Internet-Based Therapy for Adolescents With Chronic Fatigue Syndrome: Long-term Follow-up

WHAT’S KNOWN ON THIS SUBJECT: Cognitive behavioral therapy is an effective and safe treatment of chronic fatigue syndrome in children and adolescents. After 6 months, Internet-based cognitive behavioral therapy in the form of FITNET led to an 8 times higher chance of recovery compared with usual care.

WHAT THIS STUDY ADDS: The positive effects of FITNET were maintained at long-term follow-up (>2.5 years). Patients following usual-care treatment achieve similar recovery rates at long-term follow-up.

abstract

OBJECTIVE: Cognitive behavioral therapy (CBT) is known to be an effective treatment of adolescents with chronic fatigue syndrome (CFS), but its availability is limited. Fatigue in Teenagers on the Internet (FITNET), an Internet-based CBT program for adolescents with CFS, has been developed as an alternative to face-to-face CBT. Recently, its short-term effectiveness has been proven in a randomized clinical trial. Here we aimed to assess the long-term outcome of CFS in adolescents after FITNET treatment and after usual care. In addition, factors related to recovery at long-term follow-up (LTFU) for adolescents treated with the FITNET program were investigated.

METHODS: The study was an LTFU of participants of the FITNET trial. Data were completed for 112 (88.2%) of 127 approached FITNET study participants. Primary outcomes were fatigue severity (Checklist Individual Strength–20), physical functioning (87-item Child Health Questionnaire), and school/work attendance.

RESULTS: After a mean follow-up of 2.7 years, 66 (58.9%) adolescents had recovered from CFS. Most adolescents who recovered directly after treatment with FITNET were still recovered at LTFU. At LTFU there was no difference between the recovery rates for the different treatment strategies (original randomization: FITNET [64%] versus any form of usual care [52.8%]). Per additional month of “pretreatment disease duration,” the odds for recovery were 4% lower (odds ratio: 0.96; 95% confidence interval: 0.93–0.99; P = .016), and per added point on “focus on bodily symptoms” (Body Consciousness Scale) of the mother (0–20 points) the odds for recovery were 11% lower (odds ratio: 0.89; 95% confidence interval: 0.80–0.99; P = .029).

CONCLUSIONS: The short-term effectiveness of Internet-based CBT on adolescent CFS is maintained at LTFU. At LTFU, usual care led to similar recovery rates, although these rates were achieved at a slower pace. Pediatrics 2013;131:e1788–e1795

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KEY WORDS chronic fatigue, adolescents, FITNET, Fatigue in Teenagers on the Internet, follow-up, cognitive behavioral therapy, Internet, functioning, recovery

ABBREVIATIONS CBT—cognitive behavioral therapy CDC—Centers for Disease Control and Prevention CFS—chronic fatigue syndrome CHQ-CF87—87-item Child Health Questionnaire CI—confidence interval CIS-20—Checklist Individual Strength–20 FITNET—Fatigue in Teenagers on the Internet FN—Direct Start FITNET LTFU—long-term follow-up OR—odds ratio RCT—randomized clinical trial SRI—self-rated improvement UC—Usual Care Only XO—FITNET Cross-over After Usual Care

Dr Nijhof and Ms Priesterbach contributed equally to this work.

Dr Nijhof was the principal investigator and together with Ms Priesterbach was responsible for data gathering and analysis and drafting the report; Dr van de Putte, Mr Bleijenberg, Dr Uiterwaal, and Mr Kimpen designed and supervised the study; Dr van de Putte was responsible for diagnosis of chronic fatigue syndrome in adolescents; and Ms Priesterbach, Dr Nijhof, and Dr Uiterwaal performed the data analysis. All authors read and approved the final article. Dr Nijhof had full access to all the data in the study and had final responsibility for the decision to submit for publication.

(Continued on last page)
Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue that persists for longer than 6 months (according to the definition by the US Centers for Disease Control and Prevention [CDC]), is not alleviated by rest or sleep, and is often accompanied by other symptoms such as muscle pain and unrefreshing sleep.1–3 Adolescent CFS is uncommon compared with chronic fatigue in adolescents4–6 but leads to high disability and subsequent negative effects on physical, educational, and social development.6,7 One of the most successful potential treatments for adolescents with CFS is cognitive behavioral therapy (CBT), which has been shown to be effective in two-thirds of adolescents with CFS.8–10 CBT is considered a safe treatment of CFS11,12 but requires specialized therapeutic skills that are not always available within driving distance.8,10 Fatigue in Teenagers on the Internet (FITNET), an Internet-based CBT program for adolescents with CFS, has been developed as an alternative to face-to-face CBT.10,13 The FITNET program was found to be successful in the treatment of CFS in adolescents, because it led to an 8 times higher chance of short-term recovery compared with usual care.10 FITNET is the first Internet-based therapy for CFS. It makes CBT more accessible to patients who live in an area without a specialized therapist and teenagers seem to prefer Internet-based therapy.10 Untreated CFS in adolescents seems to have a better prognosis than CFS in adults; however, the disruption of development and education requires prompt recognition and treatment.8,10,14 Reports on long-term prospects after treatment are variable. Study results of significant improvement vary between 50% (mean follow-up period of 2.2 years)15 and 70% in adolescents who were initially treated with face-to-face CBT (mean follow-up period of 2.1 years).16 The factors that influence treatment outcomes in adolescent CFS are largely unknown. Several patient and parental factors have been suggested to be associated, such as age at inclusion,15 presence of pain,15 mental health,15 self-esteem,15 and general health perception15 and the fatigue severity of the mother.16 An earlier study has suggested the role of family, especially the mother, as a factor related to treatment success.16 If factors related to long-term recovery from CFS in adolescents treated with FITNET can be established, results can be used to adjust content, focus, and duration of treatment of both the adolescent and/or parent(s) to enhance recovery rates and to determine which adolescents are most likely to benefit.

The primary goal of this study was to determine long-term recovery rates of adolescent CFS patients who participated in the FITNET trial. In addition, factors related to recovery were assessed.

METHODS

Design and Participants

This study was designed to assess the long-term outcome of participants of the FITNET study. The FITNET study design15 and short-term outcomes10 were published elsewhere.

Between January 2008 and February 2010, 135 CFS patients aged 12 to 18 years were enrolled in the original FITNET trial.13 All patients complied with CDC criteria for CFS diagnosis3 and were randomly assigned to either FITNET (n = 68) or usual care (n = 67). Usually care consisted mainly of individual or group-based rehabilitation programs, face-to-face CBT, and graded exercise therapy with a physical therapist.

After 6 months of treatment, the randomized part of the trial ended and nonrecovered patients were offered to cross over to either FITNET or usual care. Thirty-two adolescents who were initially randomly assigned to usual-care treatment (n = 67), and had not recovered after 6 months, decided to cross over to FITNET. Eleven nonrecovered adolescents initially randomly assigned to FITNET (n = 68) crossed over to usual care. All randomly assigned patients were invited for assessment of primary outcomes at 12 months postrandomization. These outcomes were published with the initial FITNET results.10

For the current long-term follow-up (LTFU) study, 127 potential participants received a written invitation for follow-up assessment between August and October 2011. Of the 135 initial FITNET trial participants, 8 participants dropped out of the trial before the initiation of this LTFU study. These 8 participants were not contacted. This LTFU measurement was performed within a fixed period, resulting in a follow-up period of different lengths for each participant (with a minimum of 1.7 years and a maximum of 3.8 years).

All primary and secondary outcome measures were obtained through written questionnaires that were sent to the participants by post and e-mail. Reminders to take part in the LTFU assessment were sent by e-mail and provided through phone calls. The medical ethics committee of the University Medical Centre Utrecht approved the study. Written informed consent for follow-up assessment was obtained from patients and parent(s).

Figure 1 illustrates the relation of the LTFU study to the FITNET trial and clarifies the flow of participants.

Outcome Variables

The primary outcomes of this study were the same as the outcome measures of the original FITNET trial and were as follows: (1) fatigue, as measured by the subscale “fatigue severity” (8 items) of the Checklist Individual
Strength–20 (CIS-20; range: 8–56), which has good reliability and discriminative validity8,18,19; (2) physical functioning, as measured by the subscale “physical functioning” (9 items) of the 87-item Child Health Questionnaire (CHQ-CF87; range: 0%–100%)20; and (3) school attendance, measured retrospectively as the proportion of classes attended the 6 months before filling out the questionnaire, was expressed as a percentage of the normal school schedule. Considering that some of the adolescents were now beyond school age, the alternative primary outcome to school attendance was work attendance.

The secondary outcome measure was “self-rated improvement” (SRI), measured by using a 4-item tool in which patients can indicate whether they have completely recovered, feel much better, have the same complaints, or have become worse compared with the measurement before commencement of CFS treatment.8,10

Factors Related to Treatment Outcome
Potential factors related to nonrecovery, assessed at baseline for the original randomized clinical trial (RCT),13 were as follows: age at the time of CFS diagnosis, gender, disease duration, fatigue score (CIS-20),8,18,19 somatization score (Child Somatization Inventory),21,22 physical functioning (CHQ-CF87),20 depression score (Child Depression Inventory),23,24 anxiety score (Spielberger State-Trait Anxiety Inventory for Children),25,26 self-efficacy (Self-Efficacy Scale–28),27 and focus on (fatigue) symptoms (Illness Management Scale).28 Possible parental factors taken into account were as follows: parental fatigue score (CIS-20),8,18,19 psychological stress [Brief Symptom Inventory, short version of Symptom Checklist (SCL)-90],29 and focus on bodily symptoms (Body Consciousness Scale).30,31

**FIGURE 1**
Design of the RCT and LTFU with flow of participants in the FITNET trial.
All participants completed a general questionnaire with items relating to school, work, medication use, and participation in sports/exercise.

**Definition of Recovery**

Recovery from CFS was defined in relation to healthy peers (±2 SD) and in accordance with the FITNET trial. This combined end point consisted of a fatigue-severity score <40, a physical functioning score of ≥85%, school/work presence of ≥90%, and an SRI answered with (1) “I have completely recovered” or (2) “I feel much better.”

**Statistical Analysis**

Baseline characteristics of LTFU participants and nonparticipants were tested for dissimilarity by using independent samples t tests. Of all relevant variables, group-specific means and SDs or proportions were calculated for 12-month assessment and LTFU. After labeling of participants as recovered or nonrecovered, a $\chi^2$ test was used to assess the difference in recovery rates between the 2 groups on the basis of original randomization at LTFU.

The possible relationships between the adolescent/parental factors and the long-term outcome were quantified by estimating odds ratios (ORs) and 95% confidence intervals (CIs) by using binary logistic regression, with outcome (recovery: yes or no) as the dependent variable and the assessed factors as independent variables. Separate analyses were performed for adolescent factors and parental factors. Because the LTFU period varied, time between inclusion and LTFU assessment was taken into account as a covariate. All analyses were performed by using PASW Statistics 20.0.

**RESULTS**

**Study Population**

One-hundred twelve of 127 adolescents (88.2%) completed LTFU assessment (Fig 1). Of the 15 nonparticipants (telephone interview), 11 reported recovery, 3 reported nonrecovery, and 1 was untraceable (Fig 1). There were no significant differences in baseline characteristics between participants and nonparticipants (Table 1). Table 1 also shows baseline characteristics of this cohort and the severity of disease at study entry.

**LTFU of Treatment Effects**

The mean (±SD) follow-up period was 2.7 ± 0.5 years (range: 1.7–3.8 years).
The mean age of the participants at LTFU was 18.5 ± 1.5 years.

Table 2 shows the outcomes at LTFU compared with the 12-month assessment for all 112 LTFU participants, irrespective of initial randomization or treatment during the RCT. Thus, these adolescents received either FITNET therapy, usual care, or both. LTFU assessment showed sustained treatment effects in comparison with the 12-month assessment; mean scores on fatigue, physical functioning, school/work attendance, and SRI were similar. Analyses at other cutoff points (−1 SD) obviously changed the number of recovered patients (57 instead of 66) but did not materially change our findings concerning the relative effects (FITNET compared with usual care; data not shown).

Recovery rates per group (FN/XO/UC) from the start of the RCT through the current follow-up are shown in Fig 2. All participants at the 4 different times of assessment are included in the graph: 135 at RCT initiation, 131 at 6-month assessment, 127 at 12-month assessment, and 112 at LTFU. The FN group (n = 59 at LTFU) showed stable recovery rates (64%) at all follow-up moments. The XO group (n = 25 at LTFU) showed an increased and subsequent stable recovery rate after crossing over to FITNET (52%). The UC group (n = 28 at LTFU) showed comparable recovery rates (53.6%) at LTFU, although these were achieved at a slower pace.

Of the FN group, 18 (30.5%) LTFU participants followed ≥1 forms of usual care between 12-month follow-up and LTFU. The recovery percentage in this group was 61.1% at LTFU. Recovery percentages at LTFU for the 2 groups based on original randomization (FITNET versus usual care) were not significantly different (64.4% vs 52.8%; χ² test, P = .251). At LTFU, receiving FITNET therapy did not significantly influence recovery rates (followed FITNET [58.2%] versus no FITNET [53.6%], P = .515). Per protocol analysis of just the 112 respondents to the LTFU study for all moments of assessment did not change these findings.

A number of adolescents experienced a relapse during the follow-up period. Within the FN group, 5 (8.5%) adolescents, who were recovered at 12-month assessment, no longer met recovery criteria at LTFU. Within the XO group, 4 (16%) relapses occurred, and 3 were within the UC group (10.7%).

Most adolescents were still going to school at the time of LTFU, although some adolescents had started their working careers (n = 10). Only 3 (30%) of the adolescents with a job were currently working full-time. However, 70% of the adolescents were satisfied with working a part-time job and worked as many hours as they liked, unrestrained by CFS (results from general questionnaire, work-related items).

Factors Related to Recovery

Baseline factors related to recovery at LTFU after following the FITNET program are presented in Table 3. Of 112 LTFU participants, 84 (59 from the FN group and 25 from the XO group) followed FITNET and were included in this analysis. Only 2 factors were related to

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recovery; every additional month of pretreatment disease duration led to 4% lower odds of recovery (adolescent factor; OR: 0.96; 95% CI: 0.93–0.99; \( P = 0.016 \)), and every additional point scored on maternal focus on bodily symptoms (Body Consciousness Scale) led to 11% lower odds of recovery (parental factor; OR: 0.89, 95% CI: 0.80–0.98; \( P = 0.029 \)). Adjustment for follow-up time did not change the findings.

**DISCUSSION**

The long-term outcome of CFS in adolescents in this study was mostly favorable. On average, 2.7 years after commencing treatment and 4.5 years after onset of disease, \({\sim}60\%\) of the adolescents recovered, irrespective of the type of treatment. It was encouraging to see that the short-term treatment effects of FITNET therapy appeared stable and were sustained at LTFU. The number of relapses was limited. Patients who only followed usual-care treatment eventually achieved comparable outcomes at LTFU. However, the pace of recovery was remarkably slower; it took this group considerably more months to achieve similar recovery rates.

Nonetheless, a substantial number of adolescents did not recover and were unable to attend all required hours of school or work full-time. Factors related to recovery after FITNET treatment at LTFU were disease duration before treatment commencement and maternal focus on bodily symptoms.

**Strengths and Limitations**

The cohort of adolescents followed in our study population is, to our knowledge, the largest described for CFS thus far. Moreover, it is a well-characterized group, representative of the Dutch CFS population and strictly diagnosed with the CDC criteria.

Another particular strength is the high participation rate of 88.2%, reducing the risk of selection bias.

An additional strength is our definition of recovery, which used a combined end point of 4 criteria, which is fairly strict compared with other studies.\(^8,9,14,15\) The combination of the primary measures of disease severity with the patient’s own perception of recovery (SRI) generally creates lower recovery rates than the primary measures alone.

Some issues need additional consideration. The scope of the LTFU was to assess the sustainability of FITNET treatment, rather than to compare FITNET with usual care. Our original pragmatic study design enabled us to demonstrate the value of FITNET relative to currently locally available therapies. Availability, of course, is defined locally and differs from region to region, even in a small country such as The Netherlands. This design meant that we could and cannot provide detailed data about the specific interventions in the UC group because the quality and quantity of treatments (mostly CBT) differed according to local availability, and adolescents often combined CBT with other treatments such as graded exercise. Nonetheless, we wanted to provide insight into the long-term results of the UC group as well.

A considerable number of usual-care patients received FITNET therapy using the cross-over opportunity \((n = 32)\), which means that only 35 adolescents received solely usual-care treatment.

At LTFU, school presence was scored by using retrospective questionnaires. These are less precise than the prospective diaries used during the FITNET trial and at the 12-month assessment.

**Results in the Context of Previous Literature**

Despite significant methodologic differences and definitions of recovery with previous studies on this topic, the outcomes found in our study are in accordance with previous reports on the prognosis of adolescent CFS.\(^14,32,33\) The longest follow-up study of natural course (13 years) showed that the majority of adolescents with CFS have mild to moderate persisting symptoms with a considerable duration of school absence.\(^16\) Previous study results of

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**TABLE 3** Factors Related to Recovery After FITNET Treatment at LTFU

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0.86</td>
<td>0.62–1.19</td>
<td>0.37</td>
</tr>
<tr>
<td>Gender</td>
<td>1.54</td>
<td>0.52–4.56</td>
<td>0.44</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>0.96</td>
<td>0.93–0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Fatigue severity (CIS-20)</td>
<td>0.97</td>
<td>0.87–1.07</td>
<td>0.49</td>
</tr>
<tr>
<td>Physical functioning (CHQ-CF87)</td>
<td>1.02</td>
<td>0.99–1.05</td>
<td>0.17</td>
</tr>
<tr>
<td>Depression score (CDI)</td>
<td>0.96</td>
<td>0.88–1.05</td>
<td>0.39</td>
</tr>
<tr>
<td>Anxiety score (STAIC)</td>
<td>1.01</td>
<td>0.96–1.06</td>
<td>0.66</td>
</tr>
<tr>
<td>Somatic complaints (CSI)</td>
<td>1.01</td>
<td>0.98–1.01</td>
<td>0.46</td>
</tr>
<tr>
<td>Self-efficacy (SES-28)</td>
<td>1.10</td>
<td>0.94–1.30</td>
<td>0.24</td>
</tr>
<tr>
<td>Focus on fatigue (IMQ)</td>
<td>1.24</td>
<td>0.72–2.13</td>
<td>0.44</td>
</tr>
<tr>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue severity (CIS-20)</td>
<td>1.00</td>
<td>0.97–1.04</td>
<td>0.82</td>
</tr>
<tr>
<td>Psychological stress (BSI)</td>
<td>1.00</td>
<td>0.97–1.04</td>
<td>0.76</td>
</tr>
<tr>
<td>Focus on physical sensations (BCS)</td>
<td>0.89</td>
<td>0.80–0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>Father</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue severity (CIS-20)</td>
<td>0.99</td>
<td>0.95–1.03</td>
<td>0.64</td>
</tr>
<tr>
<td>Psychological stress (BSI)</td>
<td>1.00</td>
<td>0.96–1.04</td>
<td>0.85</td>
</tr>
<tr>
<td>Focus on physical sensations (BCS)</td>
<td>0.95</td>
<td>0.85–1.06</td>
<td>0.35</td>
</tr>
</tbody>
</table>

\(N = 84\); BCS, Body Consciousness Scale; BSI, Brief Symptom Inventory; CIS, Children’s Depression Inventory; CSI, Children’s Somatization Inventory; IMQ, Illness Management Questionnaire; SES-28, Self-Efficacy Scale-28; STAIC, State-Trait Anxiety Inventory for Children.

\(^*\) Analyzed by using univariable binary logistic regression.
significant improvement after treatment vary between 50% and 70% (mean follow-up period of 2.2 and 2.1 years, respectively).\textsuperscript{15,16}

Because a significant group of adolescents remain impaired by CFS symptoms, it is important to characterize this group to change content or choice of treatment. In previous studies, a number of predictors for outcome of CFS in adolescents have been suggested. Both patient and parental factors have been revealed to be associated with unfavorable outcome after regular care\textsuperscript{15} or after CBT.\textsuperscript{16} We could not confirm an association between older age, poor mental health,\textsuperscript{15} or higher maternal fatigue severity\textsuperscript{16} with an inferior outcome. However, our finding that maternal focus on bodily symptoms was associated with long-term recovery of the child suggests that an intergenerational vulnerability and interaction between mother and child may exist.\textsuperscript{17} More research focused on this topic is required.

**Clinical Implications**

Compared with usual care, Internet-based CBT treatment of adolescents led to earlier recovery from CFS. This shortened recovery period is crucial during adolescence, when school attendance and social contacts are crucial for social and academic development. Extensive absence from school is associated with poorer educational outcome and may increase the risk of unemployment.\textsuperscript{14} Previous literature has shown that delays in diagnosis of CFS and absenteeism because of CFS in adolescents are unfortunately (still) substantial.\textsuperscript{10,35} FITNET treatment supported quick improvement of school attendance and thereby contributed to diminishing these detrimental effects of school absence during this critical time. The finding that longer disease duration was related to long-term nonrecovery underlines the necessity for prompt diagnosis and treatment of CFS. Although attention to bodily symptoms is one of the main themes in the FITNET treatment, both for the adolescent and for the parent(s), this is apparently insufficient for a subgroup of patients characterized by high maternal scores on the focus on bodily symptoms. In the FITNET program, adolescents and parents are treated simultaneously, both in a bilateral contact with the therapist. The possible implication of this finding is that a face-to-face dynamic family approach is needed for a subgroup of adolescent CFS patients.\textsuperscript{8–10}

**CONCLUSIONS**

The treatment effects of Internet-based CBT persist at LTFU. Its therapeutic gain lies largely in rapid recovery. A challenge remains to offer Internet-based CBT in those cases that are most likely to benefit from it and to recognize situations that might require more intense forms of (family) therapy.
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Internet-Based Therapy for Adolescents With Chronic Fatigue Syndrome: Long-term Follow-up

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