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The Effect of Ondansetron, a 5-HT₃ Receptor Antagonist, in Chronic Fatigue Syndrome: A Randomized Controlled Trial

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Background: Accumulating data support the involvement of the serotonin (5-hydroxytryptamine [5-HT]) system in the pathophysiology of chronic fatigue syndrome. Neuropharmacologic studies point to a hyperactive 5-HT system, and open-label treatment studies with 5-HT, receptor antagonists have shown promising results. In this randomized controlled clinical trial, the effect of ondansetron, a 5-HT, receptor antagonist, was assessed on fatigue severity and functional impairment in adult patients with chronic fatigue syndrome.

Method: A randomized, placebo-controlled, double-blind clinical trial was conducted at Radboud University Nijmegen Medical Centre, The Netherlands. Sixty-seven adult patients who fulfilled the US Centers for Disease Control and Prevention (CDC) criteria for chronic fatigue syndrome and who were free from current psychiatric comorbidity participated in the clinical trial. Participants received either ondansetron 16 mg per day or placebo for 10 weeks. The primary outcome variables were fatigue severity (Checklist Individual Strength fatigue severity subscale [CIS-fatigue]) and functional impairment (Sickness Impact Profile-8 [SIP-8]). The effect of ondansetron was assessed by analysis of covariance. Data were analyzed on an intention-to-treat basis. All patients were recruited between June 2003 and March 2006.

Results: Thirty-three patients were allocated to the ondansetron condition, 34 to the placebo condition. The 2 groups were well matched in terms of age, sex, fatigue severity, functional impairment, and CDC symptoms. Analysis of covariance showed no significant differences between the ondansetron- and placebo-treated groups during the 10-week treatment period in fatigue severity and functional impairment.

Conclusions: This clinical trial demonstrates no benefit of ondansetron compared to placebo in the treatment of chronic fatigue syndrome.

Trial Registration: www.trialregister.nl: ISRCTN02536681


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Chronic fatigue syndrome is a medically unexplained syndrome, characterized by severe disabling fatigue for a period of at least 6 months that has led to considerable impairment in daily functioning. Various accompanying symptoms may be present, such as headache, joint and muscle pain, sore throat, and impaired memory and concentration. In The Netherlands, a country with 16 million inhabitants, there are probably between 30,000 and 40,000 patients with chronic fatigue syndrome. Of the many therapeutic interventions that have been undertaken, so far only cognitive behavioral therapy and graded exercise therapy are of proven effectiveness.

Neuroendocrinologic investigations have tried to elucidate the pathophysiology of chronic fatigue syndrome. Data in the literature support an important role for serotonin (5-hydroxytryptamine [5-HT]) in the pathophysiology of chronic fatigue syndrome. Serotonin plays a diverse and important role in the regulation of sleep and wakefulness, mood regulation, impulse control, memory, and perception of pain and in behavior that involves a high cognitive demand. Increased activity or metabolism of the 5-HT system have been implicated in the pathophysiology of chronic fatigue syndrome. An increased activity or metabolism of the 5-HT system may contribute to the pathophysiology of chronic fatigue syndrome. An increased 5-HT metabolism in fatigue is supported by a rise in plasma tryptophan, the precursor of 5-HT during and after sustained exercise in healthy persons.

Positive results of the use of 5-HT, inhibitors in the treatment of patients with chronic fatigue due to chronic hepatitis or fibromyalgia are in line with a role of serotonin in fatigue and support further research into this type of pharmacologic interventions.

Results of an open-label pilot study performed by our research group showed positive results during 1-month treatment with granisetron, a 5-HT, receptor antagonist. The results of the pilot study encouraged us to investigate...
the effect of ondansetron in a well-defined chronic fatigue syndrome population using validated outcome measures in a randomized, double-blind, placebo-controlled design.

METHOD

The study was approved by the medical ethical committee of the Radboud University Nijmegen Medical Centre. Written informed consent was obtained from all participants prior to enrollment.

Participants

Patients were recruited through the outpatient clinic of the Department of General Internal Medicine of the Radboud University Nijmegen Medical Centre. Furthermore, patients with chronic fatigue syndrome who were referred by general practitioners to the Nijmegen Expert Centre Chronic Fatigue for treatment were also asked to participate in the clinical trial.

Patients were eligible for participation if they met the following inclusion criteria: aged between 18 and 65 years, satisfying the 1994 US Centers for Disease Control and Prevention (CDC) consensus criteria for chronic fatigue syndrome, and scoring above clinical cut-off on the Checklist Individual Strength fatigue severity subscale and the Sickness Impact Profile-8 (see below).

At the end of 2003, the International Chronic Fatigue Syndrome Study Group presented recommendations for better application of the 1994 case definition of chronic fatigue syndrome. The 1994 CDC criteria for defining chronic fatigue syndrome have been superseded by the revised 2003 CDC criteria. In our clinical trial, we did not use the 2003 CDC criteria because the inclusion of the study started before the publication of the revised 2003 CDC criteria. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was performed by the investigator with a clinical background, who was trained in the SCID-I interview, to exclude patients with current psychiatric comorbidity. Pregnant or lactating women were excluded, as were patients with lactose intolerance and patients taking psychotropic drugs or experimental medications.

Interventions

Ondansetron (8-mg tablets) and an identical placebo were delivered by the manufacturer GlaxoSmithKline, The Netherlands. There was no difference in taste, appearance, or packaging between the active supplements and the placebo tablets. During 10 weeks, the chronic fatigue syndrome patients took either ondansetron (two 8-mg ondansetron tablets) or 2 placebo tablets at night. The dose of 16 mg per day was based on the results of the pilot study performed before this clinical trial. In the pilot study, we observed a positive treatment effect with an equipotent dose of 16 mg ondansetron per day at night, and the patients tolerated the medication relatively well.

Späth et al reported positive effects in patients with chronic fatigue syndrome treated with 16 mg per day, as well.

Design and Procedures

The study was a prospective, randomized, double-blind, placebo-controlled trial. The study was fully designed by the investigators and executed independently of the manufacturer of the study drugs.

The outcome measures were assessed before the start of the pharmacologic interventions and at the end of the 10-week treatment period, when the patients were still taking the medication. All participants, investigators, and laboratory technicians were blinded to the treatment condition.

Randomization

Before the start of the clinical trial, the hospital pharmacy prepared 70 treatment packages. Randomization and allocation to the treatment or placebo group was based on a patient’s study number. The pharmacy held the randomization list that correlated the study number with the treatment group. To maintain balance over time, the concealed randomization was done in blocks of 10. Treatments were generated randomly within the blocks using a computer program (Excel, Microsoft, Redmond, Washington, http://www.microsoft.com). After acceptance of a patient by the junior researcher (G.K.H.T.) and the clinical psychologist (G.B.), the eligible patient received the lowest study number available (1–70).

Primary Outcome Measures

Fatigue severity. The Checklist Individual Strength is a reliable and validated self-report questionnaire. We used the CheckList Individual Strength fatigue severity subscale (CIS-fatigue). The score on this 8-item scale ranges from 8 (no fatigue) to 56 (maximally fatigued). The cut-off point for severe fatigue was set at 35. Patients who had chronic fatigue syndrome with a fatigue severity score of 35 or higher were included.

Functional impairment. The Sickness Impact Profile-8 (SIP-8) measures the influence of symptoms on daily functioning, using the following 8 subscales to rate both physical and psychological disability: home management, mobility, alertness behavior, sleep/rest, ambulation, social interactions, work, and recreation and pastimes. A total score was calculated by addition of the weights of items. This widely used measure has good reliability and validity. Patients with chronic fatigue syndrome with substantial functional impairments, ie, a score of 800 or higher, were included.

Patients had to fulfill both the fatigue severity and functional impairment criteria to participate in the study.

Secondary Outcome Measures

Activity level. Besides self-reported outcome measures, we measured physical activity with an actometer (Medical
of accelerations per 5-minute interval was calculated.30,31

the mean activity level over the 12 days in the mean number
activity score that is stored into the internal memory of the
counter is set at 5 minutes, providing every 5 minutes an
adds the value to the integration counter. The integration
actometer is read and reset by the micro controller, which
memory of the actometer. Each second, the counter of the
are considered as activity and are stored into an internal
movements of the leg (eg, during walking or climbing stairs).
Electric sensor that is sensitive in 3 directions, and it detects
ankle; it was worn continuously for 12 consecutive days and
human physical activity. The actometer is attached to the
small motion-sensing device that can register and quantify

Instruments Services, Radboud University Nijmegen Medi-
cal Centre, Nijmegen, The Netherlands).29 An actometer is a
small motion-sensing device that can register and quantify
human physical activity. The actometer is attached to the
ankle; it was worn continuously for 12 consecutive days and
nights during the assessment periods. It consists of a piezo-
electric sensor that is sensitive in 3 directions, and it detects
movements of the leg (eg, during walking or climbing stairs).
Accelerations of the sensor above a predefined threshold
are considered as activity and are stored into an internal
memory of the actometer. Each second, the counter of the
actometer is read and reset by the micro controller, which
adds the value to the integration counter. The integration
counter is set at 5 minutes, providing every 5 minutes an
activity score that is stored into the internal memory of the
actometer. A general physical activity score that expressed
the mean activity level over the 12 days in the mean number
of accelerations per 5-minute interval was calculated.30,31

Daily fatigue level. During the 2-week actometer period,
patients rated their fatigue levels in a diary. They rated their
levels of fatigue 4 times a day on a 0 (no fatigue) to 4 (maxi-
mally fatigued) scale.

The 4 scores for each day were summed to produce the
daily observed fatigue (DOF) score, which ranged from 0 to
16.30 The mean of 12 consecutive DOF scores was used.

Statistical Methods
For all analyses, SPSS 14.0 (SPSS Inc, Chicago, Illinois,
http://www.spss.com) was used.

Power calculations before the start of the trial showed that
30 persons were needed in each group to detect a difference
of at least 1 standard deviation (SD) on the CIS-fatigue with
a power of 90% and a 2-tailed significance level of 5%. An-
ticipating a dropout rate of 10%, 66 persons needed to be
recruited. Analyses were performed on an intention-to-treat
basis.

Missing values were replaced by way of mean imputa-
tion.32 The effect of ondansetron was assessed by analysis
of covariance (ANCOVA) of the posttreatment scores after
10 weeks as the dependent variable, the baseline scores
as covariate, and condition as fixed factor.33 Analyses were
completed before the code was broken.

RESULTS

All patients were recruited between June 2003 and
March 2006. Figure 1 illustrates participant flow through
the trial. In total, 159 patients were given information about
the study protocol; 79 persons refused to participate, and
the main reason given for refusal was the intensity of the
study. Thirteen patients did not meet the inclusion criteria.
Seventy-four patients were screened with the SCID-I
Interview. Of those, 7 were excluded due to current psychi-
atic comorbidity. A total of 67 patients, without current
psychiatric comorbidity, were allocated randomly to the
ondansetron group or to the placebo group.

The ondansetron (n = 33) and placebo (n = 34) groups
did not differ with respect to age, gender, fatigue severity,
impairment, or number of CDC symptoms (Table 1).

There was no significant difference in age, number of
CDC symptoms, fatigue severity, or functional impairment
between the patients with chronic fatigue syndrome par-
ticipating in the clinical trial and those who chose not to
participate (data not shown).

In the placebo arm, no participants dropped out. Three
patients in the ondansetron arm dropped out within the
first 2 weeks of the trial. One patient agreed to participate
in the posttesting assessments, and 2 patients in the on-
dansetron group had missing values for the posttreatment
measurements. The main reason for discontinuing the trial

Table 1. Patient Characteristicsa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ondansetron (n = 33)</th>
<th>Placebo (n = 34)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>35.8 (9.9)</td>
<td>34.7 (9.4)</td>
<td>. . . , . . .</td>
</tr>
<tr>
<td>Sex, female</td>
<td>67</td>
<td>74</td>
<td>. . . , . . .</td>
</tr>
<tr>
<td>CIS-fatigue</td>
<td>49.4 (6.3)</td>
<td>50.0 (4.7)</td>
<td>.424, .677</td>
</tr>
<tr>
<td>SIP-8</td>
<td>1,375 (470)</td>
<td>1,359 (593.4)</td>
<td>.117, .907</td>
</tr>
<tr>
<td>CDC symptoms</td>
<td>7.4 (1.4)</td>
<td>6.8 (2.1)</td>
<td>.34, .183</td>
</tr>
<tr>
<td>Current psychiatric comorbidity</td>
<td>n = 5</td>
<td>n = 1</td>
<td>. . .</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>n = 1</td>
<td>n = 1</td>
<td>. . .</td>
</tr>
<tr>
<td>Obsessive–compulsive disorder</td>
<td>n = 1</td>
<td>n = 1</td>
<td>. . .</td>
</tr>
<tr>
<td>Current treatment for CFS</td>
<td>n = 3</td>
<td>n = 3</td>
<td>. . .</td>
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<tr>
<td>Current treatment for pain</td>
<td>n = 2</td>
<td>n = 2</td>
<td>. . .</td>
</tr>
<tr>
<td>Age</td>
<td>n = 1</td>
<td>n = 1</td>
<td>. . .</td>
</tr>
</tbody>
</table>

aValues are means (SD) except for sex, which is given as percentage.

bChi-square test.

Abbreviations: CDC = US Centers for Disease Control and Prevention,
CIS-fatigue = Checklist Individual Strength fatigue severity subscale,
SIP-8 = Sickness Impact Profile-8.
was an increased general feeling of malaise. Ondansetron and placebo treatments were relatively well tolerated. Four patients (3 ondansetron and 1 placebo) had complaints of constipation, and a laxative syrup was prescribed. No other important side effects were reported in either group.

**Primary Outcomes**

Evaluation of fatigue severity and functional impairment posttreatment scores showed no significant differences between the ondansetron and placebo groups. The posttreatment scores of both groups remained in the clinical range of severe fatigue and substantial functional impairment.

Our primary analysis was to impute the missing values of the 2 patients using mean imputation. Moreover, we performed a sensitivity analysis testing 2 imputation methods: first by imputing the last observation carried forward and second by imputing the maximum posttreatment scores of both groups using mean imputation. Both imputing methods had no significant impact on the conclusions of the primary analysis.

**Secondary Outcomes**

Posttreatment actometer activity scores and DOF scores of the ondansetron and placebo group did not differ significantly. F-statistics and mean scores of the primary and secondary outcomes are shown in Table 2.

**DISCUSSION**

This randomized, double-blind, controlled clinical trial investigated the therapeutic potential of the serotonin receptor antagonist ondansetron. We did not find significant differences between the ondansetron- and placebo-treated groups during the 10-week treatment period for any dimension of chronic fatigue syndrome. This result was rather unexpected given the promising results in an earlier open study in which we tested the effect of granisetron, a compound similar to ondansetron. Four of 5 patients showed a remarkable improvement that reversed after cessation of the drug. Of course, such an open study is prone to observer bias, and a placebo effect cannot be excluded. However, in earlier studies in chronic fatigue syndrome performed by us and others, placebo effects were minimal. Besides pharmacologic and neuroendocrine studies implicating an increased 5-HT neurotransmission, positron emission tomography (PET) supports the hypothesis of an increased serotonergic state in chronic fatigue syndrome. Cleare et al found a widespread reduction in the number or affinity of 5-HT receptors, and the results of this study may be compatible with the neuroendocrine studies. A prolonged increased 5-HT state might result in a chronic 5-HT down-regulation and, consequently, reduced 5-HT binding potential.

On the basis of all of these previous findings, the question arises why our trial met with negative results. We have scrutinized our study regarding potential confounding factors, but could not identify any. The groups were well matched, and only well-diagnosed patients with chronic fatigue syndrome fulfilling the CDC criteria were included. Furthermore, we excluded patients with current psychiatric comorbidity. In this clinical study, we investigated the effect of serotonin receptor antagonism with ondansetron. We included patients from the outpatient clinic of the department of general internal medicine and patients who were referred by the general practitioner to the Expert Center Chronic Fatigue for treatment. Patients with chronic fatigue syndrome who were taking serotonergic medication were excluded from participating in the study.

We also chose to exclude patients with current psychiatric comorbidity. Methodological differences and definition difficulties in the literature have produced conflicting results concerning the prevalence of psychiatric disorders in chronic fatigue syndrome and the impact of psychiatric disorders on the prognosis of chronic fatigue syndrome. Furthermore, evidence suggests an important role for the neurotransmitter serotonin in psychiatric disorders, such as in depression and in the pathophysiology and treatment of anxiety and panic attacks. In this way, we reduced the chance the results will be biased by current Axis I psychiatric disorders. To our knowledge, ondansetron has no significant role in the treatment of depression, anxiety disorders, or obsessive-compulsive disorders. Therefore, we do not believe that excluding patients with current psychiatric comorbidity has reduced the likelihood of achieving response to ondansetron.

In our open-label study, we used granisetron, at that time marketed by SmithKline Beecham. When we were designing the present study, SmithKline Beecham merged with GlaxoWellcome and sold granisetron to Roche. Although

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### Table 2. Scores on Outcome Measures and ANCOVA Results for Patients With Chronic Fatigue Syndrome Treated With Ondansetron or Placebo

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Mean SD</th>
<th>Mean SD</th>
<th>ANCOVA (df = 1,64)</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome measures</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CIS-fatigue</td>
<td>49.4 6.3</td>
<td>50.0 4.7</td>
<td>0.116 .73</td>
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<tr>
<td>Posttreatment</td>
<td>44.0 11.1</td>
<td>45.4 11.5</td>
<td>1.077 .30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIP-8</td>
<td>1,357 47.0</td>
<td>1,359 593.4</td>
<td>0.015 .90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttreatment</td>
<td>8.5 2.0</td>
<td>8.4 2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOF</td>
<td>7.9 2.4</td>
<td>7.8 2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcome measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actometer</td>
<td>54.1 16.5</td>
<td>58.4 16.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttreatment</td>
<td>55.0 15.5</td>
<td>60.6 17.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttreatment</td>
<td>1,063 525.5</td>
<td>1,172 694.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ANCOVA = analysis of covariance, CIS-fatigue = Checklist Individual Strength fatigue severity subscale, DOF = daily observed fatigue, SIP-8 = Sickness Impact Profile-8.
this is a fully investigator-driven study, we were not able to obtain granisetron and placebo for the randomized controlled trial. Thus, we had to redesign the study and use ondansetron. Granisetron and ondansetron are both selective 5-HT₃ receptor antagonists.

To our knowledge, no differences in efficacy and side effects are described between the different 5-HT₃ receptor antagonists. Given the similarities between the 2 drugs, we feel it is highly unlikely that the switch to ondansetron explains our negative results.

We did not monitor patient compliance on a daily basis. During the trial, patients had an appointment by telephone or at the outpatient clinic every 2 weeks. During these appointments, we assessed whether patients experienced side effects and whether the trial medication was taken as directed. Although we have not rigorously checked compliance, we do not believe that lack of adherence can explain the negative findings.

We did not assess the baseline serotonin status of the patients with chronic fatigue syndrome. As mentioned previously, results from neuroendocrine challenge studies have suggested increased central 5-HT function in patients with chronic fatigue syndrome. Several different 5-HT₃ agonists have been used to assess 5-HT function in chronic fatigue syndrome. Studies with buspirone₁₀ and d-fenfluramine¹¹,¹² showed an enhanced prolactin response in patients with chronic fatigue syndrome compared to healthy controls and depressed subjects. Others showed a normal 5-HT activity.⁴⁺,⁴⁵ Appropriateness of matching and selection of patients with chronic fatigue syndrome with heterogeneous psychiatric history could partly contribute to the inconsistent findings in the 5-HT challenge studies.¹ Three possible explanations are heterogeneity of the central serotonin biosynthetic status within the patients with chronic fatigue syndrome, measured as the ratio of serum tryptophan to the sum of its competing large neutral amino acids.⁴⁶ In our study, we do not know if the patients had a high serotonin status. If the patients in the ondansetron treatment group had a normal serotonin status, one could hypothesize that receptor antagonism could not be effective in these patients. However, we did not see any differences in the pattern of response between the placebo and the ondansetron group. For example, in both treatment groups, an equal number of 8 patients showed an improvement of more than 10 points in the CIS-fatigue severity.

In our clinical trial, we could detect changes over time in both groups. We have assessed the effects with validated instruments designed to assess different dimensions of chronic fatigue syndrome as well as treatment effects. In our trials on cognitive behavior therapy,¹⁵,¹⁶ those instruments were robust and reliable to show improvement at the group level as well as at the level of the individual patient. The negative findings in this randomized controlled trial cannot be explained by a power problem. In our opinion, it is very unlikely that a larger trial would detect a clinically relevant effect. The lack of significant differences on self-report outcome measures and physical activity strengthens our overall findings.

In conclusion, this randomized, placebo-controlled trial did not demonstrate any benefit in chronic fatigue syndrome–related outcome measures. Thus, the findings of this clinical trial do not support the use of 5-HT₃ antagonism in treating chronic fatigue syndrome–related symptoms.

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33. Van Breukelen GJ. ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. *J Clin Epidemiol*. 2006;59(9):920–925.


