included patients with long duration of disease, who had generally failed treatment with other DMARDs. Patients with early disease may respond better to treatment, and therefore it may be difficult to generalize the findings of

this review to patients with early disease. Only one trial (Shiokawa 1977) included patients with short disease duration, but the results did not appear to be substantially different from those reported in the other trials. This trial was not pooled with the others because of the way the outcomes were reported, as an aggregated index.

## AUTHORS' CONCLUSIONS

### Implications for practice

D-penicillamine appears to be efficacious in the short-term treatment of patients with RA with a clinically and statistically significant benefit on disease activity. Its effects on long-term functional status and radiological progression are not clear at this time. There appears to be no clear advantage in using d-penicillamine in doses greater than 500mg/day. Higher dosages increase toxicity without a clear benefit on efficacy. There are no clear benefits of d-penicillamine when compared to other DMARDs, so we would recommend that other drugs with a lower risk-benefit ratio be used before D-penicillamine is prescribed.

### Implications for research

Most trials included in this review were conducted over 20 years ago. Nevertheless, since the results across studies appear to be consistent and toxicity is high we would not recommend that any additional D-penicillamine, placebo-controlled trials be conducted in patients with RA. Although some direct drug-to-drug trials may be useful, more recently developed drugs increasingly being used in RA may be more promising, given their lower risk-benefit ratio. Because of the high costs involved in conducting clinical trials, research efforts may be better invested by evaluating other drugs.

## ACKNOWLEDGEMENTS

The reviewers would like to acknowledge Dr. Ann Cranney and Dr. Dan Furst for their comments and suggestions, as well as the editors of the Cochrane Musculoskeletal Group for their editorial comments.

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arthritis. *Cochrane Database of Systematic Reviews* 1998, Issue 2. [DOI: 10.1002/14651858.CD001083]
* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

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

**Andrews 1973**

| | |
|---|---|
| Methods | Allocation: Randomized [stratified by age (at 45y) sex and steroid use]<br>Blinding: double blind<br>Design: parallel study<br>Sample size entry: Penicillamine n= 52; placebo n = 53<br>Analysis: completers. |
| Participants | Country: UK, 5 centres<br>Patients with active RA (severe disease)<br>Age: mean 56.5 yrs (sd 22)<br>Duration of disease: mean 11.2 yrs (sd 8.7)<br>Females: 79%<br>RF: 65%<br>Concomitant use of steroids: 64.7%<br>Concomitant use of other DMARDS: none<br>Previous use of DMARDS: none in past 2 mo. No gold past 6 mo |
| Interventions | Penicillamine: 1500 gm/day or matching placebo<br>Treatment duration: 12 months<br>1/2 the patients in each group received 5 ml of 0.1% copper supplement daily, other 1/2 received 5 ml of 0.1% sodium bicarbonate |
| Outcomes | Articular index: Ritchie (extended to include joint swelling (scale 0- 182, 182 = worst)<br>Patient assessment: Well being (scale 0-3, 3 = very ill)<br>Physician assessment: Observer assessment scale 1-3. (3 = no value, 1 = successful)<br>Pain: (scale 0-3, 3 = severe)<br>Functional assessment: (scale 0-192, 192 = worst possible)<br>ESR<br>Xray: joints scored by CIOMS method |
| Notes | Quality score: 5<br>Allocation concealment: A<br>Reported: end of trial data, mean score only<br>Calculated:end of trial sd for articular index, function & ESR from baseline range / 3 (using baseline scores for completers only)<br>sd pain calculated using coefficient of variation from studies.<br>Observer assessment converted to 3 point scale, (3=worse). mean and sd calculated |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | A - Adequate |

**Dixon 1975**

| | |
|---|---|
| Methods | Allocation: Randomized (subgrouped by 'general' or 'nodule' groups)<br>Blinding: double blind<br>Design: parallel study, two doses vs placebo<br>Sample size at entry: penicillamine 600 mg/day n=34; 1200 mg/day n= 44; control 12mg/day n= 43<br>Analysis: completers |
| Participants | Country: UK, 5 centres<br>Patients with active RA<br>Age: mean 53.4 y (sd 9.6)<br>Duration of disease: mean 8.7y (sd 7.6)<br>Females: 68%<br>RF: 100%<br>Concomitant use of steroids: 62%<br>Concomitant use of other DMARDS: none<br>Previous use of DMARDS: excluded from study |
| Interventions | Synthetic d-penicillamine: 600 mg/day, or 1200 mg/day or control with 12 mg/day<br>Treatment duration: 24 wks |
| Outcomes | Pain (scale 0 to 4, 4 = very severe)<br>ESR |
| Notes | Quality score: 4<br>Allocation concealment: B<br>Reported: baseline & mean differences using combined results for all subgroups<br>Baseline pain score: mean & sd calculated from table 1. Baseline sd imputed to end of trial result<br>Reported: change in ESR, calculated end of trial score, imputed sd from CV = 0.7 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | B - Unclear |

**Hamilton 1977**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

***Risk of bias***

**Hamilton 1977** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | D - Not used |

**Huskisson 1976**

| | |
|---|---|
| Methods | Allocation: not reported<br>Blinding: Single blind (observer)<br>Design: not reported<br>Sample size at entry: penicillamine n= 12; levamisole n = 12; placebo n = 10.<br>Analysis: intention to treat |
| Participants | Country: UK, single centre<br>Patients with active RA<br>Age: not reported<br>Duration of disease: not reported<br>Females: not reported<br>RF: not reported<br>Concomitant use of steroids: not reported<br>Concomitant use of other DMARDS: not reported<br>Previous use of DMARDS: not reported |
| Interventions | Penicillamine 1000 mg/day or Levamisole 150 mg/day or placebo<br>Treatment duration: 6 mos |
| Outcomes | Articular index: Ritchie<br>Pain: VAS<br>ESR |
| Notes | Quality score: 2<br>Allocation concealment: C<br>Reported: Change scores, no baseline data |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | High risk | C - Inadequate |

**Mery 1976**

| | |
|---|---|
| Methods | Allocation: Randomized<br>Blinding: double blind (4 months then became open study)<br>Design: parallel study<br>Sample size at entry: 66, each treatment group subgrouped to receive zinc supplement or not. n = 31 when zinc groups not included. Penicillamine 500 mg/day n =10; penicillamine 1000 mg/day n = 10; placebo n = 11<br>Analysis: intention to treat |
| Participants | Country: France<br>Patients with active RA<br>Age: mean 52.3 yrs<br>Duration of disease: 9.5 yrs<br>Females: 71%<br>RF: 80.6%<br>Concomitant use of steroids: 76.7%<br>Concomitant use of other DMARDS: none<br>Previous use of DMARDS: none in past 3 mo. |
| Interventions | D-penicillamine 500 mg/day or d-penicillamine 1000 mg/day or placebo<br>Treatment duration: 4 mo.<br>Half of each group received 5 mg/day zinc supplement therefore six groups studied |
| Outcomes | Articular index: Ritchie<br>Patient assessment: 7 grade scale, low score = worse<br>Physician assessment: 7 grade scale, low score = worse<br>ESR |
| Notes | Quality score: 3<br>Allocation concealment: B<br>Only groups without zinc included. Zn supplement found to inhibit effect of d-penicillamine<br>Reported: Baseline & change scores, sd imputed from SE's at baseline and applied to end of trial results |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | B - Unclear |

**Shiokawa 1977**

| | |
|---|---|
| Methods | Allocation: Randomized<br>Blinding: double blind<br>Sample size at entry: penicillamine n = 90; control n = 89<br>Analysis: completers |

**Shiokawa 1977** (*Continued*)

| | |
|---|---|
| Participants | Country: Japan, multicentre<br>Patients with active RA<br>Age: mean 48.6 y<br>Duration of disease: mean 13 mo.<br>Females: 84%<br>RF: 79% Concomitant use of steroids: none<br>Concomitant use of other DMARDS: none<br>Previous use of DMARDS: none in previous two months |
| Interventions | Penicillamine: Tx group 600 mg/day, control group 30 mg/day<br>Treatment duration: 24 wks |
| Outcomes | Physician global assessment: 4 category scale<br>Xray |
| Notes | Quality score: 4<br>Allocation concealment: A<br>MD assessment converted to 4 point scale: Excellent = 1, Good = 2, Moderate = 3, Poor = 4. Mean & sd calculated<br>X-ray results not pooled with other studies.<br>Four outcomes were grouped into a 'rheumatoid activity index' and not reported separately |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | A - Adequate |

**Williams 1983**

| | |
|---|---|
| Methods | Allocation: randomized<br>Blinding: double blind<br>Design: parallel study<br>Sample size at entry: 225. d-penicillamine 125 mg/day, n = 87; d-penicillamine 500 mg/day, n = 86; placebo n = 52<br>Analysis: completers |
| Participants | Country: USA, 10 centres<br>Patients with active RA<br>Age: mean 51 yrs sd 11.4<br>Females: 68%<br>Duration of disease: mean 9.7 yrs (sd 8.2)<br>RF: not reported<br>Concomitant use of steroids: 33%<br>Concomitant use of other DMARDS: none<br>Previous use of DMARDS: not in past 2 to 3 mo. |

**Williams 1983** (*Continued*)

| | |
|---|---|
| Interventions | Penicillamine 125 mg/day or Penicillamine 500 mg/day or placebo<br>Treatment duration: 36 wks |
| Outcomes | Tender joints: count (max 60 joints)<br>Pain: Joint tenderness (scale 0-3, 3 = severe)<br>Swollen joints: count and score (scale 0-3, 3 = severe)<br>Patient's assessment: (scale 1-5, 5 = very severe)<br>Physician's assessment: (scale 1-5, 5 = very severe)<br>ESR |
| Notes | Quality score : 4<br>Allocation concealment: B<br>Reported: change scores with sd<br>Calculated end of trial scores. Used baseline sd values |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | B - Unclear |

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

| Study | Reason for exclusion |
|---|---|
| Ahern, 1984 | Studied effects of withdrawal of d-penicillamine |
| Bunch, 1984 | Combination therapy. No placebo group. |
| Eberhardt, 1996 | Long term study and data |
| Golding, 1973 | Report on MCTG study (Andrews 1973) |
| Golding, 1977 | Report on the MCTG (Andrews 1973) |
| Multicentre Trial Gr | Results at 5 yr only. No placebo group. |
| Thomas, 1979 | Placebo group data not reported |
| van Rijthoven, 1991 | No placebo group. Drug/drug comparison |
| Verstraeten, 1990 | No placebo group. |

## DATA AND ANALYSES

### Comparison 1. D-Penicillamine vs. placebo - Efficacy

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Tender joints | 3 | 316 | Mean Difference (IV, Fixed, 95% CI) | -6.79 [-10.02, -3.55] |
| 1.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 106 | Mean Difference (IV, Fixed, 95% CI) | -6.0 [-11.36, -0.64] |
| 1.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 121 | Mean Difference (IV, Fixed, 95% CI) | -6.61 [-11.37, -1.84] |
| 1.3 Dose d-penicillamine: 1000 or more mg/day | 2 | 89 | Mean Difference (IV, Fixed, 95% CI) | -8.90 [-16.63, -1.16] |
| 2 Number of swollen joints | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 2.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 106 | Mean Difference (IV, Fixed, 95% CI) | -2.0 [-5.96, 1.96] |
| 2.2 Dose d-penicillamine: 500 to < 1000 mg/day | 1 | 100 | Mean Difference (IV, Fixed, 95% CI) | -5.0 [-9.11, -0.89] |
| 3 Pain | 3 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 106 | Mean Difference (IV, Fixed, 95% CI) | -11.0 [-23.19, 1.19] |
| 3.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 176 | Mean Difference (IV, Fixed, 95% CI) | -0.63 [1.00, -0.26] |
| 3.3 Dose d-penicillamine: 1000 or more mg/day | 2 | 152 | Mean Difference (IV, Fixed, 95% CI) | -0.61 [-0.91, -0.31] |
| 4 Physician global assessment | 3 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 4.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 108 | Mean Difference (IV, Fixed, 95% CI) | -0.42 [-0.72, -0.12] |
| 4.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 234 | Mean Difference (IV, Fixed, 95% CI) | -0.77 [-0.98, -0.56] |
| 4.3 Dose d-penicillamine: 1000 or more mg/day | 1 | 82 | Mean Difference (IV, Fixed, 95% CI) | -1.07 [-1.36, -0.78] |
| 5 Patient global assessment | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 5.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 110 | Mean Difference (IV, Fixed, 95% CI) | -0.36 [-0.65, -0.07] |
| 5.2 Dose d-penicillamine: 500 to < 1000 mg/day | 1 | 101 | Mean Difference (IV, Fixed, 95% CI) | -0.56 [-0.86, -0.26] |
| 5.3 Dose d-penicillamine: 1000 or more mg/day | 1 | 68 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Functional status | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 6.1 Dose d-penicillamine: 1000 or more mg/day | 1 | 68 | Mean Difference (IV, Fixed, 95% CI) | -13.90 [-37.03, 9.23] |
| 7 ESR | 4 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 7.1 Dose d-penicillamine: 125 to < 500 mg/day (change scores) | 1 | 69 | Mean Difference (IV, Fixed, 95% CI) | -8.0 [-22.01, 6.01] |
| 7.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 98 | Mean Difference (IV, Fixed, 95% CI) | -10.65 [-20.89, -0.41] |

| | | | | |
|---|---|---|---|---|
| 7.3 Dose d-penicillamine: 1000 or more mg/day | 3 | 173 | Mean Difference (IV, Fixed, 95% CI) | -14.39 [-23.21, -5.58] |

**Comparison 2. D-Penicillaminevs. placebo - Withdrawals and dropouts**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Withdrawals and dropouts - Total | 6 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 1.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.76 [0.34, 1.69] |
| 1.2 Dose d-penicillamine: 500 to < 1000 mg/day | 4 | 415 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.63 [1.05, 2.53] |
| 1.3 Dose d-penicillamine: 1000 or more mg/day | 4 | 235 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.13 [1.12, 4.06] |
| 2 Withdrawals: lack of effect | 3 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 2.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.32 [0.07, 1.41] |
| 2.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 317 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.41 [0.13, 1.29] |
| 2.3 Dose d-penicillamine: 1000 or more mg/day | 1 | 105 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.12 [0.03, 0.56] |
| 3 Withdrawals: concurrent illness | 4 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 3.1 Dose d-penicillamine: 125 to < 500 mg/day | 0 | 0 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Dose d-penicillamine: 500 to < 1000 mg/day | 3 | 394 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.93 [0.23, 3.80] |
| 3.3 Dose d-penicillamine: 1000 or more mg/day | 2 | 108 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.99 [0.21, 19.34] |
| 4 Withdrawals: adverse reactions | 6 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 4.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.96 [0.60, 6.34] |
| 4.2 Dose d-penicillamine: 500 to < 1000 mg/day | 4 | 415 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.60 [1.51, 4.47] |
| 4.3 Dose d-penicillamine: 1000 or more mg/day | 4 | 235 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 4.95 [2.38, 10.30] |
| 5 Withdrawals:Gastrointestinal adverse reactions | 3 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 5.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.58 [0.03, 10.31] |
| 5.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 215 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.72 [0.10, 5.42] |
| 5.3 Dose d-penicillamine: 1000 or more mg/day | 2 | 192 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.99 [0.39, 10.04] |
| 6 Withdrawals:Mucosal / cutaneous adverse reactions | 4 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |

| | | | | |
|---|---|---|---|---|
| 6.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.72 [0.22, 13.32] |
| 6.2 Dose d-penicillamine: 500 to < 1000 mg/day | 1 | 138 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.17 [0.35, 13.62] |
| 6.3 Dose d-penicillamine: 1000 or more mg/day | 3 | 148 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.90 [0.77, 19.64] |
| 7 Withdrawals: Renal abnormality | 3 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 7.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 5.06 [0.48, 53.35] |
| 7.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 215 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 5.89 [0.96, 36.17] |
| 7.3 Dose d-penicillamine: 1000 or more mg/day | 1 | 21 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 8.17 [0.16, 413.39] |
| 8 Withdrawals: Hematological abnormality | 4 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 8.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 5.06 [0.48, 53.35] |
| 8.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 215 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 5.85 [1.58, 21.68] |
| 8.3 Dose d-penicillamine: 1000 or more mg/day | 3 | 130 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.81 [0.75, 19.26] |
| 9 Withdrawals: Impaired or loss of taste | 2 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 9.1 Dose d-penicillamine: 125 to < 500 mg/day | 0 | 0 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9.2 Dose d-penicillamine: 500 to < 1000 mg/day | 0 | 0 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9.3 Dose d-penicillamine: 1000 or more mg/day | 2 | 127 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 7.17 [0.74, 69.68] |

**Comparison 3. Adverse reactions not requiring withdrawal**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Adverse reactions: Gastrointestinal | 5 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 1.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 138 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.57 [0.17, 1.91] |
| 1.2 Dose d-penicillamine: 500 to < 1000 mg/day | 4 | 415 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.77 [0.44, 1.34] |
| 1.3 Dose d-penicillamine: 1000 or more mg/day | 3 | 213 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.02 [0.55, 1.87] |
| 2 Adverse reactions: Mucosal / cutaneous | 5 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 2.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.22 [0.59, 8.33] |

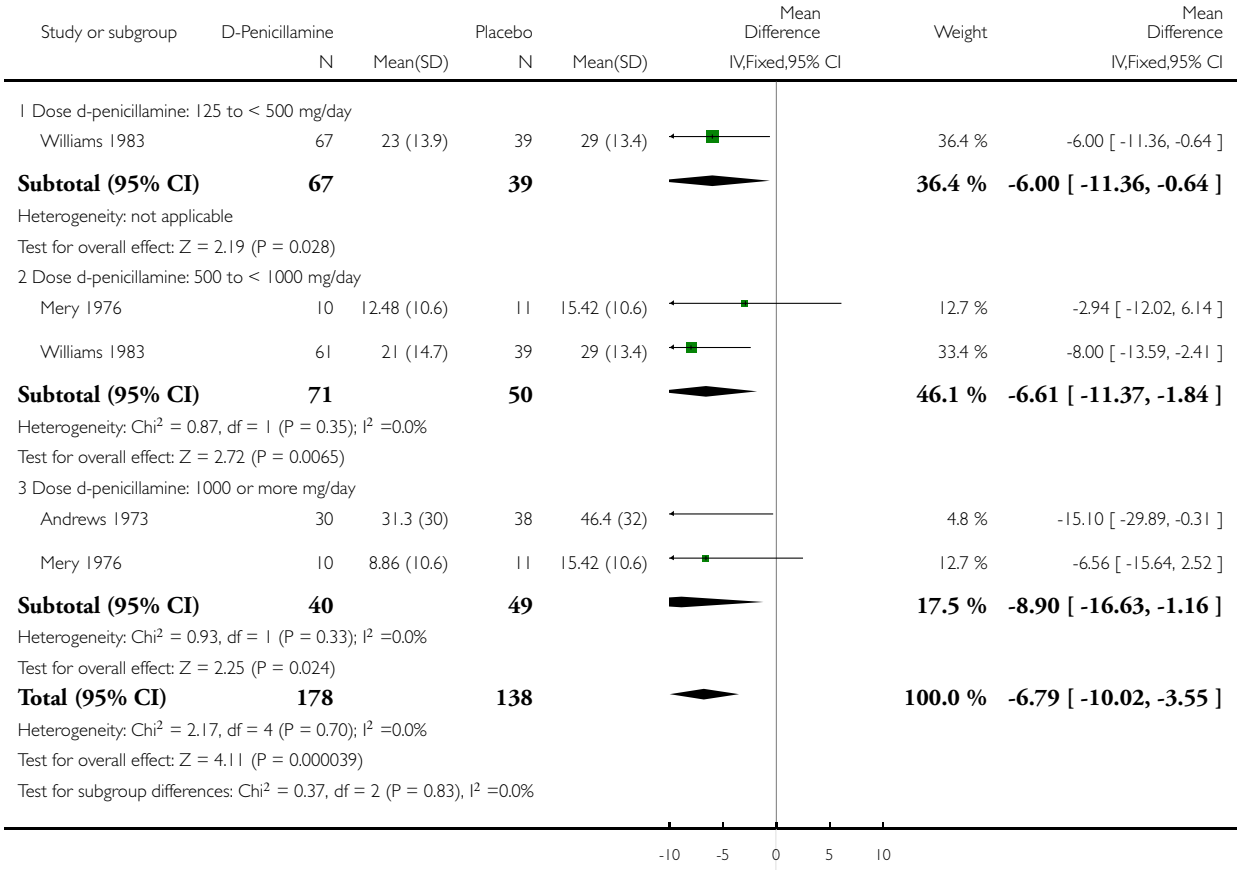
| | | | | |
|---|---|---|---|---|
| 2.2 Dose d-penicillamine: 500 to < 1000 mg/day | 4 | 415 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.66 [1.54, 4.59] |
| 2.3 Dose d-penicillamine: 1000 or more mg/day | 3 | 213 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.75 [0.89, 3.45] |
| 3 Adverse reactions: Renal | 2 | 463 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.61 [0.53, 4.83] |
| 3.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 179 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.99 [0.14, 7.14] |
| 3.2 Dose d-penicillamine: 500 to < 1000 mg/day | 1 | 179 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.99 [0.14, 7.14] |
| 3.3 Dose d-penicillamine: 1000 or more mg/day | 1 | 105 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.55 [0.59, 21.24] |
| 4 Adverse reactions: Liver | 1 | 179 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.13 [0.01, 2.13] |
| 4.1 Dose d-penicillamine: 500 to < 1000 mg/day | 1 | 179 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.13 [0.01, 2.13] |
| 5 Adverse reactions: Haematological | 1 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 5.1 Dose d-penicillamine: 500 to < 1000 mg/day | 0 | 0 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Dose d-penicillamine: 1000 or more mg/day | 1 | 105 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 6.23 [2.22, 17.53] |
| 6 Adverse reactions: Neurological (headache, dizziness, tingling) | 2 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 6.1 Dose d-penicillamine: 500 to < 1000 mg/day | 1 | 179 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.50 [0.05, 4.91] |
| 6.2 Dose d-penicillamine: 1000 or more mg/day | 1 | 105 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.02 [0.06, 16.52] |
| 7 Adverse reactions: Cardiovascular | 1 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 7.1 Dose d-penicillamine: 1000 or more mg/day | 1 | 87 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.13 [0.00, 6.67] |
| 8 Adverse reactions: Impaired or loss of taste | 5 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 8.1 Dose d-penicillamine: 125 to < 500 mg/day | 1 | 139 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 5.12 [0.66, 39.68] |
| 8.2 Dose d-penicillamine: 500 to < 1000 mg/day | 4 | 415 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.74 [1.61, 8.67] |
| 8.3 Dose d-penicillamine: 1000 or more mg/day | 3 | 213 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.07 [1.57, 5.99] |
| 9 Adverse reactions: Miscellaneous | 2 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 9.1 Dose d-penicillamine: 125 to < 500 mg/day | 0 | 0 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9.2 Dose d-penicillamine: 500 to < 1000 mg/day | 2 | 284 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.13 [0.01, 1.30] |
| 9.3 Dose d-penicillamine: 1000 or more mg/day | 1 | 105 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 7.53 [0.15, 379.68] |

## Analysis 1.1. Comparison 1 D-Penicillamine vs. placebo - Efficacy, Outcome 1 Tender joints.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 1 D-Penicillamine vs. placebo - Efficacy

Outcome: 1 Tender joints

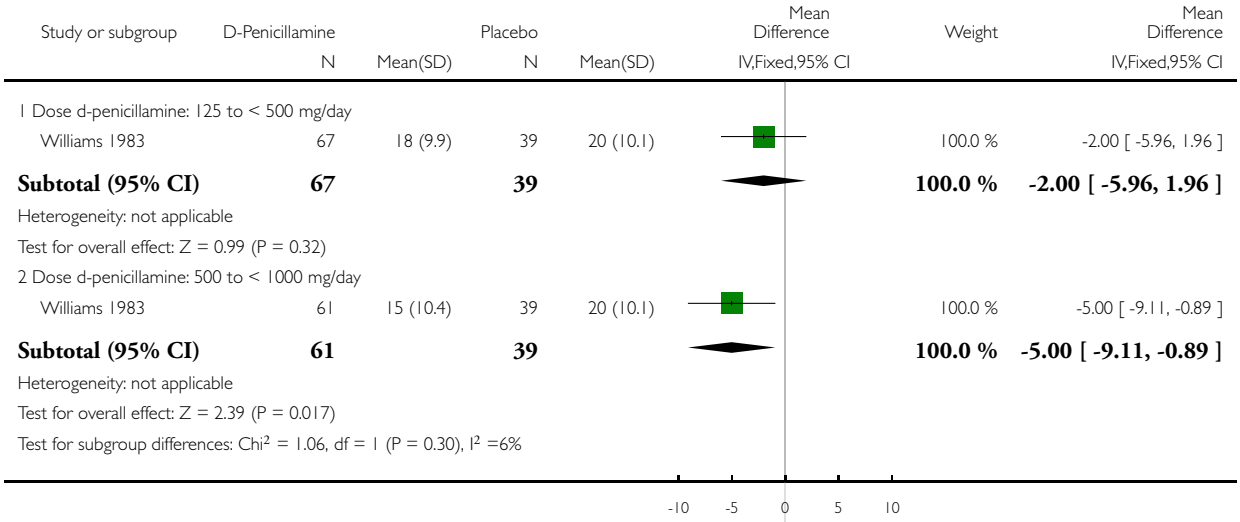


### Analysis 1.2. Comparison 1 D-Penicillamine vs. placebo - Efficacy, Outcome 2 Number of swollen joints.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 1 D-Penicillamine vs. placebo - Efficacy

Outcome: 2 Number of swollen joints

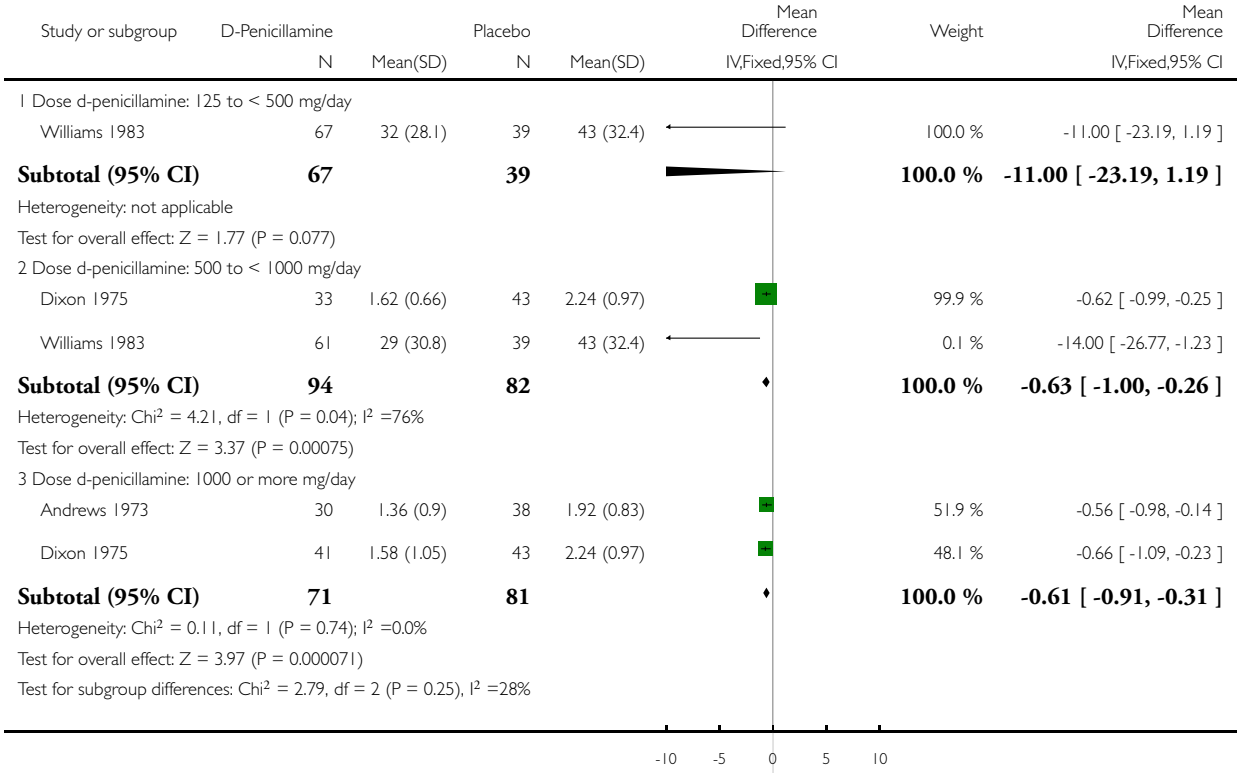


### Analysis 1.3. Comparison 1 D-Penicillamine vs. placebo - Efficacy, Outcome 3 Pain.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 1 D-Penicillamine vs. placebo - Efficacy

Outcome: 3 Pain



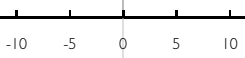
### Analysis 1.4. Comparison 1 D-Penicillamine vs. placebo - Efficacy, Outcome 4 Physician global assessment.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 1 D-Penicillamine vs. placebo - Efficacy

Outcome: 4 Physician global assessment

| Study or subgroup | D-Penicillamine N | Mean(SD) | Placebo N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | | | |
| Williams 1983 | 68 | 2.58 (0.78) | 40 | 3 (0.76) | | 100.0 % | -0.42 [ -0.72, -0.12 ] |
| **Subtotal (95% CI)** | **68** | | **40** | | | **100.0 %** | **-0.42 [ -0.72, -0.12 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.75 (P = 0.0060) | | | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | | | |
| Shiokawa 1977 | 60 | 2.15 (0.94) | 73 | 3.1 (0.87) | | 46.2 % | -0.95 [ -1.26, -0.64 ] |
| Williams 1983 | 61 | 2.38 (0.66) | 40 | 3 (0.76) | | 53.8 % | -0.62 [ -0.91, -0.33 ] |
| **Subtotal (95% CI)** | **121** | | **113** | | | **100.0 %** | **-0.77 [ -0.98, -0.56 ]** |
| Heterogeneity: $Chi^2$ = 2.33, df = 1 (P = 0.13); $I^2$ =57% | | | | | | | |
| Test for overall effect: Z = 7.17 (P < 0.00001) | | | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | | | |
| Andrews 1973 | 39 | 1.46 (0.72) | 43 | 2.53 (0.63) | | 100.0 % | -1.07 [ -1.36, -0.78 ] |
| **Subtotal (95% CI)** | **39** | | **43** | | | **100.0 %** | **-1.07 [ -1.36, -0.78 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 7.13 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 9.22, df = 2 (P = 0.01), $I^2$ =78% | | | | | | | |



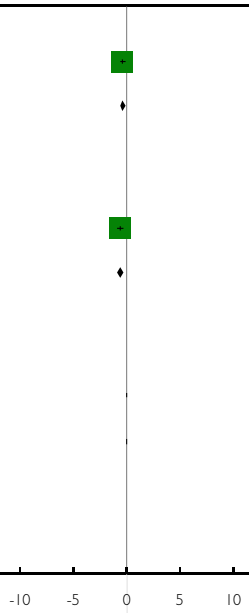
### Analysis 1.5. Comparison 1 D-Penicillamine vs. placebo - Efficacy, Outcome 5 Patient global assessment.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 1 D-Penicillamine vs. placebo - Efficacy

Outcome: 5 Patient global assessment

| Study or subgroup | D-Penicillamine N | Mean(SD) | Placebo N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | | |
| Williams 1983 | 70 | 2.61 (0.83) | 40 | 2.97 (0.7) | | -0.36 [ -0.65, -0.07 ] |
| **Subtotal (95% CI)** | **70** | | **40** | | | **-0.36 [ -0.65, -0.07 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 2.42 (P = 0.015) | | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | | |
| Williams 1983 | 61 | 2.41 (0.8) | 40 | 2.97 (0.7) | | -0.56 [ -0.86, -0.26 ] |
| **Subtotal (95% CI)** | **61** | | **40** | | | **-0.56 [ -0.86, -0.26 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 3.71 (P = 0.00020) | | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | | |
| Andrews 1973 | 30 | 0.75 (0) | 38 | 1 (0) | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **30** | | **38** | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.89, df = 1 (P = 0.34), $I^2$ =0.0% | | | | | | |

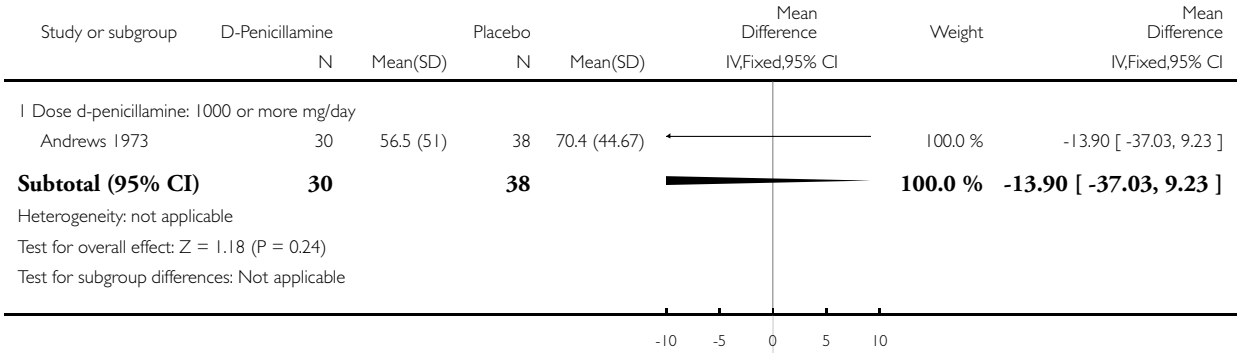


### Analysis 1.6. Comparison 1 D-Penicillamine vs. placebo - Efficacy, Outcome 6 Functional status.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 1 D-Penicillamine vs. placebo - Efficacy

Outcome: 6 Functional status

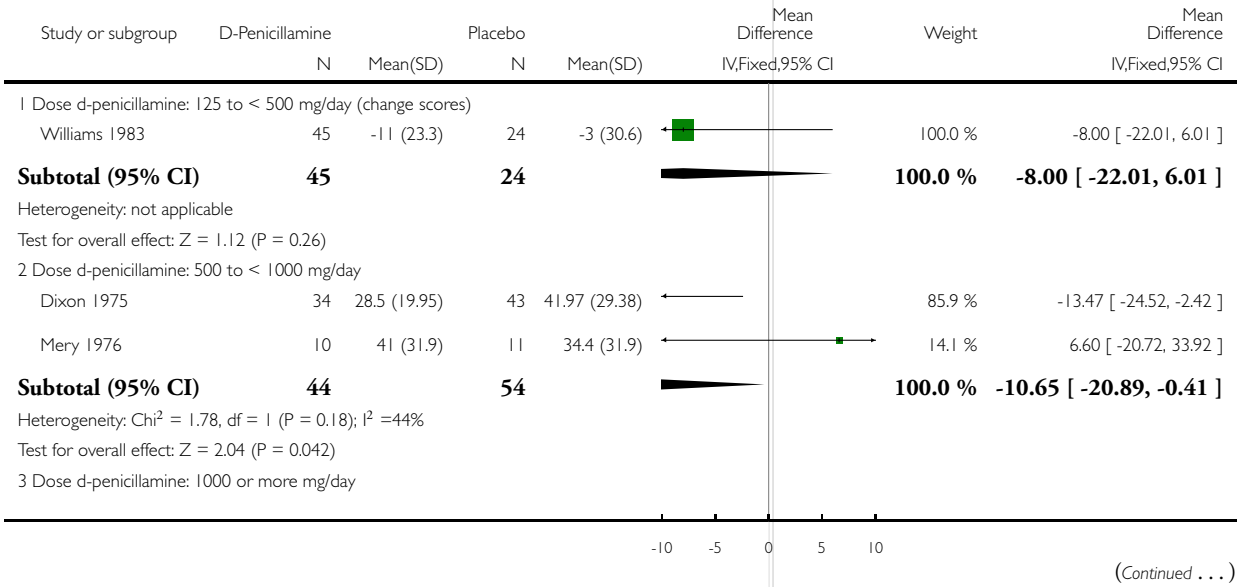



### Analysis 1.7. Comparison 1 D-Penicillamine vs. placebo - Efficacy, Outcome 7 ESR.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 1 D-Penicillamine vs. placebo - Efficacy

Outcome: 7 ESR

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| Study or subgroup | D-Penicillamine N | Mean(SD) | Placebo N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Andrews 1973 | 30 | 32 (39.67) | 38 | 56 (37.67) | | 22.5 % | -24.00 [ -42.57, -5.43 ] |
| Dixon 1975 | 41 | 29 (20.3) | 43 | 41.97 (29.38) | | 67.1 % | -12.97 [ -23.73, -2.21 ] |
| Mery 1976 | 10 | 31.6 (31.9) | 11 | 34.4 (31.9) | | 10.4 % | -2.80 [ -30.12, 24.52 ] |
| **Subtotal (95% CI)** | **81** | | **92** | | | **100.0 %** | **-14.39 [ -23.21, -5.58 ]** |

Heterogeneity: Chi² = 1.79, df = 2 (P = 0.41); I² =0.0%

Test for overall effect: Z = 3.20 (P = 0.0014)

Test for subgroup differences: Chi² = 0.66, df = 2 (P = 0.72), I² =0.0%




## Analysis 2.1. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 1 Withdrawals and dropouts - Total.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 1 Withdrawals and dropouts - Total

| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | |
| Williams 1983 | 19/87 | 14/52 | | 100.0 % | 0.76 [ 0.34, 1.69 ] |
| **Subtotal (95% CI)** | **87** | **52** | | **100.0 %** | **0.76 [ 0.34, 1.69 ]** |
| Total events: 19 (D-penicillamine), 14 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| Dixon 1975 | 10/34 | 7/43 | | 16.6 % | 2.12 [ 0.72, 6.24 ] |
| Mery 1976 | 1/10 | 2/11 | | 3.4 % | 0.53 [ 0.05, 5.77 ] |
| Shiokawa 1977 | 31/90 | 19/89 | | 45.4 % | 1.91 [ 1.00, 3.66 ] |
| Williams 1983 | 28/86 | 14/52 | | 34.6 % | 1.30 [ 0.62, 2.74 ] |
| **Subtotal (95% CI)** | **220** | **195** | | **100.0 %** | **1.63 [ 1.05, 2.53 ]** |
| Total events: 70 (D-penicillamine), 42 (placebo) | | | | | |
| Heterogeneity: Chi² = 1.66, df = 3 (P = 0.65); I² =0.0% | | | | | |




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| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z = 2.18 (P = 0.029) | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Andrews 1973 | 8/52 | 8/53 | | 37.1 % | 1.02 [ 0.35, 2.95 ] |
| Dixon 1975 | 20/44 | 7/43 | | 51.0 % | 3.85 [ 1.56, 9.49 ] |
| Huskisson 1976 | 1/12 | 0/10 | | 2.7 % | 6.25 [ 0.12, 320.40 ] |
| Mery 1976 | 2/10 | 2/11 | | 9.2 % | 1.12 [ 0.13, 9.40 ] |
| **Subtotal (95% CI)** | **118** | **117** | | **100.0 %** | **2.13 [ 1.12, 4.06 ]** |
| Total events: 31 (D-penicillamine), 17 (placebo) | | | | | |
| Heterogeneity: $Chi^2$ = 4.13, df = 3 (P = 0.25); $I^2$ =27% | | | | | |
| Test for overall effect: Z = 2.29 (P = 0.022) | | | | | |
| Test for subgroup differences: $Chi^2$ = 4.03, df = 2 (P = 0.13), $I^2$ =50% | | | | | |




## Analysis 2.2. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 2 Withdrawals: lack of effect.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 2 Withdrawals: lack of effect

| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | |
| Williams 1983 | 3/87 | 5/52 | | 100.0 % | 0.32 [ 0.07, 1.41 ] |
| **Subtotal (95% CI)** | **87** | **52** | | **100.0 %** | **0.32 [ 0.07, 1.41 ]** |
| Total events: 3 (D-penicillamine), 5 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.51 (P = 0.13) | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| Shiokawa 1977 | 1/90 | 3/89 | | 33.1 % | 0.36 [ 0.05, 2.58 ] |
| Williams 1983 | 4/86 | 5/52 | | 66.9 % | 0.45 [ 0.11, 1.79 ] |
| **Subtotal (95% CI)** | **176** | **141** | | **100.0 %** | **0.41 [ 0.13, 1.29 ]** |
| Total events: 5 (D-penicillamine), 8 (placebo) | | | | | |




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| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² =0.0% | | | | | |
| Test for overall effect: Z = 1.52 (P = 0.13) | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Andrews 1973 | 0/52 | 7/53 | | 100.0 % | 0.12 [ 0.03, 0.56 ] |
| **Subtotal (95% CI)** | **52** | **53** | | **100.0 %** | **0.12 [ 0.03, 0.56 ]** |
| Total events: 0 (D-penicillamine), 7 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.70 (P = 0.0069) | | | | | |
| Test for subgroup differences: Chi² = 1.63, df = 2 (P = 0.44), I² =0.0% | | | | | |




### Analysis 2.3. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 3 Withdrawals: concurrent illness.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 3 Withdrawals: concurrent illness

| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (D-penicillamine), 0 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| Dixon 1975 | 1/34 | 1/43 | | 25.1 % | 1.27 [ 0.08, 21.11 ] |
| Shiokawa 1977 | 2/90 | 2/89 | | 50.8 % | 0.99 [ 0.14, 7.14 ] |
| Williams 1983 | 1/86 | 1/52 | | 24.1 % | 0.59 [ 0.03, 10.40 ] |
| **Subtotal (95% CI)** | **210** | **184** | | **100.0 %** | **0.93 [ 0.23, 3.80 ]** |
| Total events: 4 (D-penicillamine), 4 (placebo) | | | | | |
| Heterogeneity: Chi² = 0.15, df = 2 (P = 0.93); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | |




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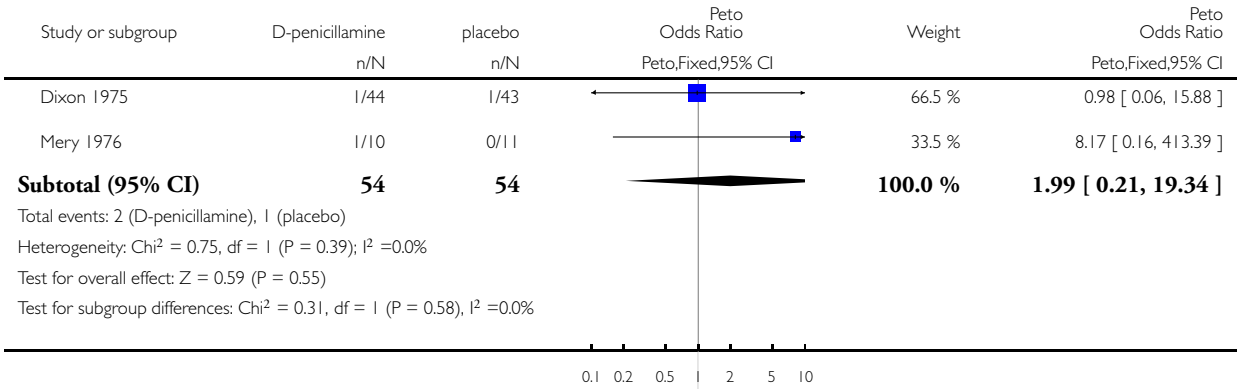
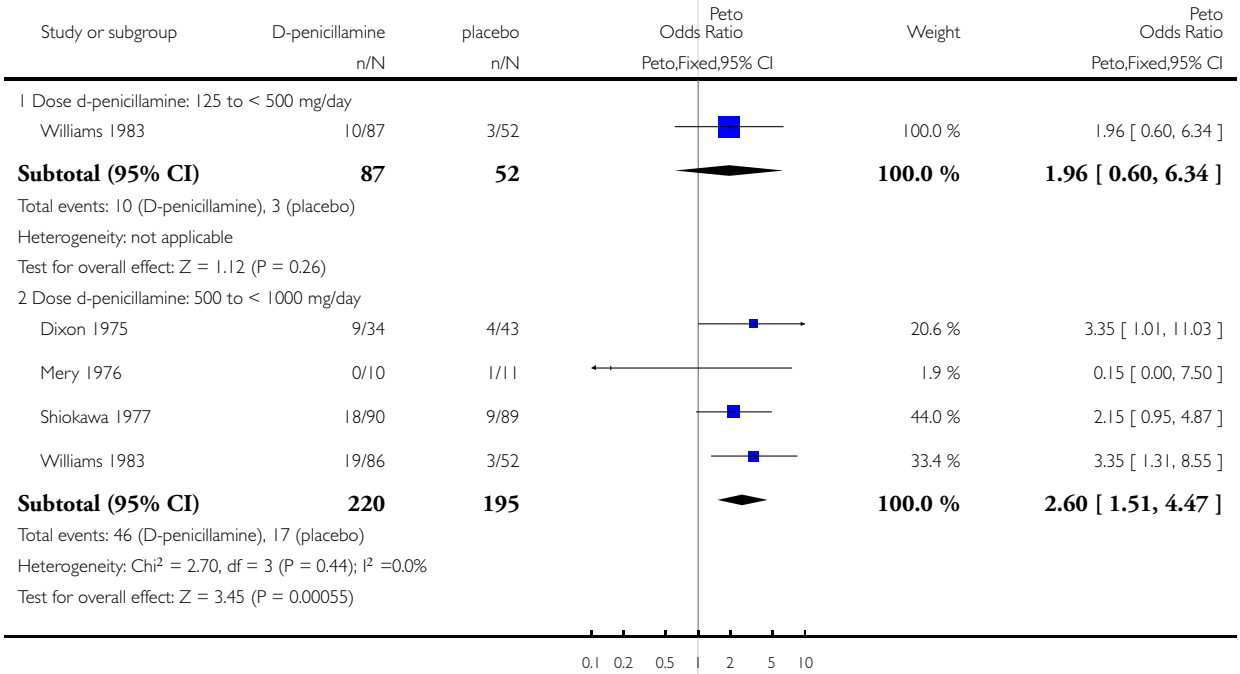



**Analysis 2.4. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 4 Withdrawals: adverse reactions.**

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 4 Withdrawals: adverse reactions

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| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Andrews 1973 | 8/52 | 1/53 | | 29.0 % | 5.51 [ 1.41, 21.46 ] |
| Dixon 1975 | 18/44 | 4/43 | | 58.1 % | 5.23 [ 2.00, 13.67 ] |
| Huskisson 1976 | 1/12 | 0/10 | | 3.5 % | 6.25 [ 0.12, 320.40 ] |
| Mery 1976 | 2/10 | 1/11 | | 9.4 % | 2.34 [ 0.21, 25.45 ] |
| **Subtotal (95% CI)** | **118** | **117** | | **100.0 %** | **4.95 [ 2.38, 10.30 ]** |
| Total events: 29 (D-penicillamine), 6 (placebo) | | | | | |
| Heterogeneity: $Chi^2$ = 0.43, df = 3 (P = 0.93); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 4.28 (P = 0.000019) | | | | | |
| Test for subgroup differences: $Chi^2$ = 2.56, df = 2 (P = 0.28), $I^2$ =22% | | | | | |


## Analysis 2.5. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 5 Withdrawals:Gastrointestinal adverse reactions.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 5 Withdrawals:Gastrointestinal adverse reactions

| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | |
| Williams 1983 | 1/87 | 1/52 | | 100.0 % | 0.58 [ 0.03, 10.31 ] |
| **Subtotal (95% CI)** | **87** | **52** | | **100.0 %** | **0.58 [ 0.03, 10.31 ]** |
| Total events: 1 (D-penicillamine), 1 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.37 (P = 0.71) | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| Dixon 1975 | 0/34 | 1/43 | | 26.2 % | 0.17 [ 0.00, 8.64 ] |
| Williams 1983 | 2/86 | 1/52 | | 73.8 % | 1.21 [ 0.11, 12.68 ] |
| **Subtotal (95% CI)** | **120** | **95** | | **100.0 %** | **0.72 [ 0.10, 5.42 ]** |
| Total events: 2 (D-penicillamine), 2 (placebo) | | | | | |
| Heterogeneity: $Chi^2$ = 0.71, df = 1 (P = 0.40); $I^2$ =0.0% | | | | | |


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| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Andrews 1973 | 3/52 | 1/53 | | 66.3 % | 2.86 [ 0.39, 20.87 ] |
| Dixon 1975 | 1/44 | 1/43 | | 33.7 % | 0.98 [ 0.06, 15.88 ] |
| **Subtotal (95% CI)** | **96** | **96** | | **100.0 %** | **1.99 [ 0.39, 10.04 ]** |
| Total events: 4 (D-penicillamine), 2 (placebo) | | | | | |
| Heterogeneity: $Chi^2$ = 0.38, df = 1 (P = 0.54); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.83 (P = 0.41) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.86, df = 2 (P = 0.65), $I^2$ =0.0% | | | | | |




### Analysis 2.6. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 6 Withdrawals:Mucosal / cutaneous adverse reactions.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 6 Withdrawals:Mucosal / cutaneous adverse reactions

| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | |
| Williams 1983 | 3/87 | 1/52 | | 100.0 % | 1.72 [ 0.22, 13.32 ] |
| **Subtotal (95% CI)** | **87** | **52** | | **100.0 %** | **1.72 [ 0.22, 13.32 ]** |
| Total events: 3 (D-penicillamine), 1 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.52 (P = 0.60) | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| Williams 1983 | 4/86 | 1/52 | | 100.0 % | 2.17 [ 0.35, 13.62 ] |
| **Subtotal (95% CI)** | **86** | **52** | | **100.0 %** | **2.17 [ 0.35, 13.62 ]** |
| Total events: 4 (D-penicillamine), 1 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.83 (P = 0.41) | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Andrews 1973 | 4/52 | 0/53 | | 66.1 % | 8.00 [ 1.09, 58.45 ] |




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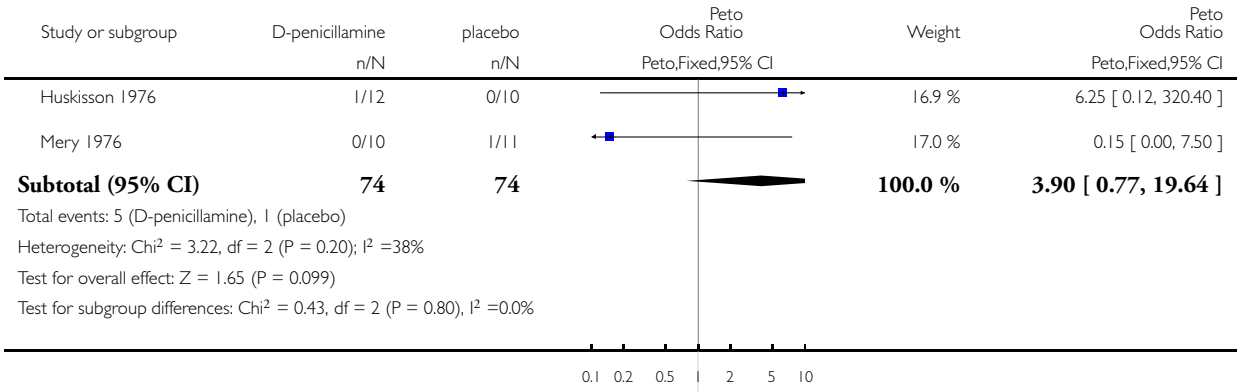
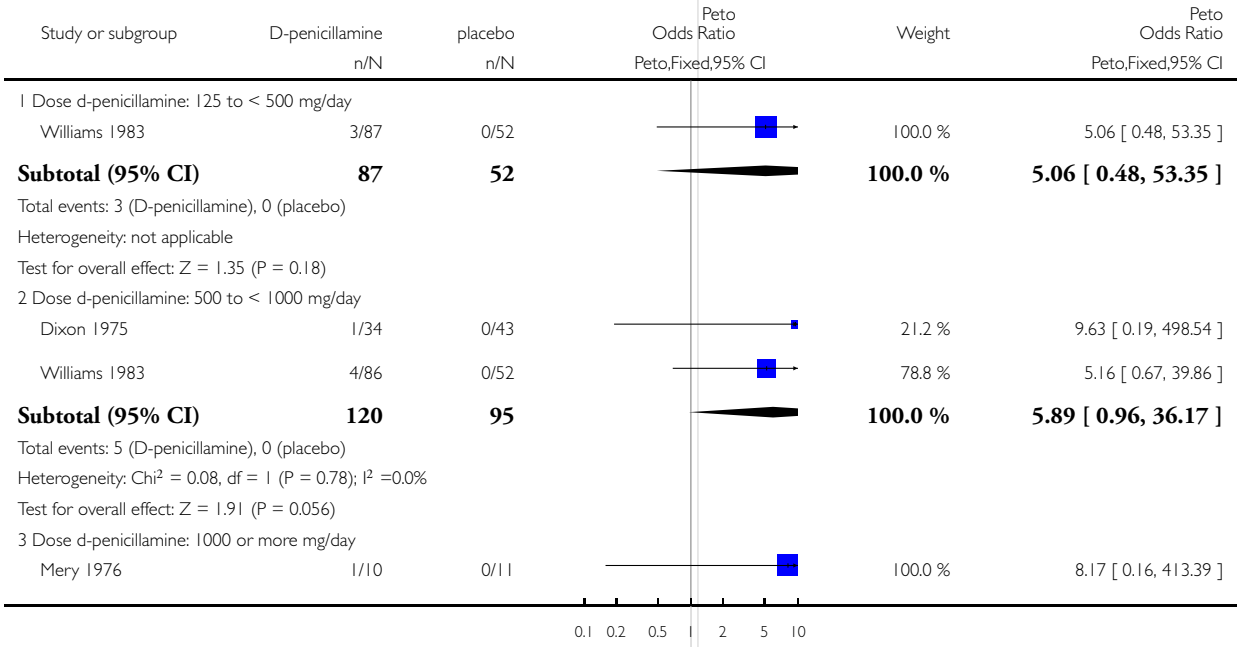



## Analysis 2.7. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 7 Withdrawals: Renal abnormality.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 7 Withdrawals: Renal abnormality

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| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **10** | **11** | | **100.0 %** | **8.17 [ 0.16, 413.39 ]** |
| Total events: 1 (D-penicillamine), 0 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.05 (P = 0.29) | | | | | |
| Test for subgroup differences: Chi² = 0.04, df = 2 (P = 0.98), I² =0.0% | | | | | |




**Analysis 2.8. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 8 Withdrawals: Hematological abnormality.**

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 8 Withdrawals: Hematological abnormality

| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | |
| Williams 1983 | 3/87 | 0/52 | | 100.0 % | 5.06 [ 0.48, 53.35 ] |
| **Subtotal (95% CI)** | **87** | **52** | | **100.0 %** | **5.06 [ 0.48, 53.35 ]** |
| Total events: 3 (D-penicillamine), 0 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.35 (P = 0.18) | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| Dixon 1975 | 1/34 | 0/43 | | 11.0 % | 9.63 [ 0.19, 498.54 ] |
| Williams 1983 | 9/86 | 0/52 | | 89.0 % | 5.50 [ 1.37, 22.06 ] |
| **Subtotal (95% CI)** | **120** | **95** | | **100.0 %** | **5.85 [ 1.58, 21.68 ]** |
| Total events: 10 (D-penicillamine), 0 (placebo) | | | | | |
| Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0% | | | | | |
| Test for overall effect: Z = 2.64 (P = 0.0083) | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Dixon 1975 | 4/44 | 0/43 | | 66.0 % | 7.76 [ 1.05, 57.05 ] |
| Huskisson 1976 | 1/12 | 0/10 | | 17.0 % | 6.25 [ 0.12, 320.40 ] |
| Mery 1976 | 0/10 | 1/11 | | 17.1 % | 0.15 [ 0.00, 7.50 ] |




(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **66** | **64** | | **100.0 %** | **3.81 [ 0.75, 19.26 ]** |
| Total events: 5 (D-penicillamine), 1 (placebo) | | | | | |
| Heterogeneity: $Chi^2$ = 3.18, df = 2 (P = 0.20); $I^2$ =37% | | | | | |
| Test for overall effect: Z = 1.62 (P = 0.11) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.16, df = 2 (P = 0.92), $I^2$ =0.0% | | | | | |

0.1 0.2 0.5 1 2 5 10

## Analysis 2.9. Comparison 2 D-Penicillaminevs. placebo - Withdrawals and dropouts, Outcome 9 Withdrawals: Impaired or loss of taste.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 2 D-Penicillaminevs. placebo - Withdrawals and dropouts

Outcome: 9 Withdrawals: Impaired or loss of taste

| Study or subgroup | D-penicillamine n/N | placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 125 to < 500 mg/day | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (D-penicillamine), 0 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 2 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (D-penicillamine), 0 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 3 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Andrews 1973 | 2/52 | 0/53 | | 66.6 % | 7.68 [ 0.47, 124.49 ] |
| Huskisson 1976 | 1/12 | 0/10 | | 33.4 % | 6.25 [ 0.12, 320.40 ] |
| **Subtotal (95% CI)** | **64** | **63** | | **100.0 %** | **7.17 [ 0.74, 69.68 ]** |
| Total events: 3 (D-penicillamine), 0 (placebo) | | | | | |
| Heterogeneity: $Chi^2$ = 0.01, df = 1 (P = 0.93); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.70 (P = 0.089) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

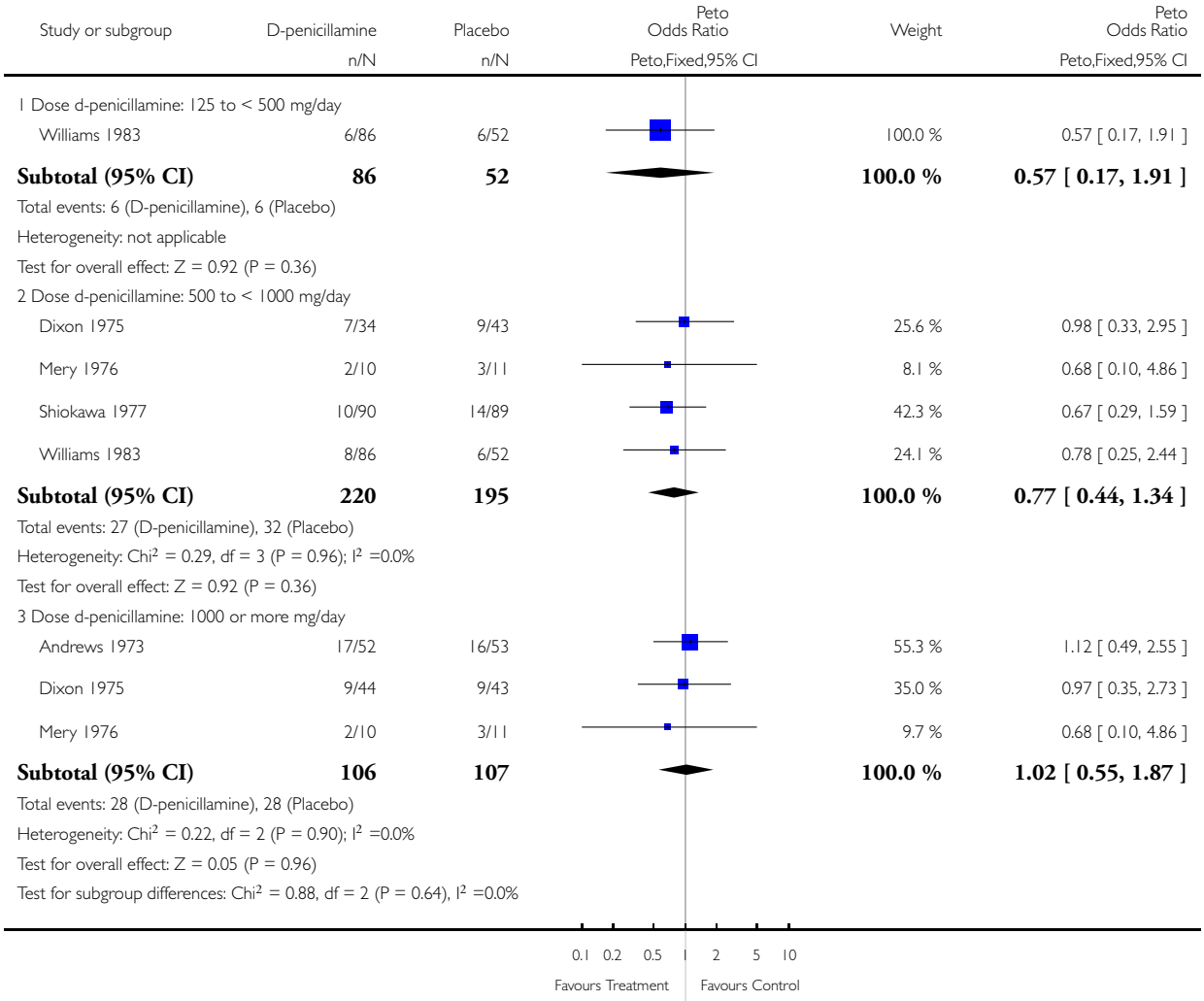
0.1 0.2 0.5 1 2 5 10

## Analysis 3.1. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 1 Adverse reactions: Gastrointestinal.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 1 Adverse reactions: Gastrointestinal

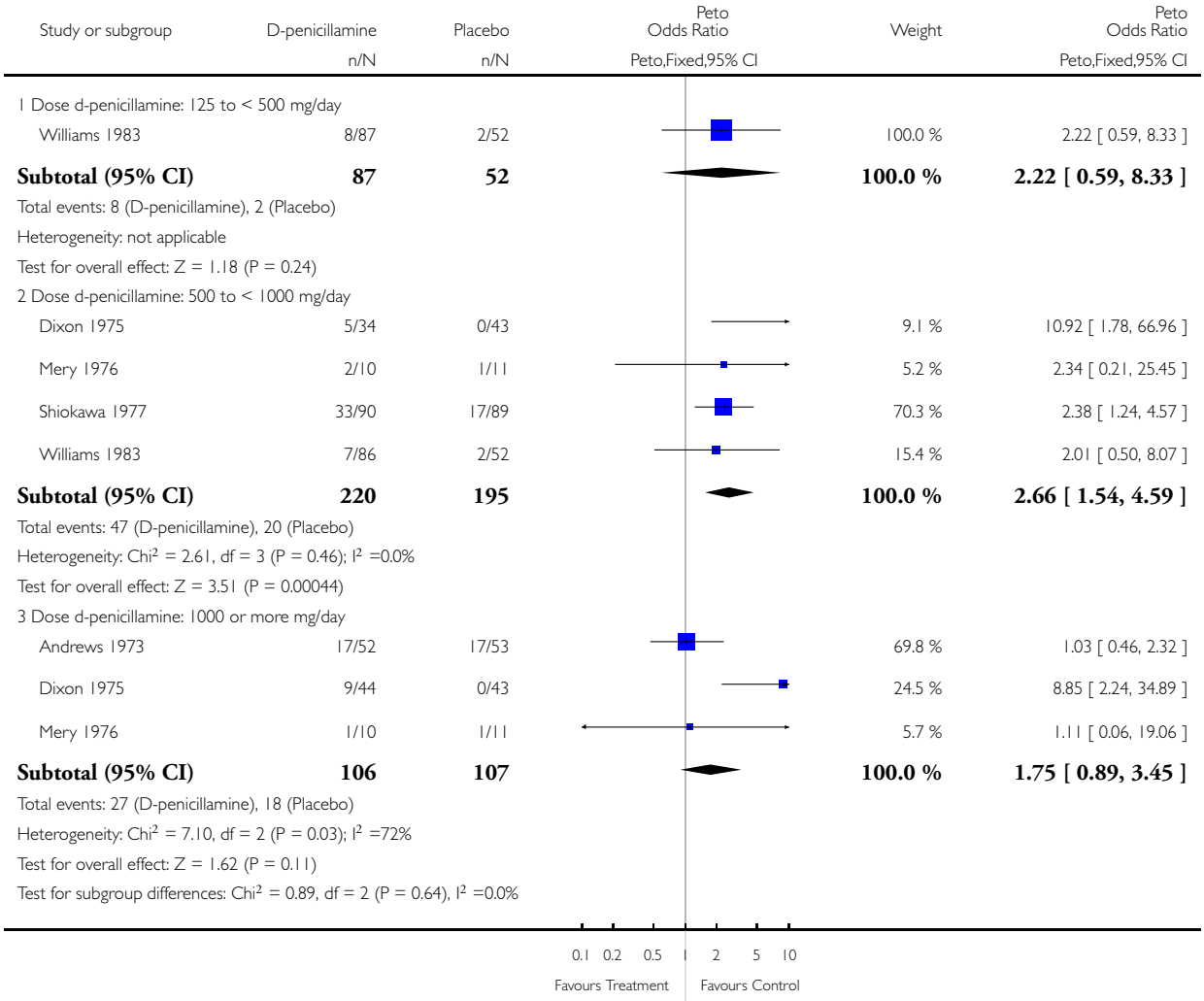


### Analysis 3.2. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 2 Adverse reactions: Mucosal / cutaneous.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 2 Adverse reactions: Mucosal / cutaneous

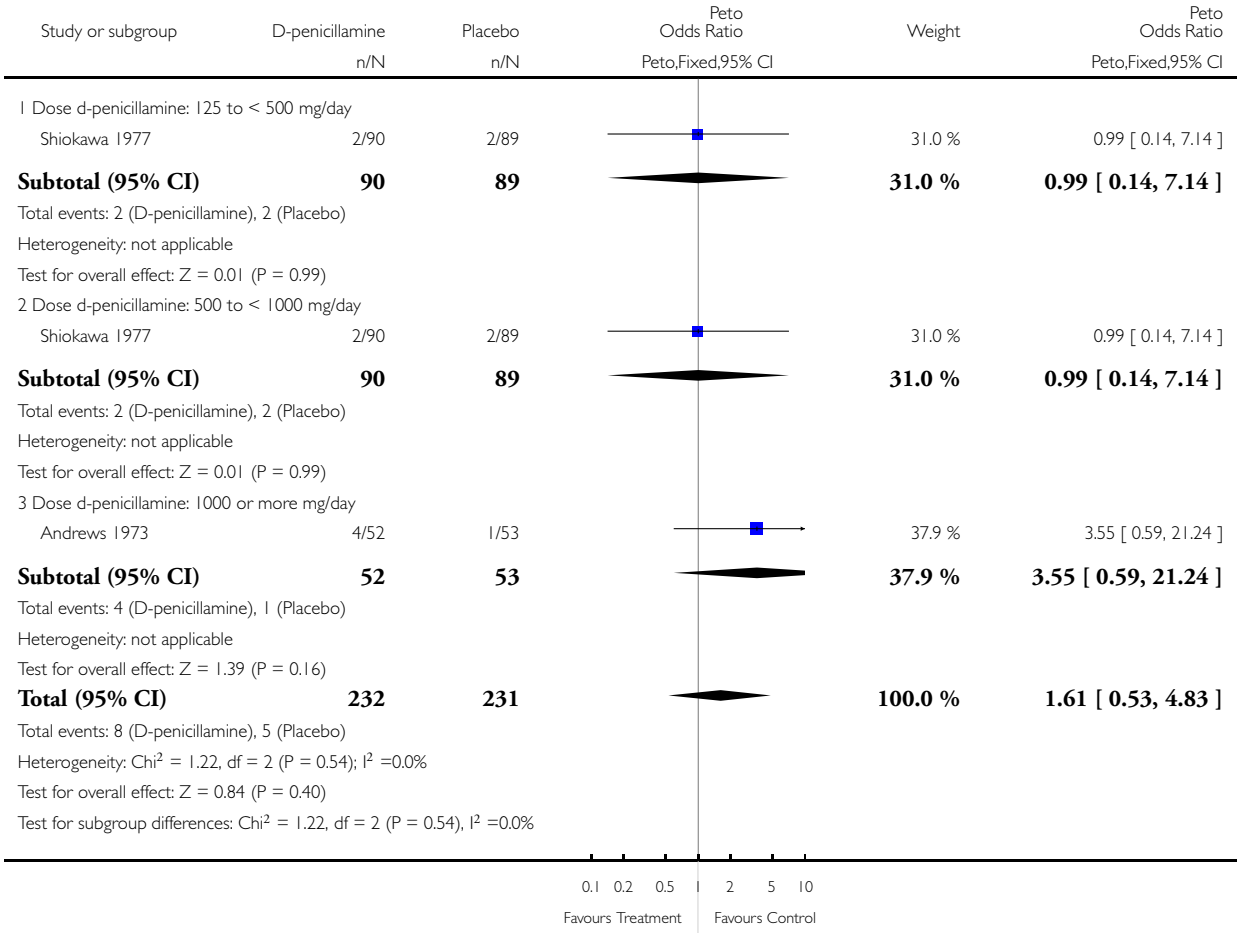


### Analysis 3.3. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 3 Adverse reactions: Renal.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 3 Adverse reactions: Renal



### Analysis 3.4. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 4 Adverse reactions: Liver.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 4 Adverse reactions: Liver

| Study or subgroup | D-penicillamine n/N | Placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| Shiokawa 1977 | 0/90 | 2/89 | | 100.0 % | 0.13 [ 0.01, 2.13 ] |
| **Total (95% CI)** | **90** | **89** | | **100.0 %** | **0.13 [ 0.01, 2.13 ]** |
| Total events: 0 (D-penicillamine), 2 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.43 (P = 0.15) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

### Analysis 3.5. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 5 Adverse reactions: Haematological.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 5 Adverse reactions: Haematological

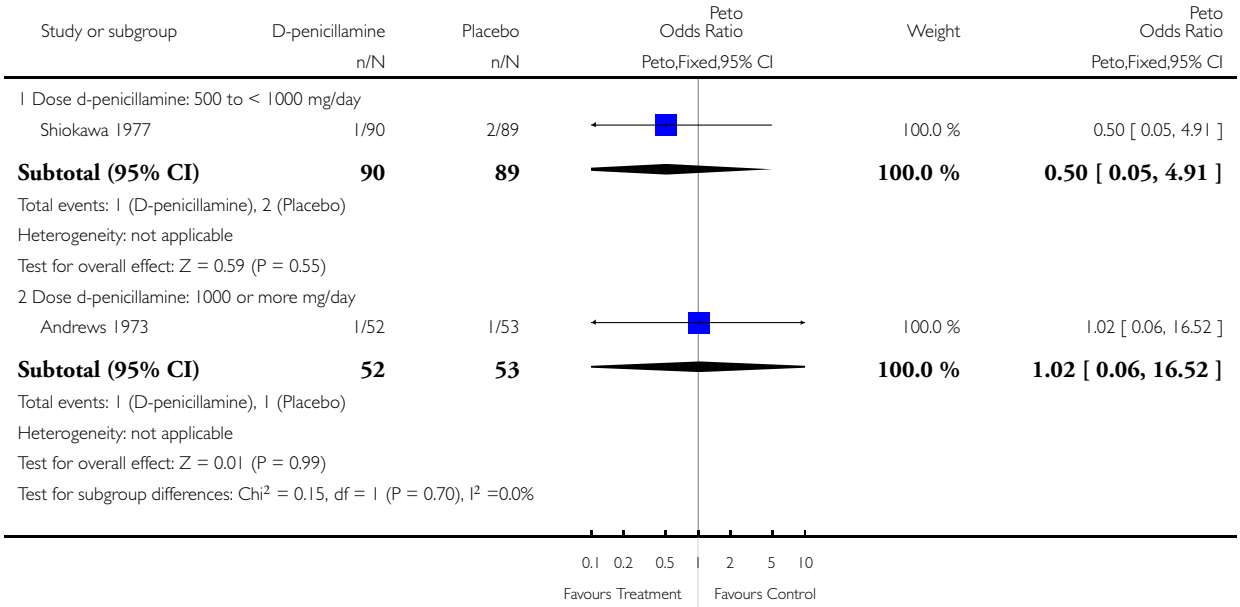
| Study or subgroup | D-penicillamine n/N | Placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 500 to < 1000 mg/day | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (D-penicillamine), 0 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 2 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Andrews 1973 | 15/52 | 2/53 | | 100.0 % | 6.23 [ 2.22, 17.53 ] |
| **Subtotal (95% CI)** | **52** | **53** | | **100.0 %** | **6.23 [ 2.22, 17.53 ]** |
| Total events: 15 (D-penicillamine), 2 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.47 (P = 0.00052) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

### Analysis 3.6. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 6 Adverse reactions: Neurological (headache, dizziness, tingling).

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 6 Adverse reactions: Neurological (headache, dizziness, tingling)



### Analysis 3.7. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 7 Adverse reactions: Cardiovascular.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 7 Adverse reactions: Cardiovascular

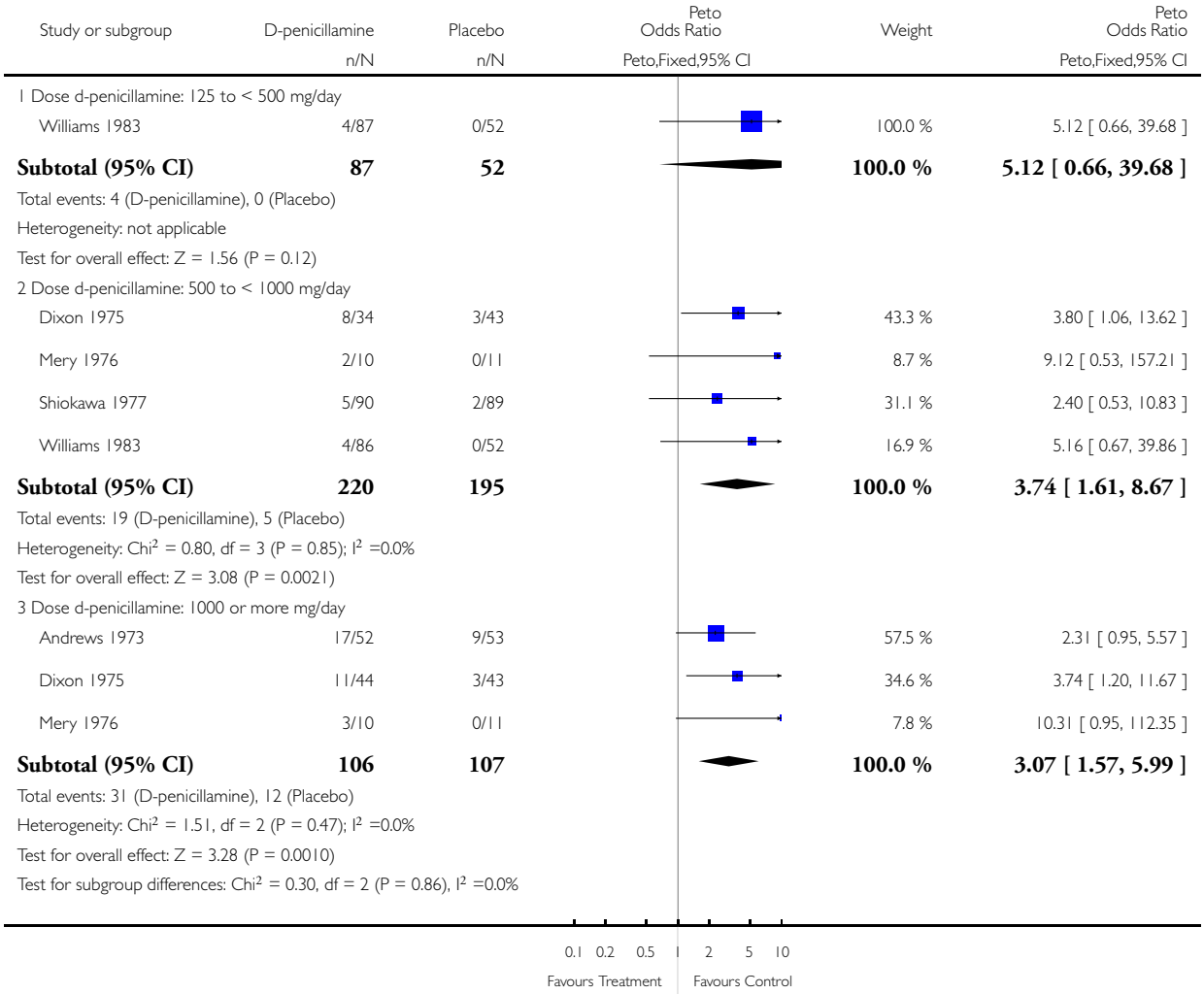
| Study or subgroup | D-penicillamine n/N | Placebo n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose d-penicillamine: 1000 or more mg/day | | | | | |
| Dixon 1975 | 0/44 | 1/43 | | 100.0 % | 0.13 [ 0.00, 6.67 ] |
| **Subtotal (95% CI)** | **44** | **43** | | **100.0 %** | **0.13 [ 0.00, 6.67 ]** |
| Total events: 0 (D-penicillamine), 1 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

## Analysis 3.8. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 8 Adverse reactions: Impaired or loss of taste.

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 8 Adverse reactions: Impaired or loss of taste

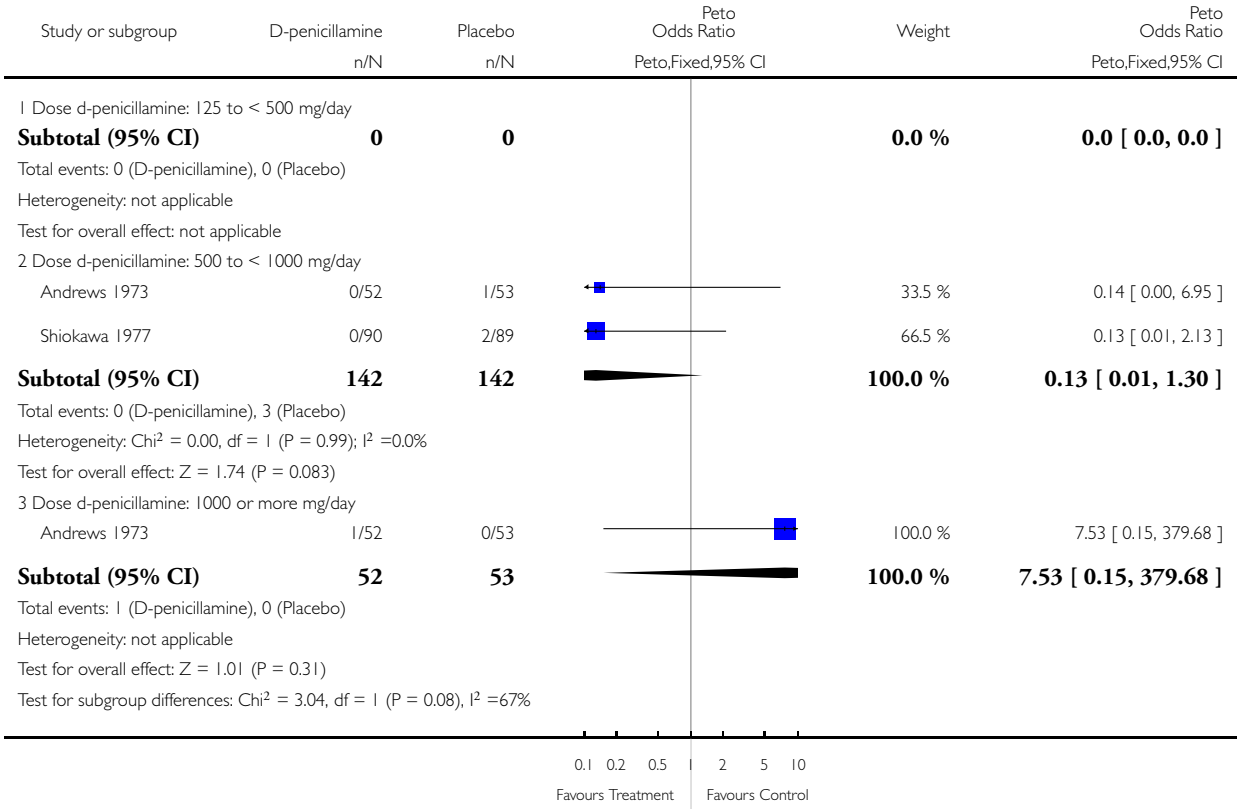


**Analysis 3.9. Comparison 3 Adverse reactions not requiring withdrawal, Outcome 9 Adverse reactions: Miscellaneous.**

Review: Penicillamine for treating rheumatoid arthritis

Comparison: 3 Adverse reactions not requiring withdrawal

Outcome: 9 Adverse reactions: Miscellaneous




## WHAT'S NEW

Last assessed as up-to-date: 29 August 2000.

| Date | Event | Description |
|---|---|---|
| 8 November 2008 | Amended | Converted to new review format.<br>CMSG ID: C064-R |

## HISTORY

Review first published: Issue 2, 1999

## CONTRIBUTIONS OF AUTHORS

Maria Suarez-Almazor was the primary reviewer including protocol development then to ??? the review. C Spooner and E Belseck helped with data collection, quality assessment and data entry.

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT


### Internal sources

- University of Alberta Hospitals Foundation, Canada.
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### External sources

- No sources of support supplied


## INDEX TERMS

### Medical Subject Headings (MeSH)

Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Controlled Clinical Trials as Topic; Penicillamine [*therapeutic use]; Randomized Controlled Trials as Topic

### MeSH check words

Humans