



# Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): Results of a systematic review

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## Objectives

To identify effective interventions in the treatment, management and rehabilitation of adults and children diagnosed with CFS/ME.

## Design

A systematic review with exhaustive literature searches was carried out to enable a transparent synthesis of the available empirical evidence. Studies with experimental and quasi-experimental designs, such as randomised controlled trials (RCTs) and studies with control groups, of any intervention or combination of interventions were eligible for inclusion in the review. Study participants could be adults or children with a diagnosis based on any existing CFS/ME case definition criteria. All treatment effects based on between-group comparisons were considered.

## Methods

Eleven electronic databases were searched; additionally, reference lists of included studies, reviews and textbooks, and submissions of stakeholders in the guideline development process of the National Institute for Health and Clinical Excellence (NICE) were screened. Two reviewers independently assessed titles and abstracts of articles, and full text papers subsequently ordered, for possible inclusion. The standardised data extraction and study quality assessment was performed by one reviewer and checked by another to reduce errors and bias. The results of the individual studies are synthesised in table 1.

## Results

Seventy studies met inclusion criteria. Studies on behavioural, immunological, pharmacological, complementary, nutritional supplements and miscellaneous interventions were identified. Graded Exercise Therapy and Cognitive Behaviour Therapy (CBT) appeared to reduce symptoms. For many other interventions, the evidence of effectiveness was inconclusive, results were in need of replication or the treatment was associated with substantial adverse effects. Very little is known about treatment for children and severely affected patients.

## Conclusions

Graded Exercise Therapy and CBT have shown promising results in reducing the symptoms of CFS/ME. There is a need for research to define the characteristics of patients who would benefit from specific interventions.

## Disclaimer

The expressed views are those of the authors and not necessarily those of NICE.

## Right: Table 1: Summary of included studies

Notes: Controlled studies are shaded, all other studies are RCTs. + indicates a positive effect of treatment; - indicates a negative effect of treatment; <> indicates no effect of treatment; rehab = rehabilitation; DLE = dialyzable leukocyte extract; \*Essential fatty acids (both studies) = 36mg gamma-linoleic acid (GLA), 17mg eicosapentaenoic acid (EPA), 11mg docosahexanoic acid (DHA), 255mg linoleic acid (LA), plus 10 IU vitamin E; fl.-hydr. = fludrocortisone; top. = topical; \$Acetyl-L-Carnitine and Propionyl-L-Carnitine. Outcome codes: PH = physical; PS = psychological; LAB = laboratory and physiological; QOL = quality of life and general health. Outcomes which showed a significant difference between intervention and control groups are highlighted in bold.

Intervention	N	Outcomes investigated	Any effect	Overall effect	Validity score (max. 20)
<b>BEHAVIOURAL</b>					
CBT (Deale 1997)	60	<b>PH; PS; QOL</b>	+	+	18
CBT (Prins 2001)	270	<b>PH; PS; QOL</b>	+	+	16
CBT (Sharpe 1996)	60	<b>PH; PS; QOL</b>	+	+	15
CBT (Stulemeijer 2005)	69	<b>PH; QOL</b>	+	+	16
CBT + DLE (Lloyd 1993)	90	<b>PH; PS; LAB; QOL</b>	+	<>	13
Rehab (Taylor 2004)	47	<b>PH; QOL</b>	+	+	9
CBT/Rehab (Cox 1999)	130	<b>PH; PS; QOL</b>	+	+	8
CBT/Rehab (Cox 2002)	97	<b>PH; PS; QOL</b>	+	<>	7
CBT (Whitehead 2002)	65	<b>PH; PS; QOL</b>	<>	<>	3
CBT/Rehab (Viner 2004)	56	<b>PH; QOL</b>	+	<>	2
CBT (Friedberg 1994)	44	<b>PH; PS; QOL</b>	<>	<>	1
GET & Fluoxetine (Wearden 1998)	136	<b>PH; PS; QOL</b>	+	<>	17
GET (Fulcher 1997)	66	<b>PH; PS; LAB; QOL</b>	+	+	17
GET (Powell 2001; 2004)	148	<b>PH; PS; QOL</b>	+	+	17
GET (Wallman 2004)	61	<b>PS; PH; LAB</b>	+	+	9
GET (Moss-Morris 2005)	49	<b>PH</b>	+	+	9
<b>IMMUNOLOGICAL</b>					
Immunoglobulin (Rowe 1997)	71	<b>PH</b>	+	+	16
Immunoglobulin (Peterson 1990)	30	<b>PH; LAB; QOL</b>	<>	<>	15
Immunoglobulin (Lloyd 1990)	49	<b>PS; QOL</b>	+	<>	13
Immunoglobulin (Vollmer-Conna 1997)	99	<b>PH; PS; LAB; QOL</b>	<>	<>	13
Staphylococcus toxoid (Zachrisson 2002)	98	<b>PH</b>	+	+	14
Staphylococcus toxoid (Andersson 1998)	28	<b>PS; QOL</b>	+	<>	9
Alpha interferon (See 1996)	30	<b>LAB; QOL</b>	+	<>	11
Interferon (Brook 1993)	20	<b>PH</b>	<>	<>	6
Acyclovir (Straus 1988)	27	<b>PH; PS; LAB; QOL</b>	-	<>	15
Ampligen (Strayer 1994)	92	<b>RU; PH; PS</b>	+	+	12
Terfenadine (Steinberg 1996)	30	<b>PH; QOL</b>	<>	<>	12
Gancyclovir (Lerner 2001)	11	<b>PH</b>	<>	<>	4
Inosine pranobex (Diaz-Mitoma 2003)	16	<b>PH; LAB; QOL</b>	+	<>	6
<b>PHARMACOLOGICAL</b>					
Hydrocortisone (Cleare 1999)	32	<b>PH; QOL</b>	+	<>	18
Hydrocortisone (McKenzie 1998)	70	<b>PH; PS; QOL</b>	<>	<>	14
Hydrocortisone (Cleare 2002)	120	<b>PH; LAB</b>	+	<>	2
Hydrocortisone & fl.-hydr. (Blockmans 2003)	80	<b>PH; PS; LAB; QOL</b>	<>	<>	14
Fludrocortisone (Rowe 2001)	100	<b>PH; PS; LAB; QOL</b>	<>	<>	18
Fludrocortisone (Peterson 1998)	25	<b>PH; PS; QOL</b>	<>	<>	16
Top. nasal corticosteroids (Kakumanu 2001)	28	<b>PH</b>	<>	<>	3
Moclobemide (Hickie 2000)	90	<b>PH; PS; LAB; QOL</b>	<>	<>	19
Fluoxetine (Vercoulen 1996)	107	<b>PH; PS; QOL</b>	<>	<>	12
Selegiline (Natelson 1998)	25	<b>PH; PS; QOL</b>	+	<>	11
Galantamine hydrobromide (Blacker 2004)	434	<b>PH; PS</b>	<>	<>	15
Galantamine hydrobrom. (Snorrason 1996)	49	<b>PH; PS; QOL</b>	<>	<>	9
Oral NADH (Forsyth 1999)	26	<b>QOL</b>	+	+	12
Oral NADH (Santaella 2004)	20	<b>PH</b>	<>	<>	3
Clonidine (Morriss 2002)	10	<b>PS</b>	<>	<>	12
Phenelzine (Natelson 1996)	24	<b>PH; PS; QOL</b>	<>	<>	10
Sulbutiamine (Tiev 1999)	326	<b>PH; QOL</b>	<>	<>	10
Dexamphetamine (Olson 2003)	20	<b>PH; QOL</b>	+	<>	8
Growth hormone (Moorkens 1998)	20	<b>PH</b>	<>	<>	5
Melatonin (Williams 2002)	30	<b>PH; PS</b>	+	+	5
<b>COMPLEMENTARY/ ALTERNATIVE</b>					
Homeopathy (Weatherley-Jones 2004)	103	<b>PH</b>	+	<>	17
Any homeopathic remedy (Awdry 1996)	64	<b>QOL</b>	<>	<>	6
Massage therapy (Field 1997)	20	<b>PH; PS; LAB</b>	+	+	9
Osteopathy (Perrin 1998)	58	<b>PH; PS; QOL</b>	<>	<>	0
<b>SUPPLEMENTS</b>					
General supplements (Brouwers 2002)	53	<b>PH</b>	<>	<>	10
General supplements (Martin 1994)	42	<b>PH; QOL</b>	<>	<>	10
General supplements (Stewart 1987)	12	<b>PH</b>	<>	<>	6
Essential fatty acids* (Behan 1990)	63	<b>LAB; QOL</b>	+	+	17
Essential fatty acids* (Warren 1999)	50	<b>PS; QOL</b>	<>	<>	16
Magnesium (Cox 1991)	34	<b>PH; PS; LAB; QOL</b>	+	+	15
Liver extract (Kaslow 1989)	15	<b>PH; PS; QOL</b>	<>	<>	10
Carnitine\$ (Vermeulen 2004)	90	<b>PH; PS</b>	+	+	10
Pollen extract (Ockerman 2000)	22	<b>PH; PS; QOL; LAB</b>	<>	<>	9
Acclodyne & amino acids (De Becker 2001)	90	<b>PH; LAB</b>	+	<>	3
Medicinal mushrooms (Rothschild 2002)	70	<b>PH</b>	<>	<>	3
<b>OTHER</b>					
Combination (Teitelbaum 2001)	72	<b>PH</b>	+	+	19
Combination (Marlin 1998)	71	<b>QOL</b>	<>	<>	3
Combination (Goudsmit 1996)	52	<b>PS; QOL</b>	+	<>	2
Low sugar low yeast diet (Hobday unpubl.)	57	<b>PH; PS</b>	<>	<>	11
Buddy/ mentor (Schlaes 1996)	12	<b>PH; PS; QOL</b>	+	<>	4
Group therapy (Söderberg 2001)	14	<b>PH; QOL</b>	<>	<>	1