Chronic Fatigue Syndrome: diagnosis, treatment and care organization - appendices

KCE reports 88S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
Belgian Health Care Knowledge Centre
2008

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Title:	Chronic Fatigue Syndrome diagnosis, treatment and care organization - appendices
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Disclaimer:	The external experts collaborated on the scientific report that was subsequently submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.

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APPENDIX

KCE-study

Chronic Fatigue Syndrome

Stordeur Sabine, Thiry Nancy, Eyssen Marijke

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2 DEFINITION, DIAGNOSIS AND TREATMENT: A LITERATURE REVIEW

2.1 APPENDIX 1. GUIDELINES PROPOSED BY 'THE CONSEIL SUPERIEUR DE LA SANTE' / 'HOGE GEZONDHEIDSRAAD'(2000)

2.1.1 Diagnostic

1ère ligne : Anamnèse complète et orientée comportant

- l'évaluation précise de **l'état d'épuisement physique** (perte d'énergie, de force musculaire)
  - durée (> 6 mois en cas de SFC)
  - sévérité selon le degré d'incapacité de réaliser des activités quotidiennes par rapport au passé récent
  - effets du sommeil, non réparateur
  - effets des efforts physiques, très mal supportés
- l'évaluation précise de l'état d'épuisement mental et de troubles comportementaux
  - absence de motivation
  - perte de dynamisme
  - pertes de mémoire et de concentration
  - répercussion sur les activités professionnelles, sociales, familiales et éducatives
  - confusion, irritabilité, dépression, idées suicidaires
  - troubles de sommeil, hypersomnie, insomnie
- l'écoute
  - des plaintes d'accompagnement
  - **syndrome polyalgique** : myalgies, arthralgies, céphalées
  - subfébrilité - troubles digestifs (épigastralgies, côlon spastique)
  - plaintes urinaires (en cas d'une éventuelle sclérose en plaques)
  - des éventuels facteurs déclenchants
- les **antécédents** de pathologies infectieuses, virales ou bactériennes
  - hépatite B et/ou C
  - infection HIV-MNI-pharyngite "virale" - CMV
  - Borreliose (Lyme disease)
  - Brucellose - toxoplasmose
- une enquête médicamenteuse
- une enquête toxicologique: alcool, drogues, tabac
- l'anamnèse familiale

2ème ligne : Examen clinique

1. Recherche de signes de focalisation et/ou d'atteinte parenchymateuse orientant vers une pathologie organique déficitaire (neurologique/locomotrice), infectieuse, parenchymateuse, endocrinienne, toxique.
2. Recherche de signes suggestifs de SFC
   - des adénopathies cervicales antérieures et axillaires
   - une pharyngite non exsudative
   - des points douloureux (tender points)

3. Test cognitif (MMS) : exclusion d'une maladie d'Alzheimer débutante

3ème ligne *: Examens complémentaires raisonnés* en 3 temps selon le profil du patient et la fréquence relative des pathologies pour s'autoriser l'exclusion de pathologies organiques

- 1. Biologie clinique :
  - Examen hématologique complet
  - Ferritine
  - Créatinine
  - Ionogramme (y compris Ca - P - Mg)
  - Glycémie
  - Enzymes hépatiques
  - Protéinogramme
  - CRP et FAN
  - TSH, cortisolurie/24 h
  - Sérologies infectieuses : hépatites B et C, syphilis
  - Borrelia, Ricketsia, Chlamydia (si suspicion clinique)
- 2. Images
  - une RX du thorax
  - un ECG et si anomalies une échocardiographie
  - une échographie abdominale in tot

PS. La place en clinique du RNAse L - assay de l'immunophénotypage et du PCR est actuellement indéterminée. Ces techniques doivent être considérées comme des outils réservés à la recherche.

- 3. Examens polysomnographiques et neuro-psychiatriques:

Les syndromes primaires et/ou secondaires psychiatriques doivent être considérés et traités, sans exclure la poursuite de l'investigation diagnostique qui devra être réalisée en fonction des éléments de l'anamnèse complète et orientée.

Objectifs : exclure troubles primaires et chroniques du sommeil, dépression majeure, schizophrénie, pathologie factice, troubles psychopathologues et autres.

Neuro-imageries: la recherche de l'utilité de la neuro-imagerie sophistiquée pour le diagnostic du CFS est actuellement en pleine expansion: RMN, positron emission tomography (PET) et single proton emission computed tomography (SPECT).

Le SPECT génère beaucoup d'intérêt, car il pourrait démontrer certains changements au niveau du système central. Cependant la signification des changements observés par SPECT reste encore largement inexpliquée. Cette technique (coûteuse) ne confirme pas par ailleurs le diagnostic spécifique du SFC. La justification de l'imagerie cérébrale à ce jour: l'exclusion de la sclérose en plaques en cas de suspicion clinique

2.1.2 Rapport de synthèse du groupe de travail "thérapie" : recommandations thérapeutiques

1. Il n'est pas nécessaire d'attendre une meilleure compréhension de la pathophysiologie du SFC, ni d'attendre une définition précise de sous-groupes éventuels pour pouvoir dès lors aider les patients touchés.
2. En ce moment, cette aide peut être optimalisée en plaçant le patient dans une perspective biopsychosociale et en organisant l'aide d'une façon pluridisciplinaire tout en adaptant les objectifs d'une façon réaliste aux possibilités et aux limites de chaque patient.
3. Selon les règles actuellement en vigueur de « evidence base medicine », une thérapie ne peut être considérée qu'efficace lorsqu'un minimum de deux trials cliniques randomisés se sont révélés positifs. En ce moment (janvier

2000), ce n'est le cas que pour la thérapie cognito-comportementale et la rééducation physique.

4. Outre les stratégies thérapeutiques susmentionnées où les effets (à court et moyen terme) ont été démontrés, il existe certaines méthodes de traitement qui se sont avérées utiles dans la clinique pratique : la psycho-éducation, le traitement de la comorbidité psychiatrique (e.a. avec anti-dépresseurs) et divers autre types de psychothérapie verbale et non verbale (oui ou non intégrées dans un paquet de traitement pluridisciplinaire).
5. Le médecin de famille est indiqué comme thérapeute pour les patients qui – p.ex. après avoir souffert d'une infection virale – se trouvent dans un état sub-chronique. Le risque d'une évolution vers la chronicité peut être limité par le biais d'une recherche somatique, une brève enquête psychosociale (p.ex. afin de tracer des attributions de dysfonctionnement ou de déceler le fait que l'on ait pas fait face au problème d'une façon adéquate ou encore afin de tracer un risque de séquelles psychiatriques) et par le biais d'informations utiles et d'avis (e.a. en ce qui concerne l'importance de reprendre progressivement une activité).
6. Les patients avec des plaintes de fatigue et de maux persistants accompagnés d'une comorbidité psychiatrique ou des plaintes qui cadrent dans un grave antécédent de traumatisme psychique prononcé ou de troubles de personnalité, doivent être encouragés à chercher de l'aide psychiatrique.
7. Les patients bloqués dans des spirales physiques et psychosociale descendantes avec comme conséquences une grave invalidité et un comportement maladif chronique (p.ex. à cause de troubles du sommeil, de dépressions secondaires et d'anxiété, déconditionnement physique progressif, complications professionnelles et médico-légales …) peuvent être aidés dans un centre spécialisé avec une approche pluridisciplinaire.
8. Le corps médical et les média doivent être tenus au courant des possibilités thérapeutiques susmentionnées. Un jugement ou des suggestions relatifs à un pronostic «catastrophique» du SFC peuvent occasionner des dommages considérables pour le patient et sont à éviter.
9. Il est nécessaire d'attacher plus d'attention à la prévention du SFC, tant chez les adultes que chez les enfants (e.a. sur le plan de troubles chroniques du sommeil. Dès lors, il s'avère nécessaire de renseigner les médecins et de leur offrir une formation continue.
10. La Sécurité sociale a pour tâche de libérer suffisamment de moyens financiers pour les centres qui se spécialisent dans les stratégies thérapeutiques susnommées et orientées vers la revalidation. En outre, il faudrait mettre des « incentives » à la disposition des patients SFC qui sont prêts à s'y engager.

2.2 APPENDIX 2. SEARCH STRATEGY (DEFINITION, DIAGNOSIS AND TREATMENT)

The following search strategy was developed:

2.2.1 Databases for Guidelines

Agency for Healthcare Research and Quality (AHRQ, USA),

Australian National Health & Medical research Council Clinical Practice Guidelines,

CDC (Centres for Disease Control, USA),

CMA Infobase (Canada),

HAS (France),

Health Services /Technology Assessment Texts (HSTAT, USA),

ICES (Institute for Clinical Evaluative Sciences, Canada)

Institute for Clinical Evaluative Sciences.

National Guideline Clearinghouse (USA),

National Institute for Clinical Excellence (NICE, UK),

New Zealand Guidelines Group,

Royal College of Paediatrics and Child Health,

Scottish Intercollegiate Guidelines Network (SIGN, UK),

2.2.2 Were searched for

Chronic fatigue syndrome OR myalgic encephalomyelitis OR myalgic encephalopathy

2.2.3 Results

3 guidelines were retained after selection on title and abstract

2.2.4 Studies in progress

Our search found 10 controlled trials completed or in progress with chronic fatigue syndrome.

Title	ISRCTN	Status	Source of record
Family focused cognitive behaviour therapy versus behaviourally oriented psycho-education for chronic fatigue syndrome in 11 to 18 year olds: a randomised controlled treatment trial	ISRCTN59388875	Completed	UK Clinical Trials Gateway
Nasal hyper-reactivity in multiple chemical sensitivity and chronic fatigue syndrome: randomised double blind, placebo-controlled, cross-over, nasal challenge study to evaluate neural and vascular responsiveness	ISRCTN52896230	Completed	UK Clinical Trials Gateway
Use of Xyrem to Improve Sleep in Chronic Fatigue Syndrome	ISRCTN00000000	Recruiting	National Institutes of Health (NIH) - randomized trial records held on NIH *ClinicalTrials.gov* website.
Should general practitioners manage chronic fatigue syndrome? A controlled trial	ISRCTN78372534	Closed to recruitment of participants: follow-up complete	National Health Service Research and Development Programme 'Time-Limited' National Programmes
Randomised controlled trial of nurse-led self-help treatment for patients in primary care with chronic fatigue syndrome. The FINE trial (Fatigue Intervention by Nurses Evaluation)	ISRCTN74156610	Open to recruitment	Medical Research Council (UK)
The effectiveness of Self-instructions in the treatment of patients with Chronic Fatigue Syndrome (CFS): a randomised controlled study	ISRCTN27293439	Completed	ISRCTN Register - trials registered with a unique identifier
The effectiveness of cognitive behavioural therapy in groups for patients with Chronic Fatigue Syndrome (CFS): a randomised controlled study	ISRCTN15823716	Ongoing	ISRCTN Register - trials registered with a unique identifier
The effect of ondansetron, a 5-Ht3 receptor antagonist, on fatigue severity and functional impairment in Chronic Fatigue Syndrome patients	ISRCTN02536681	Completed	ISRCTN Register - trials registered with a unique identifier
Efficacy of web-based cognitive behavioural treatment for adolescents with the Chronic Fatigue Syndrome	ISRCTN59878666	Ongoing	ISRCTN Register - trials registered with a unique identifier
The efficacy and predicting variables of a multidisciplinary disability resolution (MDR) program for CFS patients receiving long term disability benefits from income protection insurers	ISRCTN31632033	Ongoing	ISRCTN Register - trials registered with a unique identifier
Randomised double-blind cross-over trial of proglumide in patients with chronic pain and/or fatigue.	ISRCTN47564212	Completed	UK Clinical Trials Gateway
A comparison of high cocoa solid with absent cocoa solid chocolate in patients with chronic fatigue syndrome in a double blind randomised controlled trial	ISRCTN03090939	Completed	UK Clinical Trials Gateway
Healthcare Evaluation and Assessment of Patients with Chronic Fatigue Syndrome (CFS)	ISRCTN31455243	Completed	UK Clinical Trials Gateway

2.2.5 Medline and Embase (from 2004 to 2007).

Search string for Medline (22/10/2007): Ovid MEDLINE(R) 2004 to Present

2.2.6 Search Strategy

1 Fatigue Syndrome, chronic.mp. or exp *Fatigue Syndrome, Chronic/ (3097)

2 limit 1 to yr="2004 - 2007" (637)

3 chronic fatigue syndrome.ti,ab. (2616)

4 myalgic encephalomyelitis.ti,ab. (215)

5 1 or 3 or 4 (3545)

6 2 and 5 (637)

7 limit 6 to (clinical trial, all or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "review") (210)

8 6 and 7 (210)

9 from 8 keep 01-210 (210)

Search string for Embase (23/10/2007): 2004 to Present

#1. 'chronic fatigue syndrome':ti,ab,de AND [2004-2007]/py	1,317
#2. 'myalgic encephalomyelitis':ti,ab,de AND [2004-2007]/py	38
#3. #1 OR #2	1,317
#4. 'chronic fatigue syndrome'/de AND ([article]/lim OR [review]/lim) AND [2004-2007]/py	944
#5. #3 AND #4	944
#6. 'chronic fatigue syndrome'/exp AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2004-2007]/py	113

2.3 APPENDIX 3. CRITICAL APPRAISAL FOR SYSTEMATIC REVIEWS

Dutch Cochrane collaboration Formulier Vc	[1]	[2]	[3]	[4]
Topic	**Treatment**	**Treatment**	**Placebo response in treatment**	**Prognosis of CFS**
Vraagstelling adequaat geformuleerd?	yes	yes	yes	Yes
Zoekactie adequaat uitgevoerd?	yes	not documented	yes	yes
Adequate selectie van artikels?	yes	not documented	yes	yes
Adequate kwaliteitsbeoordeling van artikels?	yes	not documented	yes	not documented
Adequate beschrijving data-extractie?	yes	not documented	yes	yes
Belangrijkste kenmerken oorspronkelijke onderzoeken beschreven?	yes	not documented	yes	yes
Adequaat omgegaan met klinische en statistische heterogeniteit?	yes	not documented	yes	not documented
Statistische pooling correct uitgevoerd?	not applicable	not documented	yes	not applicable
Valide en toepasbaar?	valid	not valid	valid	valid

Bagnall et al. CRD Report 35, 2007	
Authors' objectives	To evaluate the interventions (or combinations of interventions) for the treatment, management and rehabilitation of adults and children with chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME), and to update a previous systematic review.
Specific interventions included in the review	Studies that evaluated any intervention or combinations of interventions used as treatment, management or rehabilitation were eligible for inclusion. The included studies assessed interventions in the following categories: pharmacological; immunological; behavioural; complementary and alternative therapies; supplements; and other (e.g. multicomponent, buddy programmes and dietary interventions). Behavioural interventions included graded exercise therapy (GET), graded activity, pacing, cognitive-behavioural therapy (CBT), psychotherapy, counselling, family therapy and rehabilitation.
Participants included in the review	Studies of adults or children (aged 5 years or older) who had been diagnosed as having CFS/ME according to any criteria were eligible for inclusion.
Outcomes assessed in the review	The review assessed physical, psychological, laboratory and physiological outcomes, quality of life, general health and adverse effects. The individual studies used a variety of measures to assess these outcomes (the measures used in the individual studies were reported).
Study designs of evaluations included in the review	Randomised controlled trials (RCTs) and non-randomised controlled clinical trials (CCTs) were eligible for inclusion in the review.
Validity Assessment	The studies were assessed for method of randomisation, allocation concealment, blinding of the participant and investigator, baseline comparability of the treatment groups, reporting of follow-up, drop-outs (use of intention-to-treat analysis), objectivity of outcome measure, statistical analysis, sample size calculation, and comparability of the treatment groups.

How were the data extracted from primary studies?	The studies were classified as showing some effect of treatment if there was a statistically significant ($p<0.05$) treatment difference for any outcome. The studies were classified as showing an overall effect of treatment if there was a statistically significant treatment difference for more than one clinical outcome.
Number of studies included in the review	Seventy controlled studies (n=4,749) were included: 58 RCTs (n=4,176) and 12 CCTs (n=573).
Results of the review	The validity scores ranged from 2 to 19 for the RCTs and from 0 to 14 for the CCTs (details of the individual validity criteria were reported). The RCTs frequently had poor allocation concealment and lacked intention-to treat analyses. ***Adults*** **Behavioural (15 RCTs, 1 CCT).** Fourteen studies reported some effect of treatment and ten reported an overall effect of treatment. One recent good-quality RCT reported a positive effect of CBT on fatigue, symptoms, physical functioning and school attendance. Most other new studies showed positive effects, but were lower quality RCTs or CCTs. The previous review reported that 3 of 4 high-quality RCTs showed positive effects. Two recent moderate-quality RCTs of GET suggested positive effects with GET on symptoms and physical functioning. The previous review reported that 2 of 3 high-quality RCTs of GET showed an overall treatment effect for this intervention. **Pharmacological (19 RCTs, 1 CCT).** Six studies reported some effect of treatment and two reported an overall effect of treatment. One recent large RCT of galantamine hydrobromide reported no difference between treatment groups. One poor-quality RCT of hydrocortisone reported a significant treatment effect, whilst 2 recent studies of steroids reported no significant treatment difference. The previous review reported that few RCTs showed a positive effect. **Immunological (11 RCTs, 2 CCTs).** Seven studies reported some effect of treatment and three reported an overall effect of treatment. Two recent studies (a CCT of inosine pranobex and a low-quality RCT of staphylococcus toxoid) reported positive effects of interventions but relatively high rates of adverse effects. The previous review reported that 2 of 5 studies evaluating immunoglobulin G showed an overall effect of treatment, but some studies reported severe adverse effects. **Complementary and alternative therapies (3 RCTs, 1 CCT).** Two studies reported some effect of treatment and one reported an overall effect of treatment. One recent study of homeopathic treatment reported positive effects on one of five measures of fatigue and one of five measures of function. The previous review reported a positive effect in one small RCT of massage therapy, one poor-quality RCT of homeopathy, and one poor CCT of osteopathy. **Supplements (10 RCTs, 1 CCT).** Four studies reported some effect of treatment and three reported an overall effect of treatment. One recent moderate quality RCT reported an overall treatment effect of acetyl-L-carnitine and propionyl-L-carnitine. The previous review reported an overall effect of treatment in 1 of 2 good-quality RCTs evaluating fatty acids and one good-quality but small RCT of magnesium. **Other (6 CCTs).** Three studies reported some effect of treatment and one reported an overall effect of treatment for combination treatment. ***Children*** Two recent studies that compared interventions that included CBT with routine care reported significant improvements in global wellness (one CCT of CBT/rehabilitation) and symptoms and school attendance (one RCT of CBT) associated with CBT interventions. One RCT on immunoglobulin G reported significant improvements in functional scores (see above for reports about adverse effects).

Authors' conclusions	There was evidence supporting the effectiveness of CBT and GET in reducing symptoms and improving physical functioning. Further research is required.
What are the implications of the review?	Practice: The authors did not state any implications for practice. Research: The authors stated that CBT should be compared with GET and both of these interventions should be compared with pacing. Research into the effect of interventions on subgroups is required, and there is an urgent need to standardise outcome measures. Future studies must combine rigorous research with acceptability to patients.

Cho, Hotopf et Wessel, 2007[3]	
Authors' objectives	To investigate the placebo response in the treatment of chronic fatigue syndrome (CFS) and to determine whether this is dependent on intervention type.
Specific interventions included in the review	Studies of any intervention aimed at treating CFS compared with placebo were eligible. Placebo was defined as 'any therapeutic procedure which has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated'. In the analysis, interventions were classified according to the hypothesised degree of placebo response (i.e. low, medium or high) with which they were believed to be associated. Interventions based on infectious or immunological assumptions, or alternative therapies, were deemed to have a high placebo effect; interventions based on psychological or psychiatric assumptions, a low effect; and interventions with an obscure or neutral theory base (e.g. neuroendocrinological agents), a medium effect.
Participants included in the review	Adults and children diagnosed with CFS or any similar condition (e.g. myalgic encephalomyelitis, chronic fatigue immune deficiency syndrome, or chronic mononucleosis) based on any criteria were eligible. Studies focusing only on fibromyalgia were excluded. Patients from primary, secondary and tertiary care, along with those recruited through advertisements and from patient organisations, were included. The majority of the participants were female (mean age 38 years) with poor baseline functioning due to a perceived physical cause, and a mean illness duration of 62 months.
Outcomes assessed in the review	The primary outcomes of interest were categorised as either physical (e.g. fatigue, pain, sleep and functional ability) or general (e.g. quality of life, well-being, clinical improvement, and overall symptom measure) outcomes using a binary measure (e.g. improved or not, response or non-response).
Study designs of evaluations included in the review	Placebo-controlled randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were eligible. The majority of the included trials were RCTs. The duration of follow-up ranged from 3 to 61 weeks (median 13).
Validity Assessment	The following criteria were adopted for the assessment of RCTs: method of randomisation; allocation concealment; blinding; baseline comparability of the groups; completeness of follow-up; drop-out analysis; intention-to-treat (ITT); objectivity of outcome assessment; appropriateness of statistical analysis; sample size; equality in how the groups were treated; description of placebo type, placebo group and placebo response. The first two criteria were adapted for the assessment of CCTs. A scoring system was used, with a maximum of 22 points attainable. One reviewer assessed the studies and a second reviewer checked them.
How were the data extracted from primary studies?	Clinical improvement data were extracted in order to calculate the percentage placebo response (number of placebo responders divided by number of participants assigned to placebo), along with the 95% confidence interval (CI). If only data reporting the number of study completers were reported, it was assumed that only completers had responded.
Number of studies included in the review	Twenty-nine trials were included in the review: 28 RCTs (n=1 002), six of which were crossover trials and one CCT (n=14). The total number of placebo arm participants was 1 016 (median 32, range: 12 to 94).
Results of the review	Eight trials were of interventions hypothesised to have a low placebo effect, five were classified as having a medium effect, and 16 a high effect. Five trials used behavioural placebos or standardised medical care; sixteen used oral and eight used injection-based placebos. The pooled placebo response was 19.6% (95% CI: 15.4, 23.7), but there was considerable

	heterogeneity amongst the trials (P<0.001). From the factors investigated, only intervention type contributed significantly to the observed heterogeneity (P=0.03). The subgroup analysis revealed an upward trend of placebo response between the groups (a 5% increase according to effect level). The low and medium effect groups had placebo responses of 14.0% (95% CI: 8.0, 19.9) and 16.5% (95% CI: 5.7, 27.4), respectively. The high effect group had the highest placebo response (24.0%, 95% CI: 18.9, 29.1).
Authors' conclusions	The placebo response in CFS treatment is low. In particular, this is characterised by a lower response to psychological-psychiatric interventions. A possible link to patient expectation theory is feasible.
What are the implications of the review?	Practice: The authors stated that more focus is required on the non-specific, contextual aspects of CFS treatment in order to increase the effect of an active treatment. The collaborative therapeutic relationship was suggested as a key factor in the management of the condition.

2.4 APPENDIX 4. CRITICAL APPRAISAL FOR RANDOMIZED CONTROLLED TRIALS

Dutch Cochrane collaboration Formulier II	[5]	[6]	[7]	[8]	[9]
Topic	**Treatment with methylphenidate**	**BioBran MGN-3**	**CBT/standard care/support & education in primary care**	**CBT+Biofeedback**	**Acclydine**
Randomisatie?	Yes	Yes	Yes	Yes	Yes
Blindering van randomisatie?	Yes	Yes	Yes	Yes	Yes
Blindering patienten?	Yes	Yes	Yes (except for SC)	Not documented	Yes
Blindering behandelaars?	Yes	Yes	No	No	Yes
Blindering effectbeoordeelaars?	Yes	Yes	Yes	Yes	Yes
Vergelijkbare groepen?	Not documented	Yes	Yes	Yes	Yes
Voldoende follow-up?	Yes	Yes	Yes	Yes	Yes
Intention-to-treat?	Yes	Yes	Yes	No	Yes
Vergelijkbare behandeling?	Yes	Yes	Yes	Yes	Yes

2.5 APPENDIX 5. KCE LEVELS OF EVIDENCE AND GRADE RECOMMENDATIONS [10]

Grade of Recommendation/ Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1/ strong recommendation A/ high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation can apply to most patients, in most circumstances without reservation
1/ strong recommendation B/ moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1/ strong recommendation C/ low-quality or very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2/ weak recommendation A/ high quality evidence	Benefits closely balanced with risks and burden	RCTs without Important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2/ weak recommendation B/ moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2/ weak recommendation C/ low quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

2.6 APPENDIX 6. ASSESSMENT TOOLS FOR OUTCOMES

2.6.1 Tool 1: Clinical Global Improvement Scale

Overall, much have you changed since the start of the study?

Please tick ONE box.

	Answers	Codes
Very much better		1
Much better		1
A little better		2
No change		2
A little worse		3
Much Worse		3
Very much worse		3

2.6.2 TOOL 2: RAND VERSION SF-36 PHYSICAL FUNCTION

These questions are about activities you might do during a typical day.

Please circle one box for each question.

Does your health limit you in these activities?

ACTIVITIES	(Circle One Number on Each Line)		
	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running lifting heavy objects, participating in strenuous sports			
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing several flights of stairs			
e. Climbing one flight of stairs			
f. Bending, kneeling or stooping			
g. Walking more than a mile			
h. Walking several blocks (about half a mile)			
i. Walking one block (about 100 yards)			
j. Bathing or dressing yourself			

http://vivisimo.rand.org/vivisimo/cgi-bin/query-meta?v%3Aproject=health&query=SF-36&Go.x=46&Go.y=9

2.6.3 Tool 3: Chalder Fatigue Scale

We would like to know more about any problems you have had with feeling tired, weak or lacking in energy in the last month. Please answer ALL the questions by ticking the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt when you were last well.

Chalder Fatigue Scale – Scoring Method

		Less than usual	No more than usual	More than usual	*Much more than usual*
P	**Do you have problems with tiredness?**	**0**	**0**	**1**	***1***
P	**Do you need to rest more?**	**0**	**0**	**1**	***1***
P	**Do you feel sleepy or drowsy?**	**0**	**0**	**1**	***1***
P	**Do you have problems starting things?**	**0**	**0**	**1**	***1***
P	**Do you lack energy?**	**0**	**0**	**1**	***1***
P	**Do you have less strength in your muscles?**	**0**	**0**	**1**	***1***
P	**Do you feel weak?**	**0**	**0**	**1**	***1***
M	**Do you have difficulty concentrating?**	**0**	**0**	**1**	***1***
M	**Do you make slips of the tongue when speaking?**	**0**	**0**	**1**	***1***
M	**Do you find it more difficult to find the correct word?**	**0**	**0**	**1**	***1***
		Better than usual	**No worse than usual**	**Worse than usual**	***Much worse than usual***
M	***How is your memory?***	***0***	***0***	***1***	***1***

Items marked **P** are physical items

Items marked **M** are mental items

2.7 APPENDIX 7. CRITICAL APPRAISAL FOR RANDOMIZED CONTROLLED TRIALS

Dutch Cochrane collaboration Formulier II	[5]	[6]	[7]	[8]	[9]
Topic	**Treatment with methylphenidate**	**BioBran MGN-3**	**CBT/standard care/support & education in primary care**	**CBT+Biofeedback**	**Acclydine**
Randomisatie?	Yes	Yes	Yes	Yes	Yes
Blindering van randomisatie?	Yes	Yes	Yes	Yes	Yes
Blindering patienten?	Yes	Yes	Yes (except for SC)	Not documented	Yes
Blindering behandelaars?	Yes	Yes	No	No	Yes
Blindering effectbeoordeelaars?	Yes	Yes	Yes	Yes	Yes
Vergelijkbare groepen?	Not documented	Yes	Yes	Yes	Yes
Voldoende follow-up?	Yes	Yes	Yes	Yes	Yes
Intention-to-treat?	Yes	Yes	Yes	No	Yes
Vergelijkbare behandeling?	Yes	Yes	Yes	Yes	Yes

2.8 APPENDIX 8. TREATMENT OF CHRONIC FATIGUE SYNDROME IN ADULT PATIENTS

Behavioural treatment (cognitive behaviour therapy)

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
[11]	Meta-analysis	January 2008	1B → 1A	+ (d=0.48)	• Positive effect of CBT on CFS and similar disorders, but large room for improvement • Unknown factors determine the extent of the treatment efficacy • No difference in effect size according to CFS definition (strict or lower standard for inclusion) • No evidence for including cognitive components in treatment of fatigue disorders • Non significant association between number of treatments hours or number of sessions and effect size • Larger effect size for physical fatigue than for mental fatigue (treatment includes gradual increase in physical activity but no emphasis on increasing mental activity) • No difference between objective and subjective measures • No difference between individual and group treatment • Longer follow-up is associated with larger effect size
[1]	Systematic review	May 2007	1B → 1A	+	Positive effects on: • physical functioning (functional status, fatigue, pain) • psychological state (depression, mood, anxiety, well-being) • quality of life and general health (work and social adjustment, long term goals, global improvement)

ID	Type of study	Search date	Level of evidence	Setting	Participants	Interventions	Outcome measures	Length of follow-up
[7]	A double-blind RCT with three arms	2000/2002	1B	A health psychology department for the management of chronic illness in a general hospital in Bristol, UK.	Adults with a diagnosis of CFS/ME referred by their GP A total of 153 patients were recruited to the trial : - 52 to CBT, - 50 to EAS, - 51 to SMC.	The three interventions were 1. group CBT incorporating graded activity scheduling, 1. education and support group (EAS), 2. standard medical care (SMC).	- SF-36 physical and mental health. - Chalder fatigue scale - Hospital Anxiety and Depression Scale - General Health Questionnaire - physical function (shuttles walked, walking speed and perceived fatigue), - health utilities index - cognitive function (mood, recall and reaction times).	Outcomes were assessed at baseline and 6 and 12 months after first assessment and results were analysed on an intention-to-treat basis.

Results	Author's conclusions / recommendations

- CBT group (compared to SMC group):
  - higher mental health scores [difference +4.35, 95% CI +0.72 to +7.97, p = 0.019],
  - less fatigue (difference -2.61, 95% CI -4.92 to -0.30, p = 0.027)
  - walk faster (difference +2.83 shuttles, 95% CI +1.12 to +5.53, p = 0.0013).
- CBT group (compared to EAS group) :
  - walk faster [difference +1.77, 95% CI +0.025 to +3.51, p = 0.047],
  - less fatigue; fatigue: [difference -3.16, 95% CI -5.59 to -0.74, p = 0.011],
Follow-up:
  - walking speed: increase by +0.87 shuttles (95% CI +0.09 to +1.65, p = 0.029) between the 6- and 12-month follow-ups,
  - At baseline, 30% of patients had an SF-36 physical score within the normal range and 52% had an SF-36 mental health score in the normal range.
  - At 12 months, the physical score was in the normal range for 46% of the CBT group, 26% of the EAS group and 44% of SMC patients. For mental health score the percentages were CBT 74%, EAS 67% and SMC 70%. Of the CBT group, 32% showed at least a 15% increase in physical function and 64% achieved a similar improvement in their mental health. For the EAS and SMC groups, this improvement in physical and mental health was achieved for 40 and 60% (EAS) and 49 and 53% (SMC), respectively.
	CBT has larger effects (compared to standard medical care) on:
	• mental health
	• fatigue
	• ability to walk faster
	CBT has larger effects (compared to education and support) on:
	• fatigue
	• ability to walk faster
	Scores are similar at 6 and 12 months follow-up, except for walking speed which increases at 12 months.
	A higher proportion of CBT patients leads to the normal range for physical scores (SF-36) at 12 months follow-up compared to the 2 other groups; no difference between groups for mental scores.
	Group CBT was effective in treating symptoms of fatigue, mood and physical fitness in CFS. It was found to be as effective as trials using individual therapy in these domains. However, it did not bring about improvement in cognitive function or quality of life. There was also evidence of improvement in the EAS group, which indicates that there is limited value in the non-specific effects of therapy.

ID	Type of study	Search date	Level of evidence	Setting	Participants	Interventions	Outcome measures	Length of follow-up
[12] based on [13]	A RCT with three arms	1996 - 1998	1A	The outpatient clinic of the departments of internal medicine of the University Medical Centre Nijmegen and the University Hospital Maastricht	Adults with a diagnosis of CFS (1994 CDC criteria, with the exception of the criterion requiring four of eight additional symptoms to be present). A total of 270 patients were recruited to the trial : - 92 to CBT, - 90 to support, - 88 to no treatment.	The two interventions were 1. group CBT (16 sessions of 1 hour over 8 months) including cognitive restructuring, building up activity, returning to work and relapse prevention 2. guiding support group (11 group meetings oh 1 hour ½, non directive and client-centered). Control : natural course without intervention	- **Concentration**: subscale concentration of CIS score - **Impact of cognitive impairment on daily functioning**: subscale Sickness Impact Profile-alertness behaviour (SIP-ab), - **Reaction time task** - **Complex attention**: symbol digit modalities task (SDMT).	Outcomes were assessed at baseline and 4 and 8 months after first assessment and results were analysed on an intention-to-treat basis. Dependent variables were the change scores at 14 months from baseline. If data at 14 months were missing, data 8-months post-treatment were uses, as available.

Results	Author's conclusions / recommendations

- CBT and support groups (treatment):
  - Significant effect on the change in concentration-CIS: [difference -7.4, 95% CI: -9.1 to -5.7] ; greater effect than support group (p=0.001) and natural course (p<0.001);
  - Significant effect on the change in SIP-ab [difference -116, 95% CI -156 to -76]; greater effect than natural course (p=0.004)
  - No significant effect on reaction time task and SDMT.
- support group (treatment):
  - Significant effect on the change in concentration-CIS: [difference -3.4, 95% CI: -5.1 to -1.8];
  - Significant effect on the change in SIP-ab: [difference -61, 95% CI -100 to -21];
  - No significant effect on reaction time task and SDMT.
- natural course (no treatment):
  - Significant effect on the change in concentration-CIS: [difference -2.7, 95% CI: -4.4to -1.0];
  - Significant effect on the change in SIP-ab: [difference -31, 95% CI -72 to -10];
  - No significant effect on reaction time task and SDMT.
	CBT has larger effects (compared to support group or natural course) on:
	• Concentration disturbances
	• Impact of cognitive impairment on physical functioning
	CBT has no effect on:
	• Neuropsychological performance

ID	Type of study	Search date	Level of evidence	Setting	Participants	Interventions	Outcome measures	Length of follow-up
[14]	Comparison between results obtained in: 1. RCT	**1. 1993-1994**	**1A**	King's College CFS Research and Treatment Unit	Adults with a diagnosis of CFS (Oxford criteria and 1994 CDC criteria) recruited from consecutive GP and consultant referrals. Patients were excluded if: 1) antidepressant or anxiolytic of greater than 10 mg/day/diazepam or equivalent, or if their dose changed during the trial or within the 3 months prior. 2) somatisation disorder, severe depression, ongoing physical investigations, concurrent treatment and/or an inability to attend all therapy sessions. 30 to CBT 30 to relaxation	The two interventions were 1. group CBT (13 sessions over 4-6 months) including cognitive restructuring, graded activity relaxation. Control : natural course without intervention	- **Fatigue**: Chalder Fatigue Scale - **Social Adjustment**: Work and Social Adjustment Scale, - **Global Improvement:** Self-rated global outcomes	Outcomes were assessed at baseline and 6 months after first assessment.
	2. routine clinical practice	**2. 1995-2000**		Routine clinical practice in the same unit	No exclusion except for alternative medical causes, severe depression, concurrent treatment. - 384 patients	11 sessions of therapy on a fortnightly basis and their progress was reviewed at 3 and at 6 months post-treatment CBT followed the same stages than in the RCT	- **Fatigue**: Chalder Fatigue Scale - **Social Adjustment**: Work and Social Adjustment Scale, - **Global Improvement:** Self-rated global outcomes	Outcomes were assessed at baseline and 6 months after first assessment.

Results	Author's conclusions / recommendations
- RCT group (compared to clinical practice): - Significantly larger overall reduction in fatigue from pre-therapy to 6-month follow-up and from post-treatment to follow-up; - Significantly larger improvement in work and social adjustment from pre-therapy to 6-month follow-up; the gains are slight between post-treatment and follow-up; - Similar effect on global improvement and patient satisfaction with the treatment outcomes.	CBT has larger effects in RCT than in clinical routine practices on: • Fatigue • Social adjustment This difference is probably due to: • The stricter selection procedure in RCTs and the exclusion of patients with comorbidities (anxiety, depression • The motivation and supervision of therapists in RCTs • The follow-up bias : in RCTs more patients completed follow-up measures • The manualised therapy in RCTs, tailored for patients (therapists are less strict and focused in routine clinical practice)

Behavioural treatment (modified cognitive behaviour therapy)

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
1	Systematic review	May 2007	2C → 1A	+	Positive effects on: • physical functioning (fatigue, pain) • psychological state (emotional distress) • illness management

Behavioural treatment (cognitive behaviour therapy associated with dialyzable leukocyte extract)

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
1	Systematic review	May 2007	1B	+	Larger effects (than placebo or CBT alone) on: • global well-being (only) Neither dialyzable leukocyte extract nor CBT (alone or in combination) provided greater benefit than the non specific treatment regimens

Behavioural treatment (Graded exercise therapy)

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
• 1 • 15	Systematic review Systematic review	May 2007 2004	1B → 1A 1B → 1A	+	Positive effects on: • physical functioning (functional status, fatigue, pain); *exercise therapy was significantly effective at 12 weeks, but not at 24 weeks* • physiological (increase in peak oxygen consumption and maximum ventilation) • psychological state (depression, mood, anxiety, well-being) • quality of life and general health (work and social adjustment, long term goals, global improvement)

Behavioural treatment (Graded exercise therapy + fluoxetine)

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
1	Systematic review	May 2007	1A	No	Adding fluoxetine to GET is not more effective than GET alone.
15	Systematic review	2004	1A	No	Adding fluoxetine to GET is not more effective than GET alone.

Behavioural treatment (Graded exercise therapy + patient education)

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
15	Systematic review	2004	1A	No	Adding patient education to GET is not more effective than GET alone.

Immunological treatment

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
Antihistamine (oral terfenadine)					
1	Systematic review	May 2007	1A	No	**No effect of Terfenadine**
Antiviral					
1	Systematic review	May 2007	2B → 1A	-	Antiviral treatment should be avoided according to the lack of beneficial effects and the presence of adverse effects such as: • reversible renal failure with Acyclovir • pericardial bleeding during invasive investigations with Gancyclovir • elevation of serum uric acid with Inosine pranobex
Immuno-modulators					
1	Systematic review	May 2007	1A		Immunological treatments with Immunoglobulin have more adverse effects than beneficial effects and should be avoided: • transient abnormal liver function tests • phlebitis • headaches (in treatment and control) • severe constitutional reaction to infusion
1	Systematic review	May 2007	1B → 1A	+	There is low evidence of benefit for immunological treatments • Interferon • Alpha Interferon • Leukocyte extract • Ampligen Moreover, risks are greater than benefits linked to the use of blood products (possible transfer of infectious diseases)

Vaccination with staphylococcus toxoid					
I	Systematic review	May 2007	2B → 1A	No	There is low evidence of benefit for vaccination with staphylococcus toxoid treatment, and only for 'the clinical global impression'

Pharmacological treatment

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
Anticholinergic					
I	Systematic review		1B → 1A	No	There is no benefit of anticholinergic agents • Galantamine hydrobromide • Sulbutiamine Adverse events were serious enough to cause patients withdrawal from the study
Antidepressant					
I	Systematic review	May 2007	1B → 1A	No	Antidepressant agents should be avoided according to the lack of beneficial effects and the presence of adverse effects: • Phenelzine • Fluoxetine
Hormone					
I	Systematic review	May 2007	1B	No / +	• Growth hormone • Melatonin o improvement in sleep, vitality, mental health o worsening of bodily pain
Monoamine oxidase					
I	Systematic review	May 2007	2A → 1A	No / +	• Moclobemide : no effect • Selegiline o Improvement in tension anxiety and vigour (only) Adverse events were serious enough to cause patients withdrawal from the study
NADH					
I	Systematic review	May 2007	1B → 1A	No	There is no benefit of oral NADH for CFS
Dexamphetamine					
I	Systematic review	May 2007	1B	+	Positive effect on fatigue
Antihypertensive					
I	Systematic review	May 2007	1B	No	There is no benefice of Clonidine for CFS
Steroids					

[1]	Systematic review	May 2007	1B → 1A	No / +	There is no beneficial effect of • Fludrocortisone • Hydrocortisone + Fludrocortisone • Topical nasal corticosteroids Hydrocortisone alone has light beneficial effects on fatigue and clinical global impression

Methylphenidate								
ID	**Type of study**	**Search date**	**Level of evidence**	**Setting**	**Participants**	**Interventions**	**Outcome measures**	**Length of follow-up**
[5]	A double-blind randomized placebo-controlled crossover study	2003/2004	1A	Outpatient department of a university hospital (referral center), Belgium	60 CFS patients were randomized (1994 CDC criteria)	Treatment with methylphenidate 10 mg taken twice daily (at 8 AM and 2 PM) compared with placebo. Both compounds were taken for 1 month each, by every participating patient, with a washout period of 1 week at crossover (t ½ of methylphenidate _ 2 hours).	**Fatigue** (Checklist Individual Strength [CIS] and Visual Analogue Scale [VAS] **Concentration** (CIS and VAS subscales) **Emotional Well-being** (VAS) **Health related QoL** (SF-36, physical factor and mental factor) **Depression and anxiety** (HADS)	9 weeks (from baseline to the end of the intervention)

Results	**Author's conclusions / recommendations**
Fatigue scores fell significantly during methylphenidate intake in comparison with baseline (mean difference: -0.7, $p < .010$ for VAS; mean difference: -11.8, $P < .0001$ for CIS) and in comparison with placebo (mean difference: -1.0, $p < .001$ for VAS; mean difference: -9.7, $p < .0001$ for CIS). Concentration disturbances improved significantly under methylphenidate treatment compared with baseline (mean difference: -1.3, $p < .0001$) and compared with placebo (mean difference: -1.1, $p < .0001$). A clinical significant effect (≥33% improvement or CIS ≤76) on fatigue was achieved in 17% of patients; on concentration in 22% of patients.	Larger effects than placebo on : • Fatigue and concentration • Physical factor (SF-36) • Vitality • Fukuda criteria: muscle pain, joint pain, sleeping disturbance and post-exertional malaise Lack of severe side effects Authors recommend this drug for CFS patients with concentration difficulties

Alternative medicine treatment

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
Homeopathy					
	Systematic review	May 2007	1B → 1A	+	There is benefit of homeopathy on fatigue and some physical dimensions in physical functioning (p value is not reported)
Massage therapy					
	Systematic review	May 2007	1B	+	There is beneficial effect of massage therapy on: • Fatigue, pain and sleep • Depression • Decrease in cortisol levels
Osteopathy					
	Systematic review	May 2007	2B	+	There is beneficial effect of osteopathy on fatigue, back pain and sleep, anxiety and cognitive function and general health. However, the quality of this study was poor.

Supplement treatment

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
Essential fatty acids					
	Systematic review	May 2007	1A	No	There is benefit of essential fatty acids for CFS
Magnesium					
	Systematic review	May 2007	1A	+	There is beneficial effect of magnesium on: • Energy and pain • Emotional reactions • General health But adverse events are reported
Liver extract					
	Systematic review	May 2007	1B	No	There is no beneficial effect of liver extract on CFS
Acetyl-L-carnitine and propionyl-L-carnitine					
	Systematic review	May 2007	1A	+	There is benefit of ALC and PLC in fatigue and cognitive function for CFS patients
Acclydine and amino acids					
	Systematic review	May 2007	2B	No	There is no beneficial effect of Acclydine and amino acids on CFS

Pollen extract					
[1]	Systematic review	May 2007	1A	No	There is no beneficial effect of pollen extract on CFS
RM-10: medicinal mushrooms					
[1]	Systematic review	May 2007	1B	No	There is no evidence for a beneficial effect of medicinal mushrooms on CFS
General supplements					
[1]	Systematic review	May 2007	2A → 1B	No	There is no beneficial effect of general supplements on CFS. Studies were scored poorly on the validity assessment

Food supplement : arabinoxylane (BioBran MGN-3)								
ID	**Type of study**	**Search date**	**Level of evidence**	**Setting**	**Participants**	**Interventions**	**Outcome measures**	**Length of follow-up**
[6]	A randomized double-blind placebo-controlled trial	2003/2004	1A	The Dorset CFS Clinic at Wareham Community Hospital	71 CFS patients were randomized (1994 CDC criteria)	BioBran, a food supplement, whose active ingredient is arabinoxylane; 2000 mg sachets (1000 mg active ingredient + 1000 mg excipient); 2 g, thrre times per day	**Fatigue** (Chalder Fatigue Scale) **Changes in the condition** (Patient Global Impression of Change, Measure Yourself Medical Outcome Profile 2, WHOQoL-BREF, HADS)	4 and 8 weeks after the beginning of treatment

Results	Author's conclusions / recommendations
Data were complete in 64/71 patients. Both groups showed marked improvement over the study duration, but without significant differences, except for the social well-being subscale of the WHOQOL-BREF, where improvement was significantly better in the placebo group.	There is no beneficial effect of arabinoxylane supplements on CFS.

Food supplement : Acclydine								
ID	**Type of study**	**Search date**	**Level of evidence**	**Setting**	**Participants**	**Interventions**	**Outcome measures**	**Length of follow-up**
[9]	A randomized placebo-controlled, double-blind clinical trial	-	1A	Radboud University Nijmegen Medical Centre, The Netherlands	57 adult CFS patients (1994 CDC criteria).	Acclydine (alkaloid from Solanum Dulcamara) or placebo for 14 weeks For Acclydine: 250 mg of the alkaloid 1x/day, with the following decreasing dosage schedule: weeks 1–2, 1,000 mg per day; weeks 3–6, 750 mg per day; weeks 7–8, 500 mg per day; weeks 9–10, 500 mg every 2 d; weeks 11–12, 250 mg per day; and weeks 13–14, 250 mg every 2 d.	**Fatigue severity** (Checklist Individual Strength, subscale fatigue severity [CIS-fatigue]) **Functional impairment** (Sickness Impact Profile-8 [SIP-8]) **Biologically active IGF1 serum concentrations**. (ratio of IGFBP3 to IGF1 reflects IGF1 biological activity)	14 weeks from baseline to the end of the intervention

Results	Author's conclusions / recommendations
There was no difference in IGF status in 22 CFS patients compared to healthy age and gender-matched control individuals. Treatment with Acclydine did not result in significant differences compared with the placebo group on any of the outcome measures: CIS-fatigue: +1.1 (95% CI: -4.4 to +6.5, p=0.70), SIP-8:+59.1 (95% CI:-201.7 to +319.8, p=0.65), and IGFBP3/IGF1 ratio= -0.5 (95% CI: -2.8 to +1.7, p = 0.63). Note. This work was supported by Optipharma, Susteren and Planet Vital, Maastricht-Airport, The Netherlands. The funder had no role in study design, data collection, data analysis, interpretation of the data, decision to publish, or preparation of the manuscript.	No differences were found in IGF1 status in CFS patients compared to healthy matched neighborhood controls. In addition, the results of this clinical trial do not demonstrate any benefit of Acclydine over placebo in the treatment of CFS. The negative results of this trial are important: Acclydine is expensive and is available without prescription on the Internet, making it available to patients potentially without a doctor's oversight.

Other treatment

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
Combination multitreatment (medical treatment of symptoms plus anxiety/affective disorder, CBT & social)					
[1]	Systematic review	May 2007	2B	+	There is benefit of combination of treatments on return to work (no significance was reported)
Group therapy (unstructured discussions)					
[1]	Systematic review	May 2007	1B	No	There is no beneficial effect of group therapy on CFS
Low sugar low yeast diet					
[1]	Systematic review	May 2007	1A	No	There is no beneficial effect of low sugar low yeast diet on CFS

Treatment of Chronic fatigue syndrome in children and adolescents

Behavioural treatment

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
CBT					
[1]	Systematic review	May 2007	1B	+	Positive effects on: physical functioning (functional status, fatigue, pain) school attendance
Modified CBT					
[1]	Systematic review	May 2007	2A	+	There is a beneficial effect of rehabilitation and CBT on global wellness for CFS children

CBT + Biofeedback								
ID	**Type of study**	**Search date**	**Level of evidence**	**Setting**	**Participants**	**Interventions**	**Outcome measures**	**Length of follow-up**
[8]	A controlled trial	2002/2005	1B	CFS clinic (Al-Jazira Polyclinic), saudi Arabia	92 CFS adolescents, ages 10-14 years (1994 CDC criteria)	Cognitive behavioural intervention + biofeedback (interventional group; n=50) Conservative and symptomatically treatment (control group, n=42)	Fatigue (ten-item CIS = FAS) Duration of school stay (hours/month) CFS symptoms	18 months after the beginning of treatment

Results	Author's conclusions / recommendations
Fatigue severity scores fell significantly in interventional group in comparison with baseline (mean difference: -23.1%; 95%CI: -19.2, -25.4%) and in comparison with control group (mean difference: -12.2; 95%CI: -7.4, -14.8). School attendance improves significantly in interventional group, both in comparison with baseline (mean difference: +34.5; 95% CI: +29.8, +36.6) and in comparison with control group (mean difference:+23.1 hours/month; 95% CI: +20.6, +26.8). Some self-rated CFS symptoms (fatigue, headache and myalgia showed statistically significant improvements ($p<0.01$) whereas joint pains and tender glands did not significantly improved.	CBT aided by biofeedback could be very effective in treatments of adolescents suffering from CFS taking in consideration the stressors and precipitating factors during settings of psychotherapy.

ID	Type of study	Search date	Level of evidence	Setting	Participants	Interventions	Outcome measures	Length of follow-up
[12] based on [16]	A RCT with two arms	**1999 - 2002**	**1B**	The paediatric outpatient clinic of the departments of child psychology (The Netherlands)	67 consecutively referred patients with CFS; - 33 to CBT; - 34 to the waiting list for therapy.	Group CBT (10 sessions over 5 months); two treatment protocols: one for patients with a passive physical activity pattern and one for relatively active patients. Control : waiting list for treatment	- **Concentration**: subscale concentration of CIS score - **Impact of cognitive impairment on daily functioning**: structured diary to evaluate the frequency of cognitive impairments (SOCI), - **Reaction time task** - **Complex attention**: symbol digit modalities task (SDMT).	Outcomes were assessed at baseline and 5 months after first assessment.

Results	Author's conclusions / recommendations
- CBT (treatment): - Significant effect on the change in concentration-CIS: [difference -6.8, 95% CI: -10.5 to -3.5] ; greater effect than waiting list (p=0.014); - Significant effect on the change in SOCI [difference -7.9, 95% CI -12.8 to -2.9]; greater effect than waiting list (p=0.015) - No significant effect on reaction time task and SDMT. - Waiting list (no treatment): - No significant effect on concentration-CIS, SOCI, reaction time task and SDMT.	CBT has larger effects (compared to waiting list) on: • Concentration disturbances • Self-observation of cognitive impairment CBT has no effect on: • Neuropsychological performance

Immunological treatment

ID	Type of study	Search Date	Level of evidence	Effect	Authors conclusions / recommendations
Immunoglobulin					
[1]	Systematic review	May 2007	1A	+	There is benefit of immunoglobulin on physical functioning for CFS children

Appendices from Chapter 3

3 ECONOMIC EVALUATION OF CFS-EVIDENCE BASED TREATMENTS: A LITERATURE REVIEW

3.1 APPENDIX 1. CLASSIFICATION OF ECONOMIC STUDIES

		Are both costs (inputs) and consequences (outputs) of the alternatives examined?		
		No		Yes
		Examines consequences only	Examines costs only	
Is there a comparison of at least two alternatives?	No	*Partial evaluation*		*Partial evaluation*
		Outcome description	Cost description	Cost-outcome description
	Yes	*Partial evaluation*		*Full economic evaluation*
		Efficacy or effectiveness evaluation	Cost comparison	Cost-minimisation analysis (CMA) Cost-effectiveness analysis (CEA) Cost-utility analysis (CUA) Cost-benefit analysis (CBA)

Adapted from Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2d edition; 1997.

3.2 APPENDIX 2. LITERATURE SEARCH STRATEGIES

Details of the searches conducted on March the 5th, 2008.

MEDLINE, OVID Search Engine, no time limit

#	Search Strategy	Results
1	chronic fatigue syndrome.ti,ab.	2 742
2	*Cognitive Therapy/	4 883
3	*Exercise Therapy/	10 173
4	2 or 3	15 024
5	1 and 4	98
6	exp "Costs and Cost Analysis"/	133 993
7	5 and 6	3

EMBASE, no time limit

#	Search Strategy	Results
1	'chronic fatigue syndrome'/de AND [embase]/lim AND [1990-2007]/py	3 867
2	'cognitive therapy'/de AND [embase]/lim AND [1990-2007]/py	13 247
3	'kinesiotherapy'/exp AND [embase]/lim AND [1990-2007]/py	14 157
4	#2 OR #3	27 111
5	#1 AND #4	314
6	'cost effectiveness analysis'/exp AND [embase]/lim AND [1990-2007]/py	51 003
7	#5 AND #6	11

3.3 APPENDIX 3. DATA EXTRACTION SHEETS

Author	Severens JL, Prins JB, Van der Wilt GJ, Van der Meer JW, Bleijenberg G
Country	The Netherlands
Conflicts	The study was financial supported by the Health Car Insurance Board of the Netherlands (College voor zorgverzekeringen).
Objective	The objective of the study was to compare the effectiveness and cost of cognitive behaviour therapy (CBT) with guided support groups (SG) or natural course (NC, no protocol-based interventions) for CFS patients.
Design	RCT-based economic evaluation (RCT: Prins et al., 2001) CEA – CUA Probabilistic economic evaluation (n=1000)
Perspective	Payers (direct medical costs + direct non-medical costs) Societal (direct medical costs + direct non-medical costs + indirect costs)
Time window	14 months (trial duration from baseline)
Interventions	Cognitive behaviour therapy (CBT) Guided support groups (SG) Current practice : No intervention – natural course (NC) <u>Description:</u> CBT consisted of 16*1-h sessions by trained therapists. GS was an alternative treatment and consisted of 11*1.5-h meetings with a therapist. NC implied no specific intervention and represented the medical-care-seeking behaviour of CFS patients as is current practice. CBT and SG lasted for 8 months.
Population	Patients, aged 18-60 years, with a major complaint of fatigue, and who were referred to the outpatient departments of internal medicine of two University hospitals in the Netherlands (Nijmegen and Maastricht) were enrolled in the study. Inclusion criteria: having a score of 40 or more on the subscale fatigue severity of the Checklist Individual strength, and a score of 800 or more on the Sickness Impact Profile (criteria for CFS)[17] Exclusion criteria: previous or current engagement in CFS research, pregnancy or engaged in pregnancy-stimulating techniques, or living more than 1.5 h travelling time from one of the three centres. The trial was powered to show an effect on physical activity. Overall, 270 patients were included: 92 in the CBT group, 90 in the SG group and 88 in the NC group. 10 patients in the CBT group and 8 in the SG group did not start therapy (reasons were not reported here).
Assumptions	RCT-based econ eval, no extrapolation to lifetime
Data source for costs	Resources used: RCT-piggy-backed (but with protocol-driven costs excluded) Patient-self-reports: monthly diaries used to collect data during the 14 months follow-up. Unit costs: National price lists National published literature Dutch general wages
Cost items included	Direct medical costs: Intervention costs: CBT (diagnostic and treatment) SG (intake consult and treatment). Other direct medical costs: CFS-related visits (GP, medical specialist, physical therapist) Medications prescribed Hospitalisations Formal home care support. Direct non-medical costs: OTC (?)

	Travelling Informal home care support Visits to practitioners for alternative medicine Indirect cost: Productivity losses.
Data source for outcomes	Change in fatigue between baseline and 14-month follow-up. Effectiveness evidence derived from. Fatigue was measured with the subscale CIS (Checklist Individual Strength) score. EuroQol questionnaires were used to calculate the quality adjusted life years (QALY) for the period of follow-up. Patient's answers on the EuroQol questions were used to indicate their health state of the past two weeks. Utility values were calculated to indicate quality of life. No explicit information was given about the valuation tool that was used to determine utilities.
Discounting	Not applicable
Costs	All costs reported as mean per patient, over the 14 months follow-up period. Direct medical costs (adjusted for baseline): Intervention costs: CBT: €1490 SG: €424 NC: €0 Other direct medical costs: CBT: €556 SG: €1184 NC: €790 Direct non-medical costs: CBT: €488 SG: €989 NC: €714 **Total direct costs** (indirect costs excluded): CBT: €2534 SG: €2597 NC: €1504 Indirect costs: CBT: €20490 SG: €15165 NC: €22353 No significant differences in productivity costs between the alternative groups.
Year of costs	Costs in 1998 euros
Outcomes	% of patients with a clinically significant decrease in fatigue (from intake to 14 months): CBT: 27% SG: 11% NC: 20% Mean QALYs gained (from intake to 14 months) CBT: 0.0737 SG: -0.0018 NC: 0.0458 No confidence interval reported – Neither specified whether the differences between treatments (mainly CBT and NC) are significant.
Cost-effectiveness	SG dominated by CBT and NC. CBT versus NC (14 months FU): ICER: € 20 516 per patient with a clinically significant improvement (Payers') ICER: € 51 642 per QALY gained (Payers')

	ICER: € 21 375 per QALY gained (Societal) COST EFFECTIVENESS PLANES **Payers perspective** **Societal perspective** Cost per QALY 36% | 64% 0% | 0% Cost per QALY 15% | 31% 20% | 34% Cost per patient improved 22% | 78% 0% | 0% Cost per patient improved 10% | 37% 13% | 40%
Sensitivity analysis	One-way sensitivity analysis (on deterministic parameters) Reducing the costs of the intervention highly impacts the ICERs (reduction) Probabilistic sensitivity analysis CEAC for cost per QALY (societal) Comparing CBT to NC, uncertainty (both in terms of costs and efficacy) remained over a wide range of cost-effectiveness thresholds.
Conclusions	CBT leads to higher clinical efficacy and lower costs to society compared to NC (current practice), but the statistical uncertainty of this finding is considerable. ICER appears high and uncertain. Longer time window is expected to reduce this ICER.
Remarks	The costs reported probably underestimate the total costs involved in current CFS treatment, as authors were unable to examine other services besides visits to care providers and use of drugs, or non-drugs costs such as special diets. However, authors argued that including these costs would enlarge the cost difference between successfully and unsuccessfully treated patients.

Author	McCrone P, Ridsdale L, Darbishire L, Seed P.
Country	UK
Conflicts	Funded by the Linbury Trust.
Objective	To examine the cost-effectiveness of cognitive behavioural therapy (CBT) versus graded exercise therapy (GET), and the cost-effectiveness of therapy (either CBT or GET) versus usual GP care plus a self-help booklet (BUC) in patients with CFS in the UK.
Design	RCT-based economic evaluation (RCT: Ridsdale et al., 2004) CEA (Net benefit approach) Probabilistic economic evaluation (n=5000)
Perspective	Not stated Costs included: Direct medical costs + direct non-medical costs (informal home care)
Time window	8 months (trial duration from baseline)
Interventions	Cognitive behavioural therapy (CBT) Graded exercise therapy (GET) Current practice: usual general practitioner care plus a self-help booklet (BUC). <u>Description</u>: CBT (6 sessions of 45 minutes) was delivered by trained cognitive behavioural therapists and included an initial assessment, activity planning, and homework, the establishment of a sleep routine, the relapse prevention and a change in lifestyle. GET (6 sessions of 45 minutes), delivered by physiotherapists, is structured and supervised activity management that aims for a gradual but progressive increase in aerobic activities, usually walking. Home exercise is programmed, with initial sessions lasting between 5 and 15 min at an intensity of 50% of the age-related estimated maximum heart rate.
Population	The study population comprised adult patients (16 -75 years old) attending their GP with a

	main complaint of unexplained fatigue that had lasted for more than 3 months. Inclusion criteria: aged 16 to 75 years; complains of fatigue as a main or important problem; duration of fatigue symptoms for ≥3 months; no recent change in drug regimen; normal full blood count, erythrocyte sedimentation rate and thyroid function test on entry or in the previous 6 months. Exclusion criteria: patient unable to read English; concurrent physical problems, which in the judgement of the doctor have caused the fatigue symptoms; patient has asthma and/or ischemic heart disease that would contraindicate a physical step-test; psychotic illness, organic brain syndrome, or substance dependency; current treatment from a psychiatrist, psychologist, community psychiatric nurse, physiotherapist, or exercise therapist. Sample size was determined on the basis of power calculations to show significant differences in clinical outcomes. Limited information on the process of sample selection was reported. Of the 144 patients referred to the randomized component of the study, 123 received the study interventions. A further group of 40 of the 47 initially identified patients entered the BUC group (7 patients refused to participate). However, the final study sample comprised 50 patients (66% women) in the GET group, 52 patients (71% women) in the CBT group and 30 patients (77% women) in the BUC group, because cost-effectiveness data was available for a smaller group of patients than that initially considered (132 patients). The mean age of the patients was 40 (+/- 10.7) years in the GET group, 40 (+/- 12.8) years in the CBT group and 36.9 (+/- 10.7) years in the BUC group. The three groups of patients were comparable in terms of their demographics and the baseline values of the outcome measures. However, when GET and CBT patients were grouped, the therapy group had a higher proportion of non-white patients and significantly higher baseline fatigue, symptom and depression scores.
Assumptions	RCT-based econ eval – no extrapolation
Data source for costs	Resources used: RCT-piggy-backed Patient-self-reports: the Client Service Receipt Inventory (CSRI) was used to retrospectively record service use for the 3 months prior to baseline and 8-month follow-up. Unit costs: National price list. National published literature.
Cost items included	Direct medical costs: Intervention costs CBT: £40 per hour GET: £41 per hour Booklet unit cost: £5 (assumption) GPs, other clinicians, nurses, inpatient stays, physiotherapists (additional to those providing GET), counsellors, nutritionists, social services and complementary therapy Direct non-medical costs: Informal home care support (time spent by friends or relatives for personal support, child care, help in or around the house, help outside the home, or other tasks) Cost of informal care giver valued at the cost of paid home care workers: £10.57 Indirect costs: Not included The unit costs were not reported separately from the quantities of resources used, but the unit costs were provided for the majority of items.
Data source for outcomes	Change in fatigue between baseline and 8-month follow-up. Effectiveness evidence derived from Ridsdale et al. (2004).[18] The primary outcome measure was fatigue measured with a fatigue scale scored using a validated 11-item Likert instrument (0 [represented fatigue less than usual], 1, 2, 3 [representing higher levels of fatigue]) with a maximum score of 33. Binary scoring (0, 0, 1, 1) was applied to the data to estimate fatigue 'caseness ', with a cut-off of ≥4 indicative of clinically significant fatigue.

Discounting	Not applicable
Costs	CBT versus GET (with sample differences controlled for): Incremental costs at baseline: £519 (90% CI: -£814 to £1 904; p=0.552) Incremental costs at 8 months: **- £193** (90% CI: -£946 to £458; p=0.620). CBT&GET versus BUC (with sample differences controlled for): Incremental costs at baseline: £385 (90% CI: -£811 to £1 702; p=0.664) Incremental cost at 8 months: **£149** (90% CI: -£708 to £1 011; p=0.791)
Year of costs	Costs in 2000/2001 £
Outcomes	CBT versus GET: % of patients with a clinically significant (at least 4 points) decrease in fatigue: CBT: 79% GET: 73% Mean unit change (improvements or deteriorations divided by 4): CBT: 2.7 (SD 2.1) GET: 2.4 (SD 2.2) CBT&GET versus BUC: % of patients with a clinically significant (at least 4 points) decrease in fatigue: CBT&GET: 76% BUC: 60% Mean unit change (improvements or deteriorations divided by 4): CBT&GET: 2.6 (SD 2.2) BUC: 1.2 (SD 1.9)
Cost-effectiveness	CBT versus GET: % of patients with a clinically significant (at least 4 points) decrease in fatigue: Probability CBT is cost-effective at £0 threshold: 0.589 Probability CBT is cost-effective at £5000 threshold: 0.766 At all values considered, CBT was more cost-effective. Mean unit change (improvements or deteriorations divided by 4): Probability CBT is cost-effective at £0 threshold: 0.663. CBT&GET versus BUC % of patients with a clinically significant (at least 4 points) decrease in fatigue: Probability CBT&GET is cost-effective at £0 threshold: 0.237 Probability CBT&GET is cost-effective at £4500 threshold: 0.818 Mean unit change (improvements or deteriorations divided by 4): Probability CBT is cost-effective at £500 threshold: 0.819.
Sensitivity analysis	One-way sensitivity analyses: <u>Cost of informal care:</u> % of patients with a clinically significant (at least 4 points) decrease in fatigue: £0 per hour: Probability CBT&GET is cost-effective at £4500 threshold: 0.880 £4.10 per hour: Probability CBT&GET is cost-effective at £4500 threshold: 0.894 £10.57 per hour: Probability CBT&GET is cost-effective at £4500 threshold: 0.818 (Baseline) Mean unit change (improvements or deteriorations divided by 4): £0 per hour: Probability CBT&GET is cost-effective at £500 threshold: 0.989 £4.10 per hour: Probability CBT&GET is cost-effective at £500 threshold: 0.951 £10.57 per hour: Probability CBT&GET is cost-effective at £500 threshold: 0.819 (Baseline) <u>Cost of therapy:</u> % of patients with a clinically significant (at least 4 points) decrease in fatigue: +30%: Probability CBT&GET is cost-effective at £4500 threshold: 0.797 Baseline: Probability CBT&GET is cost-effective at £4500 threshold: 0.818 -30%: Probability CBT&GET is cost-effective at £4500 threshold: 0.836 Mean unit change (improvements or deteriorations divided by 4): +30%: Probability CBT&GET is cost-effective at £500 threshold: 0.797 Baseline: Probability CBT&GET is cost-effective at £500 threshold: 0.819 -30%: Probability CBT&GET is cost-effective at £500 threshold: 0.837

	Results fairly robust to changes in the costs of therapy
Conclusions	Although costs and outcomes were quite similar between GET and CBT, CBT was slightly more cost-effective than GET for the treatment of patients with chronic fatigue syndrome. The cost of informal care played a key role in the cost-effectiveness analysis. Whether the improvement achieved for patients with CFS was worthwhile depended on society's willingness to pay.
Remarks	While all patients in the CBT group received therapy, only 88% of the patients in the GET group did so. More patients cited lack of faith in their allocated treatment as a reason for not starting GET. If the remaining 12% actually received therapy then – potentially – the difference between CBT and GET outcomes would have been less. Treatments need to be acceptable to patients and the fact that 12% of the GET group decided not to receive therapy is questioning. Trials in secondary care have also reported high dropout rates for GET.[19] In future it will be useful to describe patient-preferences at baseline. Physiotherapy is more available in primary care, and if exercise therapy is to develop as a treatment, therapists may need to develop better strategies to engage and retain patient participation in the treatment.

Author	Chisholm D, Godfrey E, Ridsdale L, Chalder T, King M, Seed P, Wallace P, Wessely S.
Country	UK
Conflicts	This trial was funded by the Wellcome Trust.
Objective	To compare the relative costs and outcomes of counselling versus cognitive behaviour therapy (CBT) provided in primary care settings for the treatment of fatigue.
Design	RCT-based econ eval (RCT: Ridsdale et al., 2001[20]) CEA Probabilistic economic evaluation
Perspective	Not stated Costs included: Direct medical costs ('health care payers') Direct medical costs + direct non-medical costs + indirect costs ('societal')
Time window	6 months (trial duration from baseline)
Interventions	Cognitive behavioural therapy (CBT) Counselling therapy (CT) No comparison with current practice <u>Description:</u> CBT (6 sessions of 50 minutes) was delivered by trained cognitive behavioural therapists and included providing a treatment rationale, activity planning, homework, establishing a sleep routine and other cognitive interventions. Counselling (6 sessions of 50 minutes) was delivered by trained counsellors, using a psychodynamic approach. This model of counselling is non-directive and client-centred; it offers the patient an opportunity to talk through their concerns and difficulties in a non-judgmental and supportive environment.
Population	The study population comprised adult patients (16 -75 years old) attending their GP with a main complaint of unexplained fatigue that had lasted for more than 3 months. The inclusion criteria were: aged 16 to 75 years; complains of fatigue as a main or important problem; duration of fatigue symptoms for ≥3 months; no recent change in drug regimen; normal full blood count, erythrocyte sedimentation rate and thyroid function test on entry or in the previous 6 months; may have concurrent physical problems but, in the doctor's judgement, they have not caused the fatigue symptoms. The exclusion criteria were: patient unable to read English; learning difficulty precludes completion of questionnaires; score of less than 4 on fatigue questionnaire (bi-modal scoring); psychotic illness; current treatment from a psychiatrist, psychologist, community psychiatric

	nurse, psychologist or counsellor; patient unable to attend the doctors' premises for therapy sessions. The authors stated that sample size was determined on the basis of power calculations to show significant differences in clinical outcomes: 160 patients were referred to a therapeutic group, 80 being allocated to counselling and 80 to CBT. At 6 month-follow-up, 129 (81%) patients returned completed questionnaires.
Assumptions	RCT-based econ eval, no extrapolation
Data source for costs	Resources used: RCT-piggy-backed Patient-self-reports: a variant of the Client Service Receipt Inventory (CSRI) was used to collect data at baseline and six-month follow-up. Unit costs: National price lists National published literature National wages
Cost items included	Direct medical costs Intervention costs: CBT: £40 per hour CT: £28 per hour Other direct medical costs Inpatient care Outpatient care Primary care (GP) Community care Alternative therapies Direct non-medical costs Cost of informal care giver valued at the cost of paid home care workers: £6.89 per hour Indirect costs Valuation of productive days lost with the UK average general gross wage: average of £7.10, £12.94, £5.10 and £8.90 per hour.
Data source for outcomes	Change in fatigue between baseline and 6-month follow-up. Effectiveness evidence derived from Ridsdale et al. (2001). Fatigue was measured with a validated 11-item Likert instrument (0 [represented fatigue less than usual], 1, 2, 3 [representing higher levels of fatigue]) with a maximum score of 33. Self-report measures were used to avoid interviewer bias.
Discounting	Not applicable
Costs	Direct medical costs (adjusted for baseline) Intervention costs (mean per patient): CBT: £164 (150–181) CT: £109 (96–119) Other direct medical costs CBT: -£36 (-145–81) CT: -£43 (-114–36) Total direct medical costs CBT: £129 (23–242) CT: £65 (-6–146) Direct non-medical costs and indirect costs (not reported separately) (adjusted for baseline) CBT: -£125 (-1048–645) CT: -£241 (-860–43) Total costs (adjusted for baseline) CBT: £4 (-928–822)

	CT: -£176 (-793–410)
Year of costs	Costs in 1998 £
Outcomes	Mean decrease in fatigue scores (adjusted for baseline) CBT: 7.34 (5.5–9.1) CT: 8.25 (6.5–10.0)
Cost-effectiveness	Incremental costs - CT versus CBT Intervention costs: -£55 per patient (35–76; *P*<0.001). Other direct medical costs: -£7 (-144–124) Total direct medical costs: -£63 (-258–42) Direct non-medical costs and indirect costs: -£116 (-1086–976) Total costs: -£180 (-1103–968) = non-significant cost reduction for CT Incremental reduction in fatigue score - CT versus CBT 0.90 (-1.80–3.60) = non-significant trend in favour of counselling. Computation of ICERs not possible since non significant results. The proportion of the dots in each quadrant of the cost-effectiveness plane is not reported
Sensitivity analysis	One-way sensitivity analysis – results still inconclusive
Conclusions	Counselling and CBT were both associated with some reduction in lost employment and informal care costs, and with a reduction in fatigue. CT and CBT are both effective therapies but there is no significant clinical advantage of one therapy above the other. Likewise, there is no significant cost difference between both therapies. Counselling represents a less costly treatment, but there is no statistically significant cost-effectiveness advantage associated with either form of treatment. The choice of therapy should depend on the availability of therapists and the relative cost of the time.
Remarks	A post hoc power calculation indicates that at least double the number of participants would have been required in the trial to show a significant difference (at a 5% level of significance and 80% power) in the observed costs of health care or patient and family burden. Authors have only assessed the impact of treatment over a six-month period, meaning that they are unable to comment on any longer-term effects.

Appendices from Chapter 4

4 PROGNOSIS: A LITERATURE REVIEW

4.1 APPENDIX 1. PROGNOSIS

4.1.1 Search strategy

4.1.1.1 Medline and Embase (from 2003 to 2008).

Search string for Medline (05/02/2008): Ovid MEDLINE(R) 2003 to Present

1	Chronic Fatigue Syndrome, ti.ab	2 635
2	limit 1 to yr="2003 - 2008"	759
3	prognosis.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	328 524
4	1 and 2 and 3	37

Search string for Embase (05/02/2008): 2003 to Present

#1 'chronic fatigue syndrome' AND prognosis AND [embase]/lim AND [2003-2007]/py	63

Appendices from Chapter 5

5 PATIENT ISSUES: A LITERATURE REVIEW

5.1 APPENDIX 1. SEARCH STRATEGY

PsycInfo (22/02/2008)

1	Chronic Fatigue Syndrome, ti.ab	1 234
2	treatment outcomes/ or "recovery (disorders)"/ or "relapse (disorders)"/ or relapse prevention/ or "remission (disorders)"/ or "side effects (treatment)"/ or therapeutic processes/	40 278
3	1 and 2	58
4	expectations/	14 588
5	1 and 4	2
6	exp General Practitioners/ or exp Primary Health Care/ or exp Health Care Utilization/	16 598
7	1 and 6	39
8	3 or 7	90

CSA Illumina (26/02/2008)

1	Chronic Fatigue Syndrome AND Patient	39

Appendices from Chapter 7

6 ORGANISATION AND FINANCING OF CFS CARE IN OTHER COUNTRIES

6.1 APPENDIX 1. ORGANISATIONAL MODEL OF CARE: SEARCH TERMS AND SEARCH RESULTS

Chronic Fatigue Syndrome

Date: 2007, December

CRD databases

"chronic fatigue syndrome or fibromyalgia " and "classification": 8 results, 0 retained

"chronic fatigue syndrome or fibromyalgia " and "international comparison": no results

"chronic fatigue syndrome or fibromyalgia " and "typology": no results

"chronic fatigue syndrome or fibromyalgia " and "disease management": 9 results, 0 retained

"chronic fatigue syndrome or fibromyalgia " and "model": 8 results, no additional relevant results

"chronic fatigue syndrome or fibromyalgia " and "organiz/sation": no results

Medline (PubMed)

fatigue syndrome, chronic AND "health services research": 9 results, 0 retained (however, one systematic review did not describe a model but compared first level and second level care for CFS, irritable bowel syndrome and chronic back pain, and was retained for separate discussion: Raine R et al. (2002)[21]

Google:

"chronic fatigue syndrome " and "classification"

"chronic fatigue syndrome " and "international comparison"

"chronic fatigue syndrome " and "typology" and "organiz/sation"

No relevant results (only results on typology of clinical symptoms)

Website WHO and European Observatory:

chronic fatigue syndrome or chronic fatigue or fibromyalgia : no relevant results

Chronic Condition/Disease

Date: 2007, December

CRD databases

"chronic disease" and "classification": 101 results, 0 retained

"chronic disease" and "typology": no results

"chronic disease" and "organiz/sation": 111 results, 4 retained as potentially relevant; 3 not considering a model for chronic care, 1 retained (Tsai AC 2005)[22]

Medline (PubMed)

"chronic disease" and "health services research" (712 results)

"chronic disease" and "health services research" and "typology" (1 result)

"chronic disease" and "health services research" and "organiz/sation" (498 results)

"chronic disease" and "health services research" and "disease management" (368 results)

13 results retained:[23, 24, 25, 26, 27-29, 30-32, 33-35]

Website WHO and European Observatory

"chronic" and "classification"

"chronic" and "typology"

"chronic" and "organiz/sation"

2 results retained:

- Velasco-Garrido M, Busse R, Hisashige A (2003). Are disease management programmes (DMPs) effective in improving quality of care for people with chronic conditions? Copenhagen, WHO Regional Office for Europe. Health Evidence Network report; http://www.euro.who.int/document/e82974.pdf, accessed 20-12-2007.
- Sheri Pruitt, JoAnne Epping-Jordan et al (2002). Innovative Care for Chronic Conditions: Building Blocks for Action. WHO Geneva (http://www.who.int/diabetesactiononline/about/icccglobalreport.pdf, accessed 20-12-2007).

Google

"chronic disease" and "classification" (results limited to 5 pages)

"chronic disease" and "typology" (results limited to 5 pages)

"chronic disease" and "care organiz/sation" (results limited to 5 pages)

1 additional result:

- Department of Health, UK

  "Supporting people with long term conditions: An NHS and social care model to support local innovation and integration" Department of Health, UK, 5 Jan 2005.

  http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4100252

6.2 APPENDIX 2A. QUESTIONNAIRE ON CSF CARE ORGANISATION

March, 4th 2008

Organization and financing of care for patients with Chronic Fatigue Syndrome (CFS) in your country.

Questionnaire for the study on Chronic Fatigue Syndrome

by the Belgian Superior Health Council

and

the Federal Health Care Knowledge Centre (KCE)

Please return before end March to:

Mail: Maria.Eyssen@kce.fgov.be

Fax: (32)/2/287 33 85

For more information, please feel free to contact:

Marijke Eyssen, M.D.

Belgian Federal Health Care Knowledge Centre

Wetstraat 62; B-1040 Brussel (Belgium)

tel. (32)/2/287 33 88 or (32)/2/287 33 35

fax (32)/2/287 33 85

mail: Maria.Eyssen@kce.fgov.be

http://www.kce.fgov.be

PART 1: Special Structure(s) or Service(s) for CFS in Adults

1.1 Availability:

Are special structures (services, centres or teams) for persons with CFS (adults) available in your country? Yes/no (if no, go to *PART 2*)

Where are these structures situated (more than one answer possible):

1st line- 2nd line- 3rd line

Please specify:

Are these structures recognized by the government? Are there specific agreements with the government to regulate organization and financement?

Please specify:

Who is the main financier of these structures (e.g. government- local authorities- special funds- patient out-of-pocket etc.)?

Referral is necessary - not necessary (please indicate)

If necessary, it can be by (more than one possible answer):

Family doctor- medical specialist – other, please specify:

How many centres/ services/ teams exist in the country?

1.2 Capacity:

Do these centres take in charge other patients than CFS-patients (e.g. fibromyalgia, CFS-like cases?) Yes/no. If Yes, please specify:

How many CFS patients are on average treated per centre/ service per year? (if differences between centres, please specify):

How many NEW CFS patients are seen per centre/ service per year? (if differences between centres, please specify):

Do waiting lists exist: yes/ no (please indicate)

If waiting lists exist, how many months on average (please indicate):

1-2; 3-5; 6-9; 9-12; >12 months

1.3 Organization:

Which discipline(s) contribute(s) to the special service (more than one possible answer), how many FTE (full time equivalents):

Psychiatrist of the centre or in liaison			Psychologist, psychotherapist	
Medical specialist (internal medicine) of the centre or in liaison			Physiotherapist	
Medical specialist (rehabilitation) of the centre or in liaison			Nurse (general practice)	
Medical specialist (other, specify) of the centre/liaison			Psychiatric nurse	
General practitioner of the centre/ liaison			Social worker	
			Other(s), specify:	

If several professionals work together, do they work in a coordinated, multidisciplinary way? Yes/ no

Are evidence-based guidelines used by the professional(s)? Yes/ no

If yes: these guidelines are of international - national – local origin (please indicate)

(Please send a copy of the guideline(s) in attachment)

How is the contact with the 1st and/or 2nd line professionals organized during and/or after the treatment in the centre?

Please comment:

Are clinical information systems used to support services or planning? Yes/ no.

Are patient registers kept? Yes/ no.

1.4 Services:

Which services are provided by these special centres or teams or services for persons with CFS (more than one answer possible, please indicate):

- Diagnosis: not possible – possible – obligatory to be recognized as CFS patient
    - If the centre/ service uses a diagnostic protocol, please send a copy of the protocol in attachment
- Treatment by medication: not possible – limited period – no time limits
- Rehabilitation including counselling: not available– limited period – no time limits
- Educational sessions (e.g. information) for patient(s) or family: not available – available
- Specific program/ support to promote self-care (e.g. information, leaflets…): not available – available
- Occupational rehabilitation: not available – available
- Support to (re-)gain work: not available – available
- Support to obtain reimbursement(s), maintenance costs,…: not available – available
- Outreach/ visit to support local rehabilitation teams, health and social workers: not available – available
- Assessment or treatment delivered at home for severely (bedridden) affected persons: not available – available
- Support at home by telephone: not available – available
- 24h-telephone contact ("hotline"): not available – available

If rehabilitation and/or counselling is provided:

Can it be delivered individually: yes/ no

Can it be delivered in group: yes/ no

If group therapy is possible, how many participants on average by group (please specify):

Which criteria are used to start rehabilitation and/or counselling (e.g. duration, severity, distance to centre…)? Please specify:

Which criteria are used to stop rehabilitation and/or counselling? Please specify:

Are many patients leaving treatment/rehabilitation before these criteria are reached? (please estimate attrition rate):

Are there any conditions or constraints (legal or other) to start reimbursement of (part of the) treatment/ rehabilitation/counselling (e.g. duration, severity…)? yes/ no

If yes, please specify:

Is reimbursement (if available) limited in time?

If yes, please specify:

1.5 Rehabilitation content and evaluation:

The following therapies are provided in these centres/ services (if a treatment protocol exists, please send a copy in attachment):

	0= no 1=yes	Average frequency per week	Maximal duration (months)	Reimbursement possible (0= no; 1=yes)
CBT or cognitive behavioural therapy				
Psychotherapy, other theory or not specified				
Graded exercise therapy				
Physiotherapy, other background or not specified				
Pacing				
Occupational rehabilitation				
Program to promote self-care				
Treatment delivered at home				
Pharmacological treatments		XXX		
Alternative medicines or therapies (acupuncture, homeopathy), diets,…				
Other, specify:				

If rehabilitation and/or counselling is provided:

Are patient outcomes evaluated? Yes/ no (please indicate)

If yes, which evaluations/ instruments/ scales? Please specify:

(If reports on these evaluations exist, please send a copy in attachment)

1.7 Special Structure(s) or Service(s) for CFS in Children

So far, only special services for CFS in adults were considered.

Do specific centres/teams exist for children? Yes/ no

If yes, please comment:

1.8 Other comments (PART 1):

PART 2: Other services for CFS in Adults

Apart from the services mentioned above, delivered exclusively to CFS adult patients, OR if your country does not provide special services (in centres, by teams or individual professionals) exclusively to adult CFS patients:

In your country, are there services available that are open to patients with CFS, but not exclusively? Yes/ no (please indicate)

If yes, please complete the table below:

	Available (ambulatory or hospital) 0: no 1: scarcely 2: enough 3: abundantly	Specific conditions/ restraints on *participation* in therapy (e.g. severity, duration of illness) 0: no 1: yes	Specific conditions/ restraints on *duration* of therapy (e.g. severity, duration of illness) 0: no 1: yes	Reimbursement 0: no 1: yes, like other illnesses 2: especially for CFS (all patients) 3. especially for CFS (under certain conditions)
CBT or cognitive behavioural therapy				
Psychotherapy, other	XXX			
Graded exercise therapy				
Physiotherapy, other	XXX			
Pacing				
Occupational rehabilitation				
Programs promoting self-care				
Education sessions on CFS for patients or family				
Other, specify:				

Apart from these services open to adults with CFS and also to other patients, are there services *for children* that are open to CFS as well as for other patients? Yes/ no

If yes, please comment:

PART 3: Severely affected adults with CFS

Severely affected adults, that can't (re-)start work for a long time and are not able to support themselves, how are they provided for?

If severely affected adults in need of personal assistance in daily life don't have relatives to look after them, where/ how are they looked after?

PART 4: Other questions

Do you have estimated numbers on the prevalence of adult CFS in your country? Yes/no

If yes, please specify (if possible, indicate the time period over which this prevalence has been calculated: point all-over prevalence or long-term prevalence):

Do you know about any official documents on budgets spent on CFS patients? Yes/no

If yes, please indicate the reference

Remarks:

Thank you very much for your contribution!

6.3 APPENDIX 2B. INTERNATIONAL COMPARISON: LIST OF CONTACTED EXPERTS

UK

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Chairman of CSISG & Clinical Lead

Associate Dean for Cornwall

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4. the CFS Italian Association

(see Prof. Umberto Tirelli)

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2. On behalf of the Australian ME/CFS Group:
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Workforce Planner
Directorate of Workforce Planning and Management
Materiel People and Performance Branch
Defence Materiel Organisation
R2-6-C130
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Fax: 02 6265 2001

6.4 APPENDIX 3. INTERNATIONAL COMPARISON: UNITED KINGDOM (ENGLAND) - GENERAL INFORMATION

Information UK (see www.cfspod.net)

1. Services offered: Bath & Wiltshire CFS/ME Service

(Royal National Hospital for Rheumatic Diseases NHS Foundation Trust)

Upper Borough Walls, Bath BA1 1RL

This is the referral criteria for the Bath & Wiltshire CFS/ME Service, which is a local multidisciplinary service covering B&NES, South Wiltshire, Kennet & North Wiltshire and West Wiltshire PCTs, and working with an existing service based in Swindon. The team uses a hub and spoke model to ensure that the whole patch is covered effectively and has team members based in Bath, Salisbury and Swindon. Team members include 2 part-time Specialist Occupational Therapists/Service Leads, a part-time Referrals Coordinator/Administrator, 3 GP's with a specialist interest (GPSIs) and input from additional Occupational Therapists, Psychologist and Physiotherapist. The service is run on a part-time basis.

What the service offers:

- Multi-disciplinary assessment, domiciliary and outpatient.
- Consultation and advice in liaison with Primary Health Care Team.
- Direct clinical work (group or individual) at RNHRD, Community Location or home.
- Multi-component rehabilitation package for symptom management. Complex care management.

NB: We do not offer long-term counselling

We cover a large geographical area and 150 GP practices. Due to our limited staff resources, referrals may be prioritised. In some cases, we will be expecting to advise other professionals regarding care management rather than providing direct clinical input.

Services offered: LMDT service ESSEX

- Local GPs are supported and can use referral criteria to make a diagnosis. They are also provided advice on early management (generam report p 16)
- **The GP or referring doctor is willing to provide financially relevant report** *e.g. for disability allowance, which will not be provided by LMDT staff (Essex).*
- …

Services offered: Frenchay CFS/ME Service,

Ward 22, Frenchay Hospital

Frenchay Park Road, Bristol

Frenchay CFS/ME Service is a local multidisciplinary service covering Bristol North, Bristol South West, North Somerset, and South Gloucestershire PCT areas. The team consists of a specialist Clinical Psychologist, Occupational Therapist and Physiotherapist. We work on Tuesdays and Wednesdays only. Team leader: Consultant Clinical Psychologist

"(Refer to Appropriate Specialist if Diagnosis In Doubt)"

What the service offers

- · Multi-disciplinary assessment, domiciliary and outpatient.
- · Consultation and advice in liaison with Primary Health Care Team.

- · Direct clinical work (group or individual) at Frenchay Hospital.
- · Multi-component rehabilitation package for symptom management. Complex case management.

NB: we do not offer long-term counselling / support.

Due to our large catchment area and limited staff resources, we will prioritise referrals and can only accept those that meet our criteria. In some cases, we will be expecting to advise other professionals regarding case management rather than accepting the referral ourselves.

Services offered: Chronic Fatigue Syndrome Research and Treatment Unit, King's College, London

(Source: Trudie Chalder, PhD, Head of the Service, see list of contact persons)

Staff (each staff member 0.2 FTE): 2 clinical psychologists, 1 occupational therapist, 2 physiotherapists, 2 psychiatrists, 5 cognitive behavioural therapists, 1 researcher/data manager, 3 administrators. Additionally, assessment of referrals is done by other medical staff, not included in this list.

Services provided (2004-2005): 443 referrals; 246 patients accepted for treatment; 177 patients rejected for treatment (e.g. major depression,…); 80 patients not seen because of reimbursement refused by primary care trusts.

2. Care Pathway for severe CFS/ME Domiciliary service: Greater Manchester CNCC for CFS/ME:

- Patient housebound or predominantly bedbound:
- Preassesment Stage: team discussion on available information (diagnosis and symptom list, current daily activity, medical screening, GP report, minimal data set completion, carer questionnaire)
- If patient suitable for home rehabilitation: initial assessment by CFS/ME nurse specialist and clinical psychologist
- Team discussion and feed-back to referrer on recommendations and potential package of care from CNCC (working jointly with primary care)
- Management Stage: maximum of 5 home visits, minimum of 5 telephone appointments, input from CFS/ME and primary care team, referral to outside agencies as required.
- Review meeting with GP and recommendations for future care

3. Group program Manual: Leeds and West-Yorkshire CFS/ME service

9 weeks, 1 meeting/week

Manual available www.cfspod.net

4. Bristol-Bath CFS Children: GP Information Leaflet:

We have agreed a care pathway with the clinicians in the region based on guidelines from the patient group AYME* (*AYME is Association of Young People with M.E.) and RCPCH guidelines (published soon). According to these guidelines every young person with disabling fatigue needs early assessment and screening bloods following by referral to the local paediatrician for assessment. We anticipate that GP's will continue to manage young people with Mild CFS/ME but that children with Moderate to Severe CFS/ME would be managed by the managed clinical network. This will be the local paediatrician who can refer, if necessary, to the local clinical champion or the regional specialist team.

The regional team has weekly outpatient assessment clinics in either Bath or Bristol with a Paediatrician and Psychologist. This clinic provides an opportunity to make sure that the diagnosis of CFS/ME is correct and discuss different management plans.

Most young people with CFS/ME are being managed very well by their GP and local paediatric services. For children in the Bath/Bristol area there will be additional outpatient programmes which young people can access after assessment by the regional team. This will include Life Skills courses (to help young people deal with the secondary effects of CFS/ME) and graded activity courses to help young people get fit again.

Children who are bed bound may need therapist support, nutritional input or in some cases nursing input. The regional team can provide all of these skills in an assessment with local teams who would then provide ongoing management for these patients. If necessary, we would be happy to provide training for local nurses of therapists to help them manage these children at home.

5. Minimal Data Set (MDS) (www.cfspod.net)

The data has to be collected when the patient is first seen by the service and again (only once) between 9 and 15 months after the first assessment. Patients may be sent forms by mail to complete.

The following items are included:

- Demographic information - age, ethnicity, area of residence.
- Clinical information related to diagnosis
- Outcomes for adult service users: outcome measures on employment status; severity of symptoms; mood; pain severity; physical function; perceived improvement and goal attainment.
- Outcomes for children and young people: outcome measures on educational status including weekly hours of education or training; Chalder Fatigue Scale; Visual Analogue Scale; Clinical Global Improvement scale.

MDS facilitates service evaluation, improvement and benchmarking; it allows analyzing case mix and subgroups etc. The emphasis of MDS is on outcomes rather than on process (e.g. waiting lists); process data will be audited separately.

Registration started April, 2006; data are collected locally; the national process of central collection has not yet been finalized.

6. Self Care Programmes (source: Report 2004-2006 p 24-26)

Service users and carers can be faced with a variety of sources of self-help advice that can be both confusing and conflicting. A collaborative approach to developing material that is tailored to CFS/ME patients and their degree of disability would help fill this void, but is still non-existing. In the NHS, some general initiatives to support self care are available; other self-help groups are based on initiatives of patients themselves who meet or "chat" to offer each other practical and emotional support.

NHS Professional led Programme

Many services provide patients with a group programme manual or session handouts, to reinforce course content. Some programmes encourage specific homework or goal setting on course session themes while others encourage goal setting focused on the individual's own priorities.

Expert Patient Programme (EPP)

The Expert Patient Programme (EPP) was introduced into the NHS in 2001. The EPP is a generic lay-led group workshop. Tutors must have long-term health conditions themselves and undertake a three-day training programme and accreditation to deliver the course in pairs, from a scripted manual. The EPP is a licensed product; alternative programs exist and some are web-based.

6.5 APPENDIX 4. INTERNATIONAL COMPARISON: ST HELIER CFS/ME MODEL OF SERVICE (ENGLAND, UK)

(source: www.cfspod.net; Coordinators resource)

Concerns:

St Helier Hospital CNCC and Kingston and Sutton /St Helier LMDT for CFS/ME: Proposed Model of Service for Adults, October 2005.

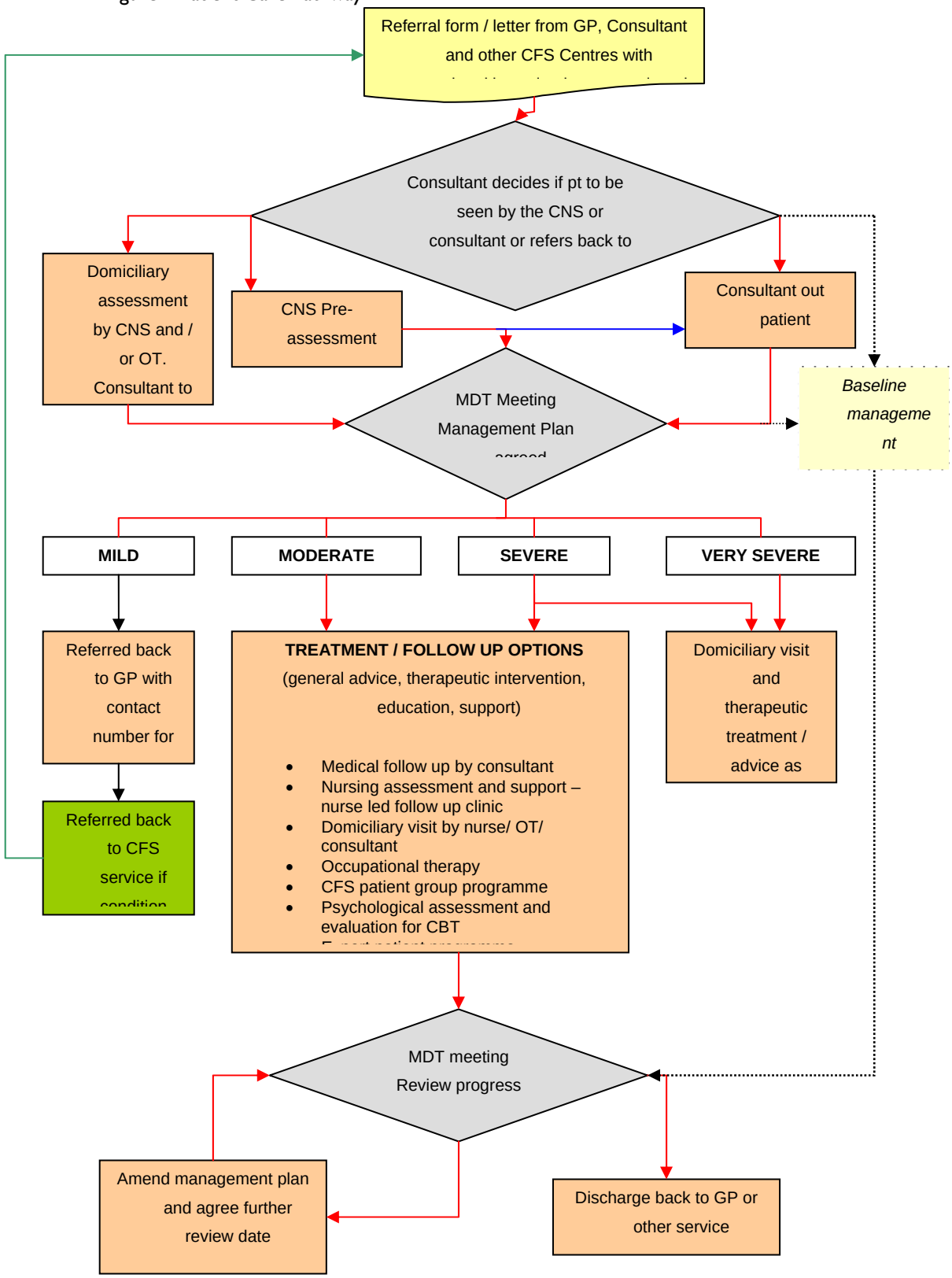
A. Clinical Members

Table 1 Proposed clinical members of the Local Multi-disciplinary Team and Roles

Title	Summary of Role	w.t.e. / sessions
Consultant in Clinical Immunology / Clinical Lead for CFS/ME Network	To triage initial referrals To diagnose CFS and exclude other causes of persistent fatigue To introduce concepts of different therapeutic strategies To initiate drug therapy if appropriate To refer to other members of the LMDT as appropriate To provide expert advice and support for complex cases To support and deliver education programmes to other professionals dealing with people with CFS/ME and other LMDTs	0.3
Clinical Psychologist	To provide a highly specialised psychological assessment for people with CFS/ME To provide evidence based therapeutic advice and interventions to individuals for a defined period of time agreed with the patient To participate in the development of and provide clinical psychology input to a group management programme To provide advice and consultation to other health professionals and clinical team members based on psychological principles and theories	1.0
Clinical Psychology Assistant (up to end March 2006)	Observing other therapeutic groups to inform the forthcoming CFS/ME group Researching and reviewing existing interventions, service models and evidence based practice and building a literature database / library for reference Actively participating in the CFS/ME programme	0.4
Clinical Nurse Specialist CFS/ME	To provide specialist advice and information to support people living with CFS/ME as well as their carers and families. To liaise with patient support groups To be the central point of contact for primary and secondary care clinicians seeking advice about CFS/ME and the service. To develop and run a pre-assessment clinic for people with mild to moderate CFS/ME. To participate in the development of and provide nursing input to a group management programme To provide domiciliary and in-patient services to patients with more severe cases of CFS/ME	2.0
Occupational Therapist	To provide a comprehensive assessment of needs for individuals referred with CFS/ME to formulate recommendations for specific therapies. To plan and implement patient centred individual or group strategies to achieve therapeutic goals and re-enable the patient in areas of self maintenance, productivity and leisure To participate in the development and delivery of a group management programme To provide a domiciliary and in-patient service for people with severe CFS/ME To provide support and advice to carers and relatives	1.0

B. Patient Care Pathway

Figure 1 Patient Care Pathway



B.1 Referral Process

The Consultant Immunologist (Clinical Lead of the network) will triage the referral (within 13 weeks) based on the information provided and decide whether the patient should initially be seen by a consultant or in the nurse led pre-assessment clinic.

The LMDT based at the SHCNCC will receive referrals from GPs within the local PCTs as well as the LMDTs that form part of the network. The service therefore needs to take this into account.

B.2 Consultant Assessment

The consultant will see all patients referred to the service with potentially complex CFS/ME and those under the age of 17 (18 if still in full time education) years.

An initial clinical evaluation of the patient's condition will be undertaken based on the information provided on the patient questionnaire, the results of the investigations and further discussion with the patient. This will help to confirm the diagnosis.

A draft management plan will then be formulated in partnership with the patient to be discussed with other members of the LMDT at the next MDT meeting.

For patients referred by other LMDTs, GPs or consultants within the clinical network, the consultant will assess the patient and liaise with the referrer and if necessary other specialists within the team

B.3 Nurse Led Pre-assessment Clinic

The nurse led pre-assessment clinic (2x/week held at Sutton) will enable patients with suspected mild, moderate or severe CFS/ME to be seen as soon as possible following referral to the service.

All referrals to the pre-assessment clinic will be from the consultant through the initial triage process.

The aim of the nurse led pre-assessment clinic is to:

- gather information about the patient's condition to be discussed at the MDT meeting to facilitate diagnosis, severity and management of the CFS/ME.
- provide a central point of contact to the service via the nurse for patients, carers and families
- provide patients and carers with information about CFS/ME and different management strategies
- provide information about other services available to meet the individual needs
- reduce waiting times
-

B.4 Domiciliary Service

For patients with very severe CFS/ME who are either bed bound or unable to leave their home, a domiciliary service will be developed. An assessment will be carried out in the patient's home by the Consultant, Clinical Nurse Specialist or Occupational Therapist and an individualised treatment plan formulated following discussion at the MDT meeting

B.5 Multi-disciplinary Team Meeting

A multi-disciplinary team meeting will be held on a fortnightly basis at Sutton Hospital.

The purpose of the MDT meeting is to:

- discuss:
  - all new patients to the service - seen by the consultant or the nurse in the pre-assessment clinic
  - new assessments undertaken by individual team members

- issues arising in relation to existing patients
- patients for review
- patients ready for discharge from the service

- agree a management plan which may include referral back to the GP or discharge from the service. A care planning proforma will be completed and attached to the front of the patient notes
- identify a key worker / care co-ordinator for each new patient

B.6 Grading and Management of Patients with CFS/ME

The severity of the illness will be confirmed at the MDT meeting and graded as:

- Mild
- Moderate
- Severe
- Very severe

B.6.1. Mild

Patients with mild CFS/ME will be referred back to the GPs to be managed in primary care with advice and support from relevant members of the LMDT.

B.6.2. Moderate and Severe

For patients with moderate to severe CFS/ME, the management plan discussed at the MDT meeting will be agreed with the patient. The letter to be sent to the GP with the proposed management plan will also be sent to the patient.

Either one or a combination of the following will be part of the management plan:

- Medical follow-up appointment with the consultant
- Psychological assessment and evaluation for cognitive behaviour therapy
- Occupational therapy assessment either at home or in the clinic
- Physiotherapy assessment
- Follow up nurse assessment either at home or in the nurse led follow up clinic to provide education and support and an individualised management plan
- CFS Group Management Programme

Each professional will work in accordance with the service framework for their own specialty.

All management strategies deployed by members of the team must be based on evidence of clinical effectiveness.

B.6.3. Very Severe

A domiciliary assessment will take place by the consultant immunologist, the clinical nurse specialist or the occupational therapist or jointly. A management plan will be developed in partnership with the patient

B.7 Clinical Psychology

B.7.1.Criteria for Referral to the Clinical Psychology Service

Patients accepted as suitable referrals to the Clinical Psychology Service need to meet the following criteria:

- Patients must be accepted as suitable referrals to the Epsom and St. Helier CNCC Chronic Fatigue Service.
- Patients must have attended either the Consultant Immunologist or Specialist CFS Nurse clinic at St. Helier prior to referral.

- The patient must agree to an initial assessment appointment with a Clinical Psychologist.
- Patients must have an initial understanding of their illness and be willing to consider a bio-psychosocial approach to their difficulties.
- Patients must not have current severe and enduring mental health problems such as psychosis and manic depression (refer to Liaison Psychiatry or local Community Mental Health Services).

B.7.2.Indications for Referral to the Clinical Psychology Service

Difficulties for a Psychological referral might include one or more of the following :

- Difficulties coming to terms with or coping with a recent diagnosis of CFS/ME.
- Unhelpful beliefs and assumptions about their CFS/ME.
- Symptoms that may be associated with depression or anxiety.
- Other mood disturbance such as anger or irritability.
- Obvious signs of stress or tension.
- Difficult family issues associated with their CFS/ME.
- Difficulties coping with work…

B.7.3. Clinical Psychology ServicePathway

All referrals to the Clinical Psychologist will be discussed at the fortnightly CFS/ME service MDT meeting. If appropriate they will be added to the Psychology waiting list.

Occasionally patients will be offered an early assessment (usually within 6 weeks) if they are considered to be in danger. Patients deemed to be at immediate risk (e.g. self harm) should be referred to either Liaison Psychiatry or their local Community Mental Health Services.

Patients may be offered individual appointments or a place on the group programme. The outcome of the assessment will communicated back to the referrer and the GP.

Drawing from the literature evidence base, patients receiving individual intervention will be offered up to 24 fortnightly sessions of 50 minutes duration. It is expected that the average will be 16 sessions, although some patients may require less. In some instances, patients may receive a small number of individual sessions before progressing to the group programme.

Both individual and group intervention will include follow-up sessions (1, 6 & 12 months for group; variable for individuals but expected to be approx. 3 month).

Following completion of the sessions patients will be discussed within the MDT meetings and either followed-up by another member of the team where appropriate, or discharged back to the care of the GP. A discharge report will be sent to both the referrer and the GP. Patients will routinely be sent a copy of their discharge report.

There are a number of scenarios in which a patient may be discharged before the intervention is complete. These would include:

- An unwillingness on the part of the patient to engage in a bio-psychosocial model of intervention.
- 2 consecutive DNAs following an initial assessment or cancellation of 3 appointments within the therapeutic contract.
- Little sign of change/progress even after a number of sessions.
- Abusive or aggressive behaviour.

<u>B.8 Nurse Led follow Up Clinic</u>

Until it is established, appointments will initially be for 30 minutes and the clinic will accommodate seven patients each week.

The aim of the nurse led follow up clinic is to:

- Support patients with varying CFS/ME severity in the management of their illness through:
  - Education on:
    - Psychological aspects of CFS/ME
    - De-conditioning and its consequences
    - Activity cycling
- Development of an individualised management plan that will include:
  - Pacing
  - Sleep Hygiene
  - Goal setting
- Evaluate the basis of any new symptom or deterioration in function
- Provide emotional support for the patient and their family /carers
- Identify barriers to treatment and discuss with other members of the MDT and refer on as necessary

B.9 CFS/ME Management Group

A weekly CFS/ME Management Group for patients with CFS/ME will be run jointly by the clinical psychologist, CFS Clinical Nurse Specialist and the Occupational Therapist.

B.10 Occupational Therapy

The patient may be offered training and advice on lifestyle changes and adaptations to their social and physical environment, addressing occupational performance and skill deficits, and enabling them in areas of self maintenance, productivity and leisure. Therapeutic interventions may be given on an individual or group basis as appropriate.

B.11 Discharge from the CFS/ME Service

CFS/ME is a long term condition and it is recognised that people with CFS/ME may need care and support over a long period of time. In order for the specialist CFS/ME service to have sufficient capacity to deal with new referrals, a formal discharge process will ensure that people are formally assessed for discharge, given a contact number for further support and advice and if necessary referred on to other support agencies.

The decision to discharge the patient from the CFS/ ME service will be agreed at the MDT. The discharge criteria for patients with CFS/ME are:

a. Improvement in the fatigue that allows return to work, school or previous levels activity.

b. Alternative diagnosis made on basis of clinical assessment and laboratory tests. Patient referred onwards for specialist management.

c. Stabilisation of the fatigue with level of functioning acceptable to the patient.

d. CFS/ME still variable but patient provided with full range of physical and mental strategies to cope with the illness. Patient discharged with support by the CFS/ME team and with the understanding that telephone advice can be provided.

e. Patient unable or chooses not to engage in treatments offered by the service

B.12 Paediatric to Adult Services

Close liaison between the paediatric team and the CFS/ME team will ensure a smooth transition of care for young people from paediatric to adult services. Planning for the transition should start several months before the transfer takes place.

All young people with CSF/ME approaching the period of transition will be discussed individually at the LMDT meeting and will be given the opportunity to meet members of the LMDT at the appropriate clinic prior to the transfer taking place. Key members of staff involved in the care of the young adult will be invited to the LMDT meeting to discuss their specific needs.

C. Calculation of New Patient Capacity

C.1 Prevalence (see Table 2)

The prevalence of CFS/ME amongst adults is between 0.2% and 0.4% - a reasonable estimate of adult population prevalence of CFS/ME is 0.4%, about half of whom will need input from the services. Approximately 25% of those needing input are severely affected by the disease and may be house bound or bed bound.

For children and adolescents, two studies suggest that the prevalence is about 0.07% although information is scanty

It has been estimated by the lead consultant for the CFS/ME Service that approximately 20% (a year) of all those with CFS/ME at any one time will be eligible to be seen by the CFS/ME service as new patients. Taking the number of people with CFS/ME needing the service as 2948, there will be a potential demand of **589** patients entering the service over a period of 12 months.

Table 2 PCT Populations and prevalence of CFS/ME

Primary Care Trust	**Total Population – all ages (taken from the PCT websites)**	**Prevalence – all ages Estimated range of no. of people with CFS/ME**		**No of patients needing the service = 50%**	**No of patients severely affected - either bed bound or house bound**
South West London SHA		0.2 %	0.4%	(based on a prevalence of 0.4%)	(based on estimate of 25% of no of patients needing the service)
Wandsworth	269,300	540	1077	540	135
Kingston	180,000	360	720	360	90
Richmond and Twickenham	200,000	400	800	400	100
Sutton and Merton	390,000	780	1560	780	195
Surrey and Sussex SHA					
East Elmbridge and Mid Surrey	275,000	550	1100	550	138
East Surrey	159,000	318	636	318	80
Total	**1,473,300**	**2948**	**5893**	**2948**	**738**

C.2 New Patient Capacity (see Table 3)

Table 3 below shows the potential capacity for new patients based on an additional nurse being recruited to the team.

Table 3 New Patient Capacity

Type of Clinic	**No of new patient appointments / slots per week**	**Potential capacity over a 12 month period based on 43 clinics (this takes into account any leave or absence)**
Consultant X one clinic a week	4	172
Nurse pre-assessment (based on 2.00 wte nurses) X 3 clinics a week	9	387
Total	13	559

The service would have the capacity to see 559 new patients each year which is 30 less patients than the estimated demand of 589.

N.B. These estimated numbers do not take into account a "Did Not Attend" factor.

C.3 Follow Up Capacity

The current referral rate to other professionals within the team is unknown as there is insufficient data and the service is in a stage of development. It is known however that there is currently a large waiting list for clinical psychology.

D. Governance

The CFS/ME service must be underpinned by a clinical governance framework in line with NHS Trust policies to ensure that all aspects of service provision are evidence based, safe, cost effective and beneficial to patients.

The framework will consist of the following elements:

- Clinical Audit – a programme of planned clinical audits over a 12 month period with clear outcome measures that can demonstrate the effectiveness of the service and benefits to patients
- Involvement of service users using a number of different methods including:
  - Patient questionnaires
  - Presentations and discussions with ME Self Help Groups
  - Patient forums / groups
  - Patient interviews
  - Patient shadowing
- Patient information – patient leaflets about the CFS/ME service and the individual treatments / therapeutic interventions will be made available to service users and carers.
- Education, Training and Continuous Professional Development –This will include amongst others:
  - An appraisal system
  - the development of personal development plans based on identified needs
  - a team training and development plan
- Research – a research programme will be developed in conjunction with other teams within the network. The development of a comprehensive data base will enable patients progress in relation to different treatment modalities to be tracked

Any other aspects of governance such as complaints handing, adverse incident reporting, probity, financial management and health and safety will be dealt with in accordance with Trust policy.

E. St Helier Hospital Clinical Network Co-ordinating centre

There are two other LMDTs within the St Helier Hospital Clinical Network, one (the Woking CFS/ME Team) has been outlined as follows:

Surrey Heath and Woking PCT currently have a Service Level Agreement with private practitioners to provide a service for people with CFS//ME. The team comprises:

- An occupational therapist
- A physiotherapist
- A clinical psychologist supported by a Consultant in Rehabilitation Medicine based at Woking Community Hospital.

F. Definition Mild-Moderate-Severe-Very Severe Cases (St Helier Model of Care)

Included in:

Referral Form (250905): Epsom and St Helier University Hospitals NHS Trust CFS CNCC

(Author: Dr Amolak Bansal, Consultant Immunologist, Immunology Department, St Helier Hospital, Wrythe Lane, Carshalton, Surrey SM5 1AA (UK))

Sutton and Kingston - St Helier Hospital CFS/ME Service

Referral Form

Date of referral ……

Patient's Name..…….. DOB…….. Occupation…….…. ….

NHS Number ……..

Patient's GP Name Address of surgery Practice Code

Name of referring GP (if different)

Onset of Fatigue: Acute or Gradual onset Viral symptoms

Brief history of Fatigue:

Criteria for Diagnosis – of six months or more **please tick**

Debilitating persistent or relapsing fatigue for at least 6 months - not life-long	
Not the result of ongoing exertion and not substantially alleviated by rest	
Severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities.	
At least 4 of the following symptoms persisted or recurred during 6 or more consecutive months of illness and did not predate the fatigue: • impaired memory or concentration; • sore throat, tender lymph nodes(symptom); • muscle pain' pain in several joints without swelling or redness; • headaches – new or different from previous headaches • non-refreshing sleep; • feeling ill after exertion.	
No clinical evidence of other causes of fatigue: 1) organ failure (eg. emphysema, cirrhosis, cardiac failure, chronic renal failure); 2) chronic infections; 3) rheumatic and chronic inflammatory diseases; 4) major neurological diseases; 5) systemic treatment for neoplasms; 6) untreated endocrine disease; 7) primary sleep disorders; 8) obesity (BMI>40); 9) alcohol/substance abuse; 10) reversible causes of fatigue such as medications, infections or recent major surgery; 11) psychiatric conditions (eg melancholic depression, bipolar disorder, psychoses, eating disorder	

Routine investigations do not suggest a cause for fatigue: FBC, ESR, U & E, LFTs, calcium, phosphate, random glucose, thyroid function, coeliac serology [endomysial abs or TTG], urinalysis.	

Severity of Fatigue: Mild □ Moderate □ Severe □ Very Severe □

Mild	Mobile, self-caring, light domestic duties, may be working but to detriment of social, family and leisure activities.
Moderate	Reduced mobility, not working, reduced ADL, sleeping in daytime, peaks and troughs of activity.
Severe	Few ADL, severe cognitive difficulties, wheelchair dependent for mobility, rarely leave house, often significant worsening of symptoms with any mental or physical exertion
Very severe	No ADL, bed-bound most of time, unable to tolerate any noise & are light sensitive, require someone else to wash toilet and feed them.

Other information (please complete or attach summaries / reports of relevant past medical history)

Past Medical History / other physical problems

Past Psychiatric History

Patient's present ability
Work, housework, walking, cooking, self care, leisure activities
Family History

Present Medication (please attach printout) Known Allergies

Investigation Protocol

Blood tests to be carried out prior to referral – please tick and attach results with form

FBC	Hb	WBC	Platelets	ESR
AANT	ANA	GPC	AMA	SMA
Ig's	IgG	IgM	IgA	IMEP
CRP	TSH	U/E	LFT	
Anti-EM abs	Positive/Negative			
ANA	Positive/Negative	Pattern	Level	

Please send / fax this referral form to:
Dr Amolak Bansal, Consultant Immunologist, Immunology Department, St Helier Hospital, Wrythe Lane, Carshalton, Surrey SM5 1AA
Fax: 020 8641 9193

6.6 APPENDIX 5. INTERNATIONAL COMPARISON: TREATMENT MANUAL (CFS RESEARCH AND TREATMENT UNIT OF KING'S COLLEGE)

Reference: Cognitive Behavior Therapy for Chronic Fatigue Syndrome:

A Randomized Controlled Trial. Alicia Deale, Trudie Chalder, Isaac Marks, and Simon Wessely. Am J Psychiatry 1997; 154:408–414.

All patients were seen individually, at weekly or fortnightly intervals. Information leaflets supplemented each phase of treatment. Each session began with a homework review and ended with agreement on homework tasks, which were recorded in daily diaries. The therapist followed detailed session-by-session treatment manuals devised for cognitive behavior therapy. The research met fortnightly to review cases and ensure protocol adherence.

Cognitive behavior therapy. This treatment was collaborative, educative, and negotiated and had a behavioral emphasis. The aim was to show patients that activity could be increased steadily and safely without exacerbating symptoms. Sessions 1 to 3 involved engaging the patients in therapy and offering a detailed treatment rationale. Presenting problems were assessed, and patients kept diaries recording hourly details of activity, rest, and fatigue. At session 4 a schedule of planned, consistent, graded activity and rest was agreed on. The initial targets were modest and small enough to be sustained despite fluctuations in symptoms. Rather than being symptom dependent, activity and rest were divided into small, manageable portions spread across the day (for example, three 5-minute walks daily rather than a 45-minute walk once a week). Patients were encouraged to persevere with their targets and not to reduce them on a bad day or exceed them on a good day. Once a structured schedule was established, activity was gradually increased and rest was reduced, step by step as tolerance developed. Therapist and patient agreed on specific daily targets covering a range of activities (such as walking, reading, visiting friends, or gardening). A sleep routine was established—for example, stopping daytime sleep, rising at a specific time each morning, reducing time in bed, and using stimulus control techniques for insomnia. Cognitive strategies were introduced at session 8 (while the graded activity program continued). Patients recorded any unhelpful or distressing thoughts and, in discussion and as homework, practiced generating alternatives. The unhelpful or distressing thoughts included fears about symptoms and treatment, perfectionism, selfcriticism, guilt, and performance expectations. In the final sessions, strategies for dealing with setbacks were rehearsed and patients drew up "action plans" to guide them through the coming months. The importance of maintaining the principles of therapy after discharge was reinforced.

7 REFERENCES

1. Bagnall A-M, Hempel S, Chambers D, Orton V, Forbes C. The treatment and management of chronic fatigue syndrome (CFS)/ myalgic encephalomyelitis (ME) in adults and children. York: University of York 2007. CRD Report 35 (CRD Report 35)
2. Reid S, Chalder T, Cleare A, Hotopf M, Wessely S. Chronic Fatigue Syndrome Clin Evid. 2007(12):1578-93.
3. Cho HJ, Hotopf M, Wessely S. The placebo response in the treatment of chronic fatigue syndrome: a systematic review and meta-analysis. Psychosom Med. 2005;67(2):301-13.
4. Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med (Oxf). 2005;55(1):20-31.
5. Blockmans D, Persoons P, Van Houdenhove B, Bobbaers H. Does methylphenidate reduce the symptoms of chronic fatigue syndrome? Am J Med. 2006;119(2):167.e23-30.
6. McDermott C, Richards SCM, Thomas PW, Montgomery J, Lewith G. A placebo-controlled, double-blind, randomized controlled trial of a natural killer cell stimulant (BioBran MGN-3) in chronic fatigue syndrome. QJM. 2006;99(7):461-8.
7. O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A. Cognitive behavioural therapy in chronic fatigue syndrome: A ramdomised controlled trial of an outpatient group programme. Health Technology Assessment. 2006;10(37):iii-51.
8. Al-Haggar MS, Al-Naggar ZA, Abdel-Salam MA. Biofeedback and cognitive behavioral therapy for Egyptian adolescents suffering from chronic fatigue syndrome. Journal of Pediatric Neurology. Vol. 2006;4(3):161-9.
9. The GKH, Bleijenberg G, van der Meer JWM. The effect of acclydine in chronic fatigue syndrome: A randomized controlled trial. PLoS Clinical Trials. 2007;2(5).
10. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest. 2006;129(1):174-81.
11. Malouff J, Thorsteinsson E, SE R, Bhullar N, Schutte N. Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: A meta-analysis. Clinical Psychology Review. 2007.
12. Knoop H, Prins JB, Stulemeijer M, van der Meer JWM, Bleijenberg G. The effect of cognitive behaviour therapy for chronic fatigue syndrome on self-reported cognitive impairments and neuropsychological test performance. J Neurol Neurosurg Psychiatry. 2007;78(4):434-6.
13. Prins J, Bleijenberg G, Rouweler EK, van der Meer J. Effect of psychiatric disorders on outcome of cognitive-behavioural therapy for chronic fatigue syndrome. British Journal of Psychiatry. 2005;187:184-5.
14. Quarmby L, Rimes KA, Deale A, Wessely S, Chalder T. Cognitive-behaviour therapy for chronic fatigue syndrome: Comparison of outcomes within and outside the confines of a randomised controlled trial. Behaviour Research and Therapy. Vol. 2007;45(6):1085-94.
15. Edmonds M, McGuire H, Price J. Exercise therapy for chronic fatigue syndrome. Cochrane Database of Systematic Reviews. 2004;3(3):CD003200.
16. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial.[see comment][erratum appears in BMJ. 2005 Apr 9;330(7495):820]. BMJ. 2005;330(7481):14.
17. Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, Komaroff A, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med. 1994;121:953-9.
18. Ridsdale L, Darbishire L, Seed PT. Is graded exercise better than cognitive behaviour therapy for fatigue? A UK randomized trial in primary care. Psychol Med. 2004;34(1):37-49.

19. Wearden AJ, Morriss RK, Mullis R, Strickland PL, Pearson DJ, Appleby L, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. Br J Psychiatry. 1998;178:485-92.

20. Ridsdale L, Godfrey E, Chalder T, Seed P, King M, Wallace P, et al. Chronic fatigue in general practice: is counselling as good as cognitive behaviour therapy? A UK randomised trial. Br J Gen Pract. 2001;51:19-24.

21. Raine R, Haines A, Sensky T, Hutchings A, Larkin K, Black N. Systematic review of mental health interventions for patients with common somatic symptoms: can research evidence from secondary care be extrapolated to primary care? BMJ. 2002;325(7372):1082.

22. Tsai AC, Morton SC, Mangione CM, Keeler EB. A meta-analysis of interventions to improve care for chronic illnesses. Am J Manag Care. 2005;11(8):478-88.

23. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Aff (Millwood). 2001;20(6):64-78.

24. Wagner EH, Davis C, Schaefer J, Von Korff M, Austin B. A survey of leading chronic disease management programs: are they consistent with the literature? Manag Care Q. 1999;7(3):56-66.

25. Bodenheimer T. Interventions to improve chronic illness care: evaluating their effectiveness. Dis Manag. 2003;6(2):63-71.

26. Nutting PA, Dickinson WP, Dickinson LM, Nelson CC, King DK, Crabtree BF, et al. Use of chronic care model elements is associated with higher-quality care for diabetes. Ann Fam Med. 2007;5(1):14-20.

27. Adams SG, Smith PK, Allan PF, Anzueto A, Pugh JA, Cornell JE. Systematic review of the chronic care model in chronic obstructive pulmonary disease prevention and management. Arch Intern Med. 2007;167(6):551-61.

28. Dorr DA, Wilcox A, Burns L, Brunker CP, Narus SP, Clayton PD. Implementing a multidisease chronic care model in primary care using people and technology. Dis Manag. 2006;9(1):1-15.

29. Vargas RB, Mangione CM, Asch S, Keesey J, Rosen M, Schonlau M, et al. Can a chronic care model collaborative reduce heart disease risk in patients with diabetes? J Gen Intern Med. 2007;22(2):215-22.

30. Daniel DM, Norman J, Davis C, Lee H, Hindmarsh MF, McCulloch DK, et al. A state-level application of the chronic illness breakthrough series: results from two collaboratives on diabetes in Washington State. Jt Comm J Qual Saf. 2004;30(2):69-79.

31. Epping-Jordan JE, Pruitt SD, Bengoa R, Wagner EH. Improving the quality of health care for chronic conditions. Qual Saf Health Care. 2004;13(4):299-305.

32. Glasgow RE, Wagner EH, Schaefer J, Mahoney LD, Reid RJ, Greene SM. Development and validation of the Patient Assessment of Chronic Illness Care (PACIC). Med Care. 2005;43(5):436-44.

33. Ofman JJ, Badamgarav E, Henning JM, Knight K, Gano AD, Jr., Levan RK, et al. Does disease management improve clinical and economic outcomes in patients with chronic diseases? A systematic review. Am J Med. 2004;117(3):182-92.

34. Solberg LI, Crain AL, Sperl-Hillen JM, Hroscikoski MC, Engebretson KI, O'Connor PJ. Care quality and implementation of the chronic care model: a quantitative study. Ann Fam Med. 2006;4(4):310-6.

35. Wellingham J, Tracey J, Rea H, Gribben B. The development and implementation of the Chronic Care Management Programme in Counties Manukau. N Z Med J. 2003;116(1169):U327.

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