Table 4.1 Effect of treatments on persons diagnosed according to the Canada criteria or ICC.

Author, year, country	Setting, intervention and comparison Diagnosis criteria	Participants	Outcome	Results
Montoya 2013 [63] USA	Research Clinic I1: Valganciclovir, for 6 months I2: Placebo, for 6 months CDC criteria + suspected infection triggered + elevated antibody titres against HHV-6 or EBV-A or EBV-B	**I1:** N = 20 (75% female) Mean Age: 50.18 (10.20) Duration disease: 12.7 (10.02) Proportion with PEM: 95% **I2:** N = 10 (50% female) Mean Age: 48.47 (12.75) years Duration disease: 13.53 (7.82) Proportion with PEM: 100 %	MFI-20 Fatigue self-assessed With FSS	Change in MFI-20 after 9 months (mean) I1: -6.15 (SD 12.06) I2: -1.10 (SD 5.90) ns Change in MFI after 9 months (values from graph) I1: -0.4 I2: 0.2 P = 0.006
Nilsson 2017 [64] Sweden	A CFS clinic I1: A drug candidate (-), -OSU6162 that had shown positive effects on fatigue after stroke. 15 x 2 mg/day for 1 week and 30 mg x 2 mg/ day for 1 week I2: Placebo ICC criteria	Not consecutive recruitment **I1:** N = 31 (84% females) Mean Age: 47.9 (9.8) Duration symptom: 9.5 (9.9) years **I2:** N = 31 (85% female) Mean Age: 45.3 (13.6) Duration symptom: 7.2 (10.0)	Fatigue self-rated with MFS Percentage of improvement (including slight improvement) estimated by clinicians using CGI -C (Likert scale 1-7)	Change in MFS after 2 weeks I1: [-4.05] (-6.11 to -2.00) I2: [-4.11] (-6.20 to -2.03) ns Proportion improved after 2 weeks I1: 55% I2: 63% ns After a further 4 weeks, the values had returned to the baseline

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Table 4.1 continued

Author, year, country	Setting, intervention and comparison Diagnosis criteria	Participants	Outcome	Results
Pinxsterhus 2017 [65] Norway	Research Clinic I1: A manual based self-help program for group treatment, based on theories of self-efficacy and Energy Envelope Theory. The program was led by an advisor with CFS. The programme involved eight meetings, 2,5 hours, every two weeks and one session for relatives. I2: Waiting list and usual treatment The Canada criteria or the CDC criteria	Recruitment from healthcare and patient organisations in six municipalities **I1:** N = 71 (94% female) Mean Age: 44.0 (11.8) years. Amount in work/studies: 5 **I2:** N = 66 (82% female) Mean Age: 43,8 (11,6) years. Amount in work/studies: 8 Significant difference between the groups regarding sex Loss of follow-up after one year: 13.9 %	Physical function self-rated with SF-36, PF (0-100 points) Fatigue self-rated with FSS (9–63 points)	Change in SF-36 after 6 months (mean) I1: [0.6] (-2.9 to 4.0) I2: [4.3] (-0.4 to 8.9) ns Change in FSS after 6 months (mean) I1: [-0.2] (-1.7 to 1.3) I2: [-2.7] (-4.7 to -0.7) P = 0.039 At follow-up 6 months later, the values had returned to the baseline
Witham 2015 [66] Scotland	Research Clinic I1: 100 000 units of vitamin D3 every two months, three times I2: Placebo, every two months, three times CDC and Canada criteria and low levels of 25g hydroxy Vitamin D (< 75 nmol/l)	Job Advertisement Recruitment **I1:** N = 25 (72% female) Mean Age: 48.1 (12.0) **I2:** N = 25 (80% female) Mean Age: 50.7 (13.1)	The study investigated mainly effects on vessels Fatigue self-assessed with Piper Fatigue scale	No differences between groups with respect to fatigue

CGI- C = Clinical Global impression of change; **EBV** = Epstein Barr virus; **FSS** = Fatigue Severity scale; **HHV-6** = Human herpes virus; **I=** Intervention; **ICC** = International consensus criteria; **MFI-20** = Multidimensional Fatigue Inventory items; **MFS** = mental Fatigue scale; **ns** = not significant; **SF-36 PF** = Medical Outcomes Study-short form -36 physical function subscale; **PEM** = Post-exertional malaise

Table 5.1 Recovery, function and ability to work in long-term follow-up.

Author, year, country	Diagnostic criteria	Study Design setting	Participants	Outcome*, Measurement method/ Analysis method	Results
Andersen et al. 2004 [119] Denmark	Holmes 1988 & CDC 1994	Longitudinal with 0 (T0) and 5-year (T1) measurement Infection clinic	N = 35 (28 female) Age: On average 41 (25– 56) Drop-out: 2 out of 35.	Self-reported work ability, and activity ability and health	Percentage not working: T0: 77% (17% still employment) T1: 91% (no one worked full-time or had regular employment) Proportion of improved health compared to measurement 1: 15 % Proportion of impaired health compared to measurement 1: 40 %
Brown et al. 2012 [120] Brown et al. 2014[37] USA	Bell & Bell 1988	Follow-up after 25 years of patients with CFS-like illness as adolescents	N = 25 (68.5% female) previously diagnosed with CFS N= 10 healthy controls Age: (Mean age 39.7) Proportion in work: 71.4% full-time, 11.4% part-time Proportion in sickness pension: 11.4% full, 5.7% partial	Self-reported current diagnosis SFFI5436 and other self-assessment forms	Still CFS N = 5 (20%) Significantly worse than controls on all subscales except Mental Health Even those who thought of themselves as being recovered, had significant worse function than the control group

Table 5.1 continued

Author, year, country	Diagnostic criteria	Study Design setting	Participants	Outcome*, Measurement method/ Analysis method	Results
Jason et al. 2011 [118] USA	CDC criteria + SCID-I interview + consensus discussion	10 years of follow-up to Patients diagnosed with CFS; 12 people could not be reached	N = 24 (79.2% female) Age: (Mean age 40 years	Clinical assessment	Proportion that still met diagnostic criteria: 67 %. Proportion in remission (i.e. not fatigue in the last 6 months): 1-24.
Huibers et al. 2004 [114] Netherlands	Severe fatigue (CIS score >35) 44% of the population met the CDC criteria	12m follow-up Of patients who had participated in RCT on CBT-treatment	N = 151 on sick leave (55% women) in the group that received CBT' Age: (Mean age 43 years)	Self-rated return to work	Proportion of those who fulfilled CDC (%) criteria and who returned to work after 12 months: 47 %
Huibers et al. 2006 [115] Netherlands See also Leone et. al. below	CFS-like caseness (CIS score >40, self-reported fatigue >6 months, low performance <60 on SF-36)	Follow-up after 4 years of CFS-like fatigue compared to those who did not meet the CFS criteria.	N = 127 (60% female) Age: (Mean age 44) Drop-out: approximately 16%	Self-assessed incapacity for work	Partial work incapacity: OR 4.4 (95% KI 1.6 to 12.2) For CFS-like fatigue compared to other fatigue Total inability to work: OR 3.9 (95% KI 1.3 to 11.8) For CFS like fatigue compared to other fatigue
Leone et al. 2006 [116]	CFS-like caseness (>35 on CIS fatigue sub scale)		Same as Huibers 2006	Self-reported full compensation due to incapacity for work	Proportion of CFS-like problems at 4 years: 27% Employment incapacity ratio: 26%
McDermott et al. 2004 [121] United Kingdom	CDC 1994	Follow-up after 18 months of patients who have received lifestyle advice and discussions with occupational therapy	N = 98 (69% female) Age: (Mean age 38.6 years)		Proportion that went back in paid or unpaid work or training: 42%

Table 5.1 continued

Author, year, country	Diagnostic criteria	Study Design setting	Participants	Outcome*, Measurement method/ Analysis method	Results
Nyland et al. 2014 [117] Norway	CDC 1994 + recent mononucleosis infection	Cohort receiving individualized cooing and activity strategies Follow-up by questionnaire after mean time 6.5 years	CFS Specialist Clinic N = 111 (67% female) Age: Approximate average age: 24 years when diagnosed 34 years at follow-up Drop out: 17%	Self-reported employment and sick leave	Proportion of full-time employees at follow-up: 27% Proportion of part-time employees: 45% Proportion with some degree of sickness benefit or reimbursement: 68% Proportion with permanents reimbursement: 16% in any grade, 42% full-time

GET = Grate exercise therapy; **KBT** = Cognitive Behavioral Therapy; **NICE Guideline criteria** = https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1962830/

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Table 5.2 Studies on factors that can predict impaired working ability, work or function.

Author, year, country	Diagnostic criteria	Setting and study design	Participant drop out	Outcome*, Measurement method/ Analysis method	Results
Crawley et al. 2013 [113]\n\nUnited Kingdom	CDC 1994	6 specialist clinics\n\nLongitudinal cohort with 8–20 months of follow-up time based on record data	N = 1,643 (77.2% female)\n\nAge: (Mean age 39.9)\n\nDrop out: Approximately 50%	Physical function (SF-36)\n\nAdjusted regression analyses	Predictors of poor physical performance: age, physical function at baseline, pain
Huibers et al. 2004 [106]\n\nNetherlands	Severe fatigue (CIS subscale >35)	Cohort of people who worked and had severe fatigue followed over 24 months	N = 2,108 (25% female)\n\nAge: (Mean age 40.6)\n\nDrop-out: Approximately 20% in register data on sick leave	Outcome: Sickness absence >42 consecutive days\n\nSick leave data from registers and self-reported sick leave	Predictors of long term sick leave: higher age, low decision-making space in work, female sex, evening shift, symptoms attributed to physical sickness, previous sick leave.
Huibers et al. 2004 [114]\n\nNetherlands	Severe fatigue (CIS Sub scale >35)\n\n44% of the population Had CFS according to CDC	In connection with RCT about CBT	N = 151 on sick leave (55% female)\n\nAge: (Mean age 43)	Return to work (Self-reported) for those who met CFS criteria	Return to work predictors for CFS cases: male sex, lower age, better self-rated health, low degree of somatization.
Leone et al. 2006 [116]\n\nHuibers et al. 2006 [115]\nNetherlands	CFS like caseness (CIS scale for fatigue >35)	Long-term monitoring of fatigue cohort.	N = 127 (60% female)\n\nAge: (Mean age 44)	Outcome: Self-reported full compensation due to incapacity for work\n\nMultiple regression	At first measurements: predictors to receive compensation for full disability at 4 years: higher age, female gender, low physical function
Nyland et al. 2014 [117]\n\nNorway	CDC 1994 + recent mononucleosis infection.	CFS Specialist Clinic\n\nCohort of people who received individualized coping options and activity strategies. Follow-up via survey (Mean age 6.5)	N = 111 (67% female)\n\nAge: (Mean 24 years of age when diagnosed and approximately 34 years at follow-up\n\nDrop out: 17%	Outcome:\n\n(1) return to work; full or partial\n\n(2) sickness pension; full or partial	PEM at first contact did not predict work outcomes after 6,5 years

CFS = Grate syndrome; **KBT** = Cognitive Behavioral Therapy; **NICE Guideline criteria** = https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1962830/;**PEM** = post-exertional malaise, fatigue-triggered

Tabel 6.1 Description of included studies.

A	Aim	Underlying philosophy, the background of researchers	Setting and recruiting	Participants	Data Collection	Method of analysis
Arroll and Senior 2008 [125] England	Investigate processes leading to participants conceptualization of their symptoms and experience of getting a diagnosis.	Phenomenology Two researchers from a psychological research institution	Two support groups for ME/ CFS in South East England Advertising in news sheets where 10 responded to the ad	N = 8, whereof 6 females Age: 35–67 (Mean age 55.5) Number of years with symptoms: 6– 53 (Mean age 21 years)	Semi-structured interviews by telephone where one question area related to the to the diagnostic process (average time 41 minutes)	IPA
Brooks et al. 2014 [126] England	Experience of living with ME/CFS or being partner to a person with ME/CFS	Phenomenology A doctoral student and two researchers from a psychological research institution	From an immunology clinic in the north of England Recruitment method is not shown	Two men of the age of 50 with symptoms in 13 and 25 years, respectively, and their wives Diagnosis according to the Fukuda criteria, 12 and 7 years earlier respectively	Semi-structured interviews with the common-sense approach as a framework	IPA
Broughton et al. 2017 [127] England	Experiences of care at NHS specialist hospital facilities for ME/CFS	Participating research A post doc and four researchers in social medicine	Consecutive recruitment of patients who ended their treatment Asked by their doctor	N = 16, whereof 14 females Number of years with symptoms: 1–17 (Mean age 7.5 years)	Semi-structured interviews at home or on the phone (average time 32 minutes) Areas of concern were raised in conjunction with a reference group of people in Action for ME Participants were encouraged to address topics other than those included in the guide	Constant comparison thematic analysis

Table 6.1 continued

Author, year, country, ID	Aim	Underlying philosophy, the background of researchers	Setting and recruiting	Participants	Data Collection	Method of analysis
de Carvalho Leite et al. 2011 [128] England	Mapping needs of support from health and social authorities and identify deficiencies equality in health care	Twelve researchers with different backgrounds e.g. physiotherapy and caring science	Recruitment by advertisement, by support groups, care and media Strategic sampling to maximize variety N = 52 answered	N = 35, whereof 28 females Age: Older than 17 years Different races, education level, working conditions and time with the disease	An initial focus group in 2 hours where the participants told their stories (n=6) followed by semi-sructured interviews with all (Mean time 45 minutes)	Thematic Analysis Triangulation and discussion of the results with support groups
Edwards et al. 2007 [129] England	Experience of living with ME/CFS	Phenomenology Three researchers in psychology and primary care	Recruitment by advertising in a ME self-help network Participants would have at least moderate disease severity according to CFS/ME Working group 2002 Pre-determined number of participants	N = 8 women, the first who signed up Age: 37– 55 years Duration of symptoms: 20 months to 12 years back	Semi-structured interviews with broad question areas in home (60 - 90 minutes)	IPA The analysis process was documented Participants validated their individual quotes and themes
Gilje et al. 2008 [130] Norway	Experiences of obstacles to good care	Three researchers in primary care	Via local patient organization	N = 12, whereof 10 females Age: 22– 54 (Mean age 41) Number of years with symptom: 1– 20 All of them were persons on disability pension	A focus group, semi structured query wizard	Systematic During a follow-up, (5/12 participated) when the analysis was presented, one year later, it was refined and completed

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Table 6.1 continued

Author, year, country, ID	Aim	Underlying philosophy, the background of researchers	Setting and recruiting	Participants	Data Collection	Method of analysis
Hannon et al. 2012 [131] England	To inform one upcoming education and training effort for physician according with MRC framework for complex interventions	Seven researchers with background in psychology, primary care and care science	Ads by ME/CFS groups and on specialist clinics	N = 16, whereof 11 females Age: 28– 64 Time from diagnosis: 0.5–22 years	Semi-structured interviews where the question guides were developed supported by literature Questions related to diagnosis, primary care support and resource needs	Thematic Analysis inspired by grounded theory Independent open encoding Data Collection was stopped when theoretical saturation was reached
Larun and Malterud 2011 [132] Norway	Experiences and perceptions about training as a knowledge base to improve the care	Two researchers with background in primary care	Strategic sampling from people who participated in one treatment program with physiotherapy and individual counselling at a rehab clinic Recruitment via clinical staff	N = 10, whereof 8 females Age: 40– 64 (Mean age 50) Time since diagnosis: 1– 7 years (Mean age 3.4) Severity factor: Near maximum value of CSS	Two focus groups on the clinic (60 minutes) The question guide covered physical activity in a broad sense	Systematic text condensation which the researchers performed together The process was documented
McDermott et al. 2011 [133] England	Hopes and expectations from people who had been referred from primary care to a ME/CFS clinic	Three researchers, whereof two with background in primary care and the third employed by the ME/CFS clinic	ME/ CFS clinic All persons (n = 56) referred during 5 months were invited by letter to participate	N = 20, whereof 17 females Age: 22– 60 year (Mean age 39)s	Semi structured interviews by phone before the people had visited the clinic for the first time (average time 45 minutes) The query guide was developed in consultation with general practitioners, ME/CFS specialists, and persons with ME/CFS	Constant comparative analysis where data collection continued until saturation reached The researcher who was employed by the clinic participated not in the initial part of the analysis

Table 6.1 continued

Author, year, country, ID	Aim	Underlying philosophy, the background of researchers	Setting and recruiting	Participants	Data Collection	Method of analysis
Ryckeghem et al. 2017 [134] Belgium	Experience and perceptions of health care as a basis to develop a role as a specialist nurse	Six researchers in hospitals, two of them nurses	Strategic sampling of patients from a department for internal medicine at a university hospital When the diagnosis was made N = 18 were invited to participate	N = 15, whereof 14 females Age: 33– 59 years (Mean age 45)	Semi-structured interviews The query guide was developed by literature review The interviews took place in the home (n = 12) or at the clinic (n = 3)	Open-encoding thematic analysis where the main researcher analysed all the data
Stormorken 2017 [135] Norway	Gain knowledge about obstacles and supporting factors which affect the course of the disease during the first years, as a support for improving care	Two nurse science researchers and a researcher with extensive experience of ME/CFS research from the USA	Strategic selection from people who received ME/CFS after an outbreak of Giardia infection, and was admitted to a neurological clinic at a university hospital in Norway	N = 26, whereof 19 females Age: 26– 59 years (Mean age 40)	In-depth interviews (60–120 minutes) 4 years after infection	Inductive qualitative content analysis The Guba & Lincoln criteria were used to increase the credibility of the results

IPA = Interpretive Phenomenological Analysis; ME/CFS = Myalgical encephalomyelitis/Chronic fatigue Syndrome; NHS = National Health Security