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# The effect of granisetron, a 5-HT<sub>3</sub> receptor antagonist, in the treatment of chronic fatigue syndrome patients – a pilot study

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## ABSTRACT

**Objective:** To explore the effect of granisetron, a 5-HT<sub>3</sub> antagonist, on fatigue and functional impairment in patients with chronic fatigue syndrome (CFS).

**Methods:** Five female patients were eligible to receive oral granisetron for one month (1 mg a day for the first two weeks and 2 mg a day for the second two weeks). The patients had to be between 18 and 65 years of age and suffering from CFS according to the CDC criteria. The effect was assessed by pre- and post-testing, using validated instruments designed to assess the different dimensions of CFS. Treatment response was also evaluated by visual analogue scales (VAS) for fatigue. Analysis was based on intention to treat.

**Results:** Treatment with granisetron resulted in significant improvement in fatigue severity and functional impairment. Activity level showed no significant increase.

**Conclusion:** The promising results of this study have encouraged us to perform a placebo-controlled, double-blind study to evaluate the efficacy of 5-HT<sub>3</sub> receptor antagonists in the treatment of CFS.

impairment in daily functioning.<sup>1</sup> Various accompanying symptoms may be present, such as headache, joint and muscle pain, sore throat, and impaired memory and concentration. Of the many therapeutic interventions that have been undertaken so far, only cognitive behaviour therapy (CBT) and graded exercise therapy (GET) have met with success.<sup>2,3</sup>

There is accumulating data in the literature supporting an important role for serotonin (5-hydroxytryptamine) in the neurobiology of CFS. Neuropharmacological studies point to an upregulated serotonin system.<sup>4,7</sup>

In a randomised controlled trial by our own research group, the selective serotonin reuptake inhibitor (SSRI) fluoxetine proved to be ineffective in CDC-diagnosed CFS subjects for the treatment of fatigue and depression,<sup>8</sup> which is also in line with upregulation of the serotonin system. Positive reports of the use of serotonin inhibitors in the treatment of patients with fatigue (due to chronic hepatitis<sup>9</sup> and to fibromyalgia<sup>10,11</sup>) support an effect. Based on these findings, we hypothesise that a serotonin antagonist could be effective in CFS. Therefore, we undertook this pilot study.

## MATERIALS AND METHODS

### Patients

Five female CDC-diagnosed patients with a high fatigue level and a substantial impairment in daily life, reflected by the Checklist Individual Strength (CIS)<sup>12,13</sup> and the

## INTRODUCTION

Chronic fatigue syndrome (CFS) is a medically unexplained syndrome, characterised by severe disabling fatigue for a period of at least six months, which has led to considerable

\*\*J.W.M. van der Meer was not involved in the handling and review process of this paper.

Sickness Impact Profile-8 (SIP-8),<sup>14,15</sup> were treated with granisetron. The cut-off point of the CIS fatigue severity subscale was set at 40 and the weighted total score of the SIP-8 was set at 800.

In a CBT multicentre, randomised controlled trial by our research group, the CBT treatment protocol did not seem to be suitable for a group of CFS patients with low activity patterns.<sup>2</sup> Therefore, we selected patients with a low activity pattern. Patients whose average daily physical activity scores stayed below the reference score in at least nine of the twelve assessment days could be included.<sup>16</sup> The activity level was assessed prior to the treatment period with an actometer. We chose only female subjects, because in CFS the ratio male/female is approximately 1:4<sup>17</sup> and combined with low activity as a disease characteristic, we created a homogeneous group.

Additional criteria were patients aged between 18 and 65 years, and no previous or current engagement in CFS research. Pregnant or lactating women and patients who were taking psychotropic medications were excluded. We received ethical clearance to perform a pilot study and obtained written informed consent from all patients.

### Design and procedures

There were four evaluation moments (E1-E4): E1 at baseline, E2+E3, in the middle and at the end of the treatment period and E4 at follow-up, two weeks after the treatment period. The treatment period was divided in two periods of two weeks. During the first period, the patients received an oral dose of granisetron of 1 mg a day. After two weeks the effect, compliance and side effects were evaluated. If the evaluation showed no significant improvement, the dose was increased to 2 mg a day.

Analysis was based on intention to treat. A linear model for repeated measures was used to analyse the effect of granisetron on the outcome measures CIS fatigue severity, CIS activity and SIP-8.

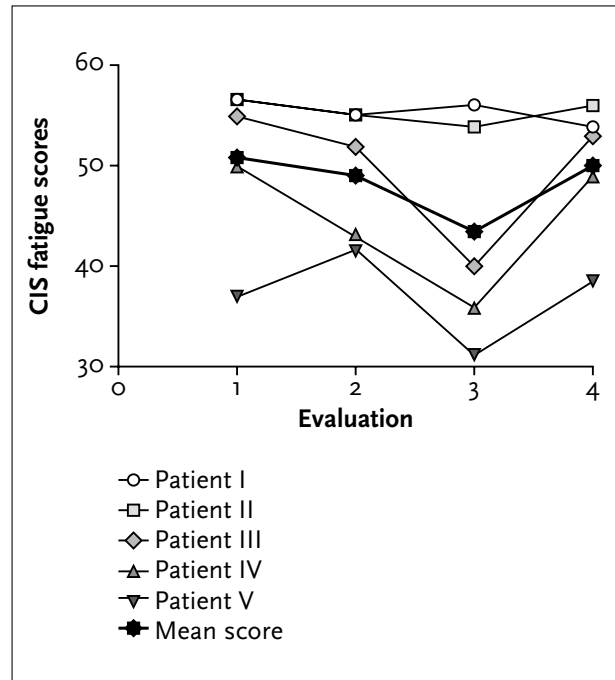
The four evaluation moments were analysed as well as the three evaluation moments during the medication period. The visual analogue scales (VAS) actual fatigue scores were analysed by the Wilcoxon signed-rank test.

## ASSESSMENTS

### Fatigue severity

The Checklist Individual Strength (CIS) is a reliable and validated self-report questionnaire. We used the subscale fatigue severity of the CIS (CIS fatigue severity).<sup>12,13</sup> The score on this eight-item scale ranges from 8 (no fatigue) to 56 (maximally fatigued).

CIS fatigue severity analysis during the medication period (E1-E3) calculated a significant decline in time ( $p=0.046$ ). The significant drop during the medication period (E1-E3) means that patients reported significantly lower fatigue levels after treatment with granisetron. Analysis over four measurements is significant in time as well ( $p=0.026$ ). Follow-up (E4) showed an increase in fatigue severity after discontinuation of granisetron (figure 1).



**Figure 1**  
Effect of granisetron in five patients on the outcome variable fatigue severity (CIS fatigue severity)

Visual analogue scales (VAS) (100 mm) are used to determine the actual fatigue severity. VAS ratings were used to evaluate the one-month treatment period. VAS assessments took place during the medication period (E1, E2 and E3). The VAS actual fatigue showed a significant drop of 29% in the mean fatigue scores ( $p=0.042$ ) during the treatment period (table 1).

**Table 1**

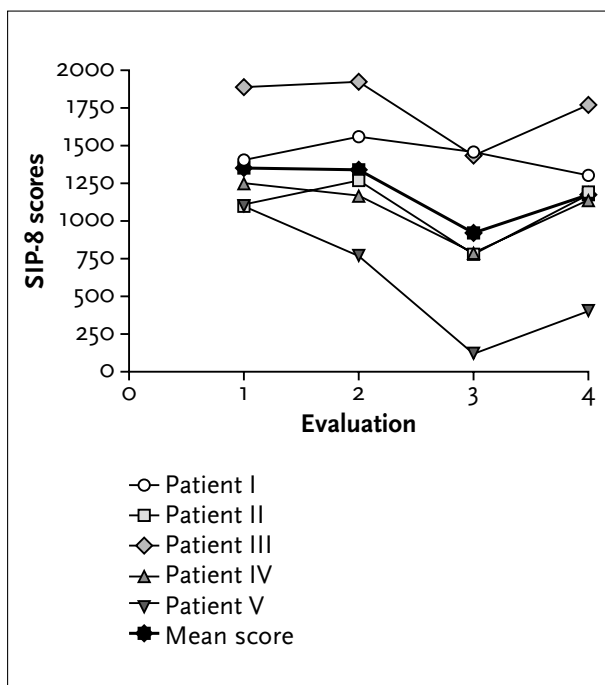
Effect of granisetron in five patients on the outcome variable VAS actual fatigue severity ( $p=0.042$ )

TREATMENT	VAS MEAN	SD	SEM	RANGE MM
E1 - actual	76.4	13.7	6.1	59-95
E2 - actual	65.2	21.4	9.6	34-93
E3 - actual	54.4	28.1	12.6	22-92

### Functional impairment

The sickness impact profile (SIP-8) measures the influence of symptoms on daily functioning, using the following eight subscales to rate both physical and psychological disability: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work and recreation, and pastimes.<sup>14,15</sup>

SIP-8 analysis during the medication period (E1-E3) showed a significant decline in time ( $p=0.008$ ). Patients reported significantly less functional impairment during the one-month medication period. Analysis over four measurements is significant in time as well ( $p=0.005$ ). Follow-up (E4) showed an increase in functional impairment after discontinuation of granisetron. Within two weeks the mean SIP-8 score returned to the baseline level (figure 2).



**Figure 2**  
*Effect of granisetron in five patients on the outcome variable functional impairment (SIP-8)*

### Activity level

The actometer is a small motion-sensing device that can register and quantify human physical activity.<sup>18</sup> Three different activity patterns can be distinguished for patients with CFS: pervasively passive, fluctuating active and pervasively active. In an earlier study identifying physical activity patterns in CFS patients, we observed that healthy controls do not fall in the category of pervasively passive. Patients wore the actometer day and night for a two-week period. After the two-week period the average scores over 12 days were computed.<sup>16</sup>

Before treatment the mean actometer score was 44.6 (SD 22.2). During the last two weeks of the treatment period the mean actometer score was 46.2 (SD 20.3).

Granisetron did not significantly change the mean actometer score ( $p=0.16$ ).

The subscale activity of the CIS was used (CIS activity). The score on this three-item scale ranges from 3 (no activity) to 21 (maximally activity level).<sup>12,13</sup>

Analysis of the CIS subscale activity showed no significant improvement during the medication period ( $p=0.16$ ).

Analysis over four measurements is not significant in time either ( $p=0.191$ ).

## RESULTS

The five women had a mean age of 34 years (range 23-44 years). Three of the five patients had a pervasively passive actometer pattern. Two patients had activity level scores lower than the mean CFS score for 9 out of the 12 days. All patients finished their study.

In the first two weeks the oral dose of 1 mg granisetron was well tolerated, but none of the patients showed significant improvement. In the second period all patients received 2 mg granisetron a day.

Four out of five patients reported marked improvement.

One patient did not report any improvement on the outcome variables fatigue severity, activity level and functional impairment. Another patient complained of constipation as a side effect of granisetron during the last few days of the treatment.

## DISCUSSION

In this pilot study we evaluated the effect of granisetron, a serotonin receptor antagonist, in chronic fatigue syndrome patients with low activity patterns. We found a substantial decrease in fatigue and functional impairment in four out of five patients as assessed by CIS fatigue severity, SIP-8 and visual analogue scale. That these changes in scores are clinically relevant can be deduced from our observations that these patients and their partners reported a remarkable improvement in fatigue and functional impairment at the end of the treatment period.

That granisetron, a serotonin antagonist, could have a favourable effect in CFS is not totally unexpected. First of all, there are reports in the literature pointing to a postsynaptic hyper-responsiveness in CFS.<sup>4,5</sup> Also the challenge test with buspirone, a 5-HT agonist and D-fenfluramine, a serotonin reuptake inhibitor, met with exaggerated prolactin responses in CFS patients, consistent with a postsynaptic serotonergic hyper-responsiveness in CFS.<sup>6,7</sup>

Second, there are reports in the literature pointing to a favourable effect of serotonin antagonist in fatigued patients. Jones reported a positive effect on fatigue in a 35-year-old woman with profound fatigue associated with chronic hepatitis-C when treated with a 5-HT<sub>3</sub> receptor antagonist.<sup>9</sup> Positive results in fibromyalgia studies<sup>10,11</sup> also support a favourable effect of serotonin antagonists in the treatment of fatigue.

A remarkable finding is that within two weeks after discontinuation of granisetron, follow-up showed a marked increased mean fatigue level score and an increased functional impairment score. Within a few days granisetron is eliminated from the system (T<sub>1/2</sub> elimination is 9-12 hours). The increase in symptoms within a short period after discontinuation of the medication supports the hypothesis that the intervention with granisetron is responsible for the reported improvement.

In this open study, a placebo effect cannot be excluded. However, in previous placebo-controlled studies<sup>8,19</sup> we have not encountered remarkable changes in fatigue severity and functional impairment in the placebo group. The actometer activity level showed no significant improvement. A possible explanation is that a reduced level of fatigue will not immediately lead to an increased physical walking activity level, which is measured by the actometer. It is possible that CFS patients have quite structured daily routines. A reduced level of fatigue will probably not immediately lead to a change in the daily routines. We treated patients with low activity patterns. In addition there may be deconditioning of the patients, which is not reversible in the short term of one month. It might take more than four weeks to change the rather static activity patterns, despite a decreased level of fatigue. Perhaps a longer treatment protocol and a longer registration period could lead to (significantly) improved actometer activity levels. However, we do not know whether wearing off effects occur with prolonged treatment.

It is striking that the outcome measures showed an improvement of CFS-related symptoms after two weeks (figures 1 and 2). It is not clear whether the reported improvement after two weeks can be explained by a dose-dependent effect. A possible explanation is that time is a key factor in the reported improvement. It is possible that granisetron induced a postsynaptic receptor modification in time or decreased the sensitivity of the postsynaptic receptors.

Data in the literature point in the direction that CFS and depression are opposing disease entities with contrasting neuroendocrine responses and 5-HT functioning.<sup>20-22</sup> The 'serotonin hypothesis' is the most widely accepted neural basis for depression. Drugs that preferentially increase serotonin activity by decreasing its reuptake (selective serotonin reuptake inhibitor, or SSRI) are effective in the treatment of depression<sup>23-25</sup> and not in the treatment of

CFS, even when the patients are depressed.<sup>8</sup>

It is worth noting that there is a therapeutic delay of two weeks in the treatment of depression with a SSRI. It is conceivable that a similar delay occurs with 5-HT receptor antagonism as applied in the presented study.

It is remarkable that one patient did not respond. This 23-year-old woman with a CFS history of three years was no different from the other patients with regard to her history, CDC criteria, CIS fatigue severity score and SIP-8 score. Whether such nonresponsiveness has a serotonergic neuroendocrine basis has to be investigated in longer studies combined with serotonergic challenge tests and with serotonin receptor-status imaging studies. It is known that granisetron concentrations in blood may vary between subjects. A lower granisetron concentration might have caused the nonresponse in this individual. In this pilot study we did not measure blood granisetron concentrations. An interesting question is also whether further dose escalation would enhance the effect.

Our favourable results in this pilot study warrant a study with a randomised placebo-controlled, double-blind design. At the present time we are conducting such a randomised clinical trial with a longer treatment protocol and longer registration periods. In the future an interesting treatment concept might be a combination of a 5-HT<sub>3</sub> receptor antagonist with CBT or GET.

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#### REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The Chronic Fatigue Syndrome Study: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121:953-9.
2. Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet* 2001;357(9259):841-7.
3. Whiting S, Bagnall A, Sowden A, Cornell J, Mulrow C, Ramirez G. Interventions for the Treatment and Management of Chronic Fatigue Syndrome A Systematic Review. *JAMA* 2001;286:1360-8.
4. Bakheit A, Behan P, Dinan T, et al. Possible up-regulation of hypothalamic 5-hydroxytryptamine receptors in patients with post-viral fatigue syndrome. *J Affect Disorder* 1996;41:71-6.
5. Cleare AJ, Bearn J, Allein T, et al. Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. *Psychoneuroendocrinology* 1995;35:283-9.

6. Sharpe M, Hawton K, Clements A, Cowen PJ. Increased prolactin response to buspirone in chronic fatigue syndrome. *J Affect Disord* 1996;41:71-6.
7. Sharpe M, Hawton K, Clements A, Cowen P. Increased brain serotonin function in men with chronic fatigue syndrome. *BMJ* 1997;315:164-5.
8. Vercoulen JHMM, Swanink CMA, Zitman FG, et al. Randomised, placebo-controlled trial of Fluoxetine in chronic fatigue syndrome. *Lancet* 1996;347:858-61.
9. Jones A. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. *Lancet* 1999;354:397.
10. Färber L, Strats W, Brückle W, et al. Efficacy and tolerability of tropisetron in primary fibromyalgia – a highly selective and competitive 5-HT<sub>3</sub> receptor antagonist. *Scan J Rheumatol* 2000;29(suppl 113):49-54.
11. Papadopoulos IA, Georgiou PE, Katsimbri PP, Drosos AA. Treatment of fibromyalgia with tropisetron, a 5-HT<sub>3</sub> serotonin antagonist: a pilot study. *Clin Rheumatol* 2000;19(1):6-8.
12. Vercoulen JHMM, Swanink CMA, Fennis JFM, Galama JMD, Meer JWM van der, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38:383-92.
13. Vercoulen JHMM, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS). *Gedragstherapie* 1999;32:131-6.
14. Bergner M, Bobbit RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 1981;19:787-805.
15. Jacobs HM, Luttik A, Touw-Otten FW, Melker RA de. De sickness impact profile: resultaten van een valideringsonderzoek van de Nederlandse versie. *Ned Tijdschr Geneesk* 1990;134:1950-4.
16. Werf S van der, Prins J, Vercoulen J, Meer JWM van der, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome in chronic fatigue syndrome using actigraphic assessment. *J Psychosom Res* 2000;49:373-9.
17. Bazelmans E, Vercoulen J, Galama J, Weel C van, Meer JWM van der, Bleijenberg G. Prevalence of chronic fatigue syndrome and primary fibromyalgia syndrome in the Netherlands. *Ned Tijdschr Geneesk* 1997;141:1520-3.
18. Tyrone W. Activity measurement in psychology and medicine. New York: Plenum Press, 1991:47-4.
19. Brouwers FM, Werf S van der, Bleijenberg G, Zee L van der, Meer JWM van der. The effect of a polynutrient supplement on fatigue and physical activity of patients with chronic fatigue syndrome: a double-blind randomized controlled trial. *QJM* 2002;95(10):677-83.
20. Cleare AJ, Bearn J, Allain T, et al. Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. *J Affect Disord* 1995;34(4):283-9.
21. Parker AJR, Wessely S, Cleare AJ. The neuroendocrinology of chronic fatigue syndrome and fibromyalgia. *Psychol Med* 2001;31:1331-45.
22. Scott LV, Dinan TG. The neuroendocrinology of chronic fatigue syndrome: focus on the hypothalamic-pituitary-adrenal axis. *Funct Neurol* 1999;14:3-11.
23. Dursun SM, Blackburn JR, Kutcher SP. An exploratory approach to the serotonergic hypothesis of depression: bridging the synaptic gap. *Med Hypotheses* 2001;56(2):235-43.
24. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem* 1994;40:288-95.
25. Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. *Lancet* 1997;349:915-9.

