

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

Gerard K. H. The, MD; Gijs Bleijenberg, PhD;
Jan K. Buitelaar, MD, PhD; and Jos W. M. van der Meer, MD, PhD, FRCP

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Corresponding author: Gerard K. H. The, MD, Radboud University Nijmegen Medical Centre, Department of Psychiatry, 966, Reinier Postlaan 10, 6525 GC Nijmegen, The Netherlands (g.the@aig.umcn.nl).

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-HT₃ receptor antagonists have shown promising results. In this randomized controlled clinical trial, the effect of ondansetron, a 5-HT₃ 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.¹ 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.² Of the many therapeutic interventions that have been undertaken, so far only cognitive behavioral therapy and graded exercise therapy are of proven effectiveness.^{3,4}

Neuroendocrinologic investigations have tried to elucidate the pathophysiology of chronic fatigue syndrome.⁵ Data in the literature support an important role for serotonin (5-hydroxytryptamine [5-HT]) in the pathophysiology of chronic fatigue syndrome.^{6–8} 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.⁹ Increased activity or metabolism of the 5-HT system have been implicated in the pathophysiology of chronic fatigue syndrome.^{10–13} 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.^{14–16}

Positive results of the use of 5-HT₃ inhibitors in the treatment of patients with chronic fatigue due to chronic hepatitis^{17,18} or fibromyalgia^{19,20} 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-HT₃ receptor antagonist.²¹ 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,¹ 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.²² 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)²³ 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.²¹ 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 al²⁴ 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).^{4,25,26} 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 35.²⁷ Patients who had chronic fatigue syndrome with a fatigue severity score of 35 or higher were included.

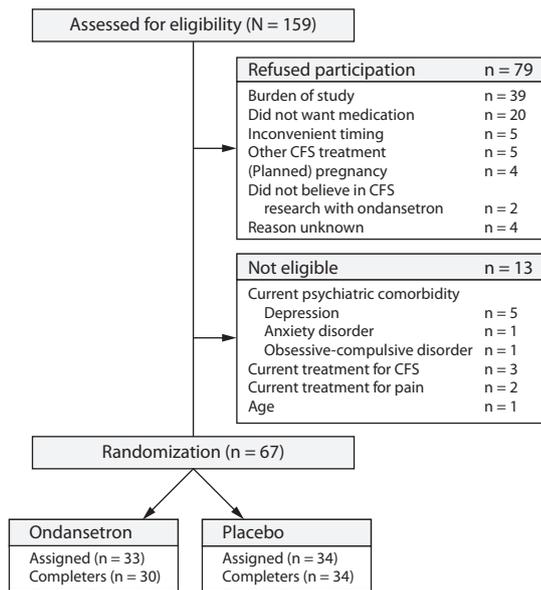
Functional impairment. The Sickness Impact Profile-8 (SIP-8) measures the influence of symptoms on daily functioning, using the following 8 subscales to rate both physical and psychological disability: home management, mobility, alertness behavior, sleep/rest, ambulation, social interactions, work, and recreation and pastimes.⁴ A total score was calculated by addition of the weights of items. This widely used measure has good reliability and validity.²⁸ 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

Figure 1. Participant Flow



Abbreviation: CFS = chronic fatigue syndrome.

Instruments Services, Radboud University Nijmegen Medical 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 (maximally 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

Table 1. Patient Characteristics^a

Characteristic	Ondansetron	Placebo	Significance	
	(n = 33)	(n = 34)	t	P
Age, y	35.8 (9.9)	34.7 (9.4)64
Sex, female	67	7454 ^b
CIS-fatigue	49.4 (6.3)	50.0 (4.7)	0.424	.67 ^c
SIP-8	1,375 (470)	1,359 (593.4)	0.117	.907 ^c
CDC symptoms	7.4 (1.4)	6.8 (2.1)	1.34	.183 ^c

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

^bChi-square test.

^cIndependent sample t test.

Abbreviations: CDC = US Centers for Disease Control and Prevention, CIS-fatigue = Checklist Individual Strength fatigue severity subscale, SIP-8 = Sickness Impact Profile-8.

of at least 1 standard deviation (SD) on the CIS-fatigue with a power of 90% and a 2-tailed significance level of 5%. Anticipating 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 imputation.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 psychiatric 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).

During the screening process, we obtained data from all the patients who did not want to participate.

There was no significant difference in age, number of CDC symptoms, fatigue severity, or functional impairment between the patients with chronic fatigue syndrome participating 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 ondansetron group had missing values for the posttreatment measurements. The main reason for discontinuing the trial

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

Outcome Measure	Ondansetron (n = 33)		Placebo (n = 34)		ANCOVA (df = 1,64)	
	Mean	SD	Mean	SD	F	P
Primary outcome measures						
CIS-fatigue					0.116	.73
Pretreatment	49.4	6.3	50.0	4.7		
Posttreatment	44.0	11.1	45.4	11.5		
SIP-8					1.077	.30
Pretreatment	1,375	470.0	1,359	593.4		
Posttreatment	1,063	525.5	1,172	694.6		
Secondary outcome measures						
Actometer					0.773	.38
Pretreatment	54.1	16.5	58.4	16.6		
Posttreatment	55.0	15.5	60.6	17.9		
DOF					0.015	.90
Pretreatment	8.5	2.0	8.4	2.0		
Posttreatment	7.9	2.4	7.8	2.8		

Abbreviations: ANCOVA = analysis of covariance, CIS-fatigue = Checklist Individual Strength fatigue severity subscale, DOF = daily observed fatigue, 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 score (worst case scenario) of the primary outcome measures. 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.²¹ 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^{34,35} and others,³⁶ 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 al³⁷ found a widespread reduction in the number or affinity of 5-HT_{1A} 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.³⁷

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.³⁸ Furthermore, evidence suggests an important role for the neurotransmitter serotonin in psychiatric disorders, such as in depression^{39,40} and in the pathophysiology and treatment of anxiety and panic attacks.^{41,42} 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.⁴³ 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

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-HT agonists have been used to assess 5-HT function in chronic fatigue syndrome. Studies with buspirone¹⁰ and *d*-fenfluramine^{11,12} 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.^{44,45} 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.⁵ One possible explanation is 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,^{4,26} 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.

Drug names: buspirone (BuSpar and others), granisetron (Sancuso, Kytril, and others), ondansetron (Zofran and others).

Author affiliations: Department of General Internal Medicine, Nijmegen Expert Centre Chronic Fatigue (Drs The, Bleijenberg, and van der Meer); and Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen Medical Centre (Drs The and Buitelaar), The Netherlands.

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