



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Original article

The effect of Hepar Magnesium D10 on fibromyalgia syndrome: A pilot study

Erik W. Baars^{a,*}, Ernst L. Ellis^{b,1}^a *Louis Bolk Instituut, Department of Healthcare & Nutrition, Hoofdstraat 24, NL-3972 LA Driebergen, The Netherlands*^b *Therapeuticum Venkelveld, Venkelveld 64, NL-7006 TL Doetinchem, The Netherlands*

Received 18 September 2009; received in revised form 13 December 2009; accepted 14 December 2009

Abstract

Objectives: To evaluate the effect of the anthroposophic drug Hepar Magnesium D10 intravenously administered weekly on fibromyalgia symptoms.

Methods: Forty-two patients attending their general practitioner for FM complaints were included by 18 general practitioners. Patients were asked to complete the Fibromyalgia Impact Questionnaire (FIQ) at baseline, after five and ten weeks of treatment. Forty-one patients completed the FIQ at baseline and after five weeks. Thirty patients completed the FIQ at baseline and after ten weeks. Cohen's delta effect sizes were calculated for all FIQ items.

Results: After five weeks, nine out of ten FIQ items demonstrated a statistically significant improvement. Cohen's delta effect size was small in two items, medium in seven items and large in one item. In nine FIQ items the mean improvement was at least 20%. After ten weeks seven FIQ items demonstrated a statistically significant improvement. Cohen's delta effect size was zero in one item, small in two items, medium in six items, and large in one item. In four FIQ items the mean improvement was at least 20%. Total FIQ score improved by at least 20% in 41.5% and 50% of patients after, five and ten weeks, respectively.

Conclusion: There are clear indications that Hepar Magnesium D10 intravenously administered can have a positive effect on FM symptoms after five and ten weeks of treatment. There are indications that a large subgroup benefits from this treatment. A randomized controlled trial is indicated to study the effects of Hepar Magnesium on FM symptoms.

© 2009 Elsevier GmbH. All rights reserved.

Keywords: Fibromyalgia; Pilot study; Hepar Magnesium; Anthroposophic medicine**Introduction**

An estimated 1–2% of the adult population and an estimated 10–15% of new referrals seen in rheumatology clinics suffer from fibromyalgia syndrome (FM) [1]. FM patients experience a wide range of symptoms: chronic widespread musculoskeletal pain, stiffness, paresthesia, disturbed sleep, and easy fatigueability along with multiple painful tender points, which are widely and symmetrically distributed and a severe loss of quality of life

[2]. FM affects predominantly women in a ratio of 9:1 compared to men. Its pathogenesis is for a great part unclear. FM is associated with genetic factors, stress, suffering from illnesses, defects in neurotransmitters, and neuro-endocrinological disorders in the central nervous system [3,4].

Currently, treatment in general is not satisfying [1]. Some antidepressants and anti-epileptics are known to be helpful for FM symptoms for a short period (6–8 weeks). A review on the efficacy of antidepressant medications for FM showed that these medications are associated with short term (median treatment time: 8 weeks) improvements in pain, depression, fatigue, sleep disturbances, and health-related quality of life in patients [5]. Non-drug treatment research showed that combination therapy had only a temporary effect on FM symptoms and quality of life [6]. A review on multi-component treatment of FM (at least

* Corresponding author. Tel.: +31 343 523860; fax: +31 343 515611.

E-mail addresses: e.baars@louisbolk.nl (E.W. Baars), eellis@nlzorg.net (E.L. Ellis).¹ Tel.: +31 314 346278; fax: +31 314 366646.

one educational or other psychological therapy with at least one exercise therapy) showed that there is strong evidence that this treatment approach has beneficial short-term effects (median treatment time: 240.16h) on the most important FM symptoms [7]. Since treatment in general is not satisfying, there is a need for new and/or unconventional treatment options. Research shows that an estimated 90% of people with fibromyalgia use some form of complementary and alternative medicine (CAM). Only a few well designed clinical trials on CAM treatment have been executed, demonstrating some effective unconventional treatment modalities. More well designed clinical trials on CAM treatment are needed [8].

In anthroposophic healthcare, Hepar Magnesium D10 has been prescribed for decades. Hepar Magnesium consists of 0.60.16ng hepar (bovine liver) and 0.40.16ng magnesium hydroxide in 100.16ml physiological salt solution and is administered intravenously. Magnesium performs many functions in the human body. About 350 functions are described [9]. Some of these functions might be of particular interest in explaining the possible effect of magnesium treatment on fibromyalgia symptoms. First of all magnesium is known to play an important role in glycolysis. It enables, by forming a complex with some oxygen groups of the phosphoryl groups of cytosolic ATP, the activity of kinases, a group of enzymes that are responsible for transfer of the γ -phosphoryl-group from ATP to an intermediate and vice versa to ADP. One group of these kinases, on their part, play a main role in the control of glycolysis, glyconeogenesis, and glycogenolysis. The end-product of the mentioned metabolic processes, pyruvate, is one of the two main fuels for the mitochondrion, the main source of energy in human cells [10–12]. Furthermore kinases play a role in the distribution of synthesized ATP in the cytosol (i.e. creatinekinase). In fibromyalgia research several investigators found (1) that small changes in free intracellular magnesium concentrations within the normal physiological range may significantly modulate important cellular functions [13]; (2) significant alterations in serum magnesium concentration and intracellular magnesium concentration [9,14–20]; (3) glycolysis related disturbances such as lowered intracellular ATP and increased pyruvate levels [18]; and (4) that treatment with high doses magnesium has shown some beneficial results in fibromyalgia [21]. Furthermore a remarkable correlation is observed between the degree of mitochondrial dysfunction and the severity of illness in chronic fatigue syndrome, a syndrome considered to be related to fibromyalgia [22–25]. All these findings suggest a relationship between magnesium-related energetic dysfunction and fibromyalgia, although a consistent view on the role of magnesium and glycolysis/mitochondrial/ATP-distribution disturbances in the pathogenesis of fibromyalgia lacks.

Hepar Magnesium D10 is a D10 potency of hepar bovis (60%) and magnesium hydroxide (40%). It is a medicament that has its roots in anthroposophic medicine. The pharmaceutical production of Hepar Magnesium D10 and the use of hepar bovis or cow liver, is executed under strict safety and quality procedures.

In 1973, it was presented for the first time by the anthroposophic psychiatrist Treichler regarding its capability to cure depressive patients and especially those patients who are depres-

sive and have fatigue. The underlying anthroposophic treatment concept is to enhance the influence of the so-called “I” in the liver by enhancing the forces of light in the fluid medium of the liver. In anthroposophic medicine, it is conceptualized that the liver plays a role in the origin of vitalization of the body by means of stimulation of the etheric body. It is also conceptualized that this function of the liver can be influenced by certain substances which, for example, work in an alkaline way and are water soluble, whereas substances that show a relationship to light in their chemical behavior are supposed to be able to influence a kind of so-called light physiology within the body. For this reason, the substance magnesium hydroxide was chosen for this indication. Magnesium shows in its characteristics a strong relationship to light. For example, in the past it was used as a flashlight in photography. In plants, it works in the center of the chlorophyll molecule and enables photosynthesis to occur. It helps with capturing light and transforming this with the help of water and carbon dioxide in sucrose, a glucose-fructose disaccharide. The hydroxide form of magnesia is a strong basic substance. Treatment with magnesium hydroxide in combination with cow liver enables the light-working to focus on the liver and the etheric body, which will theoretically result in an increase of vitality. Finally, it is conceptualized that the potentiation process of the substances results in a transformation of the quality of the (substances of the) medicine. The potentiation process promotes the possibility of the medicament to stimulate the etheric body more than to generate biochemical reactions.

In recent years hundreds of patients with FM-related fatigue, chronic fatigue syndrome, and the ‘subsyndromal seasonal affective disorder’ have been treated with Hepar Magnesium D10 in clinical practice. According to the subjective judgment of both prescribing general practitioners and treated patients there is a large group that subjectively experiences a clinical relevant improvement of their fatigue symptoms and other syndrome related symptoms due to the treatment. In a pilot study in which 23 patients with ‘subsyndromal seasonal affective disorder’ were treated with Hepar Magnesium D10 administered intravenously, clear indications for improvement of fatigue symptoms were found [26]. Based on these positive clinical and research experiences and results we decided to start a pilot study to examine the effects of Hepar Magnesium D10 on FM symptoms.

Materials and methods

Subjects

Patients were included from February to September 2008 from 18 Dutch anthroposophic general practitioner practices. Inclusion criteria were: (1) FM diagnosis established by a rheumatologist, (2) age: 21–65 years old, (3) willingness to complete FIQ questionnaires at baseline and after five and ten weeks of treatment, and (4) willingness to receive Hepar Magnesium treatment.

Exclusion criteria were other (psychiatric or somatic) diseases with accompanying musculoskeletal pain and/or fatigue, and additional therapies for FM during the study period.

Treatment consisted of a weekly dose of 100.16ml Hepar Magnesium D10 given intravenously for a period of ten weeks.

Questionnaires

Patients completed the Fibromyalgia Impact Questionnaire (FIQ, Dutch translation) at baseline, after five and ten weeks of treatment. The FIQ contains 10 items concerning FM symptoms, is a valid and reliable measuring instrument and has a good responsivity [5]. Patients described also if they had used other FM treatment at baseline, after five and ten weeks of treatment in order to assess compliance to additional therapies for FM.

Statistical analyses

FIQ data were entered in and subsequently analyzed with the statistical program SPSS 15.0. Mean scores were calculated for each individual FIQ item and its total score. After checking for normal distribution, paired sample *t*-tests were performed to analyze statistical significant differences between scores at baseline and after five and ten weeks of treatment. Cohen's delta effect sizes, after correction for within subject correlation, were calculated for differences between scores at baseline and after five and ten weeks. Cohen's delta effect size were categorized as: no effect (0–0.2), small (0.2–0.5), medium (0.5–0.8), and large (≥ 0.8). Finally, the percentages of change from baseline to five and ten weeks of treatment were calculated. Based on an estimated placebo effect of 10% [1] and the literature on clinical relevant treatment effect size of 10% [7], we also analyzed the percentages of patients that demonstrated a change of symptom severity of more than 20% when compared to baseline.

Since this study was an observational study without a control group, a number of factors apart from the experimental therapy might have contributed to the outcome, for example: natural recovery, adjunctive therapies, and regression to the mean. Hamre et al. [27] propose several methods for reliable suppression of individual bias factors without a control group. We therefore added three additional analyses in order to minimize the influence of attrition bias, bias from natural recovery and bias from adjunctive therapies. Attrition bias is a kind of selection bias caused by attrition (loss of participants), discounting trial subjects/tests that did not run to completion. It includes dropout, non-response (lower response rate), withdrawal and protocol deviators. It gives biased results where it is unequal in regard to exposure and/or outcome. To minimize the potential for attrition bias, missing values were replaced with the baseline value carried forward. To minimize the potential bias from natural recovery the sample was restricted to patients with disease duration of >12 months. In order to minimize bias from adjunctive therapies the sample was restricted to patients that did not change their FM related adjunctive therapies during the five and ten weeks of treatment. After each sample restriction, data were reanalyzed. Since there were not two or more baseline scores we were not able to minimize the potential for bias from regression to the mean.

Medical ethical committee

A member of a medical ethical committee was consulted before the onset of the study. Since the design was a routine outcome measurement in anthroposophic general practitioner's practices, Hepar Magnesium D10 treatment was no experimental treatment, but a treatment usual for these practices, and the including general practitioners were fully free to treat their patients according to their own insights, the study was regarded as a dossier study. Therefore no further medical ethical procedures, e.g. given of informed consent by patients, were necessary.

Results

Subjects

Fourty-two patients, 39 women and three men, with a mean age of 47 (range: 22–65) and a mean duration of the disease at baseline of 9.5 years (range: 1–40 years) were included. From this group, 41 patients completed the FIQ at both baseline measurement and after five weeks of treatment. 30 patients completed the FIQ both at baseline and after ten weeks of treatment. One patient dropped out because of worsening of symptoms, seven patients stopped for unknown reasons and three patients could not complete the FIQ because they had received less than ten weeks of treatment at the time the research period ended.

FIQ scores

After five weeks of treatment nine FIQ items demonstrated a statistically significant improvement when compared to baseline measurement ranging from 0.9 to 1.8. One item ('work days missed') showed a small, but statistically significant worsening. Cohen's delta effect size was small for two items (item 'work days missed' demonstrated a negative effect), medium for seven items and large for one item. Nine items showed more than 20% improvement (range: 18.5–62%) (Table 1). The FIQ total score, based on the sum scores of eight items, demonstrated a statistically significant improvement of 9.6 when compared to baseline measurement. Cohen's delta effect size was 0.98 (large effect). The percentage of improvement was 23.5% (Table 1.).

After ten weeks of treatment seven FIQ items demonstrated a statistically significant improvement when compared to baseline measurement ranging from 0.4 to 1.8. One item ('work days missed') showed a small, but statistically significant worsening. Cohen's delta effect size demonstrated no effect for one item, was small for two items (with item 'work days missed' a worsening), medium for six items and large for one item. Four items showed more than 20% improvement (range: 11.1–77.8%) (Table 2). The FIQ total score, based on the sum scores of eight items, demonstrated a statistically significant improvement of 7.7 when compared to baseline measurement. Cohen's delta effect size was 0.68 (medium effect). The percentage of improvement was 19.2% (Table 2.).

Finally, we analyzed the percentages of patients with (a) a worsening of the total FIQ score of more than 20%; (b) a wors-

Table 1
FIQ results at baseline and after five weeks of treatment.

N=41	Baseline mean (SD)	Five weeks treatment mean (SD)	Change mean	Percentage of change	Cohen's delta effect size (categories of effect sizes)
Physical functioning (0–10)	5.1 (1.5)	4.2 (2.1)	−0.9**	−17.6%	0.59 (medium)
Days felt good (0–7)	1.8 (1.6)	3.0 (1.9)	1.2**	62.8%	0.52 (medium)
Work days missed (0–7) ^a	1.4 (1.8)	1.8 (2.3)	0.4**	29.1%	−0.21 (small)
Job ability (0–10)	6.3 (1.7)	5.0 (2.2)	−1.3***	−20.4%	0.64 (medium)
Pain (0–10)	6.0 (1.5)	4.8 (2.1)	−1.2***	−20.7%	0.56 (medium)
Fatigue (0–10)	6.6 (1.3)	5.2 (2.0)	−1.4***	−21.1%	0.72 (medium)
Morning tiredness (0–10)	7.3 (1.7)	5.5 (2.4)	−1.8***	−24.0%	0.82 (large)
Stiffness (0–10)	6.5 (1.9)	4.9 (2.0)	−1.6***	−23.8%	0.78 (medium)
Anxiety (0–10)	4.1 (2.7)	3.1 (2.3)	−1.0*	−24.1%	0.42 (small)
Depression (0–10)	3.6 (3.1)	2.3 (2.5)	−1.3***	−35.7%	0.57 (medium)
Total score (0–80) ^b	40.9 (7.6)	31.3 (11.0)	−9.6***	−23.5%	0.98 (large)

Higher scores indicate worse condition, except for item 'days felt good'.

* $p \leq 0.05$.

** $p \leq 0.01$.

*** $p \leq 0.001$.

^a The results are based on 22 patients. The other patients had no work so the item did not apply to them.

^b Total scores are sum scores of all FIQ items without the items 'days felt good' and 'work days missed'.

ening of the total FIQ score ranging from 0 to 20%; (c) an improvement of the total FIQ score ranging from 0% to 20%; or (d) an improvement of the total FIQ score of more than 20% (Fig. 1). Both after five and ten weeks the category of patients that demonstrated more than 20% worsening was very small: 2.4% and 6.7%, respectively. On the contrary, both after five and ten weeks the category of patients that demonstrated more than 20% improvement was very large: 41.5% and 50%, respectively. An improvement of more than 30% was found in 34.1% after five weeks and 20% after ten weeks.

Bias suppression

Attrition bias

The reanalyzes of the total FIQ scores at baseline and after five weeks, in order to control possible attrition bias, demonstrate a very small worsening of the results (Table 3).

Table 2
FIQ results at baseline and after ten weeks of treatment.

N=30	Baseline mean (SD)	Five weeks treatment mean (SD)	Change mean	Percentage of change	Cohen's delta effect size (categories of effect sizes)
Physical function	4.9 (1.3)	4.0 (2.0)	−0.9***	−17.9%	0.55 (medium)
Days felt good	1.8 (1.7)	3.2 (1.9)	1.4***	77.8%	0.72 (medium)
Work days missed ^a	1.6 (2.0)	1.9 (2.4)	0.3**	19.0%	−0.15 (no effect)
Job ability	6.0 (1.6)	5.0 (2.4)	−1.0*	−16.6%	0.59 (medium)
Pain	6.0 (1.5)	5.0 (1.9)	−1.0**	−16.7%	0.69 (medium)
Fatigue	6.5 (1.5)	5.1 (2.0)	−1.4**	−21.4%	0.74 (medium)
Morning tiredness	7.3 (1.9)	5.5 (2.4)	−1.8**	−24.0%	1.03 (large)
Stiffness	6.3 (2.1)	5.1 (2.2)	−1.2**	−18.9%	0.53 (medium)
Anxiety	3.7 (2.5)	3.3 (2.0)	−0.4	−11.1%	0.23 (small)
Depression	3.8 (3.1)	2.9 (2.0)	−0.9	−22.0%	0.27 (small)
Total score ^b	40.1 (8.4)	32.4 (11.0)	−7.7**	−19.2%	0.68 (medium)

Higher scores indicate worse condition, except for item 'days felt good'.

* $p \leq 0.05$.

** $p \leq 0.01$.

*** $p \leq 0.001$.

^a The results are based on 16 patients.

^b Total scores are sum scores of all FIQ items without the items 'days felt good' and 'work days missed'.

The reanalyzes of the total FIQ scores at baseline and after ten weeks, in order to control for possible attrition bias, demonstrate a worsening of the results (Table 4). The change mean changed from −7.7 into −6.0, the percentage of change changed from −19.2% into −14.6% and Cohen's delta changed from 0.68 into 0.59. Although results are less favorable than those of the completers analysis, the effect size of 0.59, still indicates a medium effect.

Bias from natural recovery

For all 41 patients (difference between baseline and five weeks of treatment) respectively 30 patients (difference between baseline and ten weeks of treatment) it was clear that FM symptoms were present for more than 12 months. So there was no need to reanalyze the data to control for possible bias from natural recovery.

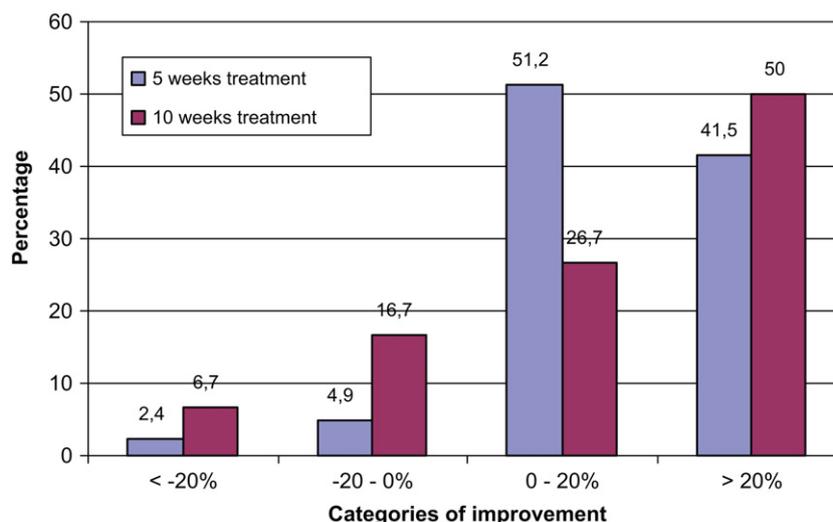


Fig. 1. Percentages of improvement after five and ten weeks of treatment.

Bias from adjunctive therapies

For all 41 patients (difference between baseline and five weeks of treatment) respectively 30 patients (difference between baseline and ten weeks of treatment) it was clear that no additional therapies were given during the research period. Both prescribing doctors and participating patients did not report additional therapies. So there was no need to reanalyze the data to control for possible bias from adjunctive therapies.

Discussion

In this observational pilot study we studied the effect of Hepar Magnesium D10 on FM symptoms by means of routine outcome measurements with the Fibromyalgia Impact Questionnaire (FIQ) at baseline, after five and ten weeks of treatment. After five weeks, nine out of ten FIQ items demonstrated a statistically significant improvement. Cohen's delta effect size was small in two items, medium in seven items and large in one item. In nine FIQ items the mean improvement was at least 20%. After

ten weeks seven FIQ items demonstrated a statistically significant improvement. Cohen's delta effect size was zero in one item, was small in two items, medium in six items and large in one item. In four FIQ items the mean improvement was at least 20%. Total FIQ score improved by at least 20% in 41.5% and 50% of patients after five and ten weeks, respectively.

Since all patients had their FM symptoms for more than 12 months and no additional therapies were given during the research period, respectively, bias from natural recovery and bias from additional therapies could be excluded as explanations for the observed effects. Reanalyzes after replacing the missing values of the dropped out patients with the baseline value carried forward, in order to control for possible attrition, demonstrated a 3% lower change mean after five weeks of treatment (one of 42 patients) and a 22% lower change mean after ten weeks of treatment (eight of 38 patients). However, after reanalyzing the data for both five and ten weeks of treatment, the Cohen's delta effect size categories remained the same, large and medium, respectively.

Table 3

Total FIQ scores at baseline and after five weeks of treatment before and after control for attrition bias.

	Baseline mean (SD)	Five weeks treatment mean (SD)	Change mean	Percentage of change	Cohen's delta effect size
Total score (0–80) ^a (N=41)	40.9 (7.6)	31.3 (11.0)	−9.6***	−23.5%	0.98 (large)
Total score (0–80) ^a (N=42) (control for attrition bias)	40.9 (7.5)	31.6 (11.0)	−9.3***	−22.7%	0.95 (large)

*** $p \leq 0.001$.

^a Total scores are sum scores of all FIQ items without the items 'days felt good' and 'work days missed'.

Table 4

Total FIQ scores at baseline and after ten weeks of treatment before and after control for attrition bias.

	Baseline mean (SD)	Ten weeks treatment mean (SD)	Change mean	Percentage of change	Cohen's delta effect size
Total score (0–80) ^a (N=30)	40.1 (8.4)	32.4 (11.0)	−7.7**	−19.2%	0.68 (medium)
Total score (0–80) ^a (N=38) (control for attrition bias)	41.1 (8.0)	35.1 (11.3)	−6.0***	−14.6%	0.59 (medium)

** $p \leq 0.01$, *** $p \leq 0.001$.

^a Total scores are sum scores of all FIQ items without the items 'days felt good' and 'work days missed'.

Limitations of this observational study are that there was no control for bias from regression to the mean and for a possible placebo effect of the intravenous route of administration. Although we estimated the placebo effect on the basis of the results of comparable clinical trials (1), higher percentages of placebo effects in the treatment of fibromyalgia have been measured. Therefore (some part of) the observed effects might be explained by these types of bias.

The results of this study confirm the general positive clinical experiences and the empirical outcome study results in the treatment of fatigue-related diseases or syndromes like fibromyalgia with Hepar Magnesium D10. Furthermore, the results are in line with the positive results of a study in which seasonal fatigue disorder patients were intravenously treated with Hepar Magnesium, demonstrating improvement of fatigue symptoms [26]. This is a very interesting finding, since as far as we know only antidepressants may be able to treat both conditions.

When compared to other outcome studies it is clear that Hepar Magnesium treatment demonstrates similar effect sizes when for example compared to the mean effect size of the efficacy of 120 treatment interventions on patients with fibromyalgia, which was a medium effect [28].

The results of a large subgroup that demonstrates an improvement of more than 20% and a smaller group (34% after five weeks and 20% after ten weeks) that demonstrates an improvement of more than 30% (up to 81%) of the total FIQ-score might be interesting for future research into the pathophysiology of FM. Since the pathogenesis of FM is for a great part unclear, fibromyalgia might not be one distinct disease but perhaps should be regarded as a syndrome with multiple pathogenetic origins and therefore different treatment effects per subgroup. Future studies could aim at distinguishing these subgroups and detecting relevant biomarkers for each subgroup.

Considering the present lack of understanding in pathogenesis of FM and the small scale of evidence based effective, short term and long term treatment methods, we consider it justified to execute further outcome research for short term and long term effects of Hepar Magnesium, an anthroposophic medicine that in clinical practice and in two pilot studies demonstrated promising results. A randomized, controlled trial can provide insights that are both clinically and scientifically relevant.

Conflict of interest

No conflict of interest declared.

Acknowledgements

First of all we would like to thank the participating patients and the general practitioners for their contribution to the study. Secondly we would like to thank Dr. T.R. Zijlstra, rheumatologist, for his advice during preparation and execution of the study and his constructive comments on this article. Thirdly we would like to thank Mrs. Leverington for patiently coaching the many doctors that participated in the study and Mrs. van den Bosch for her contribution to collecting the data. Finally we thank Weleda

Nederland and the Bernard Lievegoed Fonds for their financial grant that enabled us to perform the study.

References

- [1] Zijlstra TR. No pain, no gain. Measuring treatment effects in fibromyalgia. Universiteit Twente; 2007.
- [2] Fauci AS. In: Anthony S Fauci, et al., editors. *Harrison's principles of internal medicine*/editors. 17th ed New York: McGraw-Hill Medical; 2008.
- [3] Mease PJ, Clauw DJ, Arnold LM, Goldenberg DL, Witter J, Williams DA, et al. Fibromyalgia syndrome. *J Rheumatol* 2005;32(11):2270–7.
- [4] Gur A, Oktayoglu P. Central nervous system abnormalities in fibromyalgia and chronic fatigue syndrome: new concepts in treatment. *Curr Pharm Des* 2008;14(13):1274–94.
- [5] Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA* 2009;301(2):198–209.
- [6] Zijlstra TR, Braakman-Jansen LM, Taal E, Rasker JJ, van de Laar MA. Cost-effectiveness of spa treatment for fibromyalgia: general health improvement is not for free. *Rheumatology (Oxford)* 2007;46(9):1454–9.
- [7] Häuser W, Bernardy K, Arnold B, Offenbächer M, Schiltenswolf M. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. *Arthritis Rheum* 2009;29(61):216–24.
- [8] Holdcraft LC, Assefi N, Buchwald D. Complementary and alternative medicine in fibromyalgia and related syndromes. *Best Pract Res Clin Rheumatol* 2003;17(4):667–83.
- [9] Romani AM, Scarpa A. Regulation of cellular magnesium. *Front Biosci* 2000;5:D720–34.
- [10] Koeppen BM, Stanton BA, Berne RM. *Berne & Levy physiology*. 6th ed Philadelphia: Mosby Elsevier; 2008.
- [11] Stryer L. *Biochemistry*. W.H. Freeman & Company; 1995.
- [12] Lodish H, Berk A, Matsudaira P, Kaiser AC, Krieger M, Scott MP, et al. *Molecular cell biology*. New York: W.H. Freeman and Company; 2004.
- [13] Takaya J, Higashino H, Kobayashi Y. Can magnesium act as a second messenger? Current data on translocation induced by various biologically active substances. *Magnes Res* 2000;13(2):139–46.
- [14] Romani A. Regulation of magnesium homeostasis and transport in mammalian cells. *Arch Biochem Biophys* 2007;458(1):90–102.
- [15] Romani AM. Magnesium homeostasis in mammalian cells. *Front Biosci* 2007;12:308–31.
- [16] Trzeciakiewicz A, Opolski A, Mazur A. TRPM7: a protein responsible for magnesium homeostasis in a cell. *Postepy Hig Med Dosw (Online)* 2005;59:496–502.
- [17] Bazzichi L, Giannaccini G, Betti L, Fabbrini L, Schmid L, Palego L, et al. ATP, calcium and magnesium levels in platelets of patients with primary fibromyalgia. *Clin Biochem* 2008;41(13):1084–90.
- [18] Eisinger J, Plantamura A, Ayavou T. Glycolysis abnormalities in fibromyalgia. *J Am Coll Nutr* 1994;13(2):144–8.
- [19] Magaldi M, Moltoni L, Biasi G, Marcolongo R. Changes in intracellular calcium and magnesium ions in the pathophysiology of the fibromyalgia syndrome. *Minerva Med* 2000;91(7-8):137–40.
- [20] 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;28(11):1117–21.
- [21] 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;22(5):953–8.
- [22] Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999;354(9182):936–9.
- [23] Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. *Int J Clin Exp Med* 2009;2(1):1–16.
- [24] Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 2001;134(9 Pt 2):868–81.

- [25] Wolfe F, Rasker JJ. The symptom intensity scale, fibromyalgia, and the meaning of fibromyalgia-like symptoms. *J Rheumatol* 2006;33(11):2291–9.
- [26] Baars EW, Gans S, Ellis EL. The effect of hepar magnesium on seasonal fatigue symptoms: a pilot study. *J Altern Complement Med* 2008;14(4):395–402.
- [27] Hamre HJ, Glockmann A, Kienle GS, Kiene H. Combined bias suppression in single-arm therapy studies. *J Eval Clin Pract* 2008;14(5):923–9.
- [28] Garcia-Campayo J, Magdalena J, Magallon R, Fernandez-Garcia E, Salas M, Andres E. A meta-analysis of the efficacy of fibromyalgia treatment according to level of care. *Arthritis Res Ther* 2008;10(4):R81.