

## The Effect of Hepar Magnesium on Seasonal Fatigue Symptoms: A Pilot Study

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### ABSTRACT

**Objectives:** To evaluate the effect of the anthroposophic drug hepar magnesium D10 intravenously administered on seasonal fatigue symptoms.

**Design:** Time series with two measurements per week, starting before onset of treatment until three measurements after finishing treatment in a regular way.

**Settings:** Six anthroposophic general practitioner practices in the Netherlands.

**Subjects:** Twenty-three (23) patients with seasonal fatigue symptoms.

**Interventions:** Hepar magnesium D10 intravenously administered every week.

**Outcome measures:** Mean division of 24 hours in categories: sleep, rest, everyday activities, and activities that require a large effort; fatigue-related single questions: unusual emotional response to events, problems with short-term memory, the degree to which fatigue after effort continues for longer than 2 hours, the degree to which people at the end of the day have a complete lack of energy; and the degree to which people are still fit after the evening meal; Multidimensional Fatigue Index: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue; subjective experiences with regard to the effect of the treatment.

**Results:** (1) No changes in division in 24-hour categories were found; (2) pretreatment versus post-treatment analyses (after 1 and 2.5 weeks, at the end of treatment, and 1.5 weeks after the end of treatment) demonstrated overall large statistically significant differences. Eighteen (18) of 22 patients (82%) who completed the final questionnaire judged that treatment overall had been effective for their fatigue symptoms. Nine (9) patients (41%) judged a strong improvement and 9 patients (41%) a light improvement as a result of the treatment. Four (4) patients reported no change. On average, patients received treatment 4.5 times.

**Conclusions:** There are clear indications that hepar magnesium D10 intravenously administered can have a positive effect on subsyndromal seasonal affective disorder symptoms of fatigue. A more controlled trial is indicated to study the (long-term) effects of hepar magnesium.

### INTRODUCTION

In the beginning of the 1980s, seasonal affective disorder (SAD) was described for the first time in scientific literature.<sup>1</sup> SAD is a type of seasonal depression, usually occurring in the winter, which affects millions of people a year between September and April, with the peak occurring in the winter months of December, January, and February. True SAD is a seriously disabling illness, preventing people from

functioning normally. In addition, millions of others suffer from a milder version called “subsyndromal SAD” or “winter blues,” less disabling but still impairing and uncomfortable. There is a more rare form of summer SAD in which symptoms occur in the summer and remit in the winter.<sup>2</sup>

Symptoms of (subsyndromal) SAD keep coming back year after year, and they tend to come and go at about the same time every year. The changes in mood are not necessarily related to obvious things that would make a certain

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season stressful (such as regularly being unemployed during the winter). According to some, a diagnosis can be made after three or more consecutive winters of symptoms, which include a number of the following: sleep problems, lethargy, overeating, depression, social problems, anxiety, mood problems, and loss of libido. In subsyndromal SAD, symptoms such as tiredness, lethargy, and sleep and eating problems occur, but depression and anxiety are absent or mild.<sup>3</sup>

SAD and subsyndromal SAD may begin at any age, but the main age of onset is between 18 and 30 years. It occurs throughout the northern and southern hemispheres but is extremely rare in those living within 30 degrees of the equator, where daylight hours are long, constant, and extremely bright. It affects 1 in 100 adults in western countries. As many as half a million people in the United States may have winter depression. Another 10% to 20% may experience mild SAD. SAD is more common in women than in men (<http://sada.org.uk/symptoms.htm>).

SAD and subsyndromal SAD are associated with chronobiologic disorders and lack of sunlight.<sup>4</sup> Until now, the treatment of choice has been light therapy.<sup>5-7</sup>

### HEPAR MAGNESIUM TREATMENT

Hepar magnesium D10 is a D10 potency of hepar bovis (60%) and magnesium hydroxydatum (40%). It is a medication that has its roots in anthroposophic medicine. In 1973, it was presented for the first time by the anthroposophic psychiatrist Treichler regarding its capability to cure depressive

TABLE 1. DATES OF TREATMENT

Patient number	Treatment start	Treatment end
1	November 30, 2006	Feb. 13, 2007
2	December 6, 2006	Dec. 21, 2006
3	December 9, 2006	Jan. 9, 2007
4	December 13, 2006	Dec. 19, 2006
5	December 21, 2006	Feb. 6, 2007
6	December 26, 2006	Mar. 16, 2007
7	January 8, 2007	Feb. 13, 2007
8	January 19, 2007	Feb. 16, 2007
9	January 23, 2007	Mar. 31, 2007
10	January 23, 2007	Feb. 7, 2007
11	January 23, 2007	Feb. 20, 2007
12	January 24, 2007	Feb. 13, 2007
13	January 30, 2007	Mar. 20, 2007
14	February 2, 2007	Mar. 31, 2007
15	February 6, 2007	Mar. 20, 2007
16	February 10, 2007	Mar. 21, 2007
17	February 12, 2007	Mar. 20, 2007
18	February 14, 2007	Mar. 31, 2007
19	February 15, 2007	Mar. 31, 2007
20	February 25, 2007	Mar. 31, 2007
21	March 7, 2007	Mar. 31, 2007
22	March 7, 2007	Mar. 31, 2007
23	March 9, 2007	Mar. 31, 2007

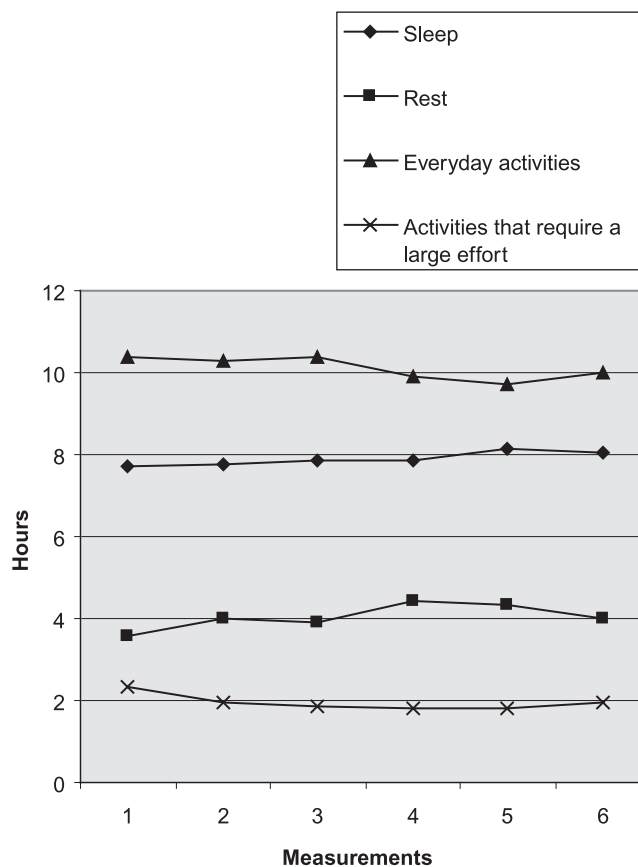


FIG. 1. Mean number of hours per 24 hours (N = 19).

patients and especially those patients who are depressive 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 depressions. It is also conceptualized that the 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 glucose. The hydroxide form of magnesia is a strong basic substance.

Treatment with magnesium hydroxatum in combination with cow liver enables the light-working to focus on the

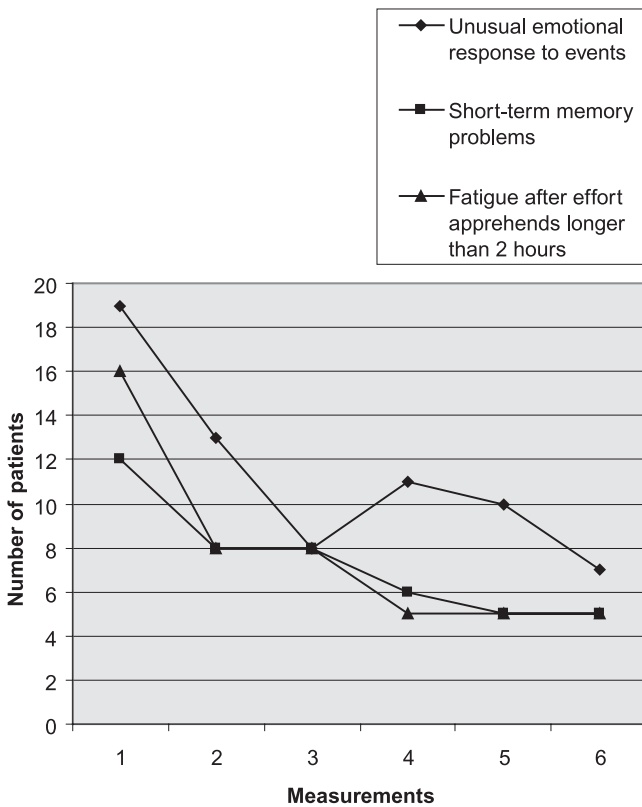
liver. In homeopathic medicine, it is especially recommended for nervous and hypersensible symptoms as well as for depressive symptoms. However, the hydroxide form is not mentioned in the classic reports of Kent and Boericke.<sup>8,9</sup>

In clinical practice, hepar magnesium did not fulfill expectations with regard to depression. However, a Dutch general practitioner discovered its effect on subsyndromal SAD. In the last 2 years, he treated hundreds of subsyndromal SAD patients with major symptoms of fatigue with 10 cm<sup>3</sup> hepar magnesium D10 intravenous injections, administered weekly. The experience of both doctor and patients was that fatigue symptoms in most cases disappeared or greatly improved. A very large group reacted positively within 3–5 weeks of therapy. In a subgroup, symptoms even disappeared the same day. However, a very small number of patients, especially young people, showed a light and transitory deterioration of symptoms. Based on the good clinical results, a pilot study was designed and executed in order to study the effect of hepar magnesium D10 on subsyndromal SAD fatigue symptoms.

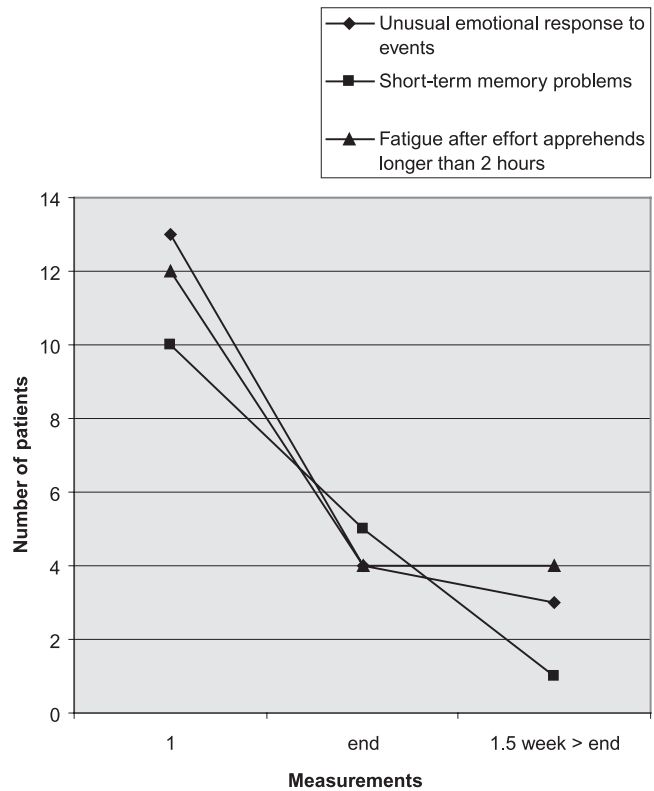
**MATERIALS AND METHODS**

*Participants*

From November 1, 2006, until March 31, 2007, patients from six anthroposophic general practitioner practices were

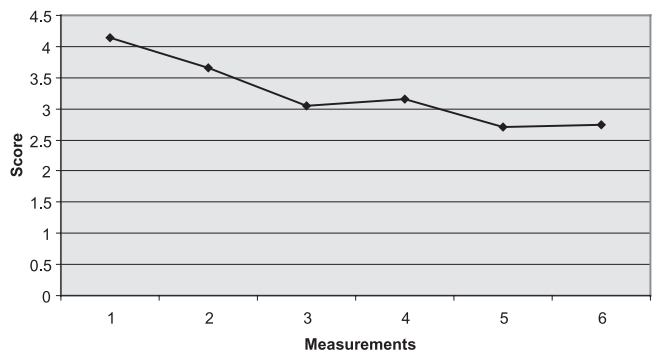


**FIG. 2.** Three fatigue-related questions (measurements 1–6). *N* = 19.



**FIG. 3.** Three fatigue-related questions (measurements start versus end/1,5 weeks after end of treatment). *N* = 15.

recruited who were willing and able to attend a pilot study in which the effect of hepar magnesium for the treatment of subsyndromal SAD symptoms of fatigue was studied. Patients were recruited if they met three diagnostic criteria: (1) the presence of unexplained fatigue symptoms that had started in the winter season; (2) fatigue symptoms were there for more than a month; and (3) fatigue symptoms come and go about the same time each year. By means of the anamnesis, other somatic and psychiatric diagnoses related to fatigue were eliminated at first. Furthermore, blood and urine tests were performed to exclude several somatic diseases as-



**FIG. 4.** At the end of the day a complete lack of energy (*N* = 19).

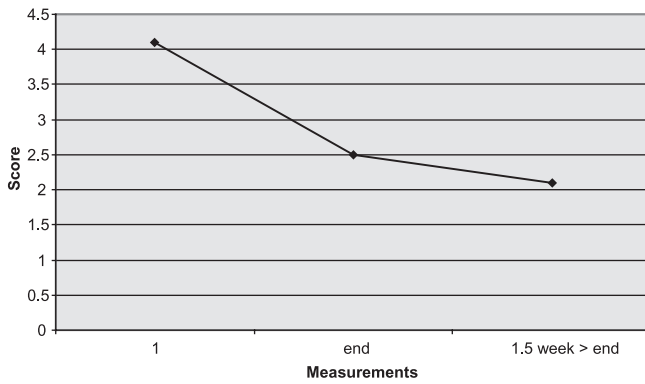


FIG. 5. At the end of the day a complete lack of energy (N = 15).

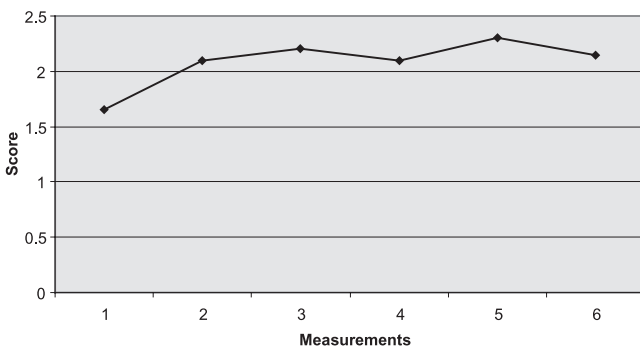


FIG. 6. Still fit after the evening meal (N = 19).

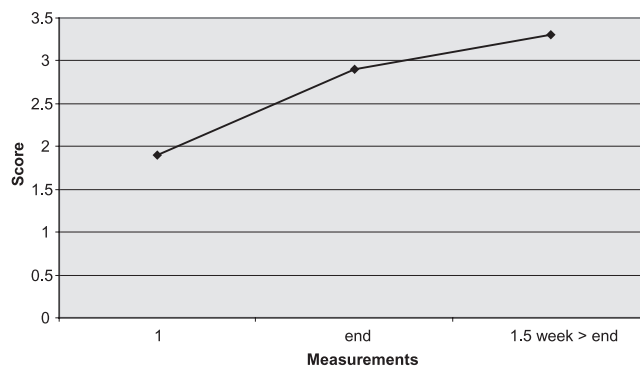


FIG. 7. Still fit after the evening meal (N = 15).

sociated with fatigue symptoms, such as, for example, infections, diabetes, thyroid dysfunctions, kidney and liver dysfunctions. Sixteen (16) patients reported mild depressive symptoms, but did not meet the criteria for a DSM-IV mood disorder. One patient suffered from endometriosis and was therefore excluded.

So ultimately 23 patients with subsyndromal SAD symptoms of fatigue could be monitored, of whom 15 stopped treatment regularly before the end date of the research (on March 31, 2007) and 8 were still treated after that time by their general practitioners for their fatigue symptoms.

*Treatment*

Patients received hepar magnesium D10, 10 cm<sup>3</sup> intravenously administered, once a week.

*Treatment period*

Patients were treated in the period from November 30, 2006 to March 31, 2007. Exact dates are presented in Table 1.

*Monitoring procedure*

After recruitment, patients received a link to an online questionnaire by e-mail. During the whole monitoring period (first measurement: before the first treatment with hepar magnesium; last measurement: 1.5 weeks after the last treatment) patients received an e-mail with a link to an online questionnaire two times a week. A final questionnaire in which the total treatment was evaluated was send at the end of April 2007, 1 month after the end of the “2 times a week” measurements.

*Measures*

Fatigue symptoms were measured by means of the following questionnaires:

- A self-made questionnaire in which patients are able to indicate how on average during the previous days (after the last measuring moment) the 24 hours per day have been divided concerning sleep, rest, everyday activities, and activities that require a large effort.
- A set of single questions that are used often in fatigue research, as follows:

In case you recognize one or more of the following symptoms in the last 3 or 4 days, please mark the symptom.

TABLE 2. NUMBER OF PATIENTS WITH FATIGUE-RELATED PROBLEMS (N = 19)

McNemar test	T1	T3	T1 versus T3 p =	T6	T1 versus T6 p =
Unusual emotional response to events	19	8	0.001	7	<0.001
Short-term memory problems	12	8	0.219	5	0.125
Fatigue after effort continues for longer than 2 hours	16	8	0.008	5	0.001

TABLE 3. NUMBER OF PATIENTS WITH FATIGUE-RELATED PROBLEMS (N = 15)

<i>McNemar test</i>	<i>T1</i>	<i>End</i>	<i>T1 versus end</i> <i>p =</i>	<i>1.5 week</i> <i>&gt; end</i>	<i>T1 versus 1.5 week &gt; end</i> <i>p =</i>
Unusual emotional response to events	13	4	0.004	3	0.004
Short-term memory problems	10	5	0.125	1	0.004
Fatigue after effort continues for longer than 2 hours	12	4	0.004	4	0.016

- unusual emotional response to the feeling of tiredness (e.g., sadness, frustration, or irritable reaction)
- problems with short-term memory
- fatigue after effort continues for longer than 2 hours

Please apply the answer that best fits your situation in the last 3 or 4 days (not at all, a little bit, moderately, quite a bit, extremely):

- at the end of the day I have a complete lack of energy
  - I am still fit after the evening meal
- The Multidimensional Fatigue Index, a validated questionnaire that measures the following domains of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.<sup>10</sup>

The subjective experiences with regard to the effect of the treatment were measured by means of a questionnaire often used in anthroposophic medical drug research.<sup>11</sup>

*Statistical analyses*

Data from completed online questionnaires were stored in a database and transported in and subsequently analyzed with the statistical program SPSS (14.0). Descriptive statistics were performed with regard to the following: demographic characteristics of the target population, course in time of fatigue symptoms, length of the observed effect, and the subjective experienced effect of the treatment.

Two types of analyses were performed to determine statistical significant differences between pre-treatment and post-treatment symptom scores. The first analysis con-

cerned determining the statistical significant difference in symptom scores before treatment (T1) and after 1 week (= 3rd measurement) (T3) and after 2.5 weeks of treatment (= 6th measurement) (T6). Both parametric and nonparametric tests were used. For these analyses, the data of only 19 (instead of 23 patients) patients were used because 4 patients already had stopped treatment before the 6th measurement. The second analysis concerned determining the statistically significant difference in symptom scores before treatment and at the end of treatment (= the measurement at the end of treatment, which took place at a different time point for each patient) and 1.5 weeks after the end of treatment. Again, both parametric and nonparametric tests were used. In these analyses, the data of 15 patients could be used, because they had ended treatment before the end of March 2007.

**RESULTS**

*Demographics*

The mean age of the research population of 23 patients (3 men and 20 women) was 41.9 (range: 16–62).

*Treatment*

On average, patients were treated 4.5 times (range: 1–13 times) in 4.5 weeks. One patient stopped treatment before March 31, 2007 because symptoms did not change. Another patient stopped because symptoms worsened slightly. The other 13 patients stopped before March 31, 2007, because symptoms, by their own judgment, had improved enough.

TABLE 4. WILCOXON TEST: SINGLE FATIGUE QUESTIONS

	<i>T1 versus T3</i> (N = 19) <i>p =</i>	<i>T1 versus T6</i> (N = 19) <i>p =</i>	<i>T1 versus end</i> (N = 15) <i>p =</i>	<i>T1 versus 1.5</i> <i>week &gt; end</i> (N = 15) <i>p =</i>
At the end of the day a complete lack of energy	0.003	0.002	0.004	0.003
Still fit after the evening meal	0.008	0.013	0.015	0.003

*Fatigue symptoms*

No statistically significant differences were found when the pretreatment scores and the treatment scores after 1 week and 2.5 weeks of the 24-hour categories (sleep, rest, everyday activities, and activities that require a large effort) were analyzed (Fig. 1).

All statistical analyses demonstrated both large statistical significant pretreatment versus post-treatment differences with regard to the following single questions: unusual emotional response to events; the degree to which fatigue after effort continues for longer than 2 hours; the degree to which people at the end of the day have a complete lack of energy; and the degree to which people still are fit after the evening meal. A nonsignificant trend was observed with regard to short-term memory problems (Figs. 2–7; Tables 2–4).

The analyses of three Multidimensional Fatigue index domains showed statistical pretreatment versus post-treatment significances in all analyses: *general fatigue*, *physical fatigue*, and *mental fatigue*. The analyses of the domain *reduced activity* demonstrated significant differences between pretreatment and post-treatment after both 1 week and 2.5 weeks of treatment, but no statistical difference between pretreatment and the end of treatment and 1.5 weeks after the end of treatment. The analyses of the domain *reduced motivation* demonstrated significant differences between pretreatment and post-treatment after both 1 week and 2.5 weeks of treatment

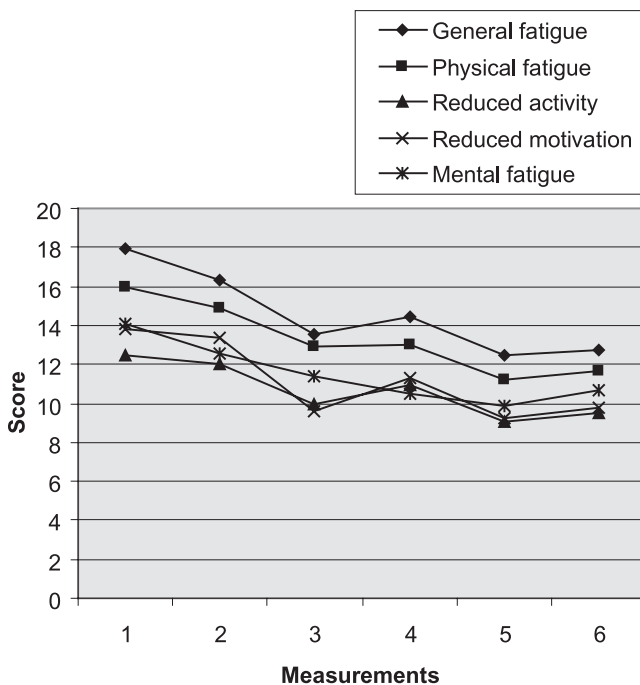


FIG. 8. Multidimensional Fatigue Index (MFI) (N = 19).

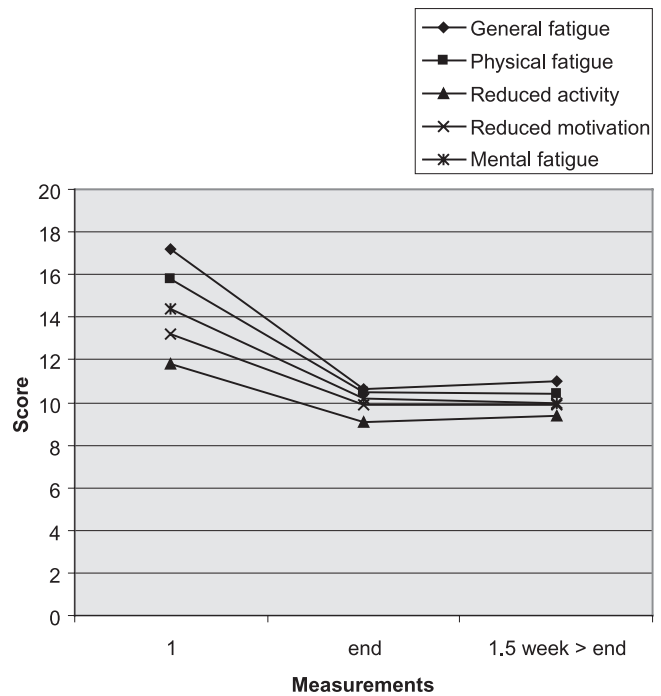


FIG. 9. Multidimensional Fatigue Index (MFI) (N = 15).

and between pretreatment and the end of treatment, but no statistical difference between pretreatment and 1.5 weeks after the end of treatment (Figs. 8 and 9) (Table 5).

*Subjective experiences*

Eighteen (18) of 22 patients (82%) who completed the final questionnaire judged that the hepar magnesium treatment overall had been effective for their fatigue symptoms. Nine (9) patients judged (41%) a strong improvement and 9 patients (41%) a light improvement as a result of the treatment. Four (4) patients reported no positive or negative change (Fig. 10).

**DISCUSSION**

We performed a pilot study in order to take a first step in gaining scientific evidence on the effect of hepar magnesium on subsyndromal SAD fatigue symptoms. On the basis of the results of the study, there are some arguments that are in favor of a positive effect of hepar magnesium treatment. First, the observed effect appeared quickly, whereas fatigue symptoms were already there for more than a month: already within 1 week and after 1 treatment, a statistically significant difference could be measured on most fatigue scores.<sup>12</sup> Second, 18 of 22 patients (82%) who completed the final question-



TABLE 5. PAIRED *t*-TEST: MULTIDIMENSIONAL FATIGUE INDEX

	<i>T1 versus T3</i> (N = 19) p =	<i>T1 versus T6</i> (N = 19) p =	<i>T1 versus end</i> (N = 15) p =	<i>T1 versus 1.5</i> <i>week &gt; end</i> (N = 15) p =
General fatigue	0.001	<0.001	<0.001	<0.001
Physical fatigue	0.003	<0.001	<0.001	0.003
Reduced activity	0.025	0.025	0.076	0.252
Reduced motivation	<0.001	0.002	0.037	0.115
Mental fatigue	0.009	0.017	0.015	0.044

naire judged that, according to their own experience, hepar magnesium treatment overall had been effective for their fatigue symptoms.

However, some other explanations for the observed effect can be hypothesized; for example: regression to the mean, natural course, or recall bias. Because the natural course of SAD is that symptoms tend to disappear at the end of March or the beginning of April, this might have influenced the results, at least with some of the patients. Therefore, increased controlled research (e.g., randomized clinical trials) is both indicated and necessary to determine the specific effect of hepar magnesium treatment. In these studies, hepar magnesium can be compared to placebo treatment and treatment as usual (light therapy) and long-term effects can be studied.

With regard to the working mechanism of subsyndromal SAD treatment, the interesting and exciting thing is that light therapy seems to be central. Treatment with both a daylight lamp and with daylight-like substances such as magnesium hydroxatum seems to be able to cure (a large subgroup of) these patients.

## CONCLUSIONS

There are clear indications from both clinical experiences and this pilot study that hepar magnesium D10 intravenously

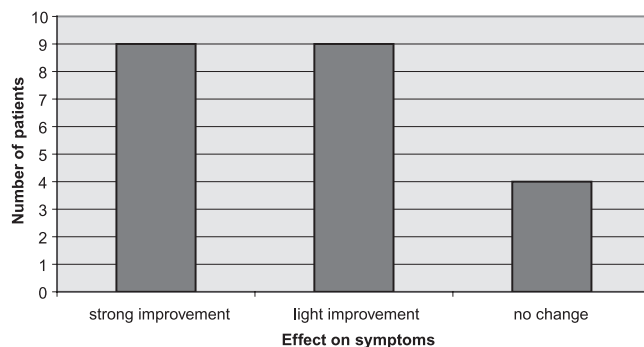


FIG. 10. Subjective judgment of the effect (N = 22).

administered can have a positive effect on subsyndromal SAD symptoms of fatigue. However, in this study other explanations for the presence of (a part of) the observed effect (e.g., natural course, regression to the mean, etc.) are also possible. Nevertheless, on the basis of the outcomes of this pilot study, it can be justified to design and perform a larger and more controlled trial (e.g., a randomized controlled trial) to study the specific effect of hepar magnesium and its long-term effects, compared to placebo and treatment as usual (light therapy).

## ACKNOWLEDGMENTS

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