



# Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial

Sanne L Nijhof, Gijs Bleijenberg, Cuno S P M Uiterwaal, Jan L L Kimpen, Elise M van de Putte

## Summary

Lancet 2012; 379: 1412–18

Published Online

March 1, 2012

DOI:10.1016/S0140-6736(12)60025-7

See Comment page 1372

Department of Paediatrics, Wilhelmina Children's Hospital (S L Nijhof MD, Prof Jan L L Kimpen PhD, E M van de Putte PhD), and Julius Centre for Health Sciences and Primary Care (C S P M Uiterwaal PhD), University Medical Centre Utrecht, Netherlands; and Expert Centre for Chronic Fatigue, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands (Prof G Bleijenberg PhD)

Correspondence to: Dr Sanne L Nijhof, University Medical Centre Utrecht, Department of Paediatrics, Office KE 04.133.1, Postbox 85090, 3508 AB, Utrecht, Netherlands s.l.nijhof@umcutrecht.nl

**Background** Chronic fatigue syndrome is characterised by persistent fatigue and severe disability. Cognitive behavioural therapy seems to be a promising treatment, but its availability is restricted. We developed Fatigue In Teenagers on the interNET (FITNET), the first dedicated internet-based therapeutic program for adolescents with this disorder, and compared its effectiveness with that of usual care.

**Methods** Adolescents aged 12–18 years with chronic fatigue syndrome were assigned to FITNET or usual care in a 1:1 ratio at one tertiary treatment centre in the Netherlands by use of a computer-generated blocked randomisation allocation schedule. The study was open label. Primary outcomes were school attendance, fatigue severity, and physical functioning, and were assessed at 6 months with computerised questionnaires. Analysis was by intention to treat. Thereafter, all patients were offered FITNET if needed. This trial is registered, number ISRCTN59878666.

**Findings** 68 of 135 adolescents were assigned to FITNET and 67 to usual care, and 67 and 64, respectively, were analysed. FITNET was significantly more effective than was usual care for all dichotomised primary outcomes at 6 months—full school attendance (50 [75%] vs 10 [16%], relative risk 4·8, 95% CI 2·7–8·9;  $p < 0\cdot0001$ ), absence of severe fatigue (57 [85%] vs 17 [27%], 3·2, 2·1–4·9;  $p < 0\cdot0001$ ), and normal physical functioning (52 [78%] vs 13 [20%], 3·8, 2·3–6·3;  $p < 0\cdot0001$ ). No serious adverse events were reported.

**Interpretation** FITNET offers a readily accessible and highly effective treatment for adolescents with chronic fatigue syndrome. The results of this study justify implementation on a broader scale.

**Funding** Netherlands Organisation for Health Research and Development.

## Introduction

Chronic fatigue syndrome, also known as myalgic encephalomyelitis or myalgic encephalopathy, is characterised by disabling persistent (>6 months) or relapsing severe unexplained fatigue that is not the result of ongoing exertion and cannot be alleviated by rest. This fatigue is accompanied by other symptoms such as muscle pain and difficulty concentrating.<sup>1</sup> In adolescents, chronic fatigue syndrome often has a protracted course that can lead to much absence from school and long-term detrimental effects on their academic and social development.<sup>2–5</sup>

The prevalence of chronic fatigue syndrome has been estimated to be between 0·11% and 1·29% in Dutch, British, and US adolescent populations, with a female-to-male ratio from 2:1 to 5:1.<sup>6–11</sup> Most recent estimations of incidence and prevalence based on diagnosis by the physician are lower than those based on population surveys.<sup>6</sup> The lack of treatment options might contribute to physicians being reticent about diagnosing chronic fatigue syndrome.

The results of a 13 years' follow-up study showed that most adolescents had persistent mild-to-moderate symptoms and disruption of school attendance.<sup>11</sup> Although untreated chronic fatigue syndrome has a better prognosis in adolescents than in adults, the risk of

disruption to social development and education in adolescents requires prompt diagnosis of the syndrome and an effective and accessible treatment.<sup>11–13</sup>

The cause of chronic fatigue syndrome is not known, but research has shown that differentiation of triggering, sustaining, and precipitating factors at the biological and psychosocial levels, especially for treatment, would be useful.<sup>12,14</sup> Patients' cognition of perpetuating factors is used in cognitive behavioural therapy, which seems promising in adolescents. Until now, cognitive behavioural therapy for adolescents with chronic fatigue syndrome has only been compared with patients being on a waiting list or receiving psychoeducation, but not treatment as usual, and resulted in a clinically significant improvement of 60–70% directly after treatment.<sup>12,15</sup> The biggest challenge associated with cognitive behavioural therapy is its restricted availability due to the requirement for specialised skills,<sup>12,15</sup> leading to unequal access for adolescent patients. Therefore, alternative ways to enhance the availability of cognitive behavioural therapy are of paramount importance.

Internet-based cognitive behavioural therapy might improve access to treatment.<sup>16,17</sup> It was shown to be effective in patients with illnesses other than chronic fatigue syndrome, but mostly in adults. For adolescents, it has been developed for disorders such as depression,<sup>18</sup>

anxiety,<sup>19</sup> and headache,<sup>20</sup> and for smoking cessation,<sup>21</sup> but not for chronic fatigue syndrome.

We developed Fatigue In Teenagers on the interNET (FITNET), a comprehensive internet-based application based on existing protocols and a theoretical model of effective face-to-face cognitive behavioural therapy for adolescents,<sup>12,22,23</sup> specifically for those with chronic fatigue syndrome and their parents. In this program, a skilled therapist would provide support through regular e-mail consultations (e-consultations). We compared the short-term effectiveness of the FITNET program with usual care in reduction of fatigue, school absence, and physical dysfunction in adolescents with chronic fatigue syndrome.

## Methods

### Study population

A detailed description of the study protocol and FITNET program has been reported elsewhere.<sup>24</sup> This trial was undertaken at the Wilhelmina Children's Hospital, University Medical Centre Utrecht (UMCU), Utrecht, and the Expert Centre for Chronic Fatigue (ECCF, treatment coordinating centre), Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. All children were referred to, examined, and randomly assigned at the UMCU.

To achieve nationwide referral, all Dutch paediatricians were personally informed about the FITNET trial and referral options.<sup>24</sup> All adolescents with fatigue who were referred to the outpatient clinic of the Department of Paediatrics, UMCU, and the outpatient clinic of ECCF were assessed in the UMCU by a paediatrician specialised in chronic fatigue syndrome. They underwent a uniform diagnostic workup, consisting of a detailed history and physical and laboratory examinations. Once the diagnosis of chronic fatigue syndrome was established, study eligibility was assessed with computerised questionnaires. Patients were eligible if they were aged 12–18 years, could read and write Dutch, had access to a computer with internet connection, and met the criteria for chronic fatigue syndrome as defined by the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA.<sup>1</sup> We chose the CDC criteria because these are the most used in the Netherlands by paediatricians.<sup>6</sup> Severe fatigue was defined as a score of 40 or more on the fatigue severity subscale of the checklist individual strength-20 (CIS-20),<sup>12,25</sup> and functional impairment as a score of 85 or less on the child health questionnaire (CHQ-CF87) physical functioning subscale,<sup>26</sup> or a school attendance of 85% or less.<sup>24</sup> Exclusion criteria were primary depression, anxiety disorder, or suicidal risk, as assessed with computerised self-reported questionnaires (Dutch translation of the child depression inventory<sup>27</sup> and state-trait anxiety inventory for children<sup>28</sup>). If scores were abnormal,<sup>24</sup> a skilled psychologist undertook a clinical assessment to exclude primary depression or anxiety.

The study protocol was approved by the ethics boards of both institutions. Oral and written consent was obtained from patients who were willing to participate and their parents (one or both), according to the Declaration of Helsinki.

### Randomisation and masking

The random allocation sequence was computer-generated with a block size of six by the data management section of the Julius Centre for Health Sciences and Primary Care, Utrecht, Netherlands. Participants were randomly assigned in a 1:1 ratio. The study was open label and the primary investigator, who was not the treating physician, informed the participants about their allocated treatment. Data for primary outcomes were assessed by use of a computer.

For the FITNET program see <http://www.fitnet.umcutrecht.nl>

### Interventions

The FITNET program was run on a dedicated hospital network (in Dutch). The portal layout for the program was specifically designed for adolescents. Patients' data and e-mails were encrypted and securely stored on the UMCU mainframes to guarantee privacy and confidentiality.

The FITNET program consisted of two sections. The psychoeducational section could be accessed after the adolescents received their log-in codes. The cognitive behavioural therapy section consisted of 21 interactive modules,<sup>22,24</sup> accessible after activation by the therapist. The patients received support from trained cognitive behavioural psychotherapists from the ECCF, solely through e-consults. At the start of the trial, two therapists had several years of experience as behavioural therapists (5 years and 10 years), and three were in the first year of their practical training as behavioural therapists. All five were given equal caseloads of patients. The FITNET therapists were not involved in usual care.

Patients were able to log in and compose and send e-mails at any time. According to an individually tailored treatment, therapists responded to the e-consults on a set day once a week and thereafter once every 2 weeks. The patient would receive an immediate response to an emergency email. Additionally, for emergency situations, telephone contact details were available to the patients.

Parents followed a parallel program, and had the same frequency of e-mail contacts wherein results so far were discussed and new assignments were given. The parents' portal consisted of the module's content, psychoeducation, and an e-consult application. The patients' portal was more detailed than was the parents' with diaries, questionnaires, and a review function of all passed modules. Patients and parents had separate accounts with unique usernames and passwords, and were not able to see each other's e-consult responses, ensuring confidentiality in communication with the therapist. The parents of patients younger than 15 years were instructed to coach their children, whereas those of older patients were asked to encourage their children to take responsibility for their treatment. Return to

full-time education was the aim of treatment and was discussed early in therapy. Patients assigned to FITNET agreed not to undergo any further medical examinations or to receive other treatments for fatigue while undergoing treatment.

The FITNET therapist and school mentor had at least one communication about school attendance and the school's effort to encourage treatment compliance. The school mentor acted as a coach, adviser, or tutor when needed. School mentors were sent a standard letter at the commencement of treatment asking them for their cooperation and consideration.

The patients in the control group were given usual care, which included individual or group-based rehabilitation

programmes, cognitive behavioural therapy face-to-face, or graded exercise treatment, or both, by a physical therapist. Records were kept of all the care given. Adolescents assigned to usual care were given the opportunity to attend FITNET after 6 months.

### Outcomes

The primary outcomes were school attendance, fatigue, and physical functioning, and were assessed at 6 months and then reassessed at 12 months. School attendance was measured as the proportion of classes attended, expressed as a percentage of the normal school schedule. It was recorded daily on a 24 h timetable of the self-observation list 12 days before testing.<sup>29</sup> On the day of testing, the past 2 weeks of school attendance were validated with a general questionnaire and checked with the parents. During FITNET treatment, the therapist and school mentor were in contact about the school plan and attendance when needed. Fatigue was measured with the subscale fatigue severity of the CIS-20 (range 8–56). The questionnaire has good reliability and discriminative validity with good internal consistency (Cronbach's  $\alpha=0.93$ ).<sup>12,25</sup> Physical functioning was measured with the subscale physical functioning of the CHQ-CF87 (0–100%). This assessment method is reported to be reliable and has been validated with a good internal consistency (Cronbach's  $\alpha=0.86$ ).<sup>26</sup>

The secondary outcome was self-rated improvement, for which patients could indicate whether they were completely recovered, felt much better, had the same complaints, or had become worse than with the previous measurement.<sup>12,29</sup> It was measured at 6 months and then at the 12 months' reassessment.

### Recovery

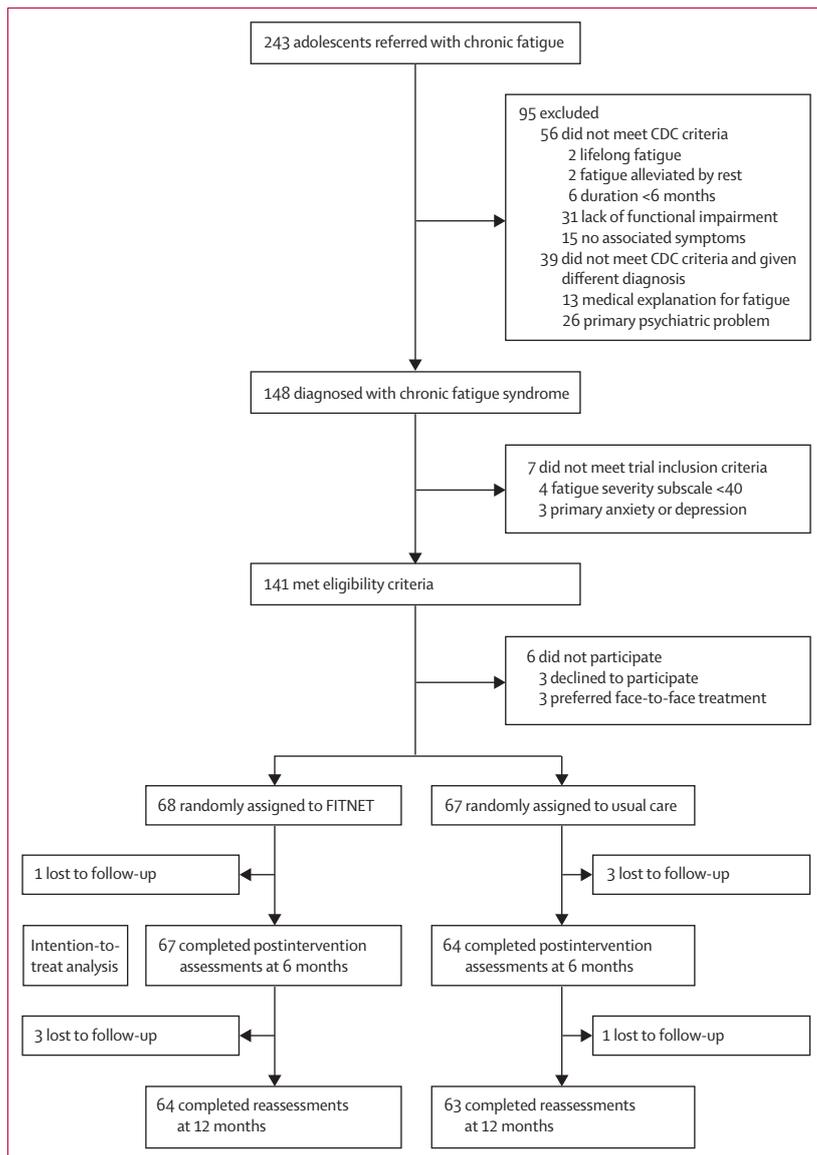
Recovery was defined post hoc, in relation to healthy peers ( $\pm 2$  SD), as having a fatigue severity score of less than 40,<sup>6,12,30</sup> physical functioning score of 85% or more,<sup>6,26</sup> and school absence of 10% or less in the past 2 weeks,<sup>6</sup> all assessed at 6 months. Additionally, patients were only judged to be recovered if they had rated themselves as being completely recovered or as feeling much better according to the secondary outcome questionnaire.<sup>12</sup>

### Semistructured interview

All patients treated with FITNET and their parents (one or both) were interviewed about their experiences and satisfaction with the intervention. The interviews were semistructured, with open questions guided by a topic list (scale of 10 points, questionnaire especially developed for this study). Different aspects of this internet-based program were assessed to evaluate and improve the FITNET program, such as text, layout, feedback by the therapist, scheduling of modules, and technical experience.

### Statistical analysis

With an estimated school absence after usual care of 40%, sample size calculations showed that 60 patients would



**Figure:** Trial profile

CDC=Centers for Disease Control and Prevention. FITNET=Fatigue In Teenagers on the interNET.

have to be allocated to each group to detect an increase in school attendance of 15% in the FITNET group, with a two-sided  $\alpha$  of 0.05 and 90% power. To compensate for a small anticipated proportion of patients and their parents not participating, we aimed to include 140 patients diagnosed with chronic fatigue syndrome. No interim analysis of the data was planned or undertaken. Data were analysed on an intention-to-treat basis.

The analysis of effectiveness was done with data obtained after 6 months of treatment with FITNET therapy or usual care. Effects on main outcomes were expressed as relative risks and mean group differences, each with 95% CIs. Differences between groups in the amount of change in the primary outcome variables were calculated with independent samples Student's *t* test. Additionally, linear regression was used to adjust for possible confounding factors, like age, sex, and baseline scores of anxiety, depression, and primary outcomes. All analyses were done with SPSS (version 16.0).

After completion of the randomly assigned treatment at 6 months, the patients who had not recovered were offered a crossover to either FITNET or usual care. All randomly assigned patients were invited for reassessments of primary outcomes at 12 months. Data for these reassessments are described without statistical analysis.

This trial is registered, number ISRCTN59878666.

### Role of the funding source

The sponsor of the study had no role in study design, data gathering, data analysis, and data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

148 adolescents who were diagnosed with chronic fatigue syndrome were screened for eligibility between January, 2008, and February, 2010. 135 (96%) of 141 eligible patients were enrolled (figure). The baseline characteristics of the enrolled adolescents ( $n=135$ ) and those who did not want to participate ( $n=6$ ) did not differ (data not shown). No patients were excluded after randomisation. Table 1 shows the baseline characteristics of both groups. All patients started the treatment they were assigned to. The baseline characteristics of four of 135 patients who were lost to follow-up did not differ from those of patients who adhered to the study schedule. Of the patients lost to follow-up (telephone interview), two had reported that they had recovered and no longer wanted to be reminded of chronic fatigue syndrome (one assigned to FITNET and one to usual care), and two who were not recovered wanted to continue the treatment but felt no need to come back for the postintervention assessment (both assigned to usual care).

In the usual care group, 38 (57%) of 67 participants received more than one treatment. Usual care involved cognitive behavioural therapy (44 [66%]), rehabilitation

treatment (inpatient or outpatient treatment, individual or group programme; 15 [22%]), physical treatment (mostly graded exercise therapy; 33 [49%]), or alternative treatment (16 [24%]). Only seven (10%) adolescents did not receive any treatment because treatment was not available within an acceptable travelling distance.

Increase in school attendance was significantly higher in the FITNET group than in the usual care group, and patients in the FITNET group were significantly less fatigued and functionally impaired (table 2). A significantly greater proportion of adolescents in the FITNET group reported improvement—ie, answered “yes” to the statement “I have completely recovered” or “I feel much better but still experience some symptoms” and more

	FITNET (n=68)	Usual care (n=67)
Age at entry (years)	15.9 (1.3)	15.8 (1.3)
Girls	54 (79%)	57 (85%)
Education level*		
Low	16 (24%)	25 (37%)
Medium	24 (35%)	21 (31%)
High	28 (41%)	21 (31%)
Duration of symptoms at entry (months)	16.0 (6–84)	19.0 (6–108)
Onset of disease		
Acute	11 (16%)	7 (10%)
Gradual	38 (56%)	43 (64%)
After infection	19 (28%)	17 (25%)
School attendance		
Continuous	39.5% (29.4)	45.1% (32.6)
$\geq 85\%$	4 (6%)	9 (13%)
$< 85\%$	64 (94%)	58 (87%)
Fatigue severity (CIS-20, range 8–56)	51.2 (4.4)	51.6 (4.6)
Physical functioning (CHQ-CF87, range 0–100)	60.7 (14.5)	56.8 (20.9)
Somatic complaints (CSI, range 0–132)	33.3 (13.6)	34.7 (12.9)
Depression score (CDI, range 0–54)	11.6 (5.2)	11.0 (5.2)
$\geq 16$	14 (21%)	9 (13%)
Anxiety score (STAIC, range 20–60)	32.7 (8.8)	32.3 (8.0)
$\geq 44$	9 (13%)	6 (9%)

Data are number (%), mean (SD), or median (range). FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire. CSI=children's somatisation inventory. CDI=children's depression inventory. STAIC=state-trait anxiety inventory for children. \*After 6 years of general primary school, at the age of 12 years, students enter low (4 years), medium (5 years), or high (6 years) secondary education.

**Table 1: Baseline characteristics of the study population in FITNET and usual care groups**

	FITNET (n=67)	Usual care (n=64)	Mean difference (95% CI)	p value
School attendance	84.3% (29.5)	51.7% (34.1)	32.6% (21.5 to 43.6)	<0.0001
Fatigue severity (CIS-20, range 8–56)	24.0 (13.4)	42.3 (13.1)	-18.3 (-22.9 to -13.7)	<0.0001
Physical functioning (CHQ-CF87, range 0–100)	88.5 (13.8)	70.1 (17.6)	18.4 (12.9 to 23.9)	<0.0001

Data are mean (SD), unless otherwise indicated. FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire.

**Table 2: Effect of treatment at 6 months on fatigue severity, functional impairment, and school attendance in FITNET and usual care groups**

	FITNET (n=67)	Usual care (n=64)	Relative risk (95% CI)	Number needed to treat	p value
<b>Primary outcomes</b>					
Full school attendance*	50 (75%)	10 (16%)	4.8 (2.7–8.9)	1.7	<0.0001
Fatigue severity (CIS-20)†	57 (85%)	17 (27%)	3.2 (2.1–4.9)	1.7	<0.0001
Physical functioning (CHQ-CF87)‡	52 (78%)	13 (20%)	3.8 (2.3–6.3)	1.8	<0.0001
<b>Secondary outcome</b>					
Self-rated improvement§	52 (78%)	17 (27%)	2.9 (1.9–4.5)	2.0	<0.0001
<b>Combined</b>					
Primary outcomes	44 (66%)	5 (8%)	8.4 (3.6–19.8)	1.7	<0.0001
Primary and secondary outcomes	42 (63%)	5 (8%)	8.0 (3.4–19.0)	1.8	<0.0001

Data are number (%), unless otherwise indicated. FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire. \*School absence of 10% or less. †Cutoff score of less than 40. ‡Cutoff score of 85% or more. §Answer “yes” to statement “I have completely recovered” or “I feel much better but still experience some symptoms”.

**Table 3: Recovery at 6 months in FITNET and usual care groups**

	Number*	School attendance	Fatigue severity (CIS-20, range 8–56)	Physical functioning (CHQ-CF87, range 0–100)
FITNET (at 6 months)	64	89.1% (22.2)	26.2 (13.5)	86.7 (18.7)
Recovered	41	96.3% (8.6)	21.0 (10.6)	89.8 (18.6)
Not recovered, continued FITNET	12	89.8% (17.6)	31.3 (12.9)	86.7 (14.0)
Not recovered, crossed over to usual care	11	59.3% (37.8)	39.8 (13.5)	75.0 (20.3)
Usual care (at 6 months)	63	75.9% (33.9)	29.2 (14.7)	84.4 (16.7)
Recovered	5	99.6% (0.9)	14.4 (6.1)	92.5 (2.6)
Not recovered, continued usual care	27	60.6% (36.3)	32.9 (12.5)	83.1 (16.2)
Not recovered, crossed over to FITNET	31	85.7% (28.6)	28.4 (16.0)	84.2 (18.3)

Data are mean (SD), unless otherwise indicated. FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire. \*Adjusted for loss to follow-up.

**Table 4: Results of reassessment at 12 months (n=127)**

achieved recovery than did those in the usual care group (table 3). The number needed to treat to achieve recovery at both primary and secondary outcomes was 1.8 (table 3).

Additional analyses with adjustments for possible confounding factors, like age, sex, baseline scores for anxiety, depression, and primary outcomes, had no effects on the results (data not shown). Analysis at other cutoff points for recovery (–1 SD) did not change our findings with respect to treatment effects (appendix).

No serious adverse events were reported. Of 68 adolescents assigned to the FITNET program, only four (6%) stopped treatment early, according to both patient and therapist. Reasons for stopping were that the internet was too impersonal (n=1), communication difficulties (n=1), and not enough self-discipline to log in frequently to the FITNET program (n=2). These four patients completed the post-treatment assessment at 6 months. Most patients and parents were satisfied with FITNET treatment; details of the experience and satisfaction with the FITNET treatment will be reported elsewhere.

The FITNET treatment lasted a mean of 26.2 weeks (SD 7.3). The mean number of times patients and parents logged in was 255.0; to maintain confidentiality, we could not differentiate between users. Treatment progression was monitored by regular e-consult contact between therapists, patients, and parents. The mean number of e-consults sent by patients was 66.6 (SD 16.3) and by parents 22.8 (10.3). The mean number of e-consults sent by the therapist was 28.7 (10.3) per patient and 19.5 (10.5) per parent. No significant differences were noted in treatment effects between the five FITNET therapists (recovery rates 61.1%, 61.5%, 66.7%, 68.4%, and 70.6%, p=0.917).

During the trial, three patients (one assigned to usual care and two to FITNET) were given new diagnoses—school phobia, personality disorder or gender identity disorder, and post-traumatic stress disorder due to family violence—by the therapist of their allocated group that were given treatment priority. We did not exclude these patients from the analysis because of the intention-to-treat principle.

127 (97%) of 131 adolescents completed the reassessment at 12 months. Patients who had recovered after FITNET showed sustainable treatment effects. Mean school attendance improved further (tables 2, 4). 12 patients, who had not recovered at the 6 months’ assessment, continued FITNET and improved at 12 months (table 4). 32 patients (including one lost to follow-up) not recovered after 6 months of usual care crossed over to FITNET. Their treatment results at 12 months were similar to the primary FITNET group (table 4).

## Discussion

Internet-based cognitive behavioural therapy was much more effective than was usual care, resulting in higher school attendance, diminished severity of fatigue, improved physical functioning, and better self-rated improvement. In patients who recovered with FITNET, treatment success persisted at the 12 months’ reassessment. Patients who continued FITNET treatment or switched to FITNET had similar success by 12 months. FITNET is the first randomised controlled trial in which the effectiveness of internet-based treatment for chronic fatigue syndrome was compared with usual care. Also, the cohort of adolescents followed up is the largest described for chronic fatigue syndrome so far (panel).

Some issues need further consideration. We chose a pragmatic study design that enabled us to assess the value of FITNET therapy relative to currently available treatments for chronic fatigue syndrome. Because of the vulnerable age, high risk of disruption to development, and general cognitive behavioural therapy lasting 5–6 months, we thought that all treatments should be assessed after 6 months. This design meant that we could not provide detailed data about the specific interventions in the usual care group because the quality and quantity of cognitive behavioural therapy differed according to local availability and adolescents often combined cognitive behavioural

See Online for appendix

therapy with other treatments such as graded exercise, but it answers the most relevant question of whether FITNET treatment is indeed an effective alternative to the heterogeneous treatments that are available.

Chronic fatigue syndrome was diagnosed or confirmed in a tertiary academic hospital setting. Since referrals were obtained nationwide and from various sources (family doctors and paediatricians),<sup>24</sup> we think that our study population is representative of the adolescent Dutch population with chronic fatigue syndrome. Physicians referring patients seemed to find the diagnosis of chronic fatigue syndrome difficult, judging by the high numbers of other primary diagnoses and patients who did not meet CDC criteria (figure). In our tertiary centre, only three adolescents were given a different diagnosis during treatment. We expect that this number will increase if FITNET treatment is made available to physicians who refer patients without assessment at a specialised tertiary centre.

There is no universal definition of recovery in patients with chronic fatigue syndrome during therapy. We constructed a post-hoc definition of recovery based on four components (fatigue, physical functioning, school participation, and self-rated improvement) that we believe are inseparable. Self-rated improvement is particularly crucial for recovery since it combines having a normal amount of fatigue and not being disabled, according to the patient's own perception.

This study had several strengths. First, the FITNET program involved parents in their children's treatment. The results of earlier studies have shown the importance of family-focused cognitive behavioural therapy in the successful treatment of adolescents.<sup>12,15,31</sup> Furthermore, hardly any loss to follow-up occurred, thus reducing the risk of bias. Only 3% of patients were lost to follow-up, which is low compared with previous studies<sup>12,15,31</sup> and other internet-based interventions.<sup>16–21</sup> The high participation rate (96% of eligible adolescents entered the study) is a sign of the low threshold and high acceptance of internet-based health care. A particular strength is that the main outcome (school attendance) was checked and double checked by the investigators, parents, teachers, and therapists.

Internet-based treatment has general advantages: it is available at any time, avoids face-to-face treatment barriers (ie, treatment delay due to poor accessibility, inconvenience of scheduling appointments, missing school or work, travelling to and from a clinician's office),<sup>32,33</sup> and reduces treatment time and costs.<sup>33</sup> This unique cognitive behavioural therapy seems to appeal to modern youth, who grow up using the internet as their main source of information. Specialised internet-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome was more effective than were the more general approaches applied in usual care, but it is not known which aspect, such as being readily accessible soon after diagnosis, 24 h availability, anonymity, or professional

### Panel: Research in context

#### Systematic review

We searched the PubMed and Cochrane databases up to June 29, 2011, for full reports of randomised controlled trials, systematic reviews, and meta-analyses with the search terms "chronic fatigue syndrome", "myalgic encephalomyelitis", or "myalgic encephalopathy"; "adolesc\*" or "childr\*"; and "treatment", "cognitive behaviour therapy", "exercise", "pacing", or "internet". There were no language restrictions. We excluded trials of adults and education and group interventions. The reports we included in the references are key pieces of evidence. Our search identified two randomised controlled trials.<sup>12,31</sup> Cognitive behavioural therapy for adolescents with chronic fatigue syndrome has only been compared with patients being on a waiting list<sup>12</sup> or receiving psychoeducation,<sup>31</sup> and resulted in a clinically significant improvement of 60–70% directly after treatment. Results of both studies also showed the importance of family-focused cognitive behavioural therapy to treatment success in adolescents. Limitations of these trials were their fairly small sizes and high dropout rates. The biggest practical challenge of cognitive behavioural therapy is its restricted availability because its administration requires specialised therapeutic skills,<sup>12,15</sup> to which there is unequal access for adolescents with chronic fatigue syndrome. Cognitive behavioural therapy has not been compared with treatment as usual in adolescents with chronic fatigue syndrome in controlled studies. No randomised trials of internet interventions or recent reviews of children and adolescents with chronic fatigue syndrome that included discussions of other randomised controlled trials of treatment, in particular cognitive behavioural therapy, were identified.

#### Interpretation

Very little evidence exists for treatment of children and adolescents with chronic fatigue syndrome. We provide new evidence in this randomised controlled trial (Fatigue In Teenagers on the interNET [FITNET]) that internet-based cognitive behavioural therapy was much more effective than was usual care within a timeframe of 6 months, resulting in higher school attendance, diminished severity of fatigue, improved physical functioning, and better self-rated improvement. In patients recovered with FITNET, treatment success persisted at the reassessment at 12 months. Patients who continued FITNET or switched to FITNET reached similar levels of success at 12 months. The sustainability of FITNET treatment success at 12 months and FITNET results after usual care reassured us of its intrinsic effectiveness. Findings from FITNET allow the following interpretations: cognitive behavioural therapy for adolescents with chronic fatigue syndrome can now be broadly made available as FITNET, and thus remove former accessibility issues and thereby improve the prognosis of chronic fatigue syndrome in adolescents. These findings emphasise the need for proper and rapid diagnosis and of making medical professionals aware of chronic fatigue syndrome in adolescents and the available treatment options.

feedback by a trained psychotherapist, is the reason for this increased effectiveness. Our results warrant a proper cost-benefit assessment of FITNET, focusing on the factors contributing to treatment success, especially the added value of a psychotherapist. We did not note any significant differences in treatment effects between the therapists despite differences in their work experiences. The same orientation and training within a specialised treatment centre in a shared supervised environment might have contributed to this equivalent effectiveness. Ultimately, knowledge of whether internet-based treatment of chronic fatigue syndrome can achieve equal results without or with less professional guidance is important.<sup>34</sup>

Chronic fatigue syndrome can only be diagnosed after 6 months of disabling fatigue.<sup>1</sup> Our patients had symptoms for almost 2 years before chronic fatigue syndrome was

diagnosed and treated, and thus the FITNET program is a promising treatment because so many patients showed improvement within 6 months of treatment. The effectiveness of FITNET was confirmed by the sustained success of the treatment at 12 months and when it was given after usual care. Prompt initiation of treatment might even further reduce the rate of morbidity, with subsequent positive effects on educational and social development. With FITNET, effective treatment is within reach for any adolescent with chronic fatigue syndrome. These findings stress the need for proper and rapid diagnosis and making medical professionals aware of adolescent chronic fatigue syndrome and the treatment options.<sup>6</sup>

Cognitive behavioural therapy for adolescents with chronic fatigue syndrome can now be broadly made available as FITNET and thus remove previous accessibility issues and thereby improve the prognosis of this disorder in adolescents.

#### Contributors

SLN was the primary investigator and responsible for data gathering and analysis, and drafting the report. EMVDP, GB, CSPMU, and JLLK designed and supervised the study. EMVDP and GB obtained funding for the study. EMVDP was responsible for diagnosis of the chronic fatigue syndrome in adolescents. GB supervised the FITNET therapists. SLN and CSPMU did the data analysis. All authors have read and approved the final report.

#### Conflicts of interest

We declare that we have no conflicts of interest.

#### Acknowledgments

This study was funded by the Netherlands Organisation for Health Research and Development (ID ZonMW 60-60800-98-013). We thank the patients and their parents who took part in this study, and Annemarie Gerritsen, Henriette Vermeer, Pauline Koetsier, Thea Berends, and Dennis Marcelissen who administered the therapy.

#### References

- Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994; **121**: 953–59.
- Crawley E, Sterne JA. Association between school absence and physical function in paediatric chronic fatigue syndrome/myalgic encephalopathy. *Arch Dis Child* 2009; **94**: 752–56.
- Marshall GS. Report of a workshop on the epidemiology, natural history, and pathogenesis of chronic fatigue syndrome in adolescents. *J Pediatr* 1999; **134**: 395–405.
- Dowsett EG, Colby J. Long-term sickness absence due to ME/CFS in UK schools—an epidemiological study with medical and educational implications. *J Chronic Fatigue Syndr* 1997; **3**: 29–42.
- Rangel L, Garralda ME, Levin M, Roberts H. The course of severe chronic fatigue syndrome in childhood. *J R Soc Med* 2000; **93**: 129–34.
- Nijhof SL, Maijer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent Chronic Fatigue Syndrome: Prevalence, Incidence, and Morbidity. *Pediatrics* 2011; **127**: e1169–75.
- Rimes KA, Goodman R, Hotopf M, Wessely S, Meltzer H, Chalder T. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. *Pediatrics* 2007; **119**: e603–09.
- Chalder T, Goodman R, Wessely S, Hotopf M, Meltzer H. Epidemiology of chronic fatigue syndrome and self reported myalgic encephalomyelitis in 5–15 year olds: cross sectional study. *BMJ* 2003; **327**: 654–55.
- Farmer A, Fowler T, Scourfield J, Thapar A. Prevalence of chronic disabling fatigue in children and adolescents. *Br J Psychiatry* 2004; **184**: 477–81.
- Jones JF, Nisenbaum R, Solomon L, Reyes M, Reeves WC. Chronic fatigue syndrome and other fatiguing illnesses in adolescents: a population-based study. *J Adolesc Health* 2004; **35**: 34–40.
- Bell DS, Jordan K, Robinson M. Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome. *Pediatrics* 2001; **107**: 994–98.
- Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *BMJ* 2005; **330**: 14.
- van Geelen SM, Sinnema G, Hermans HJ, Kuis W. Personality and chronic fatigue syndrome: methodological and conceptual issues. *Clin Psychol Rev* 2007; **27**: 885–903.
- Vercoulen JH, Swanink CM, Galama JM, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. *J Psychosom Res* 1998; **45**: 507–17.
- Chalder T, Tong J, Deary V. Family cognitive behaviour therapy for chronic fatigue syndrome: an uncontrolled study. *Arch Dis Child* 2002; **86**: 95–97.
- Emmelkamp PM. Technological innovations in clinical assessment and psychotherapy. *Psychother Psychosom* 2005; **74**: 336–43.
- Cuijpers P, van Straten A, Andersson G. Internet-administered cognitive behavior therapy for health problems: a systematic review. *J Behav Med* 2008; **31**: 169–77.
- O’Kearney R, Gibson M, Christensen H, Griffiths KM. Effects of a cognitive-behavioural internet program on depression, vulnerability to depression and stigma in adolescent males: a school-based controlled trial. *Cogn Behav Ther* 2006; **35**: 43–54.
- Spence SH, Holmes JM, March S, Lipp OV. The feasibility and outcome of clinic plus internet delivery of cognitive-behavior therapy for childhood anxiety. *J Consult Clin Psychol* 2006; **74**: 614–21.
- Trautmann E, Kroner-Herwig B. A randomized controlled trial of Internet-based self-help training for recurrent headache in childhood and adolescence. *Behav Res Ther* 2010; **48**: 28–37.
- Patten CA, Croghan IT, Meis TM, et al. Randomized clinical trial of an Internet-based versus brief office intervention for adolescent smoking cessation. *Patient Educ Couns* 2006; **64**: 249–58.
- Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet* 2001; **357**: 841–47.
- Bleijenberg G, Prins J, Bazelmans E. Cognitive behavioral therapies. In: Jason LA, Fennel PA, Taylor RR, eds. Handbook of chronic fatigue syndrome. Hoboken: Wiley and Sons, 2003: 493–526.
- Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Fatigue In Teenagers on the interNET—the FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. [ISRCTN59878666]. *BMC Neurol* 2011; **11**: 23.
- Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994; **38**: 383–92.
- Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, Essink-Bot ML. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. *Qual Life Res* 2002; **11**: 575–81.
- Kovacs M. The Children’s Depression, Inventory (CDI). *Psychopharmacol Bull* 1985; **21**: 995–98.
- Papay JP, Spielberger CD. Assessment of anxiety and achievement in kindergarten and first- and second-grade children. *J Abnorm Child Psychol* 1986; **14**: 279–86.
- Vercoulen JHMM, Hoofs MPE, Bleijenberg G, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet* 1996; **347**: 858–61.
- van Geelen SM, Bakker RJ, Kuis W, van de Putte EM. Adolescent chronic fatigue syndrome: a follow-up study. *Arch Pediatr Adolesc Med* 2010; **164**: 810–14.
- Chalder T, Deary V, Husain K, Walwyn R. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. *Psychol Med* 2010; **40**: 1269–79.
- Ritterband LM, Thorndike FP, Cox DJ, Kovatchev BP, Gonder-Frederick LA. A behavior change model for internet interventions. *Ann Behav Med* 2009; **38**: 18–27.
- Tate DF, Finkelstein EA, Khavjou O, Gustafson A. Cost effectiveness of internet interventions: review and recommendations. *Ann Behav Med* 2009; **38**: 40–45.
- Tummers M, Knoop H, Bleijenberg G. Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. *J Consult Clin Psychol* 2010; **78**: 724–31.