# Magnesium and malic acid supplement for fibromyalgia

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## Abstract

### Introduction

Fibromyalgia is characterized by myalgia and a combination of different symptoms including pain, fatigue, insomnia, morning rigidity, depression and a reduction in every-day functioning. Its aetiology is not clear, but it has been suggested that deficiency in certain minerals such as magnesium may play a role both in the physiopathology and in contributing to the symptoms.

### Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

### Results and conclusions

We identified seven systematic reviews which included 11 primary studies of which one was a randomized trial. Our conclusion is that the use of magnesium and malic acid in patients with fibromyalgia makes little or no difference on pain and on depressive symptoms.

## Problem

Fibromyalgia is a nonarticular rheumatic syndrome characterized by myalgia and multiple points of focal muscle tenderness to palpation (trigger points). This condition is often associated with general symptoms, such as sleep disturbances, fatigue, stiffness, headaches, and depression. It has a relatively high global incidence (0.5 to 5%) and affects mainly women aged 20 to 50 years[1].

Although research into this syndrome is increasing, the aetiology is not clear, although the symptoms are thought to be due to nociceptive or neurogenic mechanisms. The peripheral pain is stimulated at a spinal level through a combination of central hyperexcitability and a lack of descending inhibitory control[2].

Magnesium is involved in the modulation of muscle contraction and the regulation of enzyme reactions related to energy metabolism, neurotransmission and cerebral activity. In addition as a trace element, it has a role in the synthesis of ATP and in regulating

muscle metabolism. it has been suggested that it may have a role in the physiopathology of fibromyalgia and may contribute to the reduction of symptoms.

Malic acid also has a role in the synthesis of ATP as it contributes to the stability of the mitochondrial membrane, to mitochondrial respiration and oxidative phosphorylation.

## Key messages

- The use of magnesium and malic acid in patients with fibromyalgia makes little or no difference on pain and on depressive symptoms.

## About the body of evidence for this question

| | |
|---|---|
| What is the evidence. See evidence matrix in Epistemonikos later | We found seven systematic reviews[4-10] which included 11 primary studies[3,11-21] of which only one was a randomized controlled trial[11].<br>The table and thesummary are based on the randomized trial[11], as the observational studies did not increase the certainty of the existing evidence nor added any additional relevant information. |
| What types of patients were included* | The trial[11] included 24 patients with a diagnosis of primary fibromyalgia according to the clinical guideline of 1990 of the American College of Rheumatology.<br>The average age of the participants was 49 years old.<br>87.5% of the participants were female.<br>No exclusion criteria were specified.<br>No other information about the participants, such as severity of their symptoms or plasmatic levels of magnesium or malic acid was available from the systematic reviews. |
| What types of interventions were included* | This crossover double blind trial[11] evaluated the use of Super Malic (200 mg malic acid + 50 mg magnesium), 3 tablets taken orally twice a day for 4 weeks, compared to placebo, 3 tablets taken orally twice a day for 4 weeks.<br>The participants were randomly assigned to either the medication and placebo for four weeks, followed by a two week washout period where they took no medication.<br>After the double blinded trial, the participants had another two-week wash-out period with no medication and then entered a six month open-label dose escalation trial. |
| What types of outcomes were measured | The trials evaluated multiple outcomes, which were grouped by the systematic reviews as follows:<br>• Pain on an visual analogue scale (VAS) of 10 points<br>• Index of trigger points (a measure of the trigger severity of 18 trigger points)<br>• The average trigger (average trigger in 18 trigger points measured with a pressure algometer) |

## Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

| | |
|---|---|
| | • Physical health measured by the Health Assessment Questionnaire<br>• Depression measured using the Centre for Epidemiologic Studies-Depression Scale<br>• Psychological response to everyday events, using the Hassle Scale score.<br>• Adverse events were self-reported daily by the participants.<br><br>The outcomes were measured at weeks 0, 4, 6, 10 and 12. |

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

## Summary of Findings

The information about the effects of magnesium and malic acid is based on only one trial that included 24 participants[11].

This trial[11] reported pain (24 patients) and depression (24 patients). Functionality was not analyzed by any of the systematic reviews.

The summary of findings is as follows:

- The use of magnesium and malic acid in patients with fibromyalgia makes little or no difference on pain (high certainty evidence).
- The use of magnesium and malic acid in patients with fibromyalgia makes little or no difference on depression (high certainty evidence).

**Magnesium and malic acid for fibromyalgia**

**Patients** Fibromyalgia
**Intervention** Magnesium and malic acid supplement
**Comparison** Placebo

| Outcome | Absolute effect* | | Certainty of evidence (GRADE) |
|---|---|---|---|
| | WITHOUT magnesium and malic acid | WITH magnesium and malic acid | |
| Pain (VAS**) | 7 points | 6.8 points | ⨁⨁⨁◯[1,2] Moderate |
| | MD: 0.14 points less (Margin of error: 0.51 less to 0.23 more) | | |
| Depression (CES-D***) | 21 points | 18 points | ⨁⨁⨁⨁[1] High |
| | MD: 2.8 points less (Margin of error: 1.65 to 3.95 less) | | |
| Functionality | This outcome was not measured or reported. | | -- |

Margin of error: 95% confidence interval (CI).
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The effect WITHOUT magnesium and malic acid is based on the average risk in the control group of the trials. The effect WITH magnesium and malic acid (and its margin of error) is calculated from the mean difference (and its margin of error).
**Pain was measured on a VAS of 0-10 points, where less points means less pain.
***Depression was measured using the Center for Epidemiologic Studies-Depression (CES-D), a scale of 20 items each with 0-3 points and in which less points means fewer depressive symptoms.

[1] The certainty of the evidence was not downgraded for risk of bias because the absence of risk of bias would reinforce the conclusion of no effect.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

## About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

## Other considerations for decision-making

### To whom this evidence does and does not apply

This evidence can be applied to all patients with the diagnosis of primary fibromyalgia.

The limited evidence that is available does not allow us to identify a specific group of patients (for example those with severe fibromyalgia) that would benefit from this intervention.

This trial studied the effect of a combination of magnesium and malic acid. Any effect could not be attributed to just one of theses substances. As there appears to be no effect from the combination, we can infer that neither substance has an effect.

This evidence is not applicable to patients with chronic fatigue syndrome because although there may be substantial overlap between both syndromes, they seem to have different responses to pharmacological interventions.

### About the outcomes included in this summary

The outcomes included in the summary of findings table are those considered critical for decision-making, according to the opinion of the authors of this summary, and in general coincide with the systematic reviews identified.

In terms of adverse events, 13 of 24 patients reported adverse events in this trial[11] but none were attributed to magnesium or malic acid.

### Balance between benefits and risks, and certainty of the evidence

According to the evidence presented here, the use of magnesium and malic acid appears to have no benefit; so the balance of benefits and risks is not favourable.

It is important to mention that the low serum levels of magnesium and malic acid found in observational studies show only an association with fibromyalgia, not a cause-effect. The hypothesis that supplementing magnesium and malic acid to bring the serum levels to normal may have a clinical impact is not supported by the evidence that we present.

Side effects described in the trial were: dizziness, abdominal pain, diarrhea and postural hypotension.

### Resource considerations

Although the intervention is a vitamin/mineral supplement, it can have a considerable cost. This, together with the lack of effect makes the cost/benefit ratio not favourable.

### What would patients and their doctors think about this intervention

Given the evidence presented in this summary which shows no clinical benefit, most patients and doctors should decide against the use of a magnesium-malic acid supplement as treatment for fibromyalgia.

However, there is a positive attitude towards supplements in general and some patients and doctors may be inclined to use magnesium and malic acid supplements. In this case, it is important to inform them of the conclusions of this analysis of the evidence.

### Differences between this summary and other sources

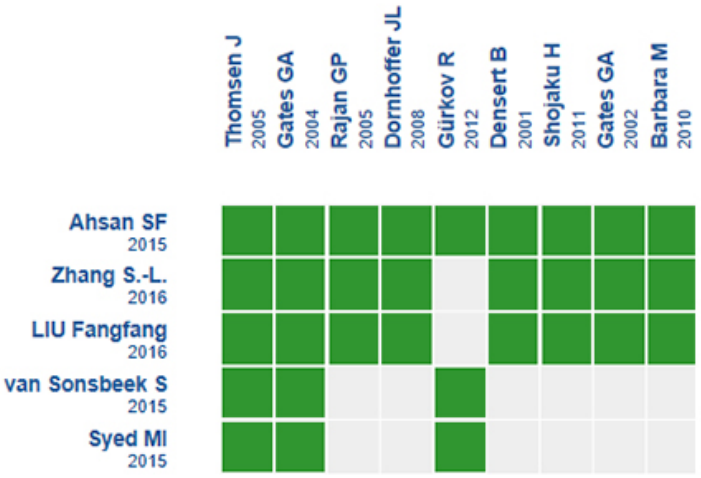
The conclusions in this summary are similar to those of most of the reviews that we analyzed.

The European League Against Rheumatism (EULAR) 2016 guidelines[21] do not include magnesium nor malic acid as therapeutic options for fibromyalgia.

### Could this evidence change in the future?

The probability that new evidence may modify the conclusions of this summary is low, given the certainty about the benefits.

We did not identify ongoing systematic reviews or trials (in the PROSPERO database or in the International Clinical Trials Registry Platform of the World Health organization respectively).




An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Magnesium and malic acid for fibromyalgia.

## Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

## Referencias


1. White KP, Harth M. Classification, epidemiology, and natural history of fibromyalgia. Curr Pain Headache Rep. 2001 Aug;5(4):320-9. | PubMed |
2. Lidbeck J. Central hyperexcitability in chronic musculoskeletal pain: A conceptual breakthrough with multiple clinical implications. Pain Research & Management. 2002;7(2):81–92.
3. Abraham GE, Flechas JD, Yunus MB, Raman KIUP, Raman KK, Wolfe, et al. Management of Fibromyalgia: Rationale for the Use of Magnesium and Malic Acid. Journal of Nutritional Medicine. 1992;3(1):49-59.
4. Joustra ML, Minovic I, Janssens KAM, Bakker SJL, Rosmalen JGM. Vitamin and mineral status in chronic fatigue syndrome and fibromyalgia syndrome: A systematic review and meta-analysis. PLoS One. 2017 Apr 28;12(4):e0176631. | CrossRef | PubMed | PMC |
5. Porter NS, Jason LA, Boulton A, Bothne N, Coleman B. Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. J Altern Complement Med. 2010 Mar;16(3):235-49. | CrossRef | PubMed |
6. Schneider M, Vernon H, Ko G, Lawson G, Perera J. Chiropractic management of fibromyalgia syndrome: a systematic review of the literature. J Manipulative Physiol Ther. 2009 Jan;32(1):25-40. | CrossRef | PubMed |
7. Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I. Combination pharmacotherapy for the treatment of fibromyalgia in adults. Cochrane Database Syst Rev. 2018 Feb 19;2:CD010585. | CrossRef | PubMed |
8. Langhorst J, Häuser W, Bernardy K, Lucius H, Settan M, Winkelmann A, Musial F; Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. [Complementary and alternative therapies for fibromyalgia syndrome. Systematic review, meta-analysis and guideline]. Schmerz. 2012 Jun;26(3):311-7. | CrossRef | PubMed |
9. ldcraft LC, Assefi N, Buchwald D. Complementary and alternative medicine in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol. 2003 Aug;17(4):667-83. | PubMed |
10. Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, Hewett JE, Johnson JC. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med. 1999 Spring;21(2):180-91. | PubMed |
11. Russell IJ, Michalek JE, Flechas JD, Abraham GE. Treatment of fibromyalgia syndrome with Super Malic: a randomized, double blind, placebo controlled, crossover pilot study. J Rheumatol. 1995 May;22(5):953-8. | PubMed |

12. Ng SY. Hair calcium and magnesium levels in patients with fibromyalgia: a case center study. J Manipulative Physiol Ther. 1999 Nov-Dec;22(9):586-93. | PubMed |
13. Kim, Young-Sang, Kim, Kwang-Min, Lee, Duck-Joo, et al. Women with Fibromyalgia Have Lower Levels of Calcium, Magnesium, Iron and Manganese in Hair Mineral Analysis. Journal of Korean Medical Science. 2011;26(10).
14. Sendur OF, Tastaban E, Turan Y, Ulman C. The relationship between serum trace element levels and clinical parameters in patients with fibromyalgia. Rheumatol Int. 2008 Sep;28(11):1117-21. | CrossRef | PubMed |
15. Bazzichi L, Giannaccini G, Betti L, Fabbrini L, Schmid L, Palego L, Giacomelli C, Rossi A, Giusti L, De Feo F, Giuliano T, Mascia G, Bombardieri S, Lucacchini A. ATP, calcium and magnesium levels in platelets of patients with primary fibromyalgia. Clin Biochem. 2008 Sep;41(13):1084-90. | CrossRef | PubMed |
16. Khalifa II, Hassan MF, AL-Deri SM, Gorial FI. Determination of Some Essential & Non-Essential Metals in Patients with Fibromyalgia Syndrome (FMS). IJPSR. 2016;8(5):306–311.
17. Eisinger J, Gandolfo C, Zakarian H, Ayavou T. Reactive oxygen species, antioxidant status and fibromyalgia. J Musculoskeletal Pain. 1997;5(4):5–15.
18. Eisinger J, Zakarian H, Pouly E, Plantamura A, Ayavou T. Protein peroxidation, magnesium deficiency and fibromyalgia. Magnes Res. 1996 Dec;9(4):313-6. | PubMed |
19. Sakarya ST, Akyol Y, Bedir A, Canturk F. The relationship between serum antioxidant vitamins, magnesium levels, and clinical parameters in patients with primary fibromyalgia syndrome. Clin Rheumatol. 2011 Aug;30(8):1039-43. | CrossRef | PubMed | PMC |
20. Rosborg I, Hyllén E, Lidbeck J, Nihlgård B, Gerhardsson L. Trace element pattern in patients with fibromyalgia. Sci Total Environ. 2007 Oct 15;385(1-3):20-7. | PubMed |
21. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017 Feb;76(2):318-328. | CrossRef |

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