Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome (Review)

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Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

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ABSTRACT

Background
Fibromyalgia (FM) syndrome is a chronic condition of unknown aetiology characterised by musculoskeletal pain that often co-exists with sleep disturbance, cognitive dysfunction and fatigue. Patients often report high disability levels and poor quality of life. Since there is no specific treatment that alters the pathogenesis of FM, drug therapy focuses on pain reduction and improvement of other bothersome symptoms.

Objectives
The objective of this review was to assess the effectiveness and safety of monoamine oxidase inhibitors (MAOIs) in the treatment of FM syndrome.

Search methods
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 10), MEDLINE (1966 to November 2010), EMBASE (1980 to November 2010) and the reference lists of reviewed articles.

Selection criteria
We selected all randomised, double-blind trials of MAOIs used for the treatment of FM pain in adult participants.

Data collection and analysis
Two authors assessed risk of bias and extracted data independently onto a specially designed pro forma and a third review author cross-checked them.

Main results
We included two studies of inconsistent risk of bias with a total of 230 patients diagnosed with FM. We evaluated two MAOIs: pirlindole and moclobemide. Pirlindole showed statistically significant results compared with placebo for several outcomes (pain, tender points and overall assessment by the patient and the physician), whereas moclobemide did not show statistically significant differences between groups. Pooled results of the two studies displayed a modest effect size in pain (mean difference (MD) -1.45 (121 patients;
95% confidence interval (CI) -2.71 to -0.20; number needed to treat (NNT) 2 (95% CI 1 to 12); $I^2 = 59\%$), implying a minimal clinically important difference (MCID) and a small effect on tender points (standardised mean difference (SMD) -0.36 (121 patients; 95% CI -0.72 to -0.00; $I^2 = 31\%$)). No effect was seen on global assessment by patient. Physical function and sleep disturbance were not measured. The most frequent adverse events were nausea and vomiting, with statistically significant differences between groups (risk ratio (RR) 7.82 (89 patients; 95% CI 1.02 to 59.97; NNT 7 (95% CI 4 to 33)).

Authors' conclusions

Data suggest that the effectiveness of MAOIs for the treatment of FM symptoms is limited. Although we observed a moderate effect size on pain and a small one on tender points, these results should be taken with caution as they are only based on two studies with a small number of patients and inconsistent risk of bias among them.

PLAIN LANGUAGE SUMMARY

Monoamine oxidase inhibitors (MAOIs) for fibromyalgia

This summary of a Cochrane review presents what we know from research about the effect of MAOIs for fibromyalgia (FM).

The review shows that in people with FM:

MAOIs may slightly improve pain and tender points in the short term compared to placebo. Of the MAOIs studied, pirlindole seems more effective than moclobemide.

We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. The most frequent side effects seen in the studies included nausea and vomiting. However, MAOIs are known to have serious and potentially fatal interactions with a variety of foods and other medications.

What is fibromyalgia and what are MAOIs?

Fibromyalgia is a chronic condition characterised by generalised pains along with other problems such as sleep disturbances, fatigue and cognitive dysfunction. MAOIs are a certain type of antidepressants that are occasionally used to treat fibromyalgia symptoms. Other antidepressants such as tricyclic agents have demonstrated that they can help to relieve pain, tender points, fatigue and sleep disturbances in people with fibromyalgia, but there is a need to know if MAOIs might also help.

Best estimate of what happens to people with fibromyalgia who take MAOIs:

Pain (higher scores mean worse or more severe pain)
- People who took MAOIs rated their pain to be 1.45 points lower on a scale of 0 to 10 compared to people who took placebo.

Global assessment (by patient)
- People who took MAOIs showed no difference in their global assessment compared to people who took placebo.

Tender points
- People who took MAOIs had a lower tender point score and a lower number of tender points (-0.36 difference) than people who took placebo after four weeks.

Physical function
- No information about physical function was provided.

Sleep disturbance
- No information about sleep disturbance was provided.

Adverse events (nausea and vomiting)
- 16 more people out of 100 who took MAOIs (pirlindole) had nausea and vomiting.
- 18 people out of 100 who took MAOIs (pirlindole) had nausea and vomiting.
- 2 people out of 100 who took placebo had nausea and vomiting.
- No information regarding people who took moclobemide is available.
Discontinuation due to adverse events

- 4 more people out of 100 who took MAOIs stopped medication due to adverse events.
- 9 people out of 100 who took MAOIs stopped medication due to adverse events.
- 5 people out of 100 who took placebo stopped medication due to adverse events.
### Summary of Findings for the Main Comparison

**MAOIs compared to placebo for fibromyalgia syndrome**

**Patient or population:** patients with fibromyalgia syndrome  
**Settings:** outpatient clinics  
**Intervention:** MAOIs  
**Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Effect size (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Pain (VAS)</td>
<td>The mean pain (VAS) in the control groups was 6.53</td>
<td>The mean pain (VAS)</td>
<td>121 (2 studies)</td>
<td>⊕⊕⊕⊕ low¹,²</td>
<td>MD = -1.45 (-2.71 to -0.2)</td>
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<tr>
<td>VAS from: 0 to 10</td>
<td>The mean pain (VAS) in the intervention groups was 1.45 lower</td>
<td>(2.71 to 0.2 lower)</td>
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<td>RPC = 96% (13% to 180%)</td>
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<td>ARD = 14.5% (2% to 27.1%)</td>
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<td>NNT = 2 (1 to 12)</td>
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<tr>
<td>Tender points</td>
<td>The number of tender points in the control group (Hannonen study at baseline) was 15.9</td>
<td>The mean tender points in the intervention groups was 0.36 standard deviations lower (0.72 lower to 0 higher)</td>
<td>121 (2 studies)</td>
<td>⊕⊕⊕⊕ low¹,²</td>
<td>Not statistically significant</td>
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<td>Tender point score and number of tender points</td>
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<td>Global assessment (by patient)</td>
<td>The mean global assessment (by patient) in the control groups was 6.59</td>
<td>The mean global assessment (by patient) in the intervention groups was 0.82 lower (2.39 lower to 0.75 higher)</td>
<td>121 (2 studies)</td>
<td>⊕⊕⊕⊕ low¹,²</td>
<td>Not statistically significant</td>
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<td>VAS from: 0 to 10</td>
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<tr>
<td>Physical function</td>
<td>Study population</td>
<td>RR 1.72</td>
<td>Medium-risk population</td>
<td>RR 7.82</td>
<td>Adverse events (nausea and vomiting)</td>
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<tr>
<td>Discontinuation due to adverse events</td>
<td>54 per 1000</td>
<td>0.53 to 5.59</td>
<td>149</td>
<td>93 per 1000</td>
<td>29 to 302</td>
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<td>Medium-risk population</td>
<td>51 per 1000</td>
<td>27 to 285</td>
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<td>88 per 1000</td>
<td>22 to 285</td>
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<tr>
<td>Adverse events (nausea and vomiting)</td>
<td>23 per 1000</td>
<td>1.02 to 59.97</td>
<td></td>
<td>180 per 1000</td>
<td>23 to 1000</td>
</tr>
</tbody>
</table>

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

ARD: absolute risk difference; CI: confidence interval; MAOIs: monoamine oxidase inhibitors; MD: mean difference; NNT: number needed to treat; SD: standard deviation; SMD: standardised mean difference; RR: risk ratio; RPC: relative percent change; VAS: visual analogue scale

GRADE Working Group grades of evidence

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

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

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

Very low quality: We are very uncertain about the estimate.

1 One study had limitations in design (sequence generation, allocation concealment and blinding not reported).

2 Both studies had low sample sizes (<50 participants per group).
BACKGROUND

Description of the condition

Fibromyalgia (FM) syndrome is a chronic condition of unknown aetiology (Cathebras 1998), affecting 3.7 million people in the United States (Lawrence 1998), with an average cost of USD 2274 per patient/year (Wolfe 1997). The disease is characterised by widespread musculoskeletal pain which commonly co-exists with cognitive dysfunction, sleep disturbance and significant fatigue (Wolfe 2010). Correspondingly, patients often report high disability levels and poor quality of life (Hawley 1988; Hawley 1991), along with extensive use of medical care (Wolfe 1997). Lacking a specific laboratory test, methods for diagnosis include both the 1990 and 2010 American College of Rheumatology (ACR) criteria (Wolfe 1990; Wolfe 2010). The more commonly used 1990 ACR criteria have been shown to be 88% accurate in identifying patients with the syndrome (Smith 1998). In the past other standardised and recognised criteria had been used to diagnose FM (Smythe 1981; Yunus 1981; Yunus 1982; Yunus 1984).

Much effort has been made to elucidate the pathophysiology of FM. Alterations in alpha-non REM sleep (Moldofsky 1989), structural (Bengtsson 1986) and functional (Bartels 1986; Bengtsson 1986; Lund 1986) alterations in muscle fibres, disturbances of hypothalamic-pituitary-adrenal axis (Crofford 1994), abnormal metabolism of substances like serotonin (Moldofsky 1989), norepinephrine and substance P (Vaeyer 1988), and alterations in regional cerebral blood flow (Bradley 1996; Gracely 2002) have been observed and postulated as aetiologic mechanisms. Despite these findings, the aetiology of this syndrome remains unknown. Since specific treatment aimed at altering the pathogenesis is not possible, drug therapy focused on pain reduction is ubiquitously employed.

Description of the intervention

The current concept of FM suggests that changes in the functioning of neurons that lead to ‘sensitisation’ of the brain and spinal cord are physiologically responsible for FM symptoms. Theoretically, medications that attenuate aberrant function of the central nervous system can be of benefit in the treatment of FM symptoms. A popular class of medications with such central effects is antidepressants and they are the most frequently prescribed medications for FM (Miller 2002).

Several studies on antidepressants have shown effectiveness compared to placebo for the symptoms associated with fibromyalgia (Rosso 1999; Arnold 2000; O’Malley 2000; Goldenberg 2007; Häuser 2009), although those have mainly centred in amitriptyline and there is a need to assess the effectiveness and safety of other antidepressants such as monoamine oxidase inhibitors (MAOIs).

Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome (Review)

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Types of interventions
We accepted trials comparing MAOIs with placebo or another active drug (this includes comparisons of different dosages of the same active drug).
We allowed co-interventions, such as non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics and physical therapy.
We considered the following antidepressants in this review: moclobemide and pirlindole.

Types of outcome measures

Primary outcomes
1. Pain (e.g. visual analogue scale (VAS), 10-point ordinal scale, pain drawings, Likert scale, McGill Pain Questionnaire, Brief Pain Inventory)
2. Side effects (including withdrawals due to side effects)

Secondary outcomes
1. Physical function (self reported physical function: e.g. Fibromyalgia Impact Questionnaire (FIQ), Physical Impairment subscale, Health Assessment Questionnaire (HAQ))
2. Global well being or patient perceived improvement (e.g. FIQ total score, Patient Global Impression of Change)
3. Physician-rated change
4. Self efficacy (e.g. Arthritis Self-efficacy Questionnaire)
5. Fatigue (e.g. FIQ fatigue subscale, Multidimensional Assessment of Fatigue Index, Fatigue Severity Scale)
6. Sleep (e.g. sleep visual analogue scale (VAS), Medical Outcomes Study (MOS) sleep scale, single-question assessment)
7. Depression (e.g. FIQ subscale for depression, Arthritis Impact Measurement Scales (AIMS) depression, other validated scales)
8. Anxiety (e.g. FIQ subscale for anxiety, AIMS anxiety, other validated scales)
9. Generic functional status or quality of life (e.g. SF-36, 15-D, Sickness Impact Profile, Health Assessment Questionnaire)
10. Tender points (e.g. pain threshold of tender points using dolorimetry, tenderness to thumb pressure)
11. Sexual function (e.g. Arizona Sexual Experience Scale)

Outcomes were measured at different time periods:
• Short-term: 4 to 12 weeks
• Medium-term: > 12 to 24 weeks
• Long-term: > 24 weeks

Data collection and analysis

Selection of studies
Two review authors (BN, RR) independently scrutinised all the titles and abstracts revealed by the searches and determined which fulfilled the selection criteria. A third review author (GU) verified that the selection had been properly realised. We obtained full texts for potentially eligible articles and followed the same process for selection.

Data extraction and management
Three review authors (BN, RR, BW) extracted data independently onto a specially designed data extraction form. There were no disagreements in this process. One author (BN) entered data into Review Manager (RevMan) 5 (RevMan 2011) and a second author (GU) checked them.

Assessment of risk of bias in included studies
Two review authors (BN, GU) independently assessed the risk of bias of each included trial. We resolved disagreements by consensus and, if needed, referral to a third review author (BW). For each included study, we assessed risk of bias against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data and selective outcome reporting, in accordance with methods recommended by The Cochrane Collaboration (Higgins 2011). We explicitly judged each of these criteria to be at low risk of bias, high risk of bias or unclear risk of bias (either lack of information or uncertainty over the potential for bias).

Measures of treatment effect
The effect measures of choice were risk ratio (RR) for dichotomous data and mean difference (MD) or standardised mean difference (SMD) (when different scales were used to measure outcomes) for continuous data. We expressed uncertainty with 95% confidence intervals (CIs).
Data synthesis

We undertook each meta-analysis using a fixed-effect model in Review Manager 5. We used the $I^2$ statistic for assessing heterogeneity and if its value was greater than 50% we inspected the trials. If no explanation could be found we repeated the analysis with a random-effects model.

'Summary of findings' table

We presented major outcomes (including benefits and adverse events) in Summary of findings for the main comparison, which provides an overall grading of the evidence and the magnitude of the intervention effect, as well as a summary of the main outcome data. We also presented an assessment of the overall quality of evidence per outcome (high, moderate, low and very low) using the GRADE approach as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We determined pooled baseline risk using the generic variance method in RevMan 2011. For dichotomous outcomes, we calculated the number needed to treat to benefit (NNT) from the control group event rate (unless the population event rate was known) (Cates 2004).

RESULTS

Description of studies

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

We initially identified 2728 studies related to FM in the 2009 search and 786 in the 2010 search. As the search strategy was designed as part of a global search strategy to identify all the RCTs on pharmacological and non-pharmacological treatments for FM (Nishishinya 2006), many of the obtained references were not related to MAOIs. We excluded 3509 references as they did not fulfil the inclusion criteria related to the interventions evaluated in this review. We identified five studies potentially related to these interventions and a full text could only be obtained for four of them. Of these five, we excluded three studies (see Characteristics of excluded studies for further details about reasons for exclusion and Figure 1 for study flow diagram). We ultimately included two studies (see Characteristics of included studies for full description of studies).

Figure 1. Flow chart of studies
Included studies
We identified two RCTs on MAOIs, one had two arms (pirlindole versus placebo) and a duration of four weeks (Ginsberg 1998) and the other had three arms (moclobemide, amitriptyline and placebo) and a duration of 12 weeks (Hannonen 1998). In both studies sample sizes were fewer than 50 participants per group. Overall 230 patients diagnosed with FM were randomised and 50 received pirlindole, 43 moclobemide, 42 amitriptyline and 95 placebo.
In both studies the American College of Rheumatology (ACR) diagnostic criteria for FM were used (Wolfe 1990). The percentage of women in both studies was 85% and 100% respectively (Ginsberg 1998; Hannonen 1998).
With regards to demographic characteristics, participants in Ginsberg 1998 were younger (mean age 39) and had a shorter duration of disease (26 to 43 months) than the participants in Hannonen 1998 (mean age 49; disease duration 7.9 to 8.6 years). Hannonen 1998 was funded by Roche Oy, Finland. Ginsberg 1998 did not provide information about study funding.

Interventions
Ginsberg 1998 compared pirlindole (150 mg) versus placebo and Hannonen 1998 compared moclobemide (450 to 600 mg) versus amitriptyline (25 to 37.5 mg) versus placebo. Both studies allowed the use of paracetamol as a co-intervention.

Outcomes
The studies assessed different outcome measures related to physical function or global assessment by the physician or the patient. In some cases different measuring instruments were used.

The outcome measures assessed with the same instrument (VAS) in both studies were: pain (0 to 10), global assessment by patient (0 to 10) and tender points (0 to 36 in Ginsberg 1998 and 0 to 18 in Hannonen 1998). Sleep disturbances and fatigue were measured with different instruments and scales.
Psychological evaluation was measured in Ginsberg 1998 using the Symptom Checklist-90-Revised and quality of life (using the Nottingham Health Profile) and disability (Sheehan’s disability scales) were only assessed in Hannonen 1998.

Risk of bias in included studies
Risk of bias was high in Ginsberg 1998 and low in Hannonen 1998. In the first study, allocation concealment, sequence generation and blinding were not reported. Additionally, the attrition rate was high (39%) and the intention-to-treat (ITT) analysis was only performed with safety data. Efficacy data were evaluated per protocol.
On the other hand, Hannonen 1998 properly described allocation concealment, sequence generation and blinding of patients and outcome assessors, and conducted an ITT analysis, although the attrition rate was also high (30%).
It was not possible to assess selective outcome reporting as we did not have access to the study protocols.
Sample sizes were small in both studies (fewer than 50 patients per group).
See Figure 2 and Figure 3 for a ‘Risk of bias’ summary and graph and Characteristics of included studies for detailed information regarding ‘Risk of bias’ assessments for every study.
Figure 2. ‘Risk of bias’ graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding (performance bias and detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)

Legend: Green = Low risk of bias, Yellow = Unclear risk of bias, Red = High risk of bias

Figure 3. ‘Risk of bias’ summary: review authors’ judgements about each risk of bias item for each included study.
Effects of interventions

See: Summary of findings for the main comparison MAOIs compared to placebo for fibromyalgia syndrome

Monoamine oxidase inhibitor (MAOI) agents versus placebo

Any MAOI agent versus placebo

Some of the results provided by the two studies included in the review could be meta-analysed. Effect measures chosen were mean difference (MD) whenever outcomes were measured with the same scale in both studies and standardised mean difference (SMD) if different scales were employed. As mentioned, if heterogeneity was greater than 50%, we used a random-effects model. Thus the MD between the treatment group and the placebo group for pain was -1.45 (121 patients; 95% confidence interval (CI) -2.71 to -0.20), with moderate heterogeneity ($I^2 = 59\%$) that could be explained by the different drugs employed and design of studies. This represents a minimal clinically important difference (MCID) of 30% (per Dworkin 2008). For tender points, the SMD favouring the treatment group was -0.36 (121 patients; 95% CI -0.72 to -0.00; $I^2 = 31\%$). On the other hand, global assessment by the physician did not show significant differences between groups (MD -0.82 (121 patients; 95% CI -2.39 to 0.75; $I^2 = 71\%$) and SMD -0.81 (121 patients; 95% CI -1.84 to 0.22; $I^2 = 86\%$)), respectively.

Pirlindole versus placebo

This comparison was studied in Ginsberg 1998. Overall, pirlindole showed statistically significant results for several outcomes (pain, tender points, global assessment by the patient and global assessment by the physician) compared with placebo. For pain, the MD between groups was -2.00 (61 patients; 95% CI -2.91 to -1.09), which would imply a MCID of 30% (per Dworkin 2008) and for tender points SMD -0.59 (61 patients; 95% CI -1.10 to -0.07). Global assessment also showed significant results for the treatment group (global assessment by the patient: MD -1.60 (61 patients; 95% CI -2.74 to -0.46) and global assessment by physician: SMD -1.34 (61 patients; 95% CI -1.90 to -0.78). On the other hand, there were no statistically significant differences between pirlindole and placebo for some other outcomes: psychological evaluation, morning stiffness duration, fatigue and sleep disturbances.

Most frequent adverse events were nausea and vomiting, with statistically significant differences between groups (risk ratio (RR) 7.82 (89 patients; 95% CI 1.02 to 59.97); number needed to treat (NNT) 7 (4 to 33)). Adverse events were observed in 18 patients (40%) in the pirlindole group and 16 patients (36.4%) in the placebo group, with no statistically significant differences. Six patients (13.3%) from the pirlindole group and three (6.8%) from the placebo group dropped out because of adverse events.

Moclobemide versus placebo

Hannonen 1998 assessed this comparison. There were no statistically significant differences between groups for the following outcomes: pain (MD -0.70 (60 patients; 95% CI -2.07 to 0.67)), tender points (SMD -0.14 (60 patients; 95% CI -0.65 to 0.36)), global assessment by patient (MD 0.00 (60 patients; 95% CI 1.24 to 1.24)) and global assessment by physician: SMD -0.29 (60 patients; 95% CI -0.80 to 0.22). In addition, the proportion of responders assessed by the physician did not significantly improve compared with placebo (54% versus 49% respectively).

In both groups there was a significant improvement in within-group comparisons, except in quality of life parameters and in functional scale areas. The percentage of patients with at least one adverse event was 77% in the moclobemide group compared with 80% in the placebo group, with no statistically significant differences. Drop outs due to adverse events did not differ statistically significantly between the treatment arms. The most common adverse events with moclobemide were headache and difficulties in falling asleep, and fatigue and headache in placebo-treated patients.

Moclobemide versus amitriptyline

This comparison was evaluated in Hannonen 1998. At 12 weeks there were no statistically significant differences between the two drugs in most of the outcomes assessed (pain, tender points, global assessment by patient, fatigue, quality of life and functional scale areas). Nonetheless, there was a statistically significant difference in sleep favouring amitriptyline compared to moclobemide (MD 2.20 (62 patients; 95% CI 0.75 to 3.65)). In addition, in the amitriptyline group the proportion of responders assessed by the physician was statistically significantly higher than that of the moclobemide group (74% versus 54%).

In both groups there were statistically significant improvements in within-group comparisons, mainly in the amitriptyline group which improved in the Nottingham Health Profile dimensions and the Sheehan’s functional scale areas.

Most typical adverse events with amitriptyline were dry mouth and fatigue. The percentage of patients with at least one adverse effect was 77% in the moclobemide group compared to 74% in the amitriptyline group. There were six drop outs (14%) due to...
adverse events in the moclobemide group and five (12%) in the amitriptyline group, with no statistically significant differences.

**DISCUSSION**

**Summary of main results**

The objective of this systematic review was to assess the effectiveness and safety of monoamine oxidase inhibitors (MAOIs) in the treatment of fibromyalgia (FM) compared with placebo or another active drug. We identified two studies with a total of 230 patients (mainly women) diagnosed with FM that evaluated two different MAOIs: pirlindole (Ginsberg 1998) and moclobemide (Hannonen 1998) in the short term (four and 12 weeks respectively) and showed inconsistent results. Pirlindole compared to placebo statistically significantly improved pain, tender points and global assessment by the patient and by the physician, whereas moclobemide did not show any statistically significant differences in comparison with placebo for the same outcomes. When moclobemide was compared to amitriptyline, the latter showed more favourable results in the percentage of responders assessed by physician and sleep quality.

Pooled results of these two studies showed a moderate effect of MAOIs on pain and a small effect in tender points. Of note, we observed moderate heterogeneity (59%) when pooling results for the outcome pain, which could be explained by the different drugs employed and different duration and design of studies. Meta-analyses of other outcomes (global assessment by the patient and the physician) did not show any significant difference between groups.

**Overall completeness and applicability of evidence**

While the two studies included in this review demonstrate short-term improvements in pain, it remains unclear if MAOIs provide any long-term benefit. FM is a chronic condition, potentially requiring treatment over an entire lifetime. When MAOIs are prescribed for the treatment of FM, it is typically with the intent that it will be a long-term therapy. The longest study reviewed only considered improvement at the end of 12 weeks. None of the studies reviewed provide any insight into the long-term efficacy of MAOIs for FM symptoms. For these reasons, we are not confident that their results adequately estimate the utility of MAOIs when applied to the general population.

The most frequent adverse effects of MAOIs were headache and insomnia, although there were no statistically significant differences with placebo. Drop outs due to adverse events did not differ either compared with placebo. In the Hannonen 1998 study, a high percentage of patients with at least one adverse event were reported in all groups (77% in the moclobemide group, 74% in the amitriptyline group and 80% in the placebo group) but only a small number of patients withdrew for that reason. It is important to be mindful that there is potential for more serious side effects to be seen in clinical practice than in these trials. MAOIs are well known to cause potentially fatal hypertensive crisis, serotonin syndrome and psychosis when they interact with foods containing tyramine (fermented beverages, liver and aged cheese) and a variety of common medications. Many of the medications that lead to MAOI interactions are commonly used in fibromyalgia treatments, such as SSRIs, tricyclics, meperidine, tramadol, dextromethorphan and St John’s Wort. The design of the two clinical trials considered had strict limitations on the use of concomitant medications; it may be more difficult to avoid unintended interactions with these medications in a clinical environment. These studies also do not include the potential for withdrawal symptoms on cessation of taking these medications.

The two medications that are the focus of this review are also more recent members of the MAOI class. These medications are reversible in their effects, unlike older MAOIs that demonstrate irreversible action. Thus, the safety data reported here should not be considered to reflect the MAOI class as a whole.

**Potential biases in the review process**

Limitations of this review include the low number of studies and issues associated with study design, such as short durations of intervention and follow-up and low numbers of patients. The long-term efficacy of treatments for FM is unknown. There are possible adverse events that might come up when using these drugs for a long time. Risk of bias is low in one study (Hannonen 1998) and high in the other one (Ginsberg 1998) as sequence generation, allocation concealment, blinding and incomplete outcome data were poorly reported. Both studies were published before the publication of the CONSORT statement (Moher 2010) which might partly explain the low quality in the reporting of the Ginsberg 1998 study. External validity is limited also because both studies were mainly conducted in women.

**Agreements and disagreements with other studies or reviews**

Our results agree with previous reviews and guidelines recommendations. The European League Against Rheumatism (EULAR) recommends the use of moclobemide and pirlindole for the treatment of pain (level of evidence Ib, recommendation grade A), although states that the evidence about these drugs is limited (Carville 2008). Häuser 2009 and Üçeyler 2008 also conclude that MAOIs showed a small effect size for reducing pain. On the other hand, other clinical practice guidelines do not mention MAOIs in their recommendations, i.e. the American Pain Society guideline...
AUTHORS’ CONCLUSIONS

Implications for practice
Data suggest that the effectiveness of monoamine oxidase inhibitors (MAOIs) for the treatment of fibromyalgia (FM) symptoms is limited. Although we observed a moderate effect size on pain and a small effect on tender points, results are only based on two studies of short duration, with a small number of patients and inconsistent risk of bias. As long-term effects of MAOIs are unknown and FM has a chronic course with pain of non-inflammatory origin, the use of these drugs is of limited value.

Implications for research
If new studies on MAOIs are to be conducted, CONSORT guidelines (Moher 2010) should be taken into account in order to improve the quality of reporting of trials. Additionally these trials should incorporate clinically relevant outcome measures and use standardised outcome measuring instruments so that results are reliable and can be compared across trials. Sample sizes should be of enough magnitude to detect relevant differences between groups, follow-up should be long term and different populations should also be included (ethnicities, ages, men). It would be useful for future studies to consider MAOIs use in both isolation as well as part of a multidisciplinary programme.

ACKNOWLEDGEMENTS
To Ivan Solà for running the searches for this review.
M. Betina Nishishinya is a PhD candidate at the Public Health and Research Methodology Programme, Universitat Autònoma de Barcelona (UAB).

REFERENCES

References to studies included in this review
Ginsberg 1998 [published data only]

Hannonen 1998 [published data only]

References to studies excluded from this review
Cerrahoglu 1995 [published data only]

Sofu 1996 [published data only]

Yavuzer 1998 [published data only]

Additional references
Arnold 2000

Bartels 1986

Bengtsson 1986

Bradley 1996

Bruhwyljer 1997

Buckhardt 2005
Buckhardt CS, Goldenberg D, Crofford L, Gerwin R, Gowens S, Jackson K, et al. Guideline for the management of...

Carville 2008

Cates 2004

Cathebras 1998

Crofford 1994

Da Prada 1994

De Wilde 1996

Dworkin 2008

Goldenberg 2007

Gracey 2002

Guidroz 2009

Hawley 1991

Higgins 2011

Holford 1994

Häuser 2009

Häuser 2012

Lawrence 1998

Lund 1986

Mease 2005

Miller 2002

Moher 2010

Moldofsky 1989

Newburn 1999
Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome (Review)

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Nishishinya 2006

Nishishinya 2012

O’Malley 2000

OMERACT 7

Papakostas 2006

Priest 1994

RevMan 2011

Rossy 1999

Smith 1998

Smythe 1981

Stabl 1989

Steinmeyer 1993

Tanghe 1997

Vaeroy 1988

Versiani 1989

Versiani 1990

Walitt 2012

Wolfe 1999

Wolfe 1997

Wolfe 2010

Yunus 1981
Yunus 1982

Yunus 1984

Üçeyler 2008

* Indicates the major publication for the study
### Characteristics of included studies

#### Ginsberg 1998

| Methods | Randomised controlled trial  
|         | Parallel  
|         | Duration: 4 weeks  
|         | Double-blind, no data about method employed |

| Participants | Source: multicentre  
|              | Inclusion criteria: ACR criteria (1990), outpatients with primary FMS, male or female, aged 18 to 75 years  
|              | Exclusion criteria: inability to give his/her informed consent, pregnancy or lactation, inability to be withdrawn from antidepressants, sleeping medications, anti-inflammatory drugs, muscle relaxants, tranquillisers and/or any other central nervous system medication, severe cardiac disease, any other disease sufficient to produce clinical problems, any clinically significant biochemical or haematological abnormality  
|              | Total n = 100  
|              | Pirlindole n = 50  
|              | Placebo n = 50  
|              | Age (mean): 39.8 (SD 8.8) placebo; 39.7 (SD 8.6) pirlindole  
|              | Women: 85% |

| Interventions | Pirlindole 75 mg p.o. twice a day  
|               | Placebo  
|               | Co-interventions: paracetamol |

| Outcomes | Pain (VAS 0 to 10)  
|          | Morning stiffness duration (minutes)  
|          | Tender point score (0 to 36)  
|          | Psychological evaluation (Symptom Checklist-90-Revised)  
|          | Global assessment by patient (VAS 0 to 10)  
|          | Global evaluation by investigator (VAS 0 to 10)  
|          | Fatigue (0 to 3)  
|          | Sleep (0 to 3)  
|          | Adverse events |

| Notes | Sample size: < 50 patients per group  
|       | Follow up: same duration for all patients: < 80% (efficacy analysis)  
|       | Intention-to-treat: yes (only for adverse events)  
|       | High attrition rate (39%)  
|       | Short period of follow-up  
|       | Withdrawals:  
|       | Pirlindole: 17/50 (34%)  
|       | Placebo: 22/50 (44%)  
|       | Total: 39/100 (39%) |

### Risk of bias
### Ginsberg 1998  
(Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Method not reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>High attrition rate. ITT only for adverse events, analysis of efficacy data conducted per protocol</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol not available</td>
</tr>
</tbody>
</table>

### Hannonen 1998

**Methods**  
Randomised controlled trial  
Parallel  
Duration: 12 weeks  
Double-blind

**Participants**  
Source: multicentre  
Inclusion criteria: female patients aged 18 to 65 years and fulfilling the ACR 1990 criteria for FM. Score at baseline a minimum of 4 (moderate) on at least 3 of the 4 self administered visual analogue scales (VAS) (0 to 10). The items were: patient’s global assessment of general health (GH), pain, sleep quality and quantity, fatigue  
Exclusion criteria: severe cardiovascular, pulmonary, hepatic, haematological or renal disease, glaucoma, pregnant or lactating, or not willing to discontinue all medication acting on the central nervous system, non-steroidal antiinflammatory drugs and analgesics (other than paracetamol). Patients with major depression, psychosis, obsessive-compulsive disorders, excessive alcohol consumption  
Total n = 130  
Moclobemide n = 43  
Amitriptyline n = 42  
Placebo n = 45  
Age: 47.6 to 49.7 years  
Women: 100%

**Interventions**  
Moclobemide: 600 mg p.o.  
Amitriptyline: 12.5 to 37.5 mg p.o.  
Placebo  
*Note: “If the patient tolerated the treatment, the dose was increased at the 2nd week check-up to the target dose (450 mg moclobemide and 25 mg amitriptyline). Further if the response was still unsatisfactory at 6 week visit, the moclobemide and amitriptyline..."
Hannonen 1998  (Continued)

Doses could be increased to 600 mg and 37.5 mg respectively, with a concomitant increase in the number of placebo capsules.

Co-interventions: Paracetamol tablets (500 mg) supplied by the sponsor (up to 4 g/day).

Outcomes

Physician’s clinical impression of change (1 to 3)
Global Health (VAS 0 to 10)
Pain (VAS 0 to 10)
Sleep quality (VAS 0 to 10)
Fatigue (VAS 0 to 10)
Sheehan’s disability scale (0 to 10)
Nottingham Health Profile (NHP)
Tender points (0 to 18)
Physician’s clinical impression of the severity (CIS) (1 to 7)
Physician’s clinical global impression of tolerability (CGI) (1 to 4)
Physician’s clinical impression of change (1 to 3)
Adverse events

Notes

Sample size: < 50 patients per group
Follow-up: same duration for all patients: < 80%
Intention-to-treat: yes
High attrition rate (30%)
Short period of follow-up
Withdrawals:
Moclobemide: 13/43 (30%)
Amitriptyline: 10/42 (24%)
Placebo: 15/45 (33%)
Total: 38/130 (30%)

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Adequate: the randomisation was organised centrally with sequentially numbered envelopes consisting of blocks of 6</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Adequate</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Described as double-blind. The placebo capsules were identical to the active drugs</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Missing outcome data described although high attrition rate. ITT</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol not available</td>
</tr>
</tbody>
</table>
ACR: American College of Rheumatology; FM: fibromyalgia; FMS: fibromyalgia syndrome; ITT: intention-to-treat; p.o.: orally; SD: standard deviation; VAS: visual analogue scale

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerrahoglu 1995</td>
<td>Not a double-blind study</td>
</tr>
<tr>
<td>Sofu 1996</td>
<td>Probably a case series. It was not possible to obtain full manuscript. (Turkish journal currently not available)</td>
</tr>
<tr>
<td>Yavuzer 1998</td>
<td>Single-blind study</td>
</tr>
</tbody>
</table>
## Data and Analyses

### Comparison 1. MAOIs vs placebo (efficacy)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pain (VAS)</td>
<td>2</td>
<td>121</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.45 [-2.71, -0.20]</td>
</tr>
<tr>
<td>2 Tender points</td>
<td>2</td>
<td>121</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.36 [-0.72, -0.00]</td>
</tr>
<tr>
<td>3 Global assessment (by patient)</td>
<td>2</td>
<td>121</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.82 [-2.39, 0.75]</td>
</tr>
<tr>
<td>4 Global assessment (by physician)</td>
<td>2</td>
<td>121</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.81 [-1.84, 0.22]</td>
</tr>
<tr>
<td>5 Psychological evaluation (SCL-90-R;NHP)</td>
<td>2</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

### Comparison 2. Moclobemide vs amitriptyline (efficacy)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pain (VAS)</td>
<td>1</td>
<td>62</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [-1.37, 1.37]</td>
</tr>
<tr>
<td>2 Tender points</td>
<td>1</td>
<td>62</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.20 [-1.65, 2.05]</td>
</tr>
<tr>
<td>3 Fatigue (VAS)</td>
<td>1</td>
<td>62</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.20 [-1.17, 1.57]</td>
</tr>
<tr>
<td>4 Sleep (VAS)</td>
<td>1</td>
<td>62</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>2.20 [0.75, 3.65]</td>
</tr>
<tr>
<td>5 Global assessment (by patient)</td>
<td>1</td>
<td>62</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.90 [-0.34, 2.14]</td>
</tr>
<tr>
<td>6 Global assessment (by physician)</td>
<td>1</td>
<td>62</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.04 [-0.49, 0.57]</td>
</tr>
</tbody>
</table>

### Comparison 3. MAOIs vs placebo (safety)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Depression</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>4.89 [0.24, 99.08]</td>
</tr>
<tr>
<td>2 Dizziness</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>3.91 [0.45, 33.63]</td>
</tr>
<tr>
<td>3 Gastric discomfort</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.96 [0.18, 20.80]</td>
</tr>
<tr>
<td>4 Headache</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.93 [0.63, 13.76]</td>
</tr>
<tr>
<td>5 Insomnia</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.93 [0.32, 27.14]</td>
</tr>
<tr>
<td>6 Nausea and vomiting</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>7.82 [1.02, 59.97]</td>
</tr>
<tr>
<td>7 Pain increase</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>4.89 [0.24, 99.08]</td>
</tr>
<tr>
<td>8 Palpitations</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.93 [0.32, 27.14]</td>
</tr>
<tr>
<td>9 Sleepy during the day</td>
<td>1</td>
<td>89</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>4.89 [0.24, 99.08]</td>
</tr>
<tr>
<td>10 Discontinuation due to adverse events</td>
<td>2</td>
<td>149</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.72 [0.53, 5.59]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison I MAOIs vs placebo (efficacy), Outcome 1 Pain (VAS).

Review: Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

Comparison: 1 MAOIs vs placebo (efficacy)

Outcome: 1 Pain (VAS)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean(SD)</th>
<th>Mean(SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
<td>IV,Random,95% CI</td>
<td></td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>Ginsberg 1998</td>
<td>33</td>
<td>28</td>
<td>4.8 (2.1)</td>
<td>6.8 (1.5)</td>
<td>-2.00 [-2.91, -1.09]</td>
<td>58.0 %</td>
<td>-2.00 [-2.91, -1.09]</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30</td>
<td>30</td>
<td>4.5 (2.7)</td>
<td>5.2 (2.7)</td>
<td>-0.70 [-2.07, 0.67]</td>
<td>42.0 %</td>
<td>-0.70 [-2.07, 0.67]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>58</td>
<td></td>
<td></td>
<td>-1.45 [-2.71, -0.20]</td>
<td>100.0 %</td>
<td>-1.45 [-2.71, -0.20]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.50; Chi² = 2.41, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 2.27 (P = 0.023)
Test for subgroup differences: Not applicable

### Analysis 1.2. Comparison I MAOIs vs placebo (efficacy), Outcome 2 Tender points.

Review: Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

Comparison: 1 MAOIs vs placebo (efficacy)

Outcome: 2 Tender points

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean(SD)</th>
<th>Mean(SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Ginsberg 1998</td>
<td>33</td>
<td>28</td>
<td>21.7 (9.9)</td>
<td>27 (7.5)</td>
<td>-0.59 [-1.10, -0.07]</td>
<td>49.2 %</td>
<td>-0.59 [-1.10, -0.07]</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30</td>
<td>30</td>
<td>14.1 (3.2)</td>
<td>14.6 (3.6)</td>
<td>-0.14 [-0.65, 0.36]</td>
<td>50.8 %</td>
<td>-0.14 [-0.65, 0.36]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>58</td>
<td></td>
<td></td>
<td>-0.36 [-0.72, 0.00]</td>
<td>100.0 %</td>
<td>-0.36 [-0.72, 0.00]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.45, df = 1 (P = 0.23); I² = 31%
Test for overall effect: Z = 1.97 (P = 0.049)
Test for subgroup differences: Not applicable
Analysis 1.3. Comparison 1 MAOIs vs placebo (efficacy), Outcome 3 Global assessment (by patient).

Review: Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

Comparison: 1 MAOIs vs placebo (efficacy)

Outcome: 3 Global assessment (by patient)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>IV,Random,95% CI</td>
<td></td>
</tr>
<tr>
<td>Ginsberg 1998</td>
<td>33</td>
<td>28</td>
<td>-1.60 [-2.74, -0.46]</td>
<td>91.2 %</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30</td>
<td>30</td>
<td>0.0 [-1.24, 1.24]</td>
<td>48.8 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>58</td>
<td>-0.82 [-2.39, 0.75]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.91; Chi² = 3.47, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 1.03 (P = 0.31)
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 MAOIs vs placebo (efficacy), Outcome 4 Global assessment (by physician).

Review: Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

Comparison: 1 MAOIs vs placebo (efficacy)

Outcome: 4 Global assessment (by physician)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>IV,Random,95% CI</td>
<td></td>
</tr>
<tr>
<td>Ginsberg 1998</td>
<td>33</td>
<td>28</td>
<td>-1.34 [-1.90, -0.78]</td>
<td>49.3 %</td>
</tr>
<tr>
<td>Hannonen 1998 (1)</td>
<td>30</td>
<td>30</td>
<td>-0.29 [-0.80, 0.22]</td>
<td>50.7 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>58</td>
<td>-0.81 [-1.84, 0.22]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.48; Chi² = 7.40, df = 1 (P = 0.01); I² = 86%
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Not applicable
Analysis 1.5. Comparison 1 MAOIs vs placebo (efficacy), Outcome 5 Psychological evaluation (SCL-90-R; NHP).

Review: Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

Comparison: 1 MAOIs vs placebo (efficacy)

Outcome: 5 Psychological evaluation (SCL-90-R; NHP)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td></td>
</tr>
<tr>
<td>Ginsberg 1998</td>
<td>33</td>
<td>153 (51)</td>
<td>28 156 (51)</td>
<td></td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30</td>
<td>15.4 (21.1)</td>
<td>30 13.2 (20.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>0</td>
<td>0</td>
<td>0.06 [-0.56, 0.45]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 = 0.0%

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

---

(1) Hannonen used the Clinical Impression of the Severity (CIS) by physician (1-7)
### Analysis 2.1. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 1 Pain (VAS).

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 2 Moclobemide vs amitriptyline (efficacy)

**Outcome:** 1 Pain (VAS)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Moclobemide</th>
<th>Amitriptyline</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30 4.5 (2.7)</td>
<td>32 4.5 (2.8)</td>
<td></td>
<td>100.0%</td>
<td>0.0 [-1.37, 1.37]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>30</td>
<td>32</td>
<td></td>
<td>100.0%</td>
<td>0.0 [-1.37, 1.37]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable

---

### Analysis 2.2. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 2 Tender points.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 2 Moclobemide vs amitriptyline (efficacy)

**Outcome:** 2 Tender points

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Moclobemide</th>
<th>Amitriptyline</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30 14.1 (3.2)</td>
<td>32 13.9 (4.2)</td>
<td></td>
<td>100.0%</td>
<td>0.20 [-1.65, 2.05]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>30</td>
<td>32</td>
<td></td>
<td>100.0%</td>
<td>0.20 [-1.65, 2.05]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.83)

Test for subgroup differences: Not applicable
### Analysis 2.3. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 3 Fatigue (VAS).

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 2 Moclobemide vs amitriptyline (efficacy)

**Outcome:** 3 Fatigue (VAS)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Moclobemide</th>
<th>Amitriptyline</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30 4.9 (2.7)</td>
<td>32 4.7 (2.8)</td>
<td>0.20 [-1.17, 1.57]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>30</td>
<td>32</td>
<td>0.20 [-1.17, 1.57]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable

### Analysis 2.4. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 4 Sleep (VAS).

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 2 Moclobemide vs amitriptyline (efficacy)

**Outcome:** 4 Sleep (VAS)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Moclobemide</th>
<th>Amitriptyline</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30 5.8 (3)</td>
<td>32 3.6 (2.8)</td>
<td>2.20 [0.75, 3.65]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>30</td>
<td>32</td>
<td>2.20 [0.75, 3.65]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 2.98 (P = 0.0029)
Test for subgroup differences: Not applicable
### Analysis 2.5. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 5 Global assessment (by patient).

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 2 Moclobemide vs amitriptyline (efficacy)

**Outcome:** 5 Global assessment (by patient)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Moclobemide</th>
<th>Amitriptyline</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV/Fixed,95% CI</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>30</td>
<td>5.3 (2.4)</td>
<td>32</td>
<td>4.4 (2.6)</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- Favorability: not applicable
- Test for overall effect: Z = 1.42 (P = 0.16)
- Test for subgroup differences: Not applicable

### Analysis 2.6. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 6 Global assessment (by physician).

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 2 Moclobemide vs amitriptyline (efficacy)

**Outcome:** 6 Global assessment (by physician)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Moclobemide</th>
<th>Amitriptyline</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV/Fixed,95% CI</td>
</tr>
<tr>
<td>Hannonen 1998 (1)</td>
<td>30</td>
<td>3.44 (1.16)</td>
<td>32</td>
<td>3.4 (0.94)</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- Favorability: not applicable
- Test for overall effect: Z = 0.15 (P = 0.88)
- Test for subgroup differences: Not applicable

(1) Clinical Impression of the Severity (CIS) by physician (1-7)
Analysis 3.1. Comparison 3 MAOIs vs placebo (safety), Outcome 1 Depression.

Review: Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

Comparison: 3 MAOIs vs placebo (safety)

Outcome: 1 Depression

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1998</td>
<td>2/45</td>
<td>0/44</td>
<td></td>
<td>100.0 %</td>
<td>4.89 [0.24, 99.08]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>45</strong></td>
<td><strong>44</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>4.89 [0.24, 99.08]</strong></td>
</tr>
</tbody>
</table>

Total events: 2 (Treatment), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 MAOIs vs placebo (safety), Outcome 2 Dizziness.

Review: Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

Comparison: 3 MAOIs vs placebo (safety)

Outcome: 2 Dizziness

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1998</td>
<td>4/45</td>
<td>1/44</td>
<td></td>
<td>100.0 %</td>
<td>3.91 [0.45, 33.63]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>45</strong></td>
<td><strong>44</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>3.91 [0.45, 33.63]</strong></td>
</tr>
</tbody>
</table>

Total events: 4 (Treatment), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Not applicable
### Analysis 3.3. Comparison 3 MAOIs vs placebo (safety), Outcome 3 Gastric discomfort.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 3 MAOIs vs placebo (safety)

**Outcome:** 3 Gastric discomfort

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed 95% CI</td>
<td></td>
<td>M-H, Fixed 95% CI</td>
</tr>
<tr>
<td>Ginsberg 1998</td>
<td>2/45</td>
<td>1/44</td>
<td>1.96 [0.18, 20.80]</td>
<td>100.0%</td>
<td>1.96 [0.18, 20.80]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>45</strong></td>
<td><strong>44</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.96 [0.18, 20.80]</strong></td>
</tr>
</tbody>
</table>

Total events: 2 (Treatment), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.56 (P = 0.58)

Test for subgroup differences: Not applicable

### Analysis 3.4. Comparison 3 MAOIs vs placebo (safety), Outcome 4 Headache.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 3 MAOIs vs placebo (safety)

**Outcome:** 4 Headache

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed 95% CI</td>
<td></td>
<td>M-H, Fixed 95% CI</td>
</tr>
<tr>
<td>Ginsberg 1998</td>
<td>6/45</td>
<td>2/44</td>
<td>2.93 [0.63, 13.76]</td>
<td>100.0%</td>
<td>2.93 [0.63, 13.76]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>45</strong></td>
<td><strong>44</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.93 [0.63, 13.76]</strong></td>
</tr>
</tbody>
</table>

Total events: 6 (Treatment), 2 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.36 (P = 0.17)

Test for subgroup differences: Not applicable
### Analysis 3.5. Comparison 3 MAOIs vs placebo (safety), Outcome 5 Insomnia.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 3 MAOIs vs placebo (safety)

**Outcome:** 5 Insomnia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1998</td>
<td>3/45</td>
<td>1/44</td>
<td>2.93 [0.32, 27.14]</td>
<td>100.0 %</td>
<td>2.93 [0.32, 27.14]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>45</strong></td>
<td><strong>44</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.93 [0.32, 27.14]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable

### Analysis 3.6. Comparison 3 MAOIs vs placebo (safety), Outcome 6 Nausea and vomiting.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 3 MAOIs vs placebo (safety)

**Outcome:** 6 Nausea and vomiting

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1998</td>
<td>8/45</td>
<td>1/44</td>
<td>7.82 [1.02, 59.97]</td>
<td>100.0 %</td>
<td>7.82 [1.02, 59.97]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>45</strong></td>
<td><strong>44</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>7.82 [1.02, 59.97]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 1.98 (P = 0.048)
Test for subgroup differences: Not applicable
### Analysis 3.7. Comparison 3 MAOIs vs placebo (safety), Outcome 7 Pain increase.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 3 MAOIs vs placebo (safety)

**Outcome:** 7 Pain increase

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1998</td>
<td>2/45</td>
<td>0/44</td>
<td>100.0 %</td>
<td>4.89</td>
<td>[0.24, 99.08]</td>
</tr>
</tbody>
</table>

Total (95% CI) 45 44 100.0 % 4.89 [0.24, 99.08]

Total events: 2 (Treatment), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

### Analysis 3.8. Comparison 3 MAOIs vs placebo (safety), Outcome 8 Palpitations.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 3 MAOIs vs placebo (safety)

**Outcome:** 8 Palpitations

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1998</td>
<td>3/45</td>
<td>1/44</td>
<td>100.0 %</td>
<td>2.93</td>
<td>[0.32, 27.14]</td>
</tr>
</tbody>
</table>

Total (95% CI) 45 44 100.0 % 2.93 [0.32, 27.14]

Total events: 3 (Treatment), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable
### Analysis 3.9. Comparison 3 MAOIs vs placebo (safety), Outcome 9 Sleepy during the day.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 3 MAOIs vs placebo (safety)

**Outcome:** 9 Sleepy during the day

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1998</td>
<td>2/45</td>
<td>0/44</td>
<td></td>
<td>100.0 %</td>
<td>4.89 [ 0.24, 99.08 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>44</td>
<td></td>
<td>100.0 %</td>
<td>4.89 [ 0.24, 99.08 ]</td>
</tr>
</tbody>
</table>

Total events: 2 (Treatment), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable

### Analysis 3.10. Comparison 3 MAOIs vs placebo (safety), Outcome 10 Discontinuation due to adverse events.

**Review:** Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

**Comparison:** 3 MAOIs vs placebo (safety)

**Outcome:** 10 Discontinuation due to adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1998</td>
<td>6/45</td>
<td>3/44</td>
<td></td>
<td>75.2 %</td>
<td>1.96 [ 0.52, 7.34 ]</td>
</tr>
<tr>
<td>Hannonen 1998</td>
<td>1/30</td>
<td>1/30</td>
<td></td>
<td>24.8 %</td>
<td>1.00 [ 0.07, 15.26 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>74</td>
<td></td>
<td>100.0 %</td>
<td>1.72 [ 0.53, 5.59 ]</td>
</tr>
</tbody>
</table>

Total events: 7 (Treatment), 4 (Control)
Heterogeneity: Chi$^2$ = 0.19, df = 1 (P = 0.66); I$^2$ =0.0%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable
### Appendix 1. Search strategies and hits retrieved

Randomised controlled trials in fibromyalgia (update November 2010)

<table>
<thead>
<tr>
<th>DATABASE (ACCESS) and date of search</th>
<th>Search strategy and hits retrieved</th>
</tr>
</thead>
</table>
#3 #1 AND #2 1682  
#4 (#2) AND #1 Limits: Publication Date from 2009 312 |
| **CENTRAL (The Cochrane Library)** 2010, Issue 10 | #1 MeSH descriptor Fibromyalgia explode all trees 449  
#2 fibromyalgi* 755  
#3 fibrositis 50  
#4 #1 OR #2 OR #3 526  
#5 (#1 OR #2 OR #3), from 2009 to 2010 137 (69 in clinical trials) |
| **EMBASE (Ovid)** 9 February 2009 | 1 exp Fibromyalgia/ 8833  
2 fibromyalgia.ti,ab. 6702  
3 exp Fibromyalgia/ 8833  
4 fibrositis.ti. 271  
5 1 or 2 or 3 or 4 9482  
6 random:.tw. or placebo:.mp. or double-blind:.mp. 776985  
7 5 and 6 1417  
8 limit 7 to yr="2009 -Current" 405 |

Randomised controlled trials in fibromyalgia (initial search February 2009)

<table>
<thead>
<tr>
<th>DATABASE (ACCESS) and date of search</th>
<th>Search strategy and hits retrieved</th>
</tr>
</thead>
</table>
#3 #1 AND #2 1316 |
| **CENTRAL (The Cochrane Library)** 2009, Issue 1 | #1 MeSH descriptor Fibromyalgia explode all trees 315  
#2 fibromyalgi* 512  
#3 fibrositis 36  
#4 #1 OR #2 OR #3 526 |
| **EMBASE (Ovid)** 9 February 2009 | 1 exp Fibromyalgia/ 5537  
2 fibromyalgia.ti,ab. 4304  
3 exp Fibromyalgia/ 354 |
HISTORY

Review first published: Issue 4, 2012

CONTRIBUTIONS OF AUTHORS

BN and GU were involved in the initial screening of articles, data extraction and 'Risk of bias' assessment with the support of ST. ST and GU wrote the manuscript, with the additional support of BW.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Iberoamerican Cochrane Centre, Spain.

External sources

- Agència d’Avaluació de Tecnologia i Recerca Mèdiques (146/24/2004), Spain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The ‘clinical relevance tables’ and the ‘grading system’ described in the original protocol have been superseded by the new guidelines about 'Summary of findings' tables and risk of bias in Cochrane reviews. Four reviews have been developed from the original protocol (Häuser 2012; Nishishinya 2012; Walitt 2012 and the present one).
INDEX TERMS

Medical Subject Headings (MeSH)
Carbazoles [therapeutic use]; Fibromyalgia [drug therapy]; Moclobemide [therapeutic use]; Monoamine Oxidase Inhibitors [therapeutic use]; Randomized Controlled Trials as Topic; Syndrome

MeSH check words
Adult; Humans