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# Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome

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## Summary

**Background** No somatic treatment has been found to be effective for chronic fatigue syndrome (CFS). Antidepressant therapy is commonly used. Fluoxetine is recommended in preference to tricyclic agents because it has fewer sedative and autonomic nervous system effects. However, there have been no randomised, placebo-controlled, double-blind studies showing the effectiveness of antidepressant therapy in CFS. We have carried out such a study to assess the effect of fluoxetine in depressed and non-depressed CFS patients.

**Methods** In this randomised, double-blind study, we recruited 44 patients to the depressed CFS group, and 52 to the non-depressed CFS group. In each group participants were randomly assigned to receive either fluoxetine (20 mg once daily) or placebo for 8 weeks. The effect of fluoxetine was assessed by questionnaires, self-observation lists, standard neuropsychological tests, and a motion-sensing device (Actometer), which were applied on the day treatment started and on the last day.

**Findings** The two groups were well matched in terms of age, sex distribution, employment and marital status, and duration of CFS. There were no significant differences between the placebo and fluoxetine-treated groups in the change during the 8-week treatment period for any dimension of CFS. There was no change in subjective assessments of fatigue, severity of depression, functional impairment, sleep disturbances, neuropsychological function, cognitions, or physical activity in the depressed or the non-depressed subgroup.

**Interpretation** Fluoxetine in a 20 mg daily dose does not have a beneficial effect on any characteristic of CFS. The lack of effect of fluoxetine on depressive symptoms in CFS suggests that processes underlying the presentation of depressive symptoms in CFS may differ from those in patients with major depressive disorder.

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## Introduction

Chronic fatigue syndrome (CFS) is characterised by persisting, disabling fatigue that does not subside with rest in bed and for which no medical explanation can be offered. As yet, no effective somatic treatment for CFS is known. Various drugs have been proposed for treatment of CFS<sup>1–4</sup> and antidepressants (notably fluoxetine) are commonly prescribed. CFS patients may tolerate first-generation tricyclic antidepressants poorly because side-effects include sedation and exacerbation of fatigue symptoms.<sup>5</sup> Lynch and colleagues<sup>6</sup> suggested the use of fluoxetine since this drug has fewer sedative and autonomic nervous system side-effects. Case-reports and uncontrolled studies suggested that fluoxetine is beneficial in CFS.<sup>2</sup> Lynch et al<sup>6</sup> reported that after 8 weeks of treatment a third of the mildly to moderately depressed CFS patients treated with fluoxetine showed reduction of at least 50% in severity of depressive symptoms, and another third showed between 25% and 50% reduction in symptom severity. However, the effectiveness of fluoxetine (or any other antidepressant) in the treatment of CFS has not been established in controlled studies.

In a previous study,<sup>7</sup> we developed and tested a multidimensional assessment method for CFS, which assessed the behavioural, cognitive, emotional, and social features of CFS. These dimensions proved to be independent of each other and contributed to the description of the patient. Therefore, in an intervention study both the effect of treatment on fatigue severity and other dimensions are of interest. We have assessed the effect of fluoxetine on the dimensions of CFS in a randomised, placebo-controlled, double-blind study. Fluoxetine is effective in treating depressive symptoms; since a proportion of patients with CFS have depression, two groups of patients were included—a depressed CFS group and a non-depressed CFS group. This design allowed us to separate any indirect effect of fluoxetine on fatigue and other dimensions through improvement in depression from a direct effect of fluoxetine.

## Patients and methods

### Patients

Patients had to fulfil criteria for CFS<sup>8</sup> and give informed written consent. Patients were randomly selected from our CFS database, acquired through self-referral, or referral by family doctors, to the outpatient clinic of the Department of General Internal Medicine, University Hospital Nijmegen. Patients had to have had fatigue for more than 1 year with substantial impairment in their daily life, which means a score of 35 or more on the subjective fatigue subscale of the checklist individual strength.<sup>7</sup> Depressed patients had to have a diagnosis of major depressive disorder<sup>9</sup> and a score on the Beck depression inventory of 16 or more (moderately to severely depressed). Non-depressed patients had to have a score on the Beck depression inventory of 10 or less (no depressive feelings at all). Psychiatric examination (SGSV supervised by FGZ) used a structured psychiatric interview. Fatigue and loss of energy were not counted as symptoms either in making the diagnosis of major depressive disorder or in calculating Beck depression inventory score.

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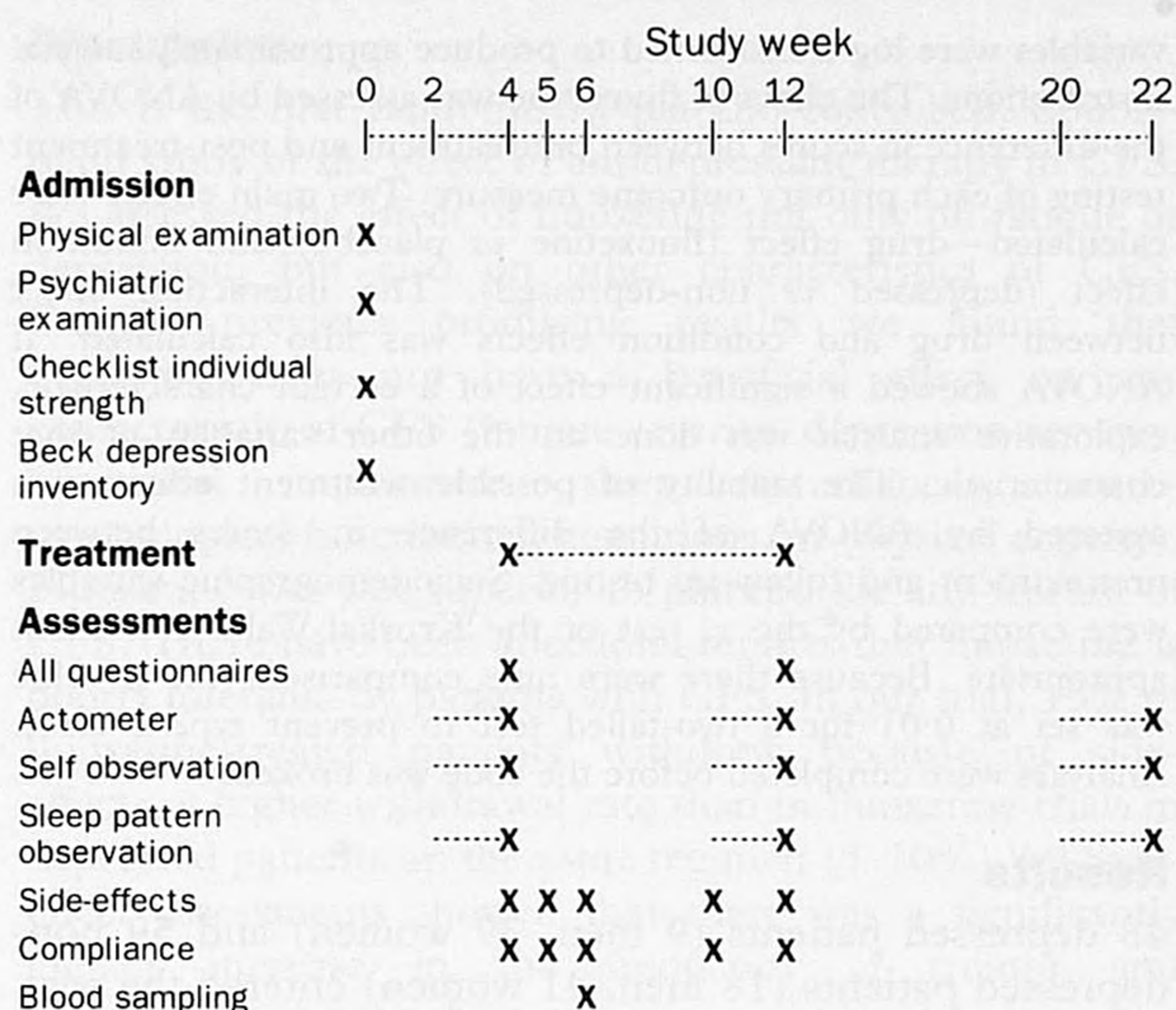


Figure 1: Study schedule

Exclusion criteria were: any physical illness that could explain the complaints; any psychiatric diagnosis besides major depressive disorder in depressed patients; any psychiatric diagnosis in non-depressed patients; pregnancy or lactation; lack of contraception in women of childbearing age; previous exposure to fluoxetine in a formal clinical trial; previous lack of satisfactory response to an adequate course of fluoxetine treatment; participation in recent clinical trials; use of any prescribed medication except incidental analgesics that could not be stopped; and current psychotherapy.

### Design

In each group patients were randomly assigned, in a double-blind manner, either fluoxetine or placebo by kit number (provided by Lilly Research Centre CT Supply Group, Windlesham, UK) per block of ten. Fluoxetine capsules (20 mg) were taken once a day. Duration of treatment with fluoxetine or placebo was 8 weeks. Compliance and side-effects were assessed after 1 week, 2 weeks, and 6 weeks of treatment (figure 1). Blood samples were taken after 2 weeks of treatment for measurement of fluoxetine concentrations by a high-performance liquid chromatography system with spectrophotometric detection at 230 nm. To assess changes in CFS features, the tests were done on the day treatment started (pretreatment) and on the last day of treatment (post-treatment). Follow-up testing took place 2 months after treatment had stopped to assess the stability of possible effects of fluoxetine. The study was approved by the ethics committee of the hospital.

### Psychological tests

The subjective feeling of fatigue was measured by the subjective fatigue subscale of the checklist individual strength.<sup>7</sup> On the self-observation list, fatigue was measured 4 times a day on a 4-point scale (daily observed fatigue score). Patients completed the self-observation list during the 12 days before the start of treatment, during the last 12 days of treatment, and during the 12 days before follow-up testing. The scores were combined as one primary outcome measure.

The Beck depression inventory<sup>10,11</sup> was used to measure severity of depression. The symptom checklist is an indicator of psychological well-being.<sup>12</sup> The total score was used as the primary outcome measure.

The sickness impact profile<sup>13,14</sup> measures the influence of symptoms in different areas of daily functioning. The total score was used as the primary outcome measure.

The physical activities subscale of the checklist individual strength measures the extent of physical activity. On the 12-day self-observation list, physical activity is rated daily on a 7-point scale (daily observed activity score). Patients wore a motion-sensing device (the Actometer), day and night, during this

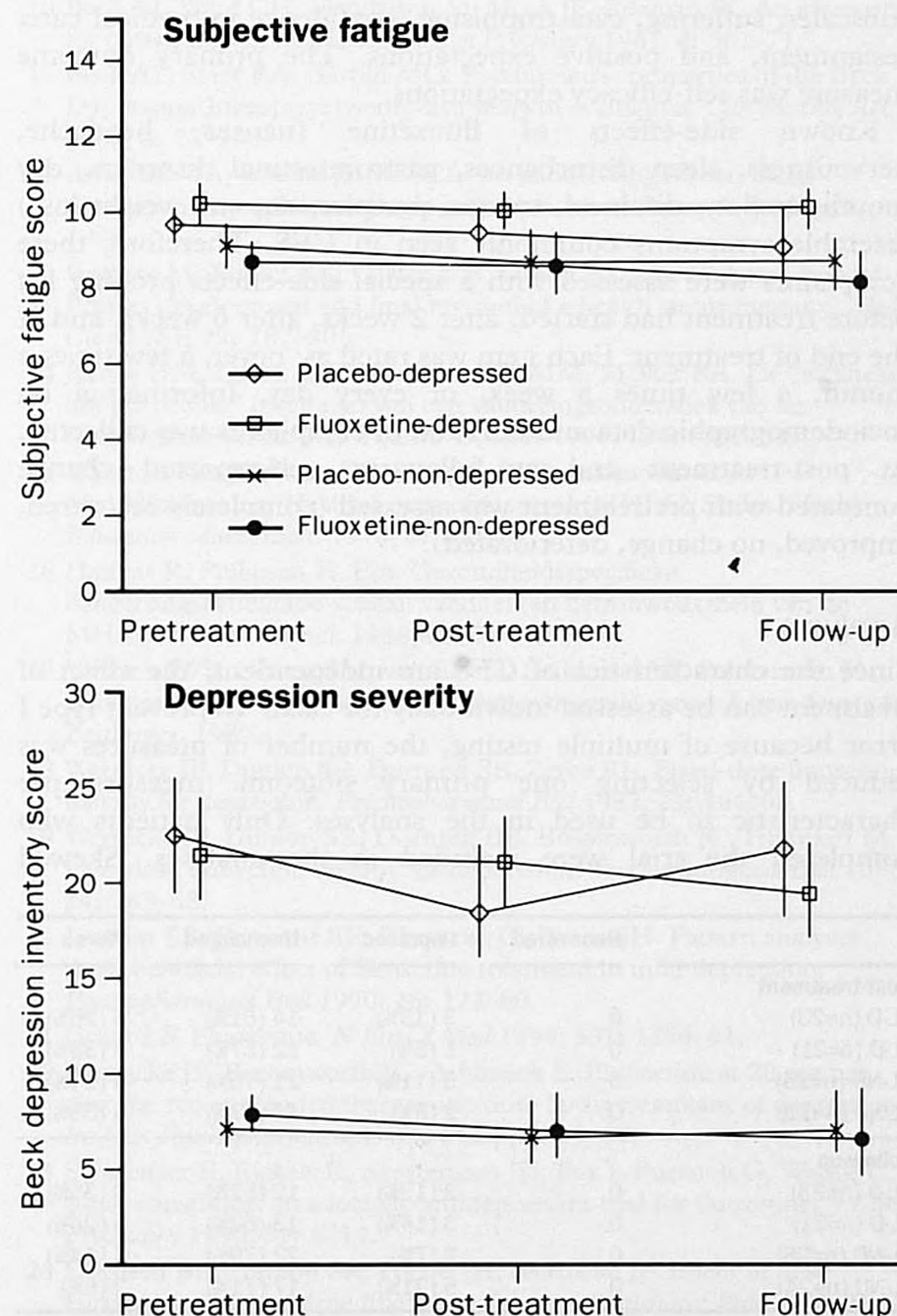
	Placebo (n=53)	Fluoxetine (n=54)
Trial completed	41 (96%)	45 (83%)
Skin reactions	1 (2%)	3 (6%)
Haematoma	..	1 (2%)
Nausea	..	2 (4%)
Headache	1 (2%)	2 (4%)
Personal reason	..	1 (2%)

Table 1: Patients entering trial and reasons for dropout

12-day period. The Actometer is the size of a matchbox and attached to the ankle; it measures the number of movements in 5-minute periods. Data are read by a personal computer and mean is calculated as the primary outcome measure.

The subscale on sleep problems of the symptom checklist<sup>12</sup> was used. On the 12-day self-observation list, quality of sleep (slept well, difficulty falling asleep, restless sleep, early awakening in the morning) is recorded daily (daily observed quality of sleep scores). Each score is expressed as a percentage of occurrence. A special sleep pattern observation list was completed in combination with the 12-day self-observation list and Actometer readings. Patients recorded daily, every 30 min, whether they were resting, asleep, or awake. The following variables were calculated over the 12-day period: hours asleep at night, hours asleep during the day, hours awake before falling asleep, hours awake during the night, hours staying in bed after waking up in the morning, and hours resting during the day (daily observed sleep pattern scores). The daily observed sleep quality score was used as the primary outcome measure.

Neuropsychological functioning was measured by the concentration subscales of the checklist individual strength and the sickness impact profile. Memory and concentration complaints were rated daily on the 12-day self-observation list. This feature was also assessed by standard neuropsychological



Data are group means with 95% CI.

Figure 2: Subjective fatigue scores and Beck depression inventory scores in four study groups



	Placebo depressed (n=23)	Fluoxetine depressed (n=21)	Placebo non-depressed (n=28)	Fluoxetine non-depressed (n=24)
Age (years)	38.5 (10.1)	39.9 (8.6)	37.8 (11.9)	39.8 (7.4)
Sex (M/F)	5/18	3/18	9/19	6/18
Median (range) duration of complaints years	6 (2-20)	5 (1-30)	6 (2-30)	5 (1-20)
<b>Marital status</b>				
Married/cohabiting	19 (38%)	14 (67%)	16 (57%)	19 (79%)
Divorced	1 (4%)	2 (9%)	1 (4%)	2 (8%)
Widowed	0	1 (5%)	1 (4%)	0
Single	3 (13%)	4 (19%)	10 (35%)	3 (13%)
<b>Employment status</b>				
Working	2 (9%)	2 (10%)	9 (32%)	4 (17%)
Housewife	7 (30%)	3 (14%)	3 (11%)	4 (17%)
Unemployed	2 (9%)	1 (5%)	0	0
Disablement benefits/ sick leave	11 (48%)	15 (71%)	13 (46%)	16 (66%)
Other	1 (4%)	0	3 (11%)	0

Table 2: Demographic data

tests. Speed of information processing was measured by the complex reaction-time test which consisted of three consecutive tasks of increasing complexity; reaction time and motor speed were separately registered. Baseline reaction time was the primary outcome measure for this dimension.

General questions were asked about satisfaction in social life and difficulties in social relationships. The social interactions subscale of the sickness impact profile was used as the primary outcome measure.

Sense of control over symptoms (self-efficacy expectations) were measured by a specific question (5-point scale) and the internal attributions subscale of the multidimensional health locus of control questionnaire.<sup>15,16</sup> The modified pain cognition list<sup>17</sup> measured fatigue-related cognitions; it contained five subscales: suffering, catastrophising, confidence in medical care, resignation, and positive expectations. The primary outcome measure was self-efficacy expectations.

Known side-effects of fluoxetine (nausea, headache, nervousness, sleep disturbances, gastrointestinal disorders, dry mouth, anxiety, dizziness, tremor, perspiration, and weight loss) resemble symptoms commonly seen in CFS. Therefore, these complaints were assessed with a special side-effects probing list before treatment had started, after 2 weeks, after 6 weeks, and at the end of treatment. Each item was rated as: never, a few times a month, a few times a week, or every day. Information on sociodemographic data and duration of complaints was collected. At post-treatment and at follow-up, self-reported change compared with pretreatment was assessed (completely recovered, improved, no change, deteriorated).

### Analysis

Since the characteristics of CFS are independent, the effect of treatment can be assessed individually for each. To prevent type I error because of multiple testing, the number of measures was reduced by selecting one primary outcome measure per characteristic to be used in the analyses. Only patients who completed the trial were included in the analyses. Skewed

variables were log-transformed to produce approximately normal distributions. The effect of fluoxetine was assessed by ANOVA of the difference in scores between pretreatment and post-treatment testing of each primary outcome measure. Two main effects were calculated—drug effect (fluoxetine *vs* placebo) and condition effect (depressed *vs* non-depressed). The interaction effect between drug and condition effects was also calculated. If ANOVA showed a significant effect of a certain characteristic, explorative analysis was done on the other variables of that characteristic. The stability of possible treatment effects was assessed by ANOVA of the difference in scores between pretreatment and follow-up testing. Sociodemographic variables were compared by the  $\chi^2$  test or the Kruskal-Wallis test when appropriate. Because there were nine comparisons the p value was set at 0.01 for a two-tailed test to prevent type I error. Analyses were completed before the code was broken.

### Results

48 depressed patients (9 men, 39 women) and 59 non-depressed patients (18 men, 41 women) entered the trial. Of the 107 patients, 96 completed the trial. 15% of patients in the fluoxetine group stopped treatment because of side-effects versus 4% of placebo-treated patients (table 1). There were no significant differences between the groups in employment or marital status, sex, age, or duration of complaints (table 2).

There was no difference between the fluoxetine-treated group and placebo groups in the change from pretreatment to post-treatment for any primary outcome measure assessing subjective fatigue (figure 2), depression (figure 2), psychological well-being, functional impairment, physical activity, sleep disturbances, neuro-psychological functioning, social interactions, or cognitions. The mean differences between fluoxetine and placebo in improvement in fatigue severity and depression severity were  $-0.164$  (95% CI  $-0.64$  to  $0.31$ ) and  $-0.186$  ( $-0.35$  to  $-0.02$ ), respectively. Thus, in the most extreme case fluoxetine would yield an improvement of 0.31 (3%) in fatigue and 2% in depression severity. In both cases the improvement is not clinically meaningful. This study therefore has sufficient power.

At follow-up there were no differences between the fluoxetine-treated and placebo groups for any variable assessing the characteristics of subjective fatigue or depression (figure 2).

No patient reported complete recovery (table 3). There was a trend for a drug effect on self-reported change at post-treatment ( $p=0.052$ ), when patients from the fluoxetine group were more likely to report deterioration. There were no effects on self-reported change at follow-up testing.

After 2 and 6 weeks of treatment, there were no differences between the actively treated and placebo groups in the frequency of any of the possible fluoxetine side-effects. At the end of treatment, more fluoxetine-treated than placebo-treated patients complained of tremor (drug effect,  $p=0.006$ ) and perspiration (drug effect,  $p=0.008$ ). For complaints that occurred at least a few times a week, 10 (22%) of fluoxetine-treated patients complained of tremor and 23 (51%) complained of perspiration at the start of treatment (placebo group, 12 [24%] and 17 [33%], respectively). At post-treatment, 18 (40%) of fluoxetine-treated patients complained of tremor and 67% of perspiration (placebo group, 30 [26%] and 20 [40%], respectively).

Fluoxetine was detected in plasma in all patients of the fluoxetine group (median 40 mg/L [range 13–134]), but in no patients of the placebo group.

	Recovered	Improved	Unchanged	Worse
<b>Post-treatment</b>				
PL-D (n=23)	0	3 (13%)	14 (61%)	6 (26%)
FL-D (n=21)	0	1 (5%)	12 (57%)	8 (38%)
PL-ND (n=28)	0	3 (11%)	21 (75%)	4 (14%)
FL-ND (n=23)	0	2 (8%)	13 (57%)	8 (35%)
<b>Follow-up</b>				
PL-D (n=23)	0	3 (13%)	12 (52%)	8 (35%)
FL-D (n=21)	0	3 (14%)	13 (62%)	5 (24%)
PL-ND (n=28)	0	2 (7%)	22 (79%)	4 (14%)
FL-ND (n=24)	0	5 (21%)	17 (71%)	2 (8%)

PL-D= placebo-depressed; FL-D=fluoxetine-depressed; PL-ND=placebo-non-depressed; FL-ND=fluoxetine-non-depressed. Percentages are row percentages.

Table 3: Self-reported change reported at post-treatment and follow-up testing



## Discussion

This is the first randomised, placebo-controlled, double-blind study of the effect of antidepressant therapy in CFS. We assessed the effect of fluoxetine not only on fatigue or depression, but also on other characteristics of CFS. Despite previous promising results we found that fluoxetine does not have a beneficial effect on any characteristic of CFS (fatigue severity, depression severity, functional impairment, sleep disturbances, neuropsychological functioning, cognitions, or physical activity). Fluoxetine was not superior to placebo for any feature of CFS. There have been anecdotal reports that fluoxetine is poorly tolerated by patients with CFS. In our trial, 15% of fluoxetine-treated patients withdrew because of side-effects, a higher withdrawal rate than in fluoxetine trials in depressed patients on the same regimen (5–10%).<sup>18–20</sup> Side-effect assessments showed that there was a significantly greater increase in the frequency of tremor and perspiration during the treatment period, compared with pretreatment, in the fluoxetine group. We found that, in patients with several complaints, the frequencies of side-effects before treatment must be taken into account. Many patients reported side-effects at the end of treatment, but most of them had reported these complaints before treatment started.

We do not know whether a dose higher than the 20 mg daily we used may yield a better effect. No dose-effect relation in fluoxetine has been established, and a dose of 5 mg daily is effective in major depressive disorder.<sup>21</sup> In depressed patients, an increase of the dose to 60 mg daily in those who did not respond to 20 mg daily was no more effective than continuation.<sup>22–24</sup> In our study 20 mg daily was ineffective for CFS, and side-effects caused 15% of patients to withdraw. Higher doses of fluoxetine may cause higher drop-out rates because of increased side-effects.<sup>21</sup> The lack of effect of fluoxetine on depressive symptoms is surprising. Gram's review of the effectiveness of fluoxetine in depressed patients<sup>21</sup> concluded that fluoxetine is an effective antidepressant. However, in our study fluoxetine was no better than placebo in treating depression. This finding cannot be explained by differences in pretreatment depression severity or by non-compliance. At intake, patients were diagnosed as depressed according to DSM III-R criteria, which include affective, somatic, and cognitive symptoms.<sup>9</sup> Somatic symptoms and cognitive symptoms are commonly reported by patients with CFS, irrespective of whether they are depressed, and therefore these symptoms may not be related to disturbed mood in CFS. Moreover, Beck depression inventory score is also based on these three symptom groups, and an effect of fluoxetine on affective symptoms might then be masked by the absence of an effect on cognitive and somatic symptoms. To test this hypothesis we did additional analyses on three subsets of Beck depression inventory items, divided into affective, cognitive, and somatic items. In the fluoxetine group there were no significant changes in any of these subscores.

Our results have theoretical implications on the role of depression in CFS. There may be differences in underlying processes of depressive symptoms between CFS patients with depressive comorbidity and patients with major depressive disorder. Even the presentation of affective symptoms may not imply disturbed mood in CFS as it does in major depressive disorder. Fluoxetine is a selective serotonin reuptake inhibitor. We found that in depressed CFS patients disturbed serotonin processes are

unlikely to be involved in the presentation of depression-like symptoms. This conclusion is supported by a study of serotonin processes in CFS.<sup>25</sup> Yatham et al found no differences in fenfluramine-induced prolactin and cortisol responses between CFS patients and healthy controls.

We conclude that prescription of 20 mg fluoxetine in CFS is unwarranted, irrespective of whether depressive symptoms are present; it does not lead to improvement in any area of the patient's functioning.

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