BMJ Paediatrics Open

Cognitive–behavioural therapy combined with music therapy for chronic fatigue following Epstein-Barr virus infection in adolescents: a randomised controlled trial

Sadaf Malik,[1] Tarjei Tørre Asprusten,[2,3] Maria Pedersen,[4] Julie Mangersnes,[1] Gro Trondalen,[5] Betty van Roy,[1] Eva Skovlund,[6] Vegard Bruun Wyller [1,2]

To cite: Malik S, Asprusten TT, Pedersen M, *et al*. Cognitive–behavioural therapy combined with music therapy for chronic fatigue following Epstein-Barr virus infection in adolescents: a randomised controlled trial. *BMJ Paediatrics Open* 2020;**4**:e000797. doi:10.1136/bmjpo-2020-000797

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjpo-2020-000797).

Received 14 July 2020
Revised 8 September 2020
Accepted 15 September 2020

For numbered affiliations see end of article.

Correspondence to
Professor Vegard Bruun Wyller; v.b.b.wyller@medisin.uio.no

ABSTRACT

Background Cognitive–behavioural therapy (CBT) is effective in chronic fatigue (CF) syndrome. However, CBT has not been investigated in postinfectious CF, nor is it known whether addition of therapeutic elements from other disciplines might be useful. We explored combined CBT and music therapy intervention for CF following Epstein-Barr virus (EBV) infection in adolescents.

Methods Adolescents (12–20 years old) participating in a postinfectious cohort study who developed CF 6 months after an acute EBV infection were eligible for the present study. A combined CBT and music therapy programme (10 therapy sessions and related homework) was compared with care as usual in a randomised controlled design. Therapists and participants were blinded to outcome evaluation. Endpoints included physical activity (steps/day), symptom scores, recovery rate and possible harmful effects, but the study was underpowered regarding efficacy. Total follow-up time was 15 months. Power analyses suggested that 120 participants would be needed in order to detect a moderate effect size.

Results A total of 91 individuals with postinfectious CF were eligible, and a total of 43 were included (21 intervention group, 22 control group). Concern regarding school absence due to therapy sessions was the main reason for declining participation. Seven individuals left the study during the first 3 months, leaving 15 in the intervention group and 21 in the control group at 3 months follow-up. No harmful effects were recorded, and compliance with appointment was high. In intention-to-treat analyses, the primary endpoint (number of steps/day) did not differ significantly between the intervention group and the control group (difference (95% CI) =−1298 (−4874 to 2278)). Secondary outcome measures were also not significantly different among the two groups.

Conclusion An intervention study of combined CBT and music therapy in postinfectious CF is feasible. A fully powered trial is needed to evaluate efficacy; participants' concern regarding school absence should be properly addressed to secure recruitment.

Trial registration number ClinicalTrials ID: NCT02499302, registered July 2015.

What is known about this subject?

- Cognitive–behavioural therapy (CBT) is effective and not harmful in chronic fatigue syndrome (CFS).
- CBT has not been investigated in postinfectious chronic fatigue (CF).
- Combined CBT and music therapy has neither been investigated in CFS nor in postinfectious CF.

What this study adds?

- Combined CBT and music therapy is feasible and acceptable in adolescent postinfectious CF.
- This study provides important baseline data for a larger trial.
- Adolescents' concerns regarding school absence might severely affect trial recruitment.

INTRODUCTION

Chronic fatigue (CF), defined as substantial fatigue lasting for more than 6 months, is a common problem after certain infections, such as Epstein-Barr virus (EBV) infection.[1 2] If accompanied by other symptoms, such as exertion intolerance, chronic pain and cognitive impairments, the patient might fulfil one of the diagnostic criteria for chronic fatigue syndrome (CSF). CSF is a major cause of disability among adolescents with an estimated prevalence of 0.1 % to 1.0 %.[3 4]

Evidence suggests a beneficial effect of cognitive–behavioural therapy (CBT) in adults[5] and adolescents[6] with chronic fatigue syndrome (CFS), as well as in CF from well-defined causes such as cancer[7] and diabetes.[8] Generally, harmful effects of CBT have never been consistently reported. Effect sizes are usually found to be moderate, and there is therefore a need to establish more effective

treatment programmes. Furthermore, it is still unclear to what extent different subgroups respond differently to CBT[9]; in particular, no study has specifically explored the effect of CBT in postinfectious CF and CFS.

Preliminary evidence suggests that a multidisciplinary approach combining CBT with other elements might improve effectiveness as compared with CBT alone in patients suffering from CFS.[10–13] *Music therapy* is an evidence-based complementary therapy form used in many different clinical contexts.[14 15] Embodiment, emotional and relational experiences in a non-verbal medium, and regulation of arousal are core elements in clinical music therapy. There are no existing studies of music therapy in CF or CFS, but it has been proven effective in patients with related problems such as fibromyalgia[16] and long-term sick leave due to stress.[17]

Based on these considerations, we have developed a mental training programme merging elements from music therapy with elements from CBT. The aim of the present study was to explore the usefulness of this mental training programme in adolescents suffering from CF after acute EBV infection. Outcome measures included physical activity, symptoms (such as fatigue, postexertional malaise, and pain), recovery from CF, and harmful effects of the training programme.

METHODS

Design overview

The project entitled Chronic Fatigue Following Acute Epstein-Barr Virus Infection in Adolescents (CEBA) encompasses a prospective postinfectious cohort study followed by a clinical trial of a mental training programme in those participants that developed CF (figure 1). The overall design of CEBA has been described elsewhere.[18] In short, from March 2015 until November 2016, EBV infected individuals fulfilling the following criteria were assessed for eligibility in the postinfectious cohort study: (1) a serological pattern indicating acute EBV infection; (2) age between 12 and 20 years; and (3) living in one of the Norwegian counties Oslo, Akershus or Buskerud. Exclusion criteria were (1) more than 6 weeks since debut of symptoms suggesting acute EBV infection; (2) any chronic disease that needed regular use of medication; (3) pregnancy.

A total of 200 adolescents with acute EBV infection were included and followed for 6 months in the postinfectious cohort study. A total of 195 participants attended the 6 months follow-up visit and were classified as non-CF or CF (dichotomised response <or ≥ 4, respectively, on the Chalder Fatigue Questionnaire (CFQ)[19]).

The CF cases (n=91) were assessed for eligibility in a separate clinical trial (ClinicalTrials ID: NCT02499302). This trial compared a mental training programme combining music therapy and CBT against care as usual within a randomised controlled design, as described in the present paper. The inclusion period of the trial lasted from September 2015 until May 2017; total follow-up time after randomisation was 15 months.

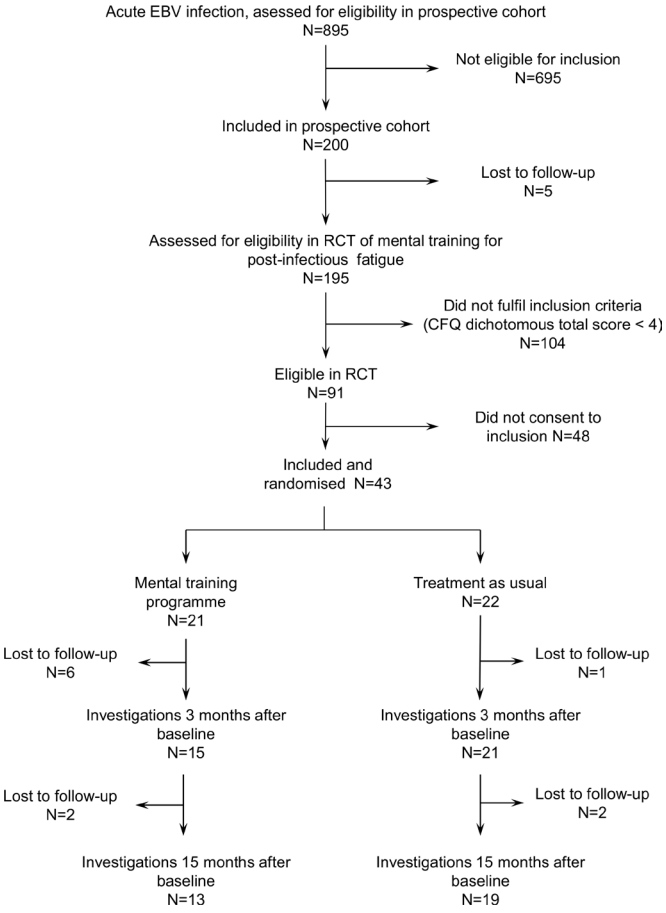

Figure 1 Flow chart of study participants. CFQ, Chalder Fatigue Questionnaire; EBV, Epstein-Barr virus; RCT, randomised controlled trial.

Participation in the trial was based on informed consent, and thorough information both orally as well as in writing was provided to the participants and (if younger than 16 years) to their parents/guardians.

Investigational program

At all encounters in CEBA, participants were subjected to a standardised investigational programme encompassing clinical assessment as well as biomarker sampling. A comprehensive overview is provided elsewhere[18]; here, only investigations relevant for the present study are detailed:

Physical activity was monitored by the activPAL accelerometer device (PAL Technologies, Glasgow, Scotland) during seven consecutive days. The accelerometer was attached in the anterior midline on the participants' thigh with custom made, waterproof adhesive tape. The participants were instructed to wear the device at all times, and only take it off when the recording period was finished. The activPAL provides reliable data on both steps and position[20]; in the present study, the mean number of steps per day was selected as the primary endpoint.

Symptoms were charted by a composite questionnaire encompassing six different instruments; in the entire postinfectious cohort, Cronbach's alpha for these instruments ranged from 0.75 to 0.94, which was considered acceptable. The CFQ[19] charts subjective experience of physical and mental fatigue, it has shown acceptable validity among adolescents,[21] and it has been translated and validated for a Norwegian population.[22] It consists of 11 items scored on four-point Likert scales; in the present study, dichotomous scoring (each item scored 0-0-1-1) was used for definition of fatigue caseness,[5] whereas ordinal scoring (0-1-2-3) was applied in the analyses of efficacy. The symptom of postexertional malaise, often considered a hallmark of CFS,[3] was charted with one single item ("How often do you experience more fatigue the day after an exertion?") and scored 1–5 on a Likert scale; higher scores imply more severe symptom burden. The Brief Pain Inventory (BPI) uses four items to assess pain severity[23]; each item is scored on 10-point Likert scales, and the total sum score (range from 0 to 40) is reported in the present paper. BPI is validated for adolescents.[24] The Karolinska Sleep Questionnaire is a validated questionnaire charting insomnia and other sleep disturbances,[25] and has previously been applied in research on adolescent fatigue.[26] It consists of 14 items scored one to six on Likert scales; the total sum score (range from 14 to 84) is reported in the present paper, and lower scores imply more symptoms of sleep problems. The Hospital Anxiety and Depression Scale charts symptoms of depression and anxiety and is validated for adolescents[27 28]; it consists of 14 items scored 0–3 on Likert scales, and total sum score (range from 0 to 42) is reported in the present paper. The Pediatric Quality of Life Inventory is translated and validated for the Norwegian population.[29] A total of 23 items are scored on five-point Likert scales, each point valued zero, 25, 50, 75 or 100; here, the mean score (range 0–100) is reported, higher scores indicate better quality of life. Functional Disability Inventory measures disability related to everyday activities, and has been thoroughly validated in different adolescent populations.[30 31] It consists of 15 items scored on five-point Likert scales; total sum score (range from 0 to 60) is applied, where higher scores suggest stronger disability.

Possible side effects related to the mental training programme was charted by a separate set of items using five-point Likert scales; the answers were dichotomised (present vs not present) prior to analyses. In addition, the questionnaire contained items related to the different diagnostic criteria of CFS as well as simple questions on demographics.

Randomisation and blinding

Participants were randomised to either mental training or care as usual in a 1:1 probability by a computer-based routine for block randomisation; block size varied randomly between 4 and 6. It was not possible to blind for treatment. End-point evaluation was concealed from patients and therapists, and allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes.

The mental training program and care as usual

The intervention consisted of a 10-week mental training programme offered to the relevant individuals as soon as possible after inclusion and randomisation. The programme encompassed one introductory session followed by nine individual therapy sessions (one per week) of 1.5 hours duration and related home-work, combining elements from CBT and music therapy (figure 2). The introductory session was carried out by a researcher, a music therapist and a cognitive therapist, with both the patient and his/her parents/guardians present. In this first session, personal experiences were also shared by a young adult voluntary patient who had himself recovered from CFS. Of the following nine treatment sessions, four were given by a music therapist (session no. 2, 3, 5 and 9) and five were given by a cognitive therapist (session no. 4, 6, 7, 8 and 10). At three of the sessions with cognitive therapists (session 4, 7 and 10), parents/guardians had the option to participate if the therapist considered it advantageous and the adolescent consented.

Normally, neither general practitioners nor paediatricians in Norway schedule appointment with postinfectious CF patients unless they have strongly reduced physical function. Thus, 'care as usual' implies that the relevant individuals would not receive any healthcare for

Figure 2 Graphical depiction of the 10 therapy sessions in the mental training programme. CBT, cognitive–behavioural therapy.

their CF condition in the follow-up period apart from the follow-up visits in the present study.

Therapists, techniques and principles in the mental training program

The mental training of all participants allocated to the intervention group was carried out by two therapists only: a child and adolescent psychiatrist holding a specialty in CBT and a Music Therapist affiliated with the Centre for Research in Music and Health at the Norwegian College of Music. Both of them had previous experiences with adolescents suffering from CF and other somatic health complaints. They participated in developing the techniques and principles of the present study; no further training was provided, but other experienced cognitive therapists and music therapists were available for supervision and discussion throughout the study period.

The first individual sessions in the mental training programme were used to chart activity and sleep patterns, altered functional abilities, withdrawal from social life and changed family dynamics. Thereafter, a variety of therapeutic principles were applied, such as psychoeducation, instructions in techniques for relaxation and visualisation by using music, challenging of automatic thoughts (primarily related to stimulus and outcome expectancies), and behavioural 'experiments'.[32] Together with the patient, the therapist sought to identify negative

Table 1 Background characteristics

	Included (n=43)		Eligible, not included (n=48)
	Treatment (n=21)	Control (n=22)	
Sex, n (%)			
Male	4 (19)	6 (27)	14 (29)
Female	17 (81)	16 (73)	34 (71)
Age, years, mean (SD)	17.7 (1.4)	16.9 (1.7)	17.4 (1.4)
BMI, kg/m^2, mean (SD)	22.5 (3.3)	21.6 (2.3)	22.1 (2.7)
Adheres to Canada 2003-criteria, n (%)			
Yes	3 (14)	7 (32)	9 (19)
No	18 (86)	15 (68)	39 (81)
Adheres to Fukuda-criteria, n (%)			
Yes	5 (24)	11 (50)	10 (21)
No	16 (76)	11 (50)	38 (79)
Epstein-Barr virus (EBV) load, copies in blood, n (%)			
Negative (<160)	9 (43)	13 (65)	22 (49)
Low (1600–2000)	7 (33)	5 (25)	14 (31)
Moderate/high (>2000)	(5 (24)	2 (10)	9 (20)
EBV-VCA-IgG, titre, median (IQR)	152 (107)	181 (212)	175.5 (198)
Blood cytotoxic T cell (CD8$^+$) count, 10^6 cells/L, mean (SD)	683 (248)	648 (232)	632 (253)
Efficacy variables			
Chalder Fatigue Questionnaire, total sum score, mean (SD)	20.0 (3.3)	19.4 (2.9)	19.1 (4.8)
Postexertional Malaise, score, mean (SD)	2.9 (1.5)	2.8 (1.3)	2.7 (1.2)
Brief Pain Inventory, total sum score, mean (SD)	10.4 (5.2)	13.1 (4.5)	11.5 (5.5)
Karolinska Sleep Questionnaire, total sum score, mean (SD)	53.0 (14.9)	45.6 (10.7)	52.0 (13.4)
Hospital Anxiety and Depression Scale, total sum score, mean (SD)	13.1 (5.8)	16.5 (6.5)	12.1 (6.2)
Paediatric Quality of Life, total average score, mean (SD)	67 (14)	62 (15)	70 (18)
Functional Disability Inventory, total sum score, mean (SD)	12.2 (8.8)	13.7 (8.3)	10.1 (10.9)
Steps/day, number, mean (SD)	7998 (4598)	8376 (3119)	9255 (3795)

P values are based on χ^2 test, Fisher's exact test, Student t-test or Mann-Whitney's test, as appropriate.
BMI, body mass index; VCA, Viral Capsid Antigen.

Table 2 Protocol deviations

	3 months after baseline				15 months after baseline			
	Treatment		Control		Treatment		Control	
	n	%	n	%	n	%	n	%
Lost to follow-up								
No	15	71	21	95	13	87	19	90
Yes	6	29	1	5	2	13	2	10
Interruption of therapy								
No	15	71	n.a	n.a	n.a	n.a	n.a	n.a
Yes*	6	29	n.a	n.a	n.a	n.a	n.a	n.a
Diagnosed with another chronic disorder								
No	15	100	21	100	13	100	19	100
Yes	0	0	0	0	0	0	0	0
Experienced severe illness/trauma								
No	15	100	21	100	13	100	19	100
Yes	0	0	0	0	0	0	0	0
Receiving other therapy for chronic fatigue								
No	15	100	21	100	12	92	19	100
Yes	0	0	0	0	1	8	0	0

*The six individuals that interrupted therapy were the same individuals that were lost to follow up in the intervention group.
n.a, not applicable.

thoughts and feelings, and to motivate for mental effort/activity to control such negative thoughts and feelings. Cognitive therapy sessions typically blend content and process issues to help make effective changes in attitudes, beliefs and expectations. Collaborative empiricism, guided discovery and the Socratic method provide a comprehensive framework for the processes involved in therapy, while remaining aligned with the core concepts of cognitive therapy.[33] A central principle throughout the training programme was to achieve *therapeutic alliance*, which may have a strong impact on treatment effect.

The treatment programme assumes active participation from the patient between the sessions, and the therapists tried to communicate the necessity of individual effort. Parents/guardians are the most essential caregivers for the patient, and can in a positive way motivate the patient and provide guidance through the principles and specific techniques which were introduced in the treatment programme. At the same time, parents/guardians may also strengthen a negative illness behaviour and disease attribution, which in turn may have a negative impact on the prognosis. Therefore, it was of great importance to involve the parents/guardians in the treatment programme. Therapist fidelity was ensured by a protocol (see online supplemental file 1) detailing the content of every therapy session,[32] as well as close supervision from senior research collaborators.

As compared with existing CBT protocols for CFS,[5 6] the present mental training programme deviated mainly on the following points:

- *Music therapy* was integrated with traditional cognitive techniques.
- *Emotions* were focused to a greater extent, and specific techniques (such as mindful presence and visualisation) were introduced to increase access to positive feelings.
- *Unconscious/automatic experiences* were given more attention. Consequently, a fixed plan for graded activity was not an integrated part in the programme, whereas spontaneous experiences not involving conscious planning were encouraged.
- There was an *individual adaption* regarding specific psychological issues, and *parents/guardians* were included in some of the treatment sessions.

Effect monitoring

Assessment of beneficial and possible harmful effects was carried out 3 months after inclusion (ie, immediately after completion of the mental training programme), and 15 months after inclusion. Endpoints included steps/day count during seven consecutive days, symptoms (such as fatigue, postexertional malaise, pain) and quality of life/functional capacity. Recovery was defined as being classified as non-CF (ie, dichotomised response<4 on the CFQ)

Patient and public involvement

Representatives from the patient organisation 'Recovery Norway' as well as representatives from the 'Youth Council' at Dept. of Paediatrics and Adolescent Medicine, Akershus University Hospital, Norway, were involved in the design of the present study. Also, we received input from a group

Table 3 Outcome of the mental training programme intervention

	3 months after baseline		15 months after baseline	
	Intention to treat	Per protocol	Intention to treat	Per protocol
CFQ—total sum score				
Treatment group, mean	18.8	19.0	15.4	14.3
Control group, mean	20.5	20.3	18.1	18.1
Difference (95% CI)	−1.8 (−6.4 to 2.9)	−1.4 (−5.3 to 2.6)	−2.7 (−8.5 to 3.2)	−3.8 (−9.6 to 2.1)
Postexertional malaise—score				
Treatment group, mean	2.6	2.4	2.0	1.7
Control group, mean	3.0	2.9	2.4	2.1
Difference (95% CI)	−0.4 (−1.1 to 0.4)	−0.5 (−1.1 to 0.01)	−0.4 (−1.1 to 0.4)	−0.4 (−1.0 to 0.3)
BPI—total sum score				
Treatment group, mean	12.4	10.7	13.0	12.9
Control group, mean	12.2	12.4	11.7	11.0
Difference (95% CI)	0.2 (−5.3 to 5.7)	−1.7 (−5.1 to 1.6)	1.4 (−4.5 to 7.3)	1.9 (−2.5 to 6.3)
KSQ—total sum score				
Treatment group, mean	45.8	44.2	42.1	41.1
Control group, mean	46.7	47.9	44.4	44.6
Difference (95% CI)	−0.9 (−9.9 to 8.1)	−3.8 (−10.9 to 3.4)	−2.4 (−14.7 to 10.0)	−3.5 (−14.4 to 7.4)
HADS—total sum score				
Treatment group, mean	14.4	13.9	12.0	10.0
Control group, mean	14.6	14.2	13.3	12.4
Difference (95% CI)	−0.2 (−5.0 to 4.5)	−0.3 (−3.8 to 3.2)	−1.3 (−7.2 to 4.6)	−2.4 (−6.0 to 1.3)
PedsQL—total average score				
Treatment group, mean	66.2	69.8	72.4	75.9
Control group, mean	64.9	66.6	71.7	74.4
Difference (95% CI)	1.3 (−9.5 to 12.0)	3.2 (−4.1 to 10.5)	0.7 (−14.1 to 15.4)	1.4 (−9.2 to 12.0)
FDI—total sum score				
Treatment group, mean	12.7	11.0	11.4	7.4
Control group, mean	12.1	12.8	10.5	10.7
Difference (95% CI)	0.6 (−4.3 to 5.5)	−1.8 (−5.5 to 1.9)	0.9 (−6.5 to 8.3)	−3.3 (−9.0 to 2.4)
Steps per day—number				
Treatment group, mean	7217	6198	5680	7540
Control group, mean	8515	8257	7587	7782
Difference (95% CI)	−1298 (−4874 to 2278)	−2059 (−3698 to −421)	−1908 (−9853 to 6037)	−242 (−2944 to 2460)

All analyses in the intention to treat columns are based on multiple imputation (55 iterations). Means and differences 3 months and 15 monhts after baseline are estimated from the parameters of the general linear model. Model diagnostics was performed by visual inspection of residual plots.
BPI, Brief Pain Inventory; CFQ, Chalder Fatigue Questionnaire; FDI, Functional Disability Inventory; HADS, Hospital Anxiety and Depression Scale; KSQ, Karolinska Sleep Questionnaire; PedsQL, Paediatric Quality of Life inventory.

of adolescent CFS/ME sufferers and their next-of-kin through a pilot test of modified CBT. We carefully assessed the burden of the trial interventions on patients. We intend to disseminate main results to the trial participants, as well as to relevant patient organisations and other stakeholders.

Power considerations and statistical analyses

In a previous research project from our institution, CFS adolescents had a mean (SD) steps/day count of approximately 4500 (2400), and a mean (SD) CFQ total score of 19.1 (6.3).[34] This given, more than 120 participants would be needed in order to detect a moderate effect size (Cohen's d≈0.5), such as an increase in steps/day of 1200 or a reduction in CFQ total score of 3 (α=0.05, β=0.2). In the present study, the total number of eligible individuals were 91 (defined as CF cases 6 months after acute EBV infection), and only 43 consented to

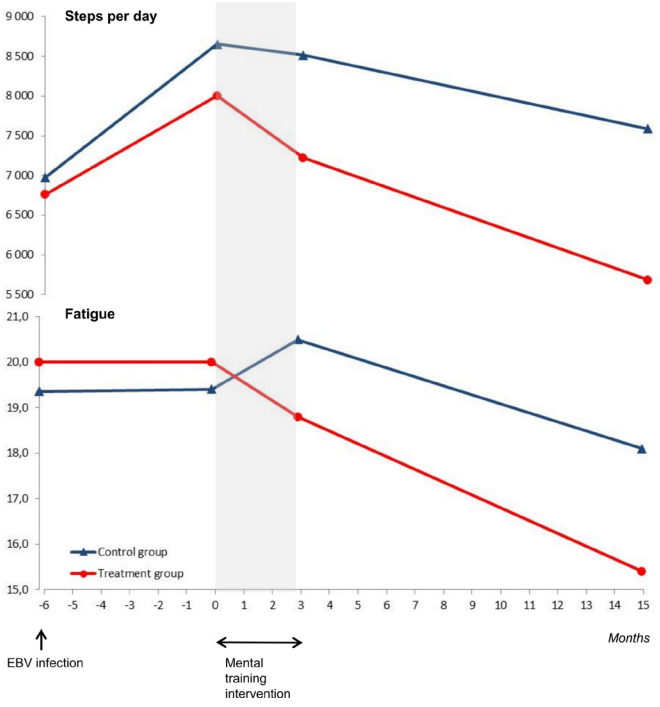

Figure 3 Development of steps/day and fatigue score over time in the intervention group (red) and the control group (blue), based on imputed data sets. The grey area represent the time period in which the mental training programme was provided. EBV, Epstein-Barr virus.

inclusion. Hence, the study was strongly underpowered regarding efficacy.

All statistical analyses were carried out using SPSS statistical software (IBM SPSS Statistic 26). The 'full analysis set' (all randomised participants) was used for intention-to-treat analyses of efficacy (see online supplemental file 2). A total of 55% of the included cases had missing data points. A convenient 'rule of thumb' suggests that the number of imputations should be similar to the percentage of cases that are incomplete.[35] Thus, multiple imputation with 55 iterations was performed using the procedure implemented in SPSS. For normally distributed variables with definite minimum and maximum, constraints were defined. In addition, a non-imputed dataset was used for per-protocol analyses. Continuous variables were reported as means or medians, as appropriate. Categorical variables were reported as numbers and percentages. General linear models (ANCOVA, analysis of covariance) were used for analyses of treatment effect; the baseline values of each efficacy endpoint were included as covariates. Safety data were summarised descriptively through appropriate data tabulations and descriptive statistics.

RESULTS

A total of 91 individuals from the postinfectious cohort study were classified as CF cases and thus eligible for inclusion in the present study (figure 1). More than half of the eligible individuals (n=48) did not consent to participation, mainly because they were concerned over school absence due to therapy sessions, leaving a total of 43 individuals for inclusion and randomisation; 21 were allocated to the intervention (mental training) arm, and 22 to the control (care as usual) arm. Background characteristics and baseline efficacy variables were similar between the included and the non-included group (table 1).

A total of seven individuals were lost to follow-up during the first 3 months of the study. Six of these individuals were allocated to the intervention group, and they all left the study prior to or immediately after therapy startup, again reporting concern over school absence as the main reason. Thus, there was a total of 15 participants in the intervention group and 21 in the control group for endpoint evaluation at 3 months follow-up. No other protocol deviations were registered during the first 3 months of the study (table 2). Of the 15 individuals completing the mental training programme, the number of attended therapy sessions divided by the total number of therapy sessions was 99% (one music therapy session missing in one individual); thus, compliance with appointments was high among those who stayed in the programme. We do not have data on compliance with recommended homework in-between appointments.

In intention-to-treat analyses, the primary endpoint (number of steps/day) did not differ significantly between the intervention group and the control group (table 3, figure 3). Also, secondary outcome measures were not significantly different among the two groups. However, most symptom scores tended to favour the

Table 4 Number of recovered patients 3 and 15 months after baseline

	3 months after baseline				15 months after baseline			
	Recovered		Not recovered		Recovered		Not recovered	
	n	%	n	%	n	%	n	%
Treatment group	3	21	11	79	8	62	5	38
Control group	4	20	16	80	7	37	12	63
Total	7	21	27	79	15	47	17	53

Recovery was defined as a total sum score ≤3 on the Chalder Fatigue Questionnaire (each item scored 0-0-1-1), analogous to the case definition of chronic fatigue used as inclusion criterion in the present study. P values are based on Fisher's exact test or χ^2 test, as appropriate.

Table 5 Adverse effects, self-reported

	3 months after baseline				15 months after baseline			
	Treatment		Control		Treatment		Control	
	n	%	n	%	n	%	n	%
Total								
No	9	60	12	57	9	69	14	74
Yes	6	40	9	43	4	31	5	26
More fatigued								
No	13	87	18	86	13	100	18	95
Yes	2	13	3	14	0	0	1	5
More attention problems								
No	13	87	15	71	12	92	17	89
Yes	2	13	6	29	1	8	2	11
More pain								
No	15	100	18	86	13	100	18	95
Yes	0	0	3	14	0	0	1	5
More sad/depressed								
No	11	73	20	95	10	77	19	100
Yes	4	27	1	5	3	23	0	0
Less schoolwork								
No	14	93	17	85	11	92	16	89
Yes	1	7	3	15	1	8	2	11
Any incident of self-harm								
No	14	93	21	100	13	100	19	100
Yes	1	7	0	0	0	0	0	0
Any thoughts/fantacies about suicide								
No	15	100	20	100	13	100	18	95
Yes	0	0	0	0	0	0	1	5

intervention group whereas physical activity tended to be higher in the control group.

An additional four individuals were lost to follow-up during the upcoming year, leaving a total of 13 in the intervention group and 19 in the control group for assessment 15 months after inclusion. There were no clear differences for any outcome variables (table 3, figure 3). However, there was a trend towards higher recovery rate with a total of 8 (62 %) recovered individuals in the treatment group, as compared with a total of 5 (39 %) recovered individuals in the control group (table 4).

As for possible harmful effects, there were no important differences between the intervention group and the control group (table 5).

DISCUSSION

This study shows that a mental training programme combining music therapy and CBT for postinfectious CF is feasible. However, the study was strongly underpowered and should be considered exploratory; a full-scale clinical trial with sufficient statistical power would be necessary to evaluate efficacy. In further research, participants' concern regarding school absence due to therapy sessions should be properly addressed to secure recruitment.

Most CBT treatment protocols for CF and CFS encompass an element of increased physical activity over time,[5 6] and graded exercise therapy (GET) in itself is shown to have beneficial effects in CFS.[36 37] Our mental training programme did not contain this element, which may explain why physical activity to our surprise actually tended to decline in the intervention group during the treatment period. Interestingly, we observed a concurrent tendency of improvement of many symptom scores, including fatigue and postexertional malaise, in the intervention group. This is in line with own experiences of patients with CSF, often reporting an initial worsening of symptoms during physical exercise which in turn might contribute to the strong controversy over studies that recommend GET in patients with CSF.[38 39] Thus, the therapeutic approach applied in the present study might be more acceptable from a patient perspective.

It has been demonstrated that postinfectious CF tends to recover spontaneously[1]; thus, only a small minority of patients develop CFS over time. Accordingly, in the present study, we observed symptom improvement over time in both the intervention group and the control group. Thus, a modest beneficial effect of the mental training programme might have been somewhat 'diluted' by the natural course of the postinfectious CF phenomenon. That said, the increased recovery rate after 15 months in the intervention group might indicate that mental training for postinfectious CF is clinically useful. This can only be determined in a full-scale clinical trial. Such a trial should be sufficiently powered to determine effects in the subgroup of CF individuals that adhere to diagnostic criteria of CFS. The low number of participants in the present study precluded us from performing such subgroup analyses.

In the present study, the compliance with appointments among those who completed the intervention was high, and the incidence of self-reported adverse events was very low and almost identical among the intervention group and the control group. Taken together, this suggests that the intervention was well tolerated, corroborating results from a recently published qualitative study which reported high levels of satisfaction among those that received the mental training programme.[40] We cannot rule out that the drop-out of six individuals in the intervention group before or immediately after startup of therapy was due to low tolerability in these participants. However, more probably, this loss to follow-up had the same cause as the poor recruitment of eligible patients into the study. The most likely explanation for these two phenomena is the introduction of a nationwide high-school sick leave precept during the study period. This precept initiated public controversies, and—in the context of the present study—caused a lot of concern among the eligible adolescents about participating in a mental training programme that would inevitably result in some school absence. This underlines the importance of considering similar contextual hindrances in the event of a future full-scale clinical trial. Furthermore, given this explanation, we assume the risk of strong selection bias to be rather low, as is supported from the lack of differences between the included and the non-included group for background and efficacy variables.

Strengths and limitations

Strengths of this study are the relatively homogeneous group of adolescent participants with the same infectious precipitation of CF and with no known comorbidities. Weaknesses encompass the poor recruitment leaving the study strongly underpowered, lack of formal fidelity checking among the therapists, and the lack of data regarding compliance with recommended homework in-between appointments.

CONCLUSION

An intervention study of combined CBT and music therapy in postinfectious CF is feasible. A fully powered trial is needed to evaluate efficacy. Participants' concern regarding school absence should be properly addressed to secure recruitment.

Author affiliations
[1]Pediatrics, Akershus University Hospital, Oslo, Norway
[2]Institutt for klinisk medisin, Universitetet i Oslo, Oslo, Norway
[3]Barne- og Ungdomsklinikken, Akershus Universitetssykehus HF, Lorenskog, Norway
[4]Department of Pediatrics and Adolescent Medicine, Drammen Hospital, Drammen, Norway
[5]Center for Music and Health, Norwegian College of Music, Oslo, Norway
[6]Department of Public Health and Nursing, NTNU—Norwegian University of Science and Technology, Trondheim, Norway

Acknowledgements The authors thank Stine Andersen Ness for invaluable secretary assistance.

Contributors SM, TTA, MP and JM collected clinical data, contributed to study design and participated in data analyses. GT and BvR contributed to study design. ES supervised statistical analyses. VBW conceived of the study, contributed to study design and participated in data analyses. All authors contributed to data interpretation and drafting of the manuscript.

Funding This study was supported by the Health South–East Hospital Trust, Norway, grant ID 2017123.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval The study was approved by The Norwegian National Committee for Ethics in Medical Research. Participation was based upon informed consent from all participants and (if younger than 16 years) their parents/guardians.

Provenance and peer review Not commissioned; externally peer-reviewed. This is an amended, republished version of a retracted paper: http://dx.doi.org/10.1136/bmjpo-2019-000620.

Data availability statement Data are available upon reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID iD
Vegard Bruun Wyller http://orcid.org/0000-0002-2537-7782

REFERENCES

1 Hickie I, Davenport T, Wakefield D, *et al*. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* 2006;333:575.
2 Katz BZ, Shiraishi Y, Mears CJ, *et al*. Chronic fatigue syndrome after infectious mononucleosis in adolescents. *Pediatrics* 2009;124:189–93.
3 Institute of Medicine. *Beyond myalgic Encephalomyelitis/Chronic fatigue syndrome: redefining an illness*. Washington, DC: The National Academies Press, 2015. http://www.iom.edu/mecfs
4 Royal College of Paediatrics and Child Health. *Evidence based guidelines for the management of CFS/ME (chronic fatigue syndrome/myalgic encephalopathy) in children and young adults*. London: Royal College of Paediatrics and Child Health, 2004.
5 White PD, Goldsmith KA, Johnson AL, *et al*. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise

therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011;377:823–36.
6 Nijhof SL, Bleijenberg G, Uiterwaal CSPM, *et al*. Effectiveness of Internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *Lancet* 2012;379:1412–8.
7 Abrahams HJG, Gielissen MFM, Donders RRT, *et al*. The efficacy of Internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: a randomized controlled trial. *Cancer* 2017;123:3825–34.
8 Menting J, Tack CJ, van Bon AC, *et al*. Web-Based cognitive behavioural therapy blended with face-to-face sessions for chronic fatigue in type 1 diabetes: a multicentre randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;5:448–56.
9 Cella M, Chalder T, White PD. Does the heterogeneity of chronic fatigue syndrome moderate the response to cognitive behaviour therapy? an exploratory study. *Psychother Psychosom* 2011;80:353–8.
10 Rimes KA, Wingrove J. Mindfulness-based cognitive therapy for people with chronic fatigue syndrome still experiencing excessive fatigue after cognitive behaviour therapy: a pilot randomized study. *Clin Psychol Psychother* 2013;20:107–17.
11 Viner R, Gregorowski A, Wine C, *et al*. Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME). *Arch Dis Child* 2004;89:615–9.
12 Crawley EM, Gaunt DM, Garfield K, *et al*. Clinical and cost-effectiveness of the lightning process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. *Arch Dis Child* 2018;103:155–64.
13 Stubhaug B, Lier HO, Aßmus J, *et al*. A 4-day Mindfulness-Based cognitive behavioral intervention program for CFS/ME. an open study, with 1-year follow-up. *Front Psychiatry* 2018;9:720.
14 Bradt J, Dileo C, Potvin N. Music for stress and anxiety reduction in coronary heart disease patients. *Cochrane Database Syst Rev* 2013;12:CD006577.
15 Bradt J, Shim M, Goodill SW, Dileo C. Dance/movement therapy for improving psychological and physical outcomes in cancer patients. *Cochrane Database Syst Rev* 2015;1:CD007103.
16 Torres E. Group Music and Imagery (GMI) for Treating Fibromyalgia. In: Grocke D, Moe T, eds. *Guided Imagery & Music (GIM) and Music Imagery Methods for Individual and Group Therapy*. London: Jessica Kingsley, 2015: 267–76.
17 Beck BD. Guided imagery and music (GIM) with adults on sick leave suffering from work-related stress Aalborg University; 2012.
18 Pedersen M, Asprusten TT, Godang K, *et al*. Predictors of chronic fatigue in adolescents six months after acute Epstein-Barr virus infection: a prospective cohort study. *Brain Behav Immun* 2019;75:94–100.
19 Chalder T, Berelowitz G, Pawlikowska T, *et al*. Development of a fatigue scale. *J Psychosom Res* 1993;37:147–53.
20 Grant PM, Ryan CG, Tigbe WW, *et al*. The validation of a novel activity monitor in the measurement of posture and motion during everyday activities. *Br J Sports Med* 2006;40:992–7.
21 Tanaka M, Fukuda S, Mizuno K, *et al*. Reliability and validity of the Japanese version of the Chalder fatigue scale among youth in Japan. *Psychol Rep* 2008;103:682–90.
22 Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res* 1998;45:53–65.
23 Klepstad P, Loge JH, Borchgrevink PC, *et al*. The Norwegian brief pain inventory questionnaire: translation and validation in cancer pain patients. *J Pain Symptom Manage* 2002;24:517–25.
24 Engel JM, Kartin D, Carter GT, *et al*. Pain in youths with neuromuscular disease. *Am J Hosp Palliat Care* 2009;26:405–12.
25 Akerstedt T, Ingre M, Broman J-E, *et al*. Disturbed sleep in shift workers, day workers, and insomniacs. *Chronobiol Int* 2008;25:333–48.
26 Pedersen M, Ekstedt M, Småstuen MC, *et al*. Sleep-Wake rhythm disturbances and perceived sleep in adolescent chronic fatigue syndrome. *J Sleep Res* 2017;26:595–601.
27 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
28 Mihalca AM, Pilecka W. The factorial structure and validity of the hospital anxiety and depression scale (HADS) in Polish adolescents. *Psychiatr Pol* 2015;49:1071–88.
29 Reinfjell T, Diseth TH, Veenstra M, *et al*. Measuring health-related quality of life in young adolescents: reliability and validity in the Norwegian version of the pediatric quality of life inventory 4.0 (PedsQL) generic core scales. *Health Qual Life Outcomes* 2006;4:61.
30 Walker LS, Greene JW. The functional disability inventory: measuring a neglected dimension of child health status. *J Pediatr Psychol* 1991;16:39–58.
31 Claar RL, Walker LS. Functional assessment of pediatric pain patients: psychometric properties of the functional disability inventory. *Pain* 2006;121:77–84.
32 Department of Pediatrics, Akershus University Hospital. Mental intervention for chronic fatigue syndrome (CFS/ME) following acute Epstein-Barr virus infection. treatment manual for the intervention part of the CEBA-project; 2015. www.ahus.no/seksjon/forskning/Documents/Forskningsgrupper/Barne-%20og%20ungdomsklinikken/Paedia/Behandlingsmanual.pdf
33 Tee J, Kazantzis N. Collaborative empiricism in cognitive therapy: a definition and theory for the relationship construct. *Clin Psychol Sci Prac* 2011;18:47–61.
34 Sulheim D, Fagermoen E, Winger A, *et al*. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. *JAMA Pediatr* 2014;168:351–60.
35 Von Hippel PT. How many imputations do you need? A two-stage calculation using a quadratic rule. *Sociological Methods & Research* 2018.
36 Larun L, Brurberg KG, Odgaard-Jensen J, *et al*. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev* 2016;2:CD003200.
37 Clark LV, Pesola F, Thomas JM, *et al*. Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomised controlled trial. *Lancet* 2017;390:363–73.
38 Kindlon T. Do graded activity therapies cause harm in chronic fatigue syndrome? *J Health Psychol* 2017;22:1146–54.
39 Vink M, Vink-Niese A. Graded exercise therapy for myalgic Encephalomyelitis/Chronic fatigue syndrome is not effective and unsafe. Re-analysis of a cochrane review. *Health Psychol Open* 2018;5:2055102918805187.
40 Trondalen G, Mangersnes J, Bonde LO, *et al*. Music therapy for chronic fatigue following Epstein-Barr virus infection in adolescents. *Music & Med* 2020;12:84–91.

Mental intervention for chronic fatigue syndrome (CSF/ME) following acute Epstein-Barr virus infection

Treatment manual for the intervention part of the CEBA-project

Children- and youth clinic, Akershus university hospital, June 2015

A. General factors

Introduction

CEBA (Chronic fatigue following acute Epstein-Barr virus infection in adolescents) is a research project investigating correlation between acute EBV-infection and the evolvement of Chronic fatigue syndrome (CSF/ME) in adolescents (12-20 years old) (9,10). An integrated part of this project is a randomized controlled intervention, where youths developing CFS/ME are offered a newly developed treatment program consisting of elements from cognitive behavioral therapy and music therapy.

The treatment program is built on a) theoretical considerations, b) clinical studies of resp. cognitive behavioral therapy and music therapy and c) user experiences from a pilot study carried out by our research group autumn 2014 (17). Here we shortly present background, goal and design, before we elaborate each element in the treatment program. A more comprehensive discussion and arguments are found in a separate research protocol (10).

Background

The "Sustained arousal" – model of CFS/ME is based on principles from cognitive theory and behavioral learning theory (35), primarily "Cognitive Activation Theory of Stress" (CATS) (30). An important premise in this model is that CFS/ME can arise as a result of classical and operant conditioning (25); for example can natural fatigue during long lasting infection gradually be automatically associated with other stimuli, like physical activity. By this the fatigue is sustained even though the infection gradually gets healed.

The validity of this model of understanding is supported by clinical research showing cognitive behavioral therapy as positive for CFS/ME patients (23,34). There is also no risk of serious side effects associated with this way of treatment (14), but at the same time the effect size is rather moderate. Therefore, more effective ways of treatment are needed; at the same time more knowledge about underlying disease mechanisms is also needed, which can be acquired if treatment studies also includes biomarkers and charting of pathophysiological processes. Finally it is important to study a patient cohort with identical actuating cause of fatigue (like EBV-infection), since earlier studies can be criticized for having a heterogeneous patient material (15).

Theoretical reflections indicate that it can be beneficial to combine cognitive behavioral therapy with other mental forms of therapy (24,31). Good effect of such interdisciplinary approach towards youths has been reported (32), but the body of knowledge is sparse, and no randomized controlled trials exist. There also exist corresponding anecdotic reports of the benefit of modified cognitive treatment programs (12).

Music therapy has effect on sensory modulation, cognition, emotions and behavior which seems functional treating CFS/ME; these effects are mediated via central nervous learning processes (18). No studies exist – and consequently no clinical documentation of the benefit of music therapy for treating CFS/ME, but there is shown positive effect in related conditions like

fibromyalgia (6,27). Combinations of music therapy and cognitive behavioral therapy are established in other clinical settings (20).

Aim

In this part of the CEBA-project we want to investigate whether a newly developed mental treatment program encompassing elements from cognitive behavioral therapy and music therapy can have a positive effect on the level of activity, symptoms and markers for disease activity among youths developing CFS/ME six months after debut of EBV-infection.

Design

The inclusion criterion is a fatigue score ≥ 4 (Chalder fatigue questionnaire, dichotomous scoring (11)). Exclusion criteria are intercurrent diseases which can explain the fatigue, and also lasting bedrest (10).

Patients included will be randomized 1:1 to either participation in the mental treatment program or routine follow-up by general practitioner. We calculate 50 participants in total, 25 in each treatment group. The patients undergoes a thorough evaluation before starting treatment (week 0), immediately after the last treatment session (week 12), and twelve months after finished treatment (week 64). Primary endpoint is physical activity (average number of steps per day) by week 12; there are good experiences from earlier research projects using this endpoint on fatigued patients (26). This study has a power of at least 80% (α=0.05) to identify a treatment effect of 2000 more steps per day (10).

The intervention – outlines of the mental treatment program

The treatment program is delivered through 10 treatment sessions á 90 minutes over a period of 10 weeks. The first session is an introduction and takes place with the patient, his/her parents/guardians and all therapists that are carrying out the treatment (figure 1). Then follow nine treatment sessions, four led by a music therapist (lesson nr. 2, 3, 5 and 9) and five led by a cognitive therapist (lesson nr. 4, 6, 7, 8 and 10). At three of the sessions with cognitive therapists (lesson 4, 7 and 10) parents/guardians participate; also, parents/guardians may attend lesson nr. 5 and 8 if the team of therapists considers it advantageous. Between the sessions each patient gets home work, and will also be called up at least once a week by either music therapist or cognitive therapist for advice and counselling.

In the first part of the treatment program music therapy will be emphasized (figure 1), with a combination of musical improvisation, songwriting, music listening and also developing personal playlists to be used in the daily living (1,2,28). Elements from cognitive therapy will be introduced gradually, and will in the end be the dominating form of treatment.

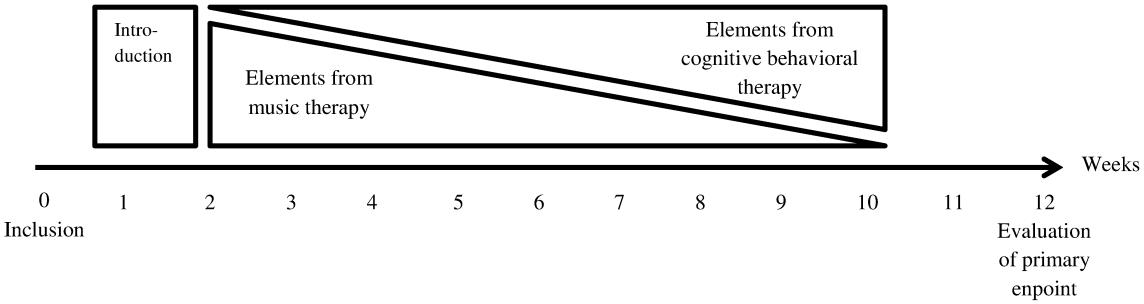

Figure 1. General model of the mental treatment program

Central principles in the mental treatment program

Therapeutic alliance

A good alliance between therapist and patient is of great importance for the effect of cognitive therapy (33). It is important that the alliance is established as soon as possible and is strengthened by positive patient experiences. Elements from music therapy stimulating positive feelings should be emphasized in the beginning of the treatment program (18,29). User experiences indicate that cognitive therapy may be experienced as "duty-oriented" and "school-alike"; therefore it is favorable if elements from this form of treatment are introduced later on (17).

Expectations and hope

One may have expectations both to specific targets and more general to "what will happen in the future". It is important charting the patients expectations, both to the disease/symptoms itself, specific situations in the everyday life, and future circumstances of life. Negative patient expectations, both what is going to happen (stimulus expectation), and how you can deal with it (response outcome expectation) have in themselves impact on the stress responses, and may be included as vicious circles in the patients (8,30,35).

The therapist must attempt to communicate to the patient a realistic hope of improvement, both from disease and life in general. This presupposes that the therapist possesses specialist authority, confidence as a therapist, empathy and a trustful relation to the patient. The patient needs to experience that his/her complaints and symptoms are taken seriously, that they can be explained in a rational way, and that no differential diagnoses are missed. User experiences indicate that histories from other patients (who have become healed) are of great importance for expectation and hope (17).

Control and coping

The feeling of having control/the belief in one's ability to cope is strongly dependent on earlier coping experiences, but is also influenced by observation of others coping, verbal persuasion about one's ability to manage something and a positive emotional/physical activation (4).

The therapist must facilitate situations where the patients can have coping experiences, with the patients circumstances of life as a starting point. The feeling of coping with a symptom the patient is struggling with, can be of great importance – then a mental control over the illness is established. Coping experiences are in themselves self-energizing: the belief in control/coping strengthen the actual ability to control/cope, and reduce bodily and mental stress activation (30). Participating actively in the treatment, and to some degree being given choices, can promote the feeling of control in the patient. In a confident therapist relation the therapist may also challenge the patients' view of mental control – together with the patient the therapist are able to identify negative thoughts and feelings, and motivating for mental individual effort/activity to take control over these negative thoughts and feelings. Here, special techniques may be helpful, like visualizing and bodily relaxing techniques. Some may have difficulties to identify negative thought patterns, for example they instead experience negative thoughts as neutral ascertains of facts. It is important to be aware of this to avoid negative thought patterns being automated and chronic, thereby blocking changes.

Experience of meaning

The patient must experience the treatment as meaningful and relevant for his/her own situation (5).The therapist may ask him-/herself: "Does what I say and do give meaning for this particular person?" A key question asking the patient may be: "What do you miss the most of the things you are not able to do because of the fatigue"?

Searching for a cause for the disease are often less expedient, since the patients often tend to misattribute (13,16) – therapist and patient should rather together concentrate on maintaining factors and what here and now may give improvement.

Positive experiences

Troublesome symptoms (like fatigue) may be triggered, not only by physical activities, but also by imagining such activities (36), which in next moment may strengthen the already established "mislearning" that all activity leads to afflictions (5). For the patient to get other experiences, the therapist may facilitate activities which to a minimal degree are an object of conscious planning. This will further make it possible to establish other, unconscious association in the central nervous system and contribute to "unlearning" of the inexpedient responses, according to fundamental principles from learning theory (5,25) and the "sustained arousal"-model of CFS/ME (35).

The therapist may also intentional arrange behavioral experiments with the patient, to test the reasonableness of the patients own understanding of the condition. For some patients it may also be required and appropriate with a plan for activities. Nevertheless it will not be established a fixed frame for graded activity, which is an important element in standard cognitive therapy for CFS/ME (8). User experiences indicate that such a plan may be experienced as a duty that must be obeyed. It may create expectations of worsening of symptoms if the plan is not followed, which in turn may trigger inexpedient anxiety.

Emotions

Negative emotions in a therapeutic situation, as anxiety and anger, may lead to learning of something totally different from what is believed by the patient and the therapist, and may block the learning of what was intended (5). If such emotions still arise, the therapist should clearly signal that these emotions are tolerated. A superior goal is still that the therapist all the time aims for a positive emotional activation in the treatment situation. This implies among others a focus on what the patient *wants* to do, rather than the duty to do something. Further may music therapeutic elements be effective in mobilizing positive emotions, which will be emphasized particularly in the first treatment sessions (18,29). The patients will learn visualization; this has been shown having a positive effect on CFS/ME and related conditions (19,21).

Concerns/rumination can be an important sustaining factor among patients with long lasting fatigue (7); it is therefore required to reduce this to a minimum. User experiences indicate moreover that negative emotions may arise in the patients if they experience that their disease is "psychologized" - one should for example not assume that the patient has a "negative way of thinking" in general, but rather present techniques usable on "bad days" (17).

Individual effort

The treatment program assumes active participation from the patient. For many patients avoidance is a (unconscious) coping strategy, which may work effective in a short perspective, but will contribute to sustain the fatigue on a long-term basis (22). The therapist must communicate the necessity of individual effort, particular towards the end of the treatment program where the intention is that the patient has learned techniques which can be used unaided.

The necessity of individual effort should nevertheless not be presented in such a way that the patient increases his/her worries or feels the treatment program more as a duty rather than pleasurable, cf. paragraphs above. User experiences indicate that instructions and homework should not be at too advanced level or remind too much of school assignments (17). Still it is important to strengthen the patients' belief in that they have the ability to affect their situation through effort. To create motivation in each individual patient must be greatly emphasized. Our experience indicates that the patients not necessarily perceive it as negative to be given tasks between the treatment sessions, but notions associated with school or school-related activities are problematic because often these patients have huge challenges with school attendance. This is the reasons for introducing homework gradually, and that it is presented on a digital platform according to the lifestyle of today's youth.

Individual adaption

As a main principle the treatment must be individually adapted (cf. the paragraph about meaning above), but still within certain frames as outlined under point B below. Individual adaption must also be done considering age and the level of maturity (in particular this happens to be the case with the cognitive techniques), and considering specific problematic areas in the patient group

that are already mapped out (trough questionnaires and cognitive tests) (10). Primarily these problematic areas are: anxiety, depression, sleeping disorders, trouble with executive functions (attention, working memory), perfectionism and worries.

Involvement of parents/guardians

Parents/guardians are the most essential caregivers for the patient, and can in a positive way motivate the patient and help guiding through the principles and specific techniques which will be introduced in the treatment program. At the same time parents/guardians may also strengthen a negative illness behavior and disease attribution, which in turn may have a negative impact on the prognosis (3). Therefore it is of great importance to involve the parents/guardians in the treatment program, and they are expected to participate in four out of ten sessions. The therapist is not intended to establish an extensive family therapy, but must be prepared for straightforward dialogue with parents/guardians which are perceived to have a clearly negative influence on the treatment plan.

Principal differences between this mental treatment program and traditional cognitive behavior therapy for CFS/ME

This treatment program is built on several of the same principles as traditional cognitive therapy for CFS/ME, but deviate on certain important points:

- It is built on a model of CFS/ME which postulates *sustained arousal* maintained through *classical and operant conditioning* (30,35). In traditional cognitive therapy one has rather emphasized factors like sickness belief, reduced and inconsistent activity, sleeping disturbances, medical uncertainty and lack of counselling as maintaining factors in CFS/ME (8).
- *Music therapy* is being integrated together with traditional cognitive techniques to an overall mental treatment program.
- *Emotions* are to a greater degree paid attention to compared to what is normal in traditional cognitive therapy, and specific techniques (like mindfulness and visualization) will be introduced to increase the access of positive feelings.
- *Unconscious/automatic experiences* are given more attention, whereas conscious processing of thoughts and planning of behavior is less emphasized. Therefore a fixed plan for graded activity is not an integrated part in the program, such as in traditional cognitive therapy; rather emphasized is spontaneous experiences not involving conscious planning.
- There will be an *individual adaption* regarding specific psychological issues, and *parents/guardians* are included in the treatment.

References

1. Baker F, Wigram T. Songwriting methods, techniques and clinical application for music therapy clinicians, educatores and students. London: Jessica Kingsley Publishers, 2004.
2. Baker F. Therapeutic Songwriting. London: Palgrave Macmillan, 2015.
3. Band R, et al. The impact of significant other expressed emotion on patient outcomes in chronic fatigue syndrome. Health Psychol 2014; 33: 1092-101.
4. Bandura A. Self-efficacy mechanisms in human agency. Am Psychol 1982; 37: 122–147.
5. Brodal P, Fadnes B, Leira K. Læringsorientert fysioterapi: teori og praksis. Oslo: Universitetsforslaget, 2013.
6. Bjellånes NAL. Musikk og autogen trening i samspill: En bedre livskvalitet for mennesker med diagnosen fibromyalgi. Musikkterapi 1994; 1: 4-21.
7. Brosschot JF, et al. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. J Psychosom Res 2006; 60: 113-24.
8. Burgess M, Chalder T. Pace. Manual for Therapists. Cognitive behavior therapy for CFS/ME. London, 2004.
9. CEBA protocol part A – a prospective and cross-sectional study of fatigue following EBV infection. Lørenskog: Dept. of Pediatrics, Akershus University Hospital, 2015. http://www.ahus.no/omoss_/avdelinger_/barne-og-ungdomsklinikken_/forskning_og_utvikling_/Documents/CEBA/Protocol%20CEBA.pdf
10. CEBA protocol part B – a randomized controlled intervention of a mental training program for fatigue following EBV infection. Lørenskog: Dept. of Pediatrics, Akershus University Hospital, 2015.
11. Chalder T, et al. Development of a fatigue scale. J Psychosom Res 1993; 37: 147-53.
12. Crawley E, et al. Comparing specialist medical care with specialist medical care plus the Lightning Process for chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME): study protocol for a randomised controlled trial (SMILE Trial). Trials 2013; 14: 444.
13. Dendy C, Cooper M, Sharpe M. Interpretation of symptoms in chronic fatigue syndrome. Behav Res Ther 2001; 39: 1369-80.
14. Dougall D, et al. Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome. J Psychosom Res 2014; 77: 20-6.
15. Fischer DB, et al. Chronic Fatigue Syndrome: The Current Status and Future Potentials of Emerging Biomarkers. Fatigue 2014; 2: 93-109.
16. Gray ML, Rutter DR. Illness representations in young people with Chronic Fatigue Syndrome. Psychology and Health 2007; 22, 159-174.
17. Heldal K. Et biopsykologisk behandlingsprogram ved kronisk utmattelsessyndrom (CFS/ME) hos ungdom. Et pilotprosjekt. Kandidatafhandling i psykologi. Aarhus: Psykologisk Institut, Aarhus universitet, 2015.
18. Koelsch S. A neursoscientific perspective on music therapy. I The Neurosciences and music III - Disorders and plasticity: Ann NY Acad Sci 2009; 1169: 374-84.
19. Lakhan SE, Schofield KL. Mindfulness-based therapies in the treatment of somatization disorders: a systematic review and meta-analysis. PLoS One 2013, 8: e71834.
20. Lund HN. "My battle of life". Musikkterapi med brug af sangskrivning, rap-performance og kognitive metoder. Musikkterapi i psykiatrien 2012; 7 (2): 81-92.
21. Menzies V, Taylor AG, Bourguignon V, et al. The Journal of Alternative and Complementary Medicine 2006; 12: 23-30.
22. Moss-Morris R. Symptom perceptions, illness beliefs and coping in chronic fatigue syndrome. Journal of Mental Health 2005, 14: 223-235.
23. Nijhof SL, Bleijenberg G, Uiterwaal CS, et al. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet 2012; 379: 1412-8.
24. Price JR, Mitchell E, Tidy E, Hunot V: Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database syst Rev 2008, 2:CD001027.
25. Skinner EA. A guide to constructs of control. J Pers Soc Psychol 1996; 71: 549–570.
26. Sulheim, D., et al., Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. JAMA Pediatr 2014; 168: 351-60.

27. Torres E. Group Music and Imagery (GMI) for Treating Fibromyalgia: Listening to Oneself as a Path of Opening and Transformation. In D. Grocke & T. Moe (Eds.), Guided Imagery & Music (GIM) and Music Imagery Methods for Individual and Group Therapy (pp. 267-276). London: Jessica Kingsley Publisers, 2015.
28. Trondalen G. Improvisasjon i musikkterapipraksis: tradisjon - kunst - teknikk. I: Nesheim E, Hanken IM, Bjøntegaard B, red. Flerstemmige Innspill. En artikkelsamling. Oslo: NMH-publikasjoner, 2005: 123-43.
29. Trondalen G, Skårderud F. Playing With Affects. And the importance of "affect attunement". Nordic Journal of Music Therapy 2007; 16:, 100-111.
30. Ursin H, Eriksen HR. The cognitive activation theory of stress. Psychoneuroendocrinology 2004; 29: 567-92.
31. Van Houdenhove B, Luyten P: Customizing Treatment of chronic fatigue syndrome and fibromyalgia: The role of perpetuating factors. Psychosomatics 2008, 49:470–477.
32. Viner R, Gregorowski A, Wine C, Bladen M, Fisher D, Miller M, El Neil S. Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME). Arch Dis Child 2004, 89:615–619.
33. Weck F, et al. Therapist competence and therapeutic alliance are important in the treatment of health anxiety (hypochondriasis). Psychiatry Res 2015; Apr 13 [Epub ahead of print]
34. White PD, Goldstmith KA, Johnson AL, et al. Comparison of adaptive pacint therapy, cognitive behaviour therapy, grader exercise therapy and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 2011; 377: 823-36.
35. Wyller VB, et al. Can sustained arousal explain the Chronic Fatigue Syndrome? Behav Brain Funct 2009; 5: 10.
36. Wyller VB, Fagermoen E, Sulheim D, Winger A, Skovlund E, Rowe PC, Saul JP. Orthostatic responses in adolescent chronic fatigue syndrome: contributions from expectancies as well as gravity. Biopsychosoc Med 2014; 8: 22.

B: Treatment sessions

1st meeting (week 1): Introduction with parents/guardians

Frames:

- Participants: The patient, parents/guardians, music therapist, cognitive therapist, responsible researcher, "speaker"
- Time: 90 minutes
- Place: Akershus University Hospital (AHUS)

Aim/focus

This is the first session in the treatment program, and is set as a psycho-educative introduction where understanding of the disease, treatment rationale and so on are being presented. Important keywords are:

- Give information about the treatment program and underlying grounds
- Clarify expectations to the treatment program
- Create motivation, hope and enthusiasm both in patients and parents/guardians
- Present the music therapist and cognitive therapist. Establish alliances.

Implementation

The first 15 min is reserved for mingling, light refreshments will be served (drinks and fruit e.g.). In this part it is important that all participating therapists actively are focused on greeting the patient and his/her parents/guardians. There will be played background music (intentionally chosen). This part finishes off with a music performance, before the chairman takes over. This one gives 2-3 min of information, before the responsible researcher is being presented. The researcher further gives a presentation on our understanding of CSF/ME. Here it is important to use the patients' own histories as a starting point. This further leads to how one is able to deal with it. Explain the concept of music changing the brain. Before a 15 min break there will be an opportunity to ask questions.

After the break a "success history" is presented. A patient who has recovered first tells his/her history, before this one is interviewed by the chairman, focusing on hope and opportunities. Open up for conversation with the patient and his/her parents/guardians, detect whether the patient recognizes some aspects in the "success history", with the aim of connecting the patients thinking and behavior pattern to the rationale earlier presented.

Further the therapists are presented, each having a short presentation of his/her treatment form. Then a new opportunity for open questions is given, before another music performance ends the session.

2nd meeting (week 2): Individual session

Frames:

- Participants: Patient, music therapist
- Time: 90 minutes
- Place: Ahus

Aim and implementation

This is the first lesson with music therapy. It is important to continue the work with building alliances, common understanding e.g., and that the patient is feeling confident in the situation. It is the patient's wish for the music therapeutic action that guides the here-and-now-meeting. The music therapist focuses on the client's resources. At the same time more specific actions are introduced, primarily:

- Mapping out the patients' music interests: music preferences and music listening in the daily living.
- Open up for an improvisatory approach to songwriting and music composition. This means a) put music to some of the patients' personal feelings and experiences, through focus on subjects from the daily life, or subjects of a more existential character, or b) have a starting point in music spontaneously referred by the patient – and put the patients' personal sayings in such a musical frame. If the patient brings a text, a poem or own music it is important to follow up this and put the texts in a positive musical frame.
- Music listening in a relaxed state. This means focus on mindfulness, focus on visualization of a "safe place", and relaxing/easing of tension/stress reduction. Visualization makes use of positive and pleasurable expressions. The music listening spend over a short time span. The patient chooses whether he/she want to sit or lay down.

Home tasks

- Choose music and listen actively to it for 5-10 minutes every day. *Pay attention to* what you think about different kinds of music. Pay attention to how different kinds of music affect you.

3rd meeting (week 3): Individual session

Frames:

- Participants: Patient, music therapist
- Time: 90 minutes
- Plave: Ahus

Aim and implementation

This is the second lesson with music therapy. There will be repetition of techniques from the previous lesson, and eventually work more on these depending on the patient's wishes and skills. Following up the patients tasks in music listening is of particular importance. In addition a goal for this lesson is to facilitate activities which to a minimal degree involve conscious planning, but focus on what is happening here and now. The intention is to create new automatic associations: Instead of the association "activity leads to fatigue" one shall facilitate associations like "activity gives energy" and "activity is fun". Here the patient's own wishes will guide the coming music activity; improvisation, songwriting and/or music listening. What kind of activity and what type of music usable for this are individual adapted. If one does not succeed, and the patient actually gets tired of the activity started, it is important to play down and rather try to use this experience for something useful – for example using a technique for resting or a technique for visualization used to chase away the feeling of fatigue and to focus on something else. Keywords are:

- Open up for an improvisatory approach to songwriting and music composition. This means a) put music to some of the patients' personal feelings and experiences, through focus on subjects from the daily life, or subjects of a more existential character, or b) have a starting point in music spontaneously referred by the patient – and put the patients' personal sayings in such a musical frame. If the patient brings a text, a poem or own music it is important to follow up this and put the texts in a positive musical frame.
- Music listening in a relaxed state. This means focus on mindfulness, focus on visualization of a "safe place", and relaxing/easing of tension/stress reduction. Visualization makes use of positive and pleasurable expressions. The music listening spends over a short time span. The patient chooses whether he/she wants to sit or lay down.
- Activities which are not consciously planned: music therapy will have a starting point in what is pleasurable, and will follow the patient's wish for musical approach.

Home tasks

- Tasks for 5th meeting (i.e. next time with music therapy) are further built on the task given in the 2nd meeting: Listen to music 5-10 min every day. *Choose* (at least) one piece of music/tune in each of the categories: a) I really like this piece of music/tune b) this piece of music/tune makes me feel calm and relaxed, and c) this piece of music/tune may give me new strength and energy. This means to choose (at least) three pieces of music/tunes. *Bring*

along these pieces of music/these tunes to the next meeting with the music therapist, i.e. 5th meeting.

4th meeting (week 4): Session with patient and parents/guardians

Frames:

- Participants: patient, parents/guardians, cognitive therapist, music therapist (teammate and observer)
- Time: 90 minutes
- Place: Ahus

Aim and implementation

This is the first individual meeting with the cognitive therapist, and also the first meeting where parents/guardians are attending after the first group session in the beginning of the treatment period. The lesson opens with the music therapist going through what have been subjects the two previous sessions, and how this may be evolved in the rest of the treatment period. The rest of the session is lead by a cognitive therapist and the structure is much like a traditional startup lesson in cognitive therapy. Keywords are:

- The patient and the family's history. Explore the patient and parents/guardians points of view, thoughts, ideas, explanation models, expectations and so on.
- Mapping out the patient and the family. Before the conversation much information regarding the patient is already known from the questionnaires (particularily anxiety, depression, sleeping problems, problems with executive functions (attention, working memory), perfectionism and worries). Use this and anamnestic information to make a fundament for individual adapted treatment in the rest of the treatment program.
- Go over the rationale once again and try to establish a common understanding. In particular it is important to draw in the music therapy, and actively use the patients experiences from the previous two sessions with music therapy, including how the music may activate different kinds of feelings. One may for example explain how techniques for relaxation, mindfulness and visualization may be used in different situations. But one shall not verbalize the principle of doing spontaneous activities – it is important that this is an unconscious experience, not an object for much mental work.
- Focus on building alliances – create good frames for learning.

Homework

Towards the end of this session more comprehensive homework than the patient has had earlier is introduced. It is important to motivate both parents/guardians and patient to do these tasks – underline the positive aspects in the possibility of being able do something with his/her own situation, and at the same time give some demands regarding individual effort. The motivation may also be strengthened by underlining that tasks are presented on a digital platform, adapted to the youths everyday life. I may be expedient to use some of the lesson working through the tasks together with the youths, so they are getting familiar with them and experience coping.
Keywords for home tasks after meeting nr 4:

- Practice techniques in mindfulness, relaxation and visualization (simple instructions are given on the digital platform).
- View a presentation of disease models for fatigue and argument for treatment (preferable together with parents/guardians).
- Keep a sleeping and activity diary.
- Listen to music for 5-10 minutes every day.

These home tasks are in the first phase meant to go on for two weeks, to session nr. 6.

5th meeting (week 5): Individual session

Frames:

- Participants: Patient, music therapist, eventually parents/guardians
- Time: 90 minutes
- Place: Ahus

Aim and implementation

This is the third meeting between the patient and the music therapist. Parents/guardians may be included if the treatment team consider it favorable. A central point in this session will be to continue and repeat already learnt techniques regarding attention, relaxation and visualization, which the patient now has received on a digital platform. It is important to integrate music therapeutic instruments with the cognitive approaches presented in the 4th session (where the music therapist participated as an observer). One should demonstrate the relevance of such techniques for the patients, and also help them to see how they can use them in everyday challenges.

The most important point in this session is still to try to experience activities which are not a result of conscious planning. The patient's homework finding at least three pieces of music/notes giving the patient positive associations can be used as a starting point. Create consciousness about elements/music so the patients are able to look for additional music giving the same feelings. The patients have brought music communicating positive emotions and which gives energy. If these attempts fail to succeed – try to turn this experience into something positive, as mentioned above.

- Open up for an improvisatory approach to songwriting and music composition. This means a) put music to some of the patient's personal feelings and experiences, through focusing on subjects from the daily life, or subjects of a more existential character, or b) have a starting point in music spontaneously referred by the patient – and put the patients' personal sayings in such a musical frame. If the patient brings a text, a poem or own music it is important to follow up this and put the texts in a positive musical frame. This may mean that the main focus is now on songwriting. Here the music therapist must "tune in" to clarify which part of the music therapy patient itself experiences as most meaningful.
- Music listening in a relaxed state. This means focus on mindfulness, focus on visualization of a "safe place", and relaxing/easing of tension/stress reduction. Visualization makes use of positive and pleasurable expressions. The music listening spend over a short time span. The patient chooses whether he/she wants to sit or lay down.

Home tasks:

Tasks for next session with music therapy are built further on the task given in session nr. 5. Task: Listen to music at least 5-10 min every day. Choose 3-5 music pieces/tunes in each of the following categories: a) I really like this piece of music/tune b) this piece of music/tune makes

me feel calm and relaxed, and c) this piece of music/tune may give me new strength and energy. *Bring with you* these music pieces/tunes to the next meeting with music therapy, i.e. session nr. 9. Maybe you want to make your own playlist at home? If the patient is not able/doesn't want to, the music therapist may support make such a list during session nr. 9.

6th meeting (week 6): Individual session

Frames:

- Participants: Patient, cognitive therapist
- Time: 90 min
- Place: Ahus

Aim and implementation

This is the second meeting with cognitive therapist, and the first where the patient is alone with the therapist. At this point the patients' main challenges are thoroughly mapped out through

- Questionnaires from earlier registrations in the CEBA-project
- Last meeting with cognitive therapist and parents/guardians (meeting nr. 4), and
- Sleeping and activity diary (homework from meeting nr. 4).

Based on this the therapist discusses with the patient which challenges are most important to handle. A goal is to make the patient an active participant in the treatment – a key question may be "what is the most important for you to do something with right away?" But the starting point must always be what one really *want* to try do something with, rather than what are dominated by duty and worries. The therapist should steer away from discussions concerning underlying causes of fatigue – the focus should be on what gives improvement. At this point it will be natural to introduce more specific elements from cognitive theory, particularily how *expectations* regarding what will happen (stimuli expectation) and *expectations* related to their own coping, and which techniques that are useful to help stopping such thoughts.

This discussion should end up with a plan for the patients' tasks until next meeting. Have as a starting point the registration already done by the patient. Have a positive focus on what one actually have been able to do. Elements in this plan may be:

- Integrate techniques which the patient already has learned in the music therapy (visualization, attention, relaxation) to stop unappropriated thought patterns.
- Introduce simple behavioral experiments to test the validity of the patients' understanding of connections between fatigue and activity – it may be based on unconscious planned behavior done earlier by the patient during the music therapy sessions. The behavioral experiments may also be related to other troublesome areas, like sleeping difficulties where provable techniques exist (stimuli control and sleeping restrictions).
- Explain to the patient the necessity of practice. Require own effort, but be convincing that the patient actually is able to cope.

Home tasks

Hometasks after this meeting are:

- Listen to music 5-10 minutes every day.

- Practice techniques in mindfulness, relaxation and visualization (simple instructions on the digital platform).
- Review the presentation of sickness models and grounds for treatment (favorable together with parents/guardians)
- Keep a diary of inexpedient/negative thoughts
- Keep a "behavioral experiments" diary

The last two elements are new, but the first three are the same as after session nr. 4. These home tasks are going to last for additional two weeks, until session nr. 8.

7th meeting (week 7); Session with patient and parents/guardians

Frames:

- Participants: Patient, parents/guardians, cognitive therapist
- Time: 90 minutes
- Place: Ahus

Aim and interpretation

This is the third meeting with cognitive therapist, and the second where the parents/guardians are participating. During meeting nr. 4 there was, in addition to mapping out the patient, done a mapping of family functions, parents/guardians understanding of the disease etc. The intention with this lesson is to:

- Further investigate the families' disease understanding, worries, explanations etc.
- Converse about how the family may be a support for a sick patient. What kind of family behavior promotes and prevents disease, viewed in the light of our understanding of underlying mechanisms for long lasting fatigue.
- Make specific plans on how the parents/guardians in a best way may help the patient in the everyday life. It is important that the parents/guardians a) strengthen the patients coping belief (worries regarding school etc should be put aside), b) motivate and supervise the patient, c) require own effort regarding practicing different mental techniques ("do the homework"), d) do not transmit own worries to the patients

Home tasks

After this lesson the parents/guardians are getting home tasks:

- Motivate and supervise the patient in techniques regarding mindfulness, relaxation and visualization
- Review the presentation of disease models and grounds for treatment. The tasks last until meeting nr 10.

8th meeting (week 8): Individual session

Frames:

- Participants: Patient, cognitive therapist, parents/guardians if suitable.
- Time: 90 minutes
- Place: Ahus

Aim and interpretation

This is the second meeting alone with the cognitive therapist. If the therapist experiences that the family dynamics to an extended degree participate in sustaining the patients' problems, parents/guardians may participate. One has as a starting point the home tasks regarding a. inexpedient thinking patterns and b. behavioral experiments, and uses this for a further discussion along the same lines as meeting nr. 6. What has been achieved so far? Is it natural to expand the perspectives and work with more of the challenges the therapist and patient together have defined as important. It may be relevant to discuss worries the patient may have, and eventually elements blocking further progression.

Cognitive theories and techniques are being introduced to a degree that seems appropriate. There should always be a positive and optimistic focus. The patient must be motivated to continue the work of learning to identify negative thought patterns, practicing techniques to stop such thoughts and experiments regarding behavior requiring increasing own effort. If the patient does "too much", and gets an increasing feeling of fatigue, it is important not to view this as a sign of failure or worsening of sickness, but a normal response everyone would experience after long lasting disease.

Home tasks

- Keep a diary over "behavioral experiments"
- Make a draft of a plan for how what is learned in the treatment program may be used further when the program is finished. How to continue the progress? How to deal with relapses if they come?
- Listen to music 5-10 minutes every day.

The tasks last until meeting nr. 10.

9th meeting (week 9): Individual session

Frames:
Participants: Patient, music therapist
Time: 90 minutes
Place: Ahus

Aim and interpretation
This is the last session with music therapist. It may be natural to repeat exercises and techniques the patient has learned and practiced through the treatment period. Main focus is although to be future-oriented:

- How to continue the progress?
- How to deal with relapses?

The goal is that the patient to a largest possible extend will be self-reliant regarding using techniques and principles acquired through the treatment period. It is important to motivate for further own effort – it may happen through pleasurable activities giving energy/joy/energy, and which give the feeling of coping. This meeting too should contain:

- Open up for an improvisatory approach to songwriting and music composition. This means a) put music to some of the patients' personal feelings and experiences, through focus on subjects from the daily life, or subjects of a more existential character, or b) have a starting point in music spontaneously referred by the patient – and put the patients' personal sayings in such a musical frame. If the patient brings a text, a poem or own music it is important to follow up this and put the texts in a positive musical frame. This may mean that the main focus is now on songwriting. Here the music therapist must "tune in" to clarify which part of the music therapy patient itself experience as most meaningful.
- Music listening in a relaxed state. This means focus on mindfulness, focus on visualization of a "safe place", and relaxing/easing of tension/stress reduction. Visualization makes use of positive and pleasurable expressions. The music listening spend over a short time span. The patient chooses whether he/she want to sit or lay down.

Home tasks:

- Task until next session: Use actively the music/notes you have chosen: 9(15) pieces of music/notes. Actively listen to these every day. Use your own playlist, which was made during the last session with music therapist.

10th meeting (week 10): Session with patient and parents/guardians

Frames:

- Participants: Patient, parents/guardians, cognitive therapist
- Time: 90 minutes
- Place: Ahus

Aim and interpretation

This is the last meeting in the treatment program. It will be natural to have as a starting point the home tasks both parents/guardians (7th meeting) and the patients (8th meeting) have received, and in particular the task regarding make a drawing on how to continue using what is learned in the treatment program when the treatment is finished. One should also discuss with the parents/guardians how they may continue to in a best way support the patients' progress. It may be appropriate to repeat a part of what has been gone through earlier, like the model of disease mechanisms and rationale for treatment, cognitive theories, techniques to distract negative thoughts, the importance of behavioral experiments and so on. The main focus should still be future-oriented:

- How to continue the progress?
- How to deal with relapses?

The goal is that the patient to a largest possible extend shall be self-reliant regarding using techniques and principles acquired through the treatment period. It is important to motivate for further own effort – it may happen through pleasurable activities giving energy/joy/energy, and which give the feeling of coping. One technique may be to listen actively to the music chosen by the patient, eventually encourage the patient to express itself through text and music, i.e. song/music/songwriting.

CEBA Chronic Fatigue following acute Epstein-Barr Virus Infection in Adolescents

AKERSHUS UNIVERSITETSSYKEHUS

Statistical analysis plan – CEBA part 2

1. AIM, STUDY DESIGN, VARIABLES

Design overview

In total, the CEBA project encompasses a prospective, a cross-sectional, and a randomised controlled intervention (RCT) design (Figure 1). For the prospective and cross-sectional part (CEBA part 1), a total of 200 adolescents with acute EBV infection will be included and followed for 6 months, as well as 70 healthy subjects for cross-sectional comparisons. A separate statistical analysis plan has been developed for this part of the project (1).

The proportion of included EBV-patients that has a sum score of dichotomized responses ≥ 4 on the Chalder Fatigue questionnaire (4) at 6 months, is defined as chronic fatigue syndrome (CFS/ME) cases (7) and will be eligible for the RCT part (CEBA part 2, ClinicalTrials ID NCT02499302), which is outlined in detail in a separate study protocol (3) and described more shortly in the present document. The patients included in CEBA part 2 are reexamined at 9 months and 21 months; ie. 12 weeks and 52 weeks after the RCT baseline.

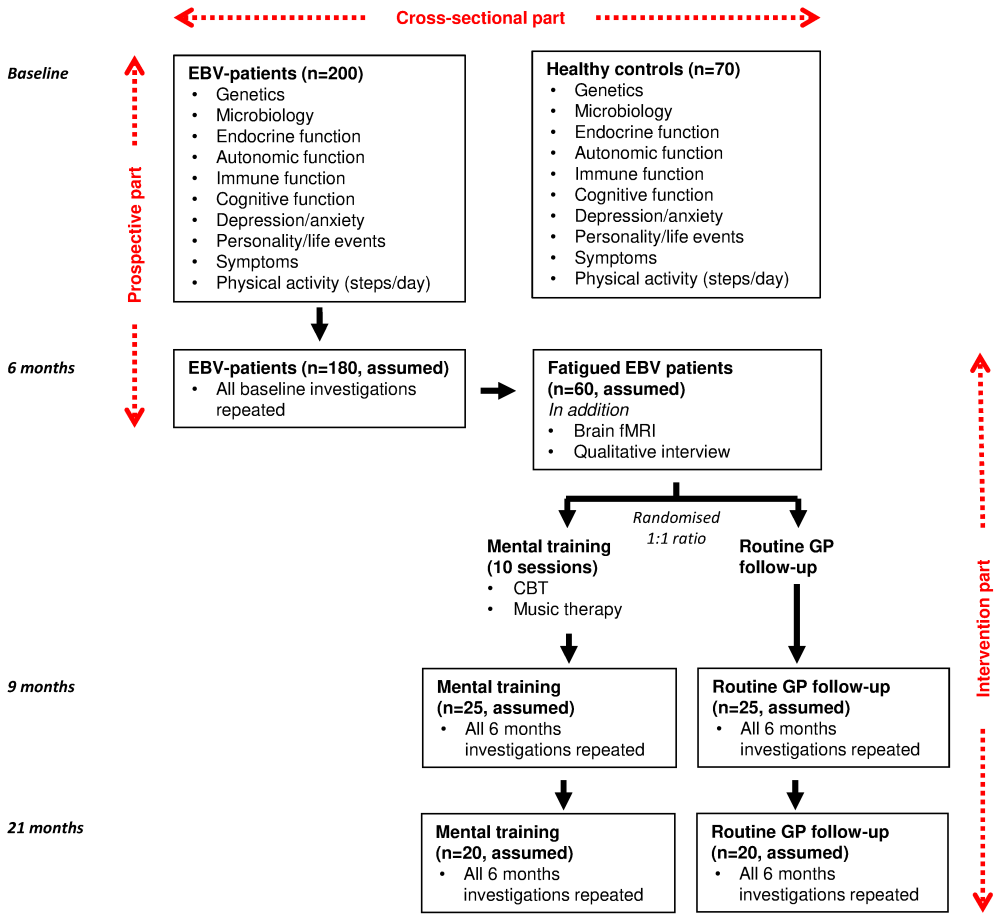

Figure 1. Design overview of CEBA. This document concerns CEBA part 2, ie. the right lower part of the figure.

CEBA Chronic Fatigue following acute Epstein-Barr Virus Infection in Adolescents

AKERSHUS UNIVERSITETSSYKEHUS

Aims

The present study explores an individually tailored mental training program built upon cognitive behavioral therapy (CBT) and music therapy to adolescents suffering from CFS/ME after EBV-infection. The general aims are:

a. To investigate the clinical effects of the training program, in particular the effect on physical activity (primary endpoint) and symptoms (fatigue, pain, insomnia).
b. To investigate the effect of the training program on important elements in CFS/ME pathophysiology, such as cardiovascular autonomic control, the HPA-axis, inflammation, cognition, affect consciousness and functional brain networks.

Patients will be recruited according to the criteria specified in Table 1.

Table 1. Criteria for inclusion and exclusion in the CEBA study

Inclusion criteria	*Exclusion criteria*
Criteria for the prospective and cross-sectional part (*applies to both patients and healthy controls)	
Age ≥ 12 years and < 20 years*	Debut of illness > 6 weeks ago (anamnestic)
Serological confirmation of acute EBV infection	Pregnancy*
Lives in one of the following Norwegian counties: Oslo, Akershus, Buskerud, Vestfold, Østfold*	Medical treatment for another disease (hormonal conterception and antibiotics against tonsillitis/pharyngitis are accepted)*
Additional criteria for the intervention part (the present protocol)	
CFS at 6 months (a sum score of dichotomized responses ≥ 4 on the Chalder Fatigue questionnaire)	Other illnesses that might explain the fatigue Bedridden

Intervention – the mental training program

The intervention consists of one introductory session followed by 9 individual therapy sessions (one each week) of 1.5 hours duration and related home-work, combining elements from CBT and music therapy (Figure 2). Important elements of the mental training program are:

- Psychoeducation: Theories of CFS/ME pathophysiology and treatment rationale
- Relaxation: Bodily stress reduction, mindfulness
- Visualization: Contact with positive emotions, techniques of worrying reduction
- Experiences: Behavioral 'experiments' (individually adjusted)
- Cognitive challenges: Challenging thoughts about disease process, stimulus and outcome expectancies, prognosis

A detailed treatment manual has been developed (2).

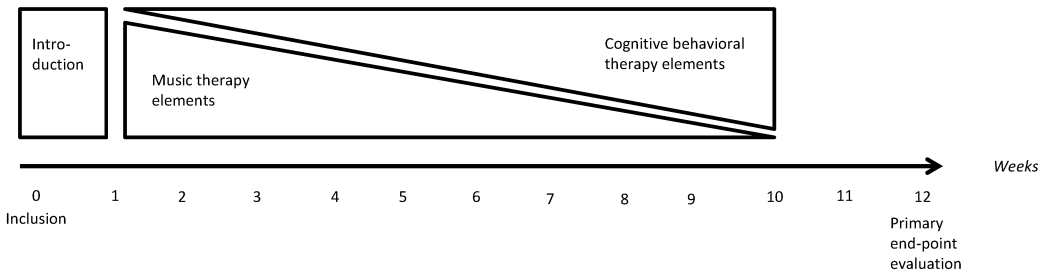

Figure 2. Principles of the mental intervention program

Randomizing and blinding

Patients eligible for the present study are randomized to either mental training or routine follow-up by the general practitioner (GP) in a 1:1 probability by a computer-based routine for block randomization; block size will vary randomly between 4 and 6. Allocation concealment will be ensured using sequentially numbered, opaque, sealed envelopes. It is not possible to blind for treatment. However, during endpoint-

evaluation, the responsible researchers will be blinded for group allocation. Likewise, both patients and therapist will be blinded for the result of the end-point evaluation.

Investigational program

At baseline, all participants are subjected to a standardized investigational program. They will be instructed to fast overnight and abstain from tobacco products and caffeine at least 48 hours. The following elements are included:

- Clinical examination
- Pain threshold assessment
- Assessment of autonomic cardiovascular control
- Cognitive assessment
- Sampling of biological material (blood, hair, urine)
- Questionnaire
- Brain fMRI
- Qualitative interview

Following the in-hospital assessment, daily physical activity will be monitored during seven consecutive days using the *activPAL* accelerometer device (PAL Technologies Ltd, Scotland) (5)

Effect monitoring

The patients are thoroughly assessed at week 12 and week 52 by an investigational program identical to the one performed at inclusion. The primary end-point is physical activity at week 12, operationalized as mean steps/day count during seven consecutive days. Secondary end-points are:

- Biomarkers (week 12 and week 52).
    - Plasma catecholamines
    - Urine cortisol/creatinine ratio
    - Cytokine network
    - Number of NK-cells
    - Plasma gene expression profiles
- Autonomic cardiovascular control (week 12 and week 52).
    - Supine heart rate (HR) and heart rate variability (HRV)
    - HRV during fixed breathing rate
    - HR and blood pressure responses to upright posture
- Cognitions/neurobiology (week 12 and week 52).
    - Working memory (digit span test)
    - Cognitive inhibition (color-word interference test, condition 3)
    - Salience network connectivity (brain fMRI)
- Symptoms/function (week 12 and week 52).
    - Fatigue score (Chalder fatigue questionnaire)
    - Pain scores (Brief pain inventory)
    - Quality of life-score (Peds QL)
    - Anxiety and depression scores (HADS)
    - Alexithymia score (TAS-20)
    - Insomnia score (KSQ)
    - Pain threshold
    - Disability score (FDI)
- Qualitative interview responses (week 12 and week 52).
- Physical activity (mean step/day) at week 52.

Side effects and unexpected events

A separate questionnaire addressing possible side effects, unexpected events, complications etc. related to the mental intervention is developed. This questionnaire will also chart other variables of interest, such as other therapies for chronic fatigue instituted by the GP. The participants will complete this questionnaire three times during the intervention period (week 3, week 6 and week 9), and also during the end-point

evaluation at week 12. The answers to the questionnaire will be analyzed and published together with the rest of the trial results

2. POWER CALCULATION

Based upon experiences from the NorCAPITAL project we assume a drop-out rate of 10 % in the prospective part of the CEBA project (8), leaving a total of 180 patients to evaluation at 6 months. Previous studies indicate that up to 1/3 might suffer from chronic fatigue (6); thus, 60 patients might be eligible for the present study. Assuming that 5 % will decline participation, and another 10 % drop-out rate during the intervention period, 50 participants will be available for endpoint evaluation (8).

The primary end-point in the present study is mean steps/day during seven consecutive days 12 weeks after inclusion. In the NorCAPITAL project, the mean (standard deviation) steps/day count for CFS/ME adolescents was approximately 4500 (2400) (8). In the present study, the power to detect an increment of 2000 steps/day is at least 80 % (α=0.05). This effect size is rather large (0.8 times the standard deviation); however, as CBT alone is documented to have moderate effect size in CFS/ME, only a substantial effect size is of direct clinical interest. Analogously, only a substantial treatment effect is of interest regarding markers of pathophysiology.

3. ANALYSIS SETS

Full analysis set
The 'full analysis set' is defined as all patients who were randomized to mental training/routine follow-up (Figure 2). This 'full analysis set' will be used for intention-to-treat analyses of efficacy. Missing values will be imputed based on the principle of 'last observation carried forward' (LOCF). In composite variables, "LOCF mixed components" will be used; that is, if only part of a composite variable is missing, that specific part will be imputed from the last observation

Per protocol analysis set
The 'per protocol analysis set' is defined as all patients in the 'full analysis set' that completed the treatment period (12 weeks) without any of the following protocol deviations:

- Interruption of therapy.
- Lost to follow-up.
- Primary endpoint measurements missing.
- Diagnosed with another chronic disorder during the study period.
- Experiencing a severe illness or trauma during the study period.
- Commencing other treatment for CFS/ME during the study period.

Missing data will not be imputed in the per protocol analysis set.

4. STATISTICAL METHODS

General considerations
Continuous variables will be reported with parametric (mean/standard deviation) or non-parametric (median, quartiles) descriptive statistics, depending on the distribution. Ordinal/nominal variables will be reported as frequency tabulation. All statistical tests will be carried out two-sided. A p-value ≤ 0.05 is considered statistically significant. For statistical tests of intervention outcome (cf below), variables having a skewed distribution will be transformed in order to achieve a normal distribution.

Analyses of intervention effect
Intention-to-treat analyses (full analysis set) will be used to compare the group allocated to mental training with the group allocated to routine follow-up using general linear models (ANCOVA). The baseline values

of each efficacy endpoint will be included as covariates. The null hypothesis is no differences in efficacy variables between the two treatment allocation groups. Primary endpoint is mean step/day count during 7 consecutive days at week 12. For each statistical analysis, the net intervention effect (the mean change in the mental intervention group minus the mean change in the routine follow-up group) will be estimated from the parameters of the fitted general linear model and reported with 95 % confidence interval. An identical methodological approach will be applied for per protocol analyses based upon the per protocol analysis set.

Safety data will be summarized descriptively through appropriate data tabulations and descriptive statistics. No interim analysis will be carried out.

5. REFRENCES

All CEBA documents (protocol, treatment manual, statistical analysis plan etc.) is available at http://www.ahus.no/omoss_/avdelinger_/barne-og-ungdomsklinikken_/forskning_og_utvikling_/Sider/CEBA.aspx

1. CEBA part 1 – Statistical analysis plan. Lørenskog: Dept. of Pediatrics, Akershus University Hospital, 2015.
2. CEBA part 2 - Manual for the mental training program. Lørenskog: Dept. of Pediatrics, Akershus University Hospital, 2015.
3. CEBA part 2 - Protocol. Lørenskog: Dept. of Pediatrics, Akershus University Hospital, 2015.
4. Chalder T, et al. Development of a fatigue scale. J Psychosom Res 1993 ; 37 : 147-53.
5. Dahlgren G, et al. Test-retest reliability of step counts with the ActivPAL device in common daily activities. Gait Posture 2010; 32: 386-90.
6. Katz BZ, et al. Autonomic symptoms at baseline and following infectious mononucleosis in a prospective cohort of adolescents. Arch Pediatr Adolesc Med 2011; 165: 765-6.
7. Loge JH, et al. Fatigue in the general Norwegian population: normative data and associations. J Psychosom Res 1998; 45: 53-65.
8. Sulheim D, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. JAMA Pediatr 2014; 168: 351-60.