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

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TABLE OF CONTENTS

[Intervention Review]

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

MAOIs compared to placebo for fibromyalgia syndrome

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

Outcomes	Illustrative comparative risks* (95% CI)		Effect size (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	MAOIs				
Pain (VAS) VAS from: 0 to 10	The mean pain (VAS) in the control groups was 6.53	The mean pain (VAS) in the intervention groups was **1.45 lower** (2.71 to 0.2 lower)		121 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	MD = -1.45 (-2.71 to -0.2) RPC = 96% (13% to 180%) ARD = 14.5% (2% to 27.1%) NNT = 2 (1 to 12)
Tender points Tender point score and number of tender points	The number of tender points in the control group (Hannonen study at baseline) was 15.9	The mean tender points in the intervention groups was **0.36 standard deviations lower** (0.72 lower to 0 higher)		121 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	Not statistically significant
Global assessment (by patient) VAS from: 0 to 10	The mean global assessment (by patient) in the control groups was 6.59	The mean global assessment (by patient) in the intervention groups was **0.82 lower** (2.39 lower to 0.75 higher)		121 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	Not statistically significant
Physical function	See comment	See comment	Not estimable	-	See comment	Not measured
Discontinuation due to adverse events	**Study population**		**RR 1.72** (0.53 to 5.59)	149 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	Not statistically significant
	54 per 1000	**93 per 1000** (29 to 302)				

	Medium-risk population					
	51 per 1000	**88 per 1000** (27 to 285)				
Adverse events (nausea and vomiting)	**Study population**		**RR 7.82** (1.02 to 59.97)	89 (1 study)	⊕⊕⊝⊝ **low** [1,2]	RPC = 682% ARD = 16% NNT = 7 (4 to 33)
	23 per 1000	**180 per 1000** (23 to 1000)				
Sleep disturbance	See comment	See comment	Not estimable	-	See comment	Not measured

*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 (Vaeroy 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 (Rossy 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).

Moclobemide is the first of a new class of reversible inhibitors of monoamine oxidase A, with high selectivity for the type A isoenzyme (MAO-A) which primarily deaminates serotonin, noradrenaline and dopamine relative to other monoamine substrates (Steinmeyer 1993; Da Prada 1994). It has been shown to modulate central nervous system neurotransmitter disposition and to have therapeutic applications (Holford 1994). It is an effective antidepressant with a mild adverse effect profile (Stabl 1989; Versiani 1989; Versiani 1990; Priest 1994; Newburn 1999; Papakostas 2006).

Pirlindole is a tetracyclic compound that has been characterised as a potential antidepressant drug. It has pharmacological characteristics in common with both tricyclic antidepressants and classical irreversible MAOIs. Its main mechanism of action consists of a selective and reversible inhibition of monoamine oxidase A (De Wilde 1996; Bruhwyler 1997; Tanghe 1997).

Other antidepressants agents (selective serotonin re-uptake inhibitors (SSRIs), tricyclic agents, serotonin–norepinephrine reuptake inhibitors (SNRIs)) have been the objective of other Cochrane reviews (Häuser 2012; Nishishinya 2012; Walitt 2012), as the original protocol for the present review has been split into different reviews (Nishishinya 2006).

OBJECTIVES

The objective was to assess the effectiveness and safety of monoamine oxidase inhibitors (MAOIs) in the treatment of FM syndrome using the key domains that derived from consensus among experts in the area (Mease 2005; OMERACT 7).

METHODS

Criteria for considering studies for this review

Types of studies

We selected all relevant randomised, double-blind, controlled trials (RCTs) with a study duration of more than four weeks (regardless of the duration of intervention).

Types of participants

Adults (over 18 years) having a clinical diagnosis of fibromyalgia by any recognised criteria (Smythe 1981; Yunus 1981; Yunus 1982; Yunus 1984; Wolfe 1990; Wolfe 2010).

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

Search methods for identification of studies

We ran an electronic search in the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 10), MEDLINE accessed through PubMed (1966 to November 2010) and EMBASE accessed through OVID (1980 to November 2010). See Appendix 1 for search strategies in all databases and retrieved results. We searched bibliographies from reviewed articles and we retrieved relevant articles. We contacted content experts for unpublished and further possible studies.

Our search included all languages. We contacted the corresponding authors of identified RCTs when possible for additional information about other relevant studies. We also searched for ongoing trials in relevant databases such as clinicaltrials.gov and controlled-trials.com.

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

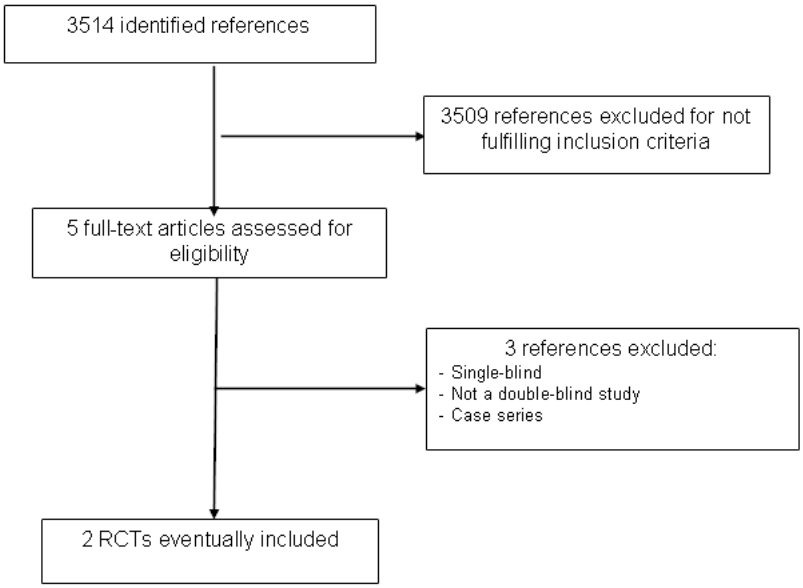
We presented major outcomes (including benefits and adverse events) in Summary of findings for the main comparison, which provides an overall grading of the evidence and the magnitude of the intervention effect, as well as a summary of the main outcome data. We also presented an assessment of the overall 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

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.

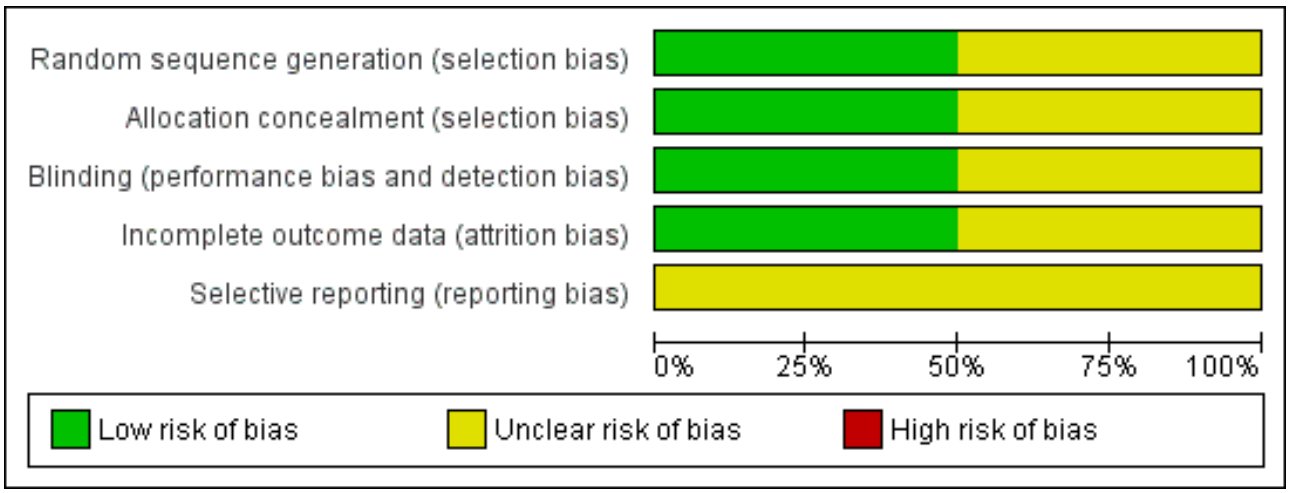
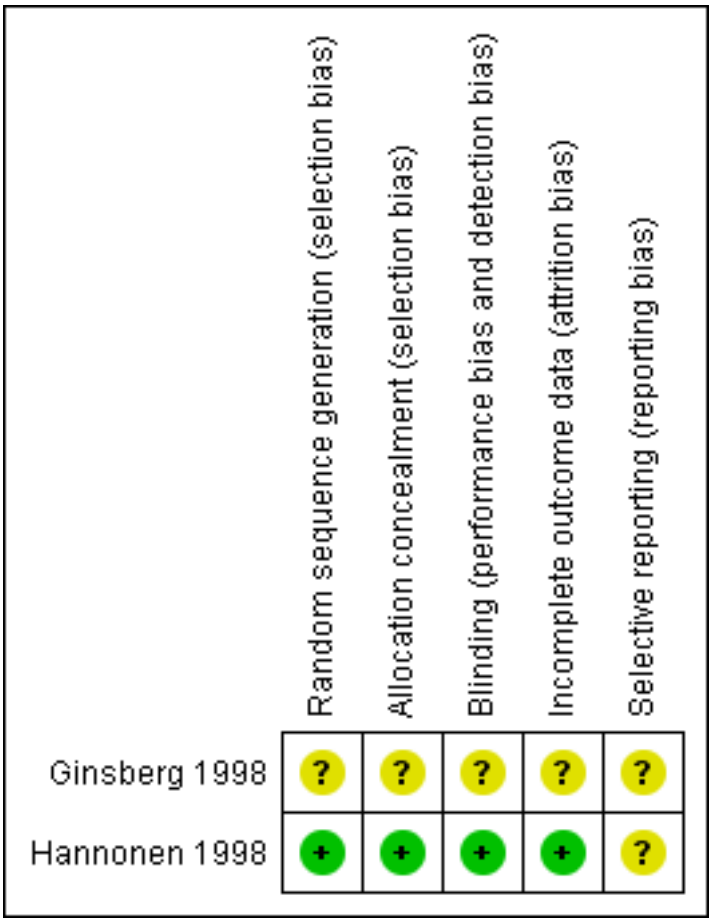


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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 patient and 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 (Buckhardt 2005) or the University of Texas School of Nursing guidelines (Guidroz 2009).

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.

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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}*

Ginsberg F, Joos E, Geczy J, Bruhwyler J, Vandekerckhove K, Famaey JP. A pilot randomized placebo-controlled study of pirlindole in the treatment of primary fibromyalgia. *Journal of Musculoskeletal Pain* 1998;**6**(2):5-17.

Hannonen 1998 *{published data only}*

Hannonen P, Malminiemi K, Yli-Kerttula U, Isomeri R, Roponen P. A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder. *British Journal of Rheumatology* 1998;**37**(12):1279-86.

References to studies excluded from this review

Cerrahoglu 1995 *{published data only}*

Cerrahoglu L, Cogalgil S, Senel K, Turkmen MB. The effects of antidepressive therapy in fibromyalgia syndrome. *Fizik Tedavi Rehabilitasyon Dergisi* 1995;**19**(4):212-6.

Sofu 1996 *{published data only}*

Sofu M, Aki S, Eskiyurt N, Oncel A. The effects of moclobemide on pain and psychological parameters in fibromyalgia syndrome. *Fizik Tedavi Rehabilitasyon Dergisi* 1996;**20**(3):115-20.

Yavuzer 1998 *{published data only}*

Yavuzer G, Kucukdeveci A, Arasil T, Elhan A. Moclobemid treatment in primary fibromyalgia syndrome. *European Journal of Physical Medicine & Rehabilitation* 1998;**8**(2):35-8.

Additional references

Arnold 2000

Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics* 2000;**41**:104-13.

Bartels 1986

Bartels EM, Danneskiold-Samsoe B. Histological abnormalities in muscle from patients with certain types fibrositis. *Lancet* 1986;**1**:755-7.

Bengtsson 1986

Bengtsson A, Henriksson KG, Larsson J. Muscle biopsy in primary fibromyalgia. Light-microscopical and histochemical findings. *Scandinavian Journal of Rheumatology* 1986;**15**:1-6.

Bradley 1996

Bradley LA, Alberts KR, Alarcón GS, Alexander MT, Mountz JM, Weigent DA, et al. Abnormal brain regional cerebral blood flow (rCBF) and cerebrospinal fluid (CSF) levels of substance P (SP) in patients and non-patients with fibromyalgia (FM). *Arthritis and Rheumatism* 1996;**39**(Suppl 9):S212.

Bruhwyler 1997

Bruhwyler J, Liégeois JF, Géczy J. Pirlindole: a selective reversible inhibitor of monoamine oxidase A. A review of its preclinical properties. *Pharmacological Research* 1997;**36**(1):23-33.

Buckhardt 2005

Buckhardt CS, Goldenberg D, Crofford L, Gerwin R, Gowens S, Jackson K, et al. Guideline for the management of fibromyalgia syndrome pain in adults and children. Glenview (IL): American Pain Society (APS), 2005.

Carville 2008

Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Annals of Rheumatic Diseases* 2008;**67**(4):536.

Cates 2004

Cates CD. Visual Rx NNT Calculator [Computer program]. Dr Chris Cates EBM website. Available from http://www.nntonline.net/. Dr Chris Cates EBM website, 2004.

Cathebras 1998

Cathebras P, Lauwers A, Rousset H. Fibromyalgia. A critical review. *Annales de Médecine Interne* 1998;**149**(7):406-14.

Crofford 1994

Crofford LJ, Pillimer SR, Kalogeras KT, Cash JM, Michelson D, Kling MA, et al. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis and Rheumatism* 1994;**37**:1583-92.

Da Prada 1994

Da Prada M, Pieri L, Cesura AM, Kettler R. The pharmacology of moclobemide. *Reviews in Contemporary Pharmacotherapy* 1994;**5**:1-18.

De Wilde 1996

De Wilde JE, Geerts S, Van Dorpe J, Bruhwyler J, Géczy J. A double-blind randomized placebo-controlled study of the efficacy and safety of pirlindole, a reversible monoamine oxidase A inhibitor, in the treatment of depression. *Acta Psychiatrica Scandinavica* 1996;**94**(6):404-10.

Dworkin 2008

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;**9**(2):105-21.

Goldenberg 2007

Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. *Best Practice and Research. Clinical Rheumatology* 2007;**21**(3):499-511.

Gracely 2002

Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis and Rheumatism* 2002;**46**(5):1333-43.

Guidroz 2009

Guidroz C, Isaac J, King B, Laird K. University of Texas, School of Nursing, Family Nurse Practitioner Program. Management of fibromyalgia syndrome in adults. Austin (TX): University of Texas, 2009.

Hawley 1988

Hawley DJ, Wolfe F, Cathey MA. Pain, functional disability, and psychological status: a 12-month study of severity in fibromyalgia. *Journal of Rheumatology* 1988;**15**:1551-6.

Hawley 1991

Hawley DJ, Wolfe F. Pain, disability, and pain/disability relationships in seven rheumatic disorders: a study of 1,522 patients. *Journal of Rheumatology* 1991;**18**:1552-7.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Holford 1994

Holford NH, Guentert TW, Dingemanse J, Banken L. Monoamine oxidase-A: pharmacodynamics in humans of moclobemide, a reversible and selective inhibitor. *British Journal of Clinical Pharmacology* 1994;**37**(5):433-9.

Häuser 2009

Häuser W, Bernardy K, Uçeyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA* 2009;**301**(2):198-209.

Häuser 2012

Häuser W, Urrútia G, Tort S, Üçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRI) for fibromyalgia syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue In press.

Lawrence 1998

Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis and Rheumatism* 1998;**41**(5):778-99.

Lund 1986

Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. *Scandinavian Journal of Rheumatology* 1986;**15**:165-73.

Mease 2005

Mease PJ. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *Journal of Rheumatology* 2005;**75**:6-21.

Miller 2002

Miller LJ, Kubes KL. Serotonergic agents in the treatment of fibromyalgia. *Annals of Pharmacotherapy* 2002;**36**(4):707-12.

Moher 2010

Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869.

Moldofsky 1989

Moldofky H. Sleep-wake mechanism in fibrositis. *Journal of Rheumatology* 1989;**16**(Suppl):47-8.

Newburn 1999

Newburn G, Edwards R, Thomas H, Collier J, Fox K, Collins C. Moclobemide in the treatment of major depressive disorder (DSM-3) following traumatic brain injury. *Brain Injury* 1999;**13**(8):637-42.

Nishishinya 2006

Nishishinya MB, Walitt B, Urrútia G, Mease PJ, Rodríguez A, Riera Lizardo RJ, et al. Anti-depressants and centrally active agents for fibromyalgia syndrome. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD006192]

Nishishinya 2012

Nishishinya MB, Walitt B, Urrútia G, Darko G, Rodríguez A, Tort S, et al. Tricyclic antidepressants agents for fibromyalgia syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue In press.

O'Malley 2000

O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. *Journal of General Internal Medicine* 2000;**15**(9):659-66.

OMERACT 7

Mease PJ, Clauw DJ, Arnold LM, Goldenberg DL, Witter J, Williams DA, et al. Fibromyalgia syndrome. *Journal of Rheumatology* 2005;**32**(11):2270-7.

Papakostas 2006

Papakostas GI, Fava M. A metaanalysis of clinical trials comparing moclobemide with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. *Canadian Journal of Psychiatry* 2006;**51**(12):783-90.

Priest 1994

Priest RG, Schmid-Burgk W. Moclobemide in the treatment of depression. *Reviews in Contemporary Pharmacotherapy* 1994;**5**:35-43.

RevMan 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Rossy 1999

Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, et al. A meta-analysis of fibromyalgia treatment interventions. *Annals of Behavioral Medicine* 1999;**21**(2):180-91.

Smith 1998

Smith WA. Fibromyalgia syndrome. *Nursing Clinics of North America* 1998;**33**(4):653-69.

Smythe 1981

Smythe HA. Fibrositis and other diffuse musculoskeletal syndromes. In: Kelley WN, Harris Jr ED, Ruddy S, Sledge CB editor(s). Textbook of Rheumatology. Philadelphia: WB Saunders, 1981:485-93.

Stabl 1989

Stabl M, Biziére K, Schmid-Burgk W, Amrein R. Review of comparative clinical trials. Moclobemide vs tricyclic antidepressants and vs placebo in depressive states. *Journal of Neural Transmission. Supplementum* 1989;**28**:77-89.

Steinmeyer 1993

Steinmeyer EM, Vorbach EU, Arnoldt KH. Efficacy and safety of moclobemide compared with maprotiline in treatment of major depressive disorder. A double-blind multicenter study with parallel groups. *Pharmacopsychiatry* 1993;**26**(6):246-53.

Tanghe 1997

Tanghe A, Geerts S, Van Dorpe J, Brichard B, Bruhwyler J, Géczy J. Double-blind randomized controlled study of the efficacy and tolerability of two reversible monoamine oxidase A inhibitors, pirlindole and moclobemide, in the treatment of depression. *Acta Psychiatrica Scandinavica* 1997;**96**(2):134-41.

Vaeroy 1988

Vaeroy H, Helle R, Forre Ø, Kåss E, Terenius L. Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. *Pain* 1988;**32**(1):21-6.

Versiani 1989

Versiani M, Oggero U, Alterwain P, Capponi R, Dajas F, Heinze-Martin G, et al. A double-blind comparative trial of moclobemide versus imipramine and placebo in major depressive episodes. *British Journal of Psychiatry. Supplement* 1989;**6**:72-7.

Versiani 1990

Versiani M, Nardi AE, Figueira IL, Stabl M. Tolerability of moclobemide, a new reversible inhibitor of monoamine oxidase-A, compared with other antidepressants and placebo. *Acta Psychiatrica Scandinavica. Supplementum* 1990;**360**:24-8.

Walitt 2012

Walitt B, Urrútia G, Tort S, Nishishinya MB, Riera Lizardo RJ. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue In press.

Wolfe 1990

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria, for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism* 1990;**33**(12):1863-4.

Wolfe 1997

Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis and Rheumatism* 1997;**40**(9):1553-5.

Wolfe 2010

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis and Rheumatism* 2010;**62**(5):600-10.

Yunus 1981

Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. *Seminars in Arthritis and Rheumatism* 1981;**11**(1):151-71.

Yunus 1982

Yunus M, Masi AT, Calabro JJ, Shah IK. Primary fibromyalgia. *American Family Physician* 1982;**25**(5):115-21.

Yunus 1984

Yunus MB. Primary fibromyalgia syndrome: current concepts. *Comprehensive Therapy* 1984;**10**(8):21-8.

Üçeyler 2008

Üçeyler N, Häuser W, Sommer C. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. *Arthritis and Rheumatism* 2008;**59**(9):1279-98.

CHARACTERISTICS OF STUDIES

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

Ginsberg 1998

Methods	Randomised controlled trial Parallel Duration: 4 weeks

Ginsberg 1998 *(Continued)*

	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%)

Ginsberg 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High attrition rate. ITT only for adverse events, analysis of efficacy data conducted per protocol
Selective reporting (reporting bias)	Unclear risk	Study protocol not available

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

Hannonen 1998 *(Continued)*

	*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 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate: the randomisation was organised centrally with sequentially numbered envelopes consisting of blocks of 6
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind. The placebo capsules were identical to the active drugs
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data described although high attrition rate. ITT

Hannonen 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study protocol not available

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]*

Study	Reason for exclusion
Cerrahoglu 1995	Not a double-blind study
Sofu 1996	Probably a case series. It was not possible to obtain full manuscript. (Turkish journal currently not available)
Yavuzer 1998	Single-blind study

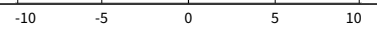
DATA AND ANALYSES

Comparison 1. MAOIs vs placebo (efficacy)

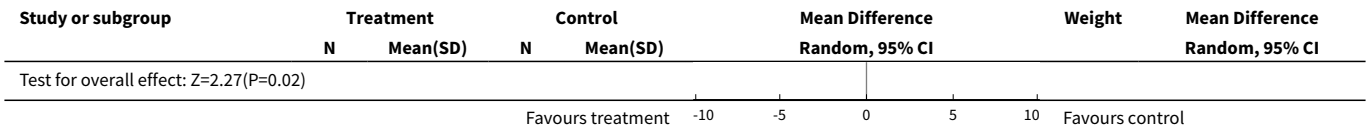
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (VAS)	2	121	Mean Difference (IV, Random, 95% CI)	-1.45 [-2.71, -0.20]
2 Tender points	2	121	Std. Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.72, -0.00]
3 Global assessment (by patient)	2	121	Mean Difference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

Analysis 1.1. Comparison 1 MAOIs vs placebo (efficacy), Outcome 1 Pain (VAS).

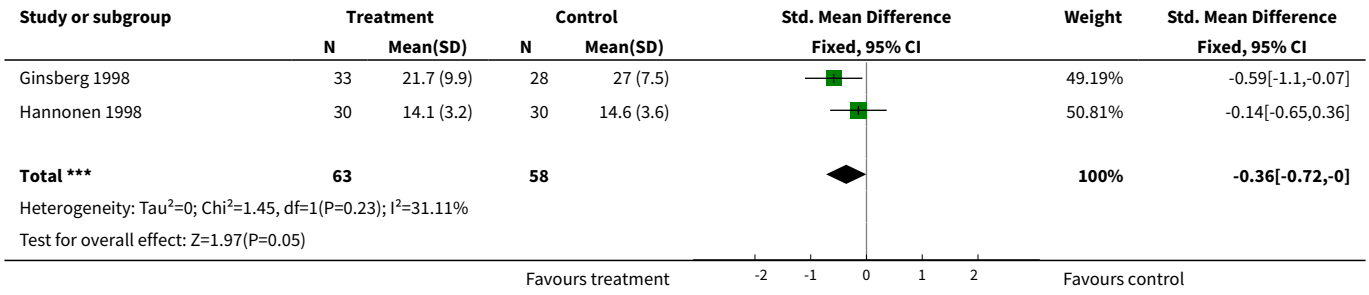
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ginsberg 1998	33	4.8 (2.1)	28	6.8 (1.5)		58.05%	-2[-2.91,-1.09]
Hannonen 1998	30	4.5 (2.7)	30	5.2 (2.7)		41.95%	-0.7[-2.07,0.67]
Total ***	**63**		**58**			**100%**	**-1.45[-2.71,-0.2]**
Heterogeneity: Tau^2=0.5; Chi^2=2.41, df=1(P=0.12); I^2=58.58%							



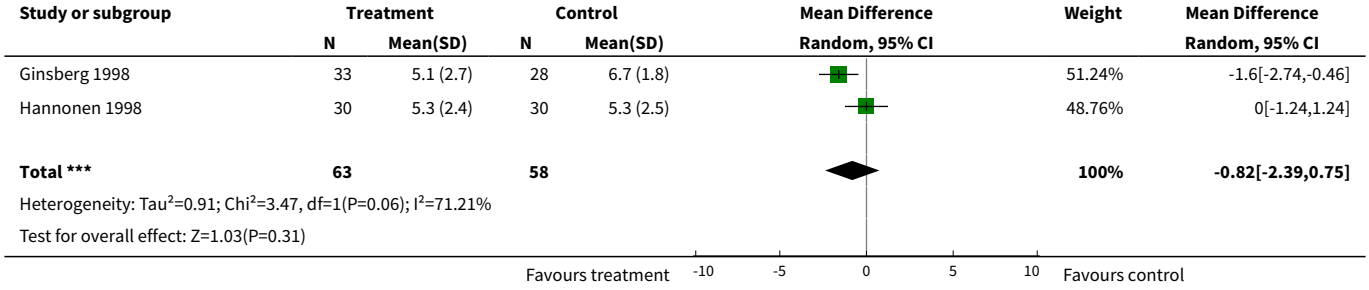
Favours treatment Favours control



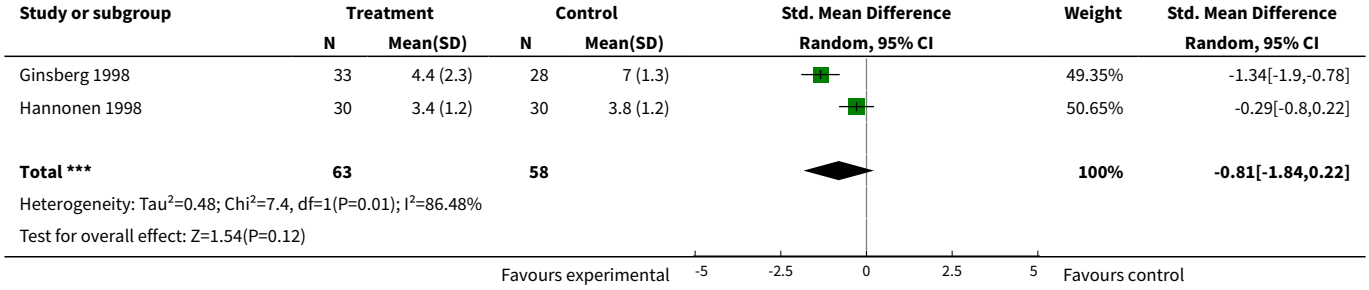
Analysis 1.2. Comparison 1 MAOIs vs placebo (efficacy), Outcome 2 Tender points.



Analysis 1.3. Comparison 1 MAOIs vs placebo (efficacy), Outcome 3 Global assessment (by patient).

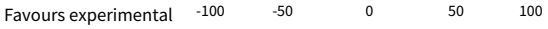


Analysis 1.4. Comparison 1 MAOIs vs placebo (efficacy), Outcome 4 Global assessment (by physician).



Analysis 1.5. Comparison 1 MAOIs vs placebo (efficacy), Outcome 5 Psychological evaluation (SCL-90-R;NHP).

Study or subgroup	Treatment		Control		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Ginsberg 1998	33	153 (51)	28	156 (51)		0%	-0.06[-0.56,0.45]
Hannonen 1998	30	15.4 (21.1)	30	13.2 (20.2)		0%	0.11[-0.4,0.61]

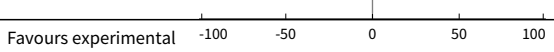


Comparison 2. Moclobemide vs amitriptyline (efficacy)

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

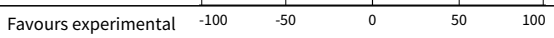
Analysis 2.1. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 1 Pain (VAS).

Study or subgroup	Moclobemide		Amitriptyline		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Hannonen 1998	30	4.5 (2.7)	32	4.5 (2.8)		100%	0[-1.37,1.37]
Total ***	**30**		**32**			**100%**	**0[-1.37,1.37]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

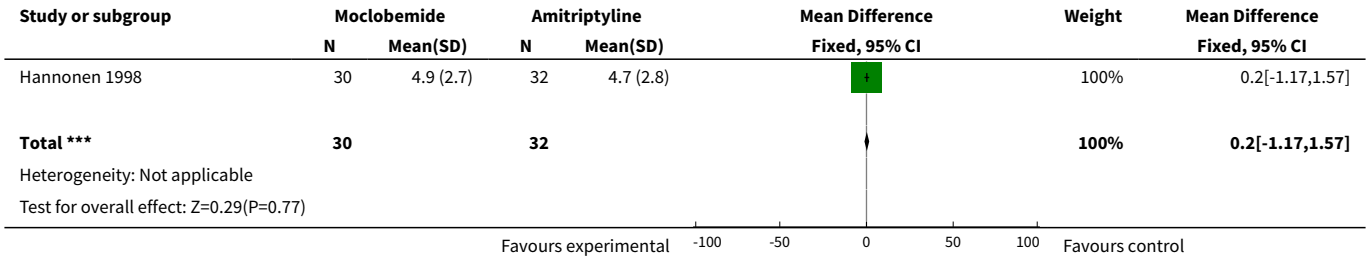


Analysis 2.2. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 2 Tender points.

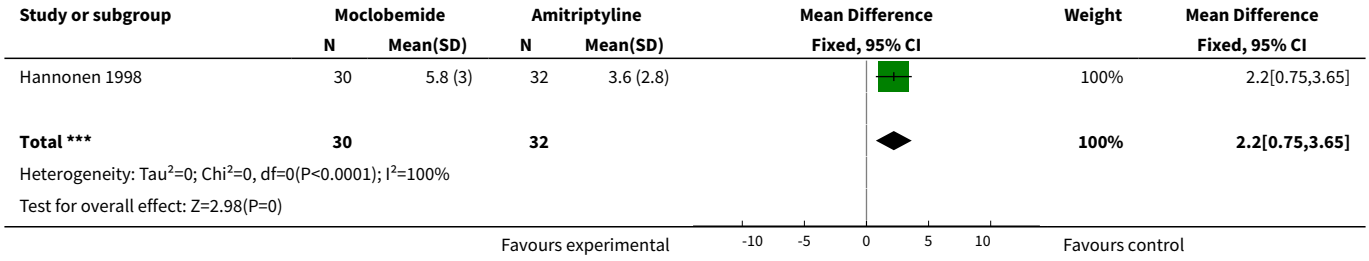
Study or subgroup	Moclobemide		Amitriptyline		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Hannonen 1998	30	14.1 (3.2)	32	13.9 (4.2)		100%	0.2[-1.65,2.05]
Total ***	**30**		**32**			**100%**	**0.2[-1.65,2.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.21(P=0.83)							



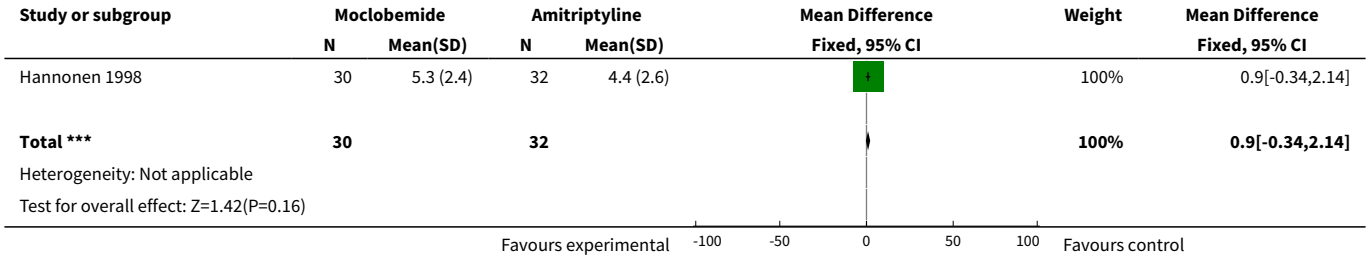
Analysis 2.3. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 3 Fatigue (VAS).



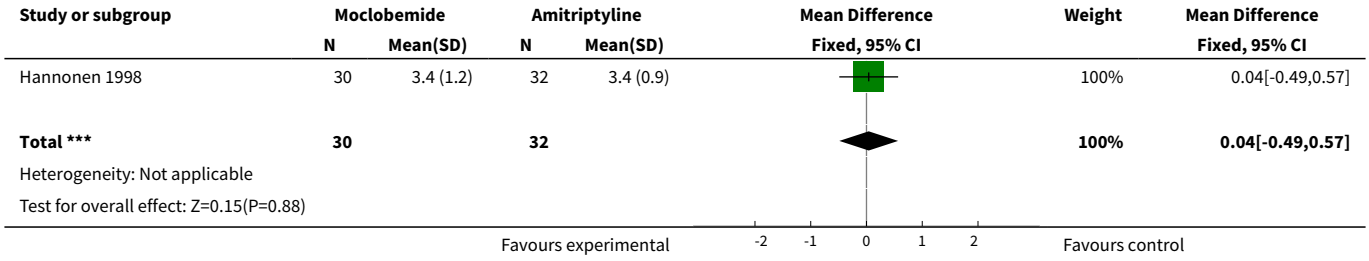
Analysis 2.4. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 4 Sleep (VAS).



Analysis 2.5. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 5 Global assessment (by patient).



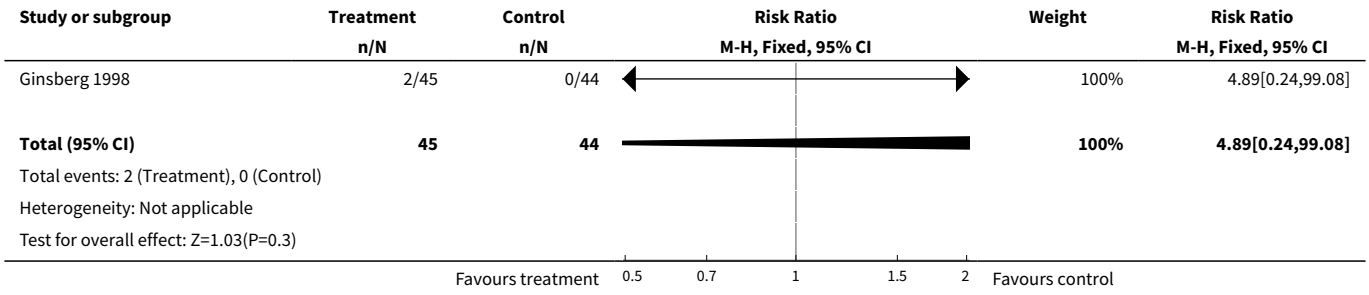
Analysis 2.6. Comparison 2 Moclobemide vs amitriptyline (efficacy), Outcome 6 Global assessment (by physician).



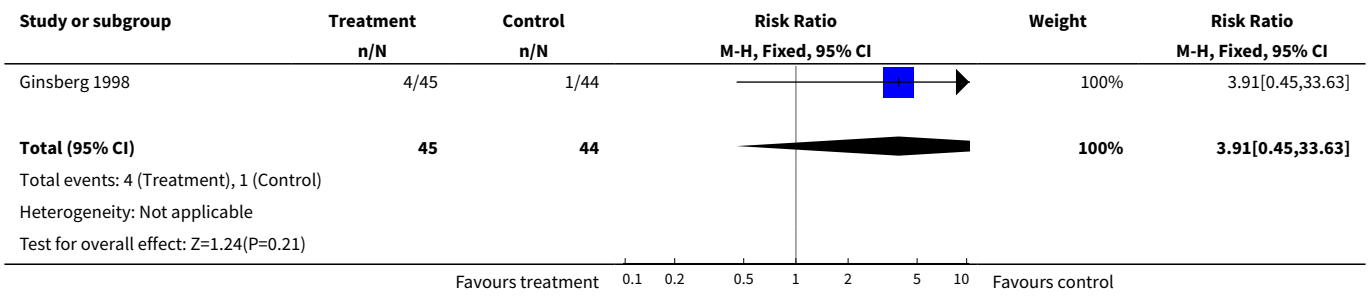
Comparison 3. MAOIs vs placebo (safety)

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

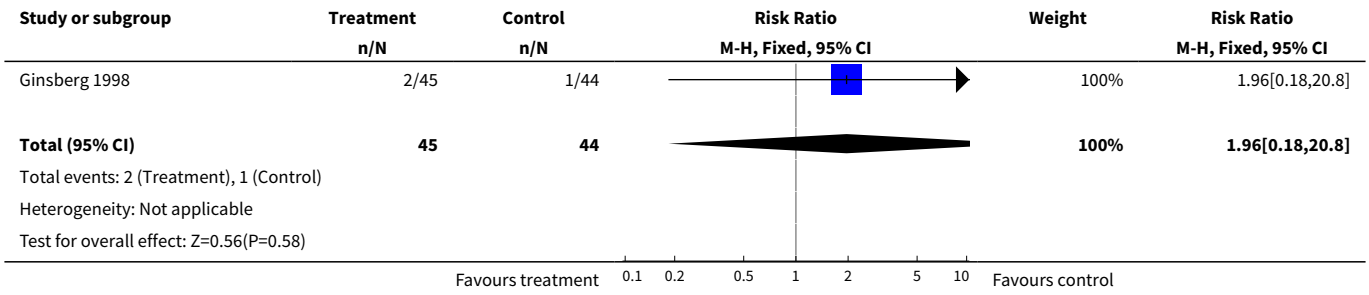
Analysis 3.1. Comparison 3 MAOIs vs placebo (safety), Outcome 1 Depression.



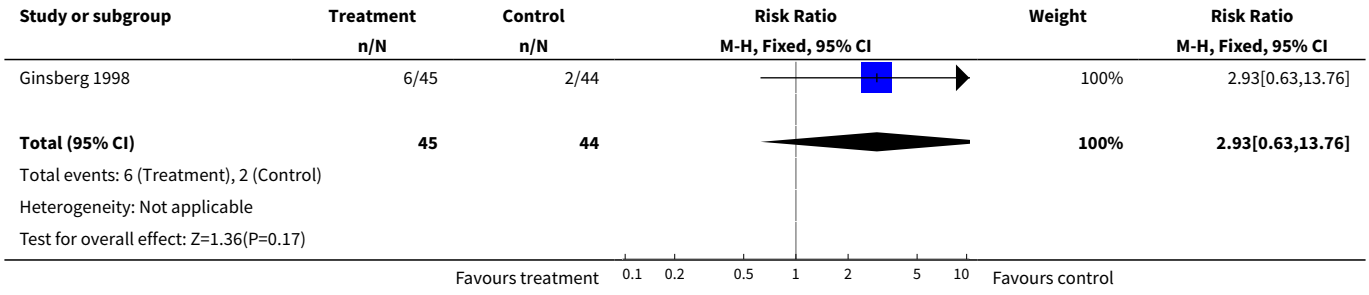
Analysis 3.2. Comparison 3 MAOIs vs placebo (safety), Outcome 2 Dizziness.



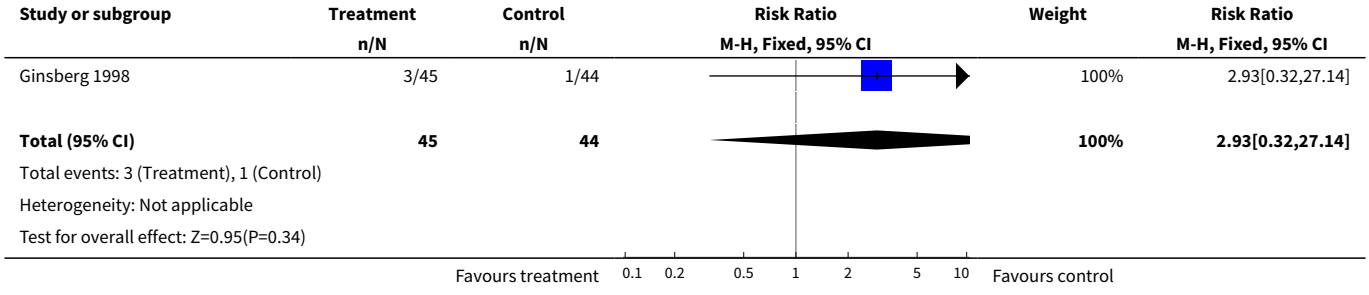
Analysis 3.3. Comparison 3 MAOIs vs placebo (safety), Outcome 3 Gastric discomfort.



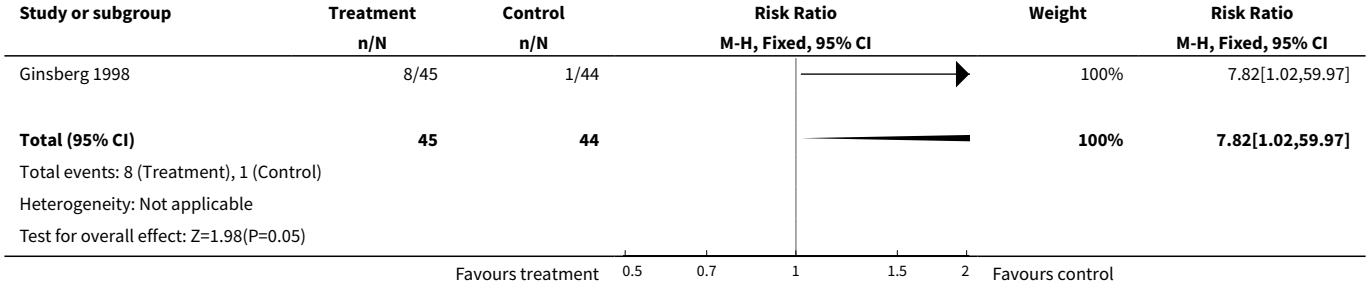
Analysis 3.4. Comparison 3 MAOIs vs placebo (safety), Outcome 4 Headache.



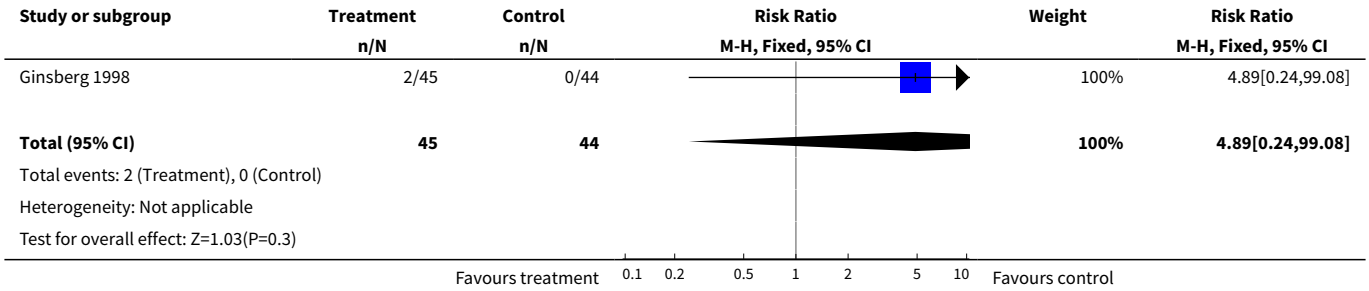
Analysis 3.5. Comparison 3 MAOIs vs placebo (safety), Outcome 5 Insomnia.



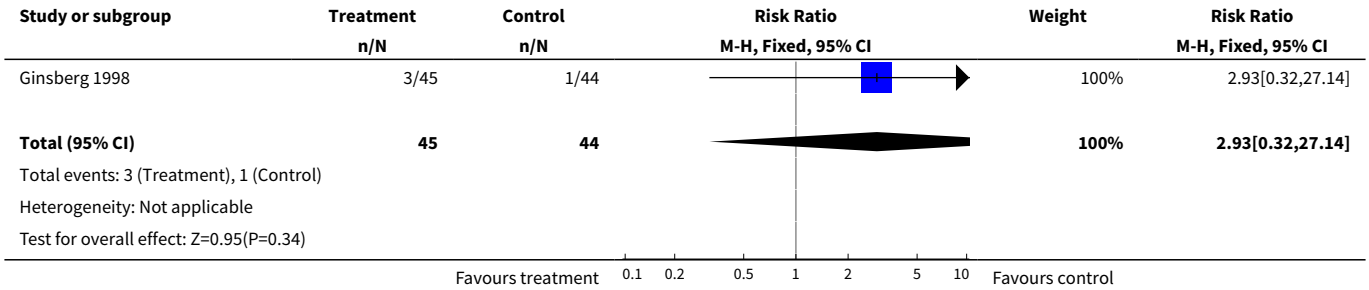
Analysis 3.6. Comparison 3 MAOIs vs placebo (safety), Outcome 6 Nausea and vomiting.



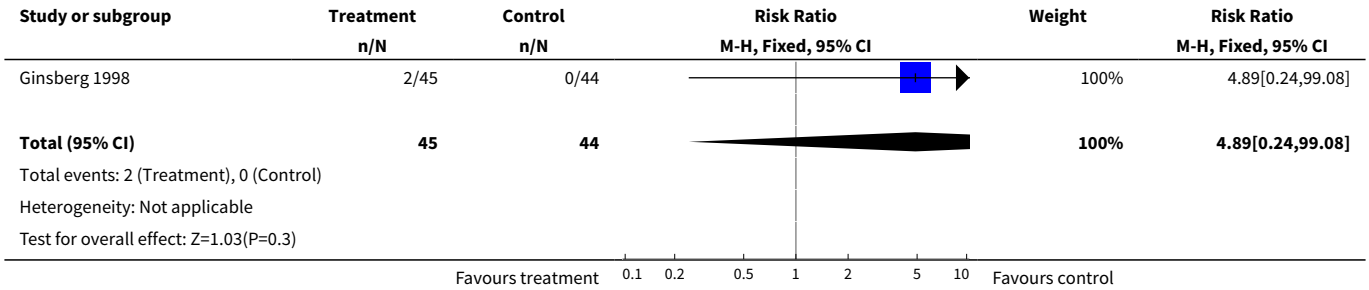
Analysis 3.7. Comparison 3 MAOIs vs placebo (safety), Outcome 7 Pain increase.



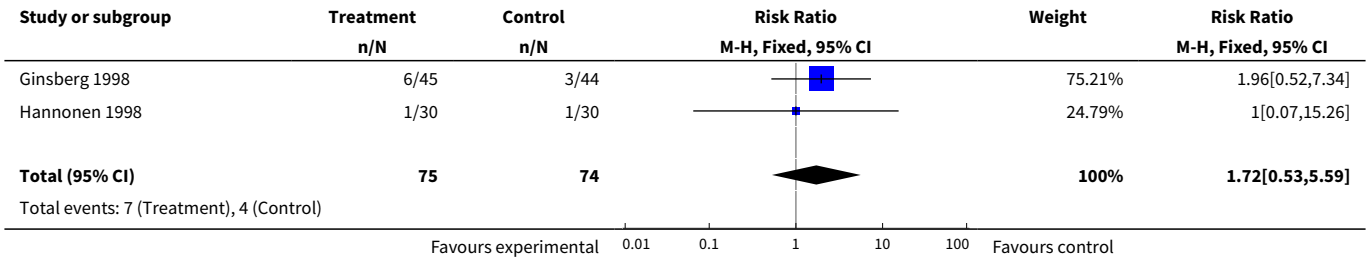
Analysis 3.8. Comparison 3 MAOIs vs placebo (safety), Outcome 8 Palpitations.

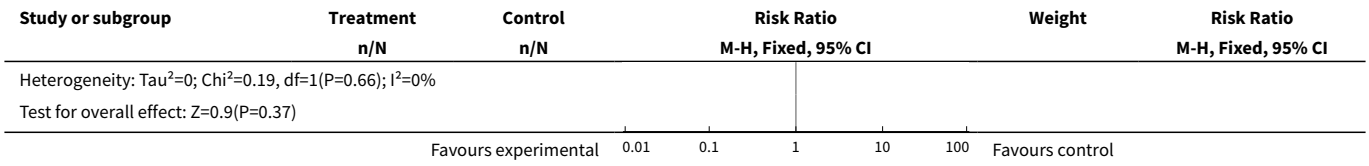


Analysis 3.9. Comparison 3 MAOIs vs placebo (safety), Outcome 9 Sleepy during the day.



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





APPENDICES

Appendix 1. Search strategies and hits retrieved

Randomised controlled trials in fibromyalgia (update November 2010)

DATABASE (ACCESS) and date of search	Search strategy and hits retrieved
MEDLINE (PubMed) 4 November 2010	#1 "Fibromyalgia"[Mesh] OR fibromyalgi*[ti] OR fibrositis[ti] **5248** #2 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])) 2309479 #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 #3 774 #5 (#1 OR #2 OR #3), from 2009 to 2010 **137 (69 in clinical trials)**
EMBASE (Ovid) 4 November 2010	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)

DATABASE (ACCESS) and date of search	Search strategy and hits retrieved
MEDLINE	#1 "Fibromyalgia"[Mesh] OR fibromyalgi*[ti] OR fibrositis[ti] **4433**
(PubMed)	#2 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND humans [mh] 1912816
9 February 2009	#3 #1 AND #2 **1316**
CENTRAL	#1 MeSH descriptor Fibromyalgia explode all trees 315
(*The Cochrane Library*)	#2 fibromyalgi* 512
2009, Issue 1	#3 fibrositis 36
	#4 #1 OR #2 OR #3 **526**
EMBASE	1 exp Fibromyalgia/ 5537
(Ovid)	2 fibromyalgia.ti,ab. 4304
9 February 2009	3 exp Fibromyalgia/ 354
	4 fibrositis.ti. 122
	5 1 or 2 or 3 or 4 **6046**
	6 random:.tw. or placebo:.mp. or double-blind:.mp. 514373
	7 5 and 6 **886**

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