

Paper 3

ILLNESS COURSE IN CHRONIC FATIGUE SYNDROMES.
A 5 YEARS FOLLOW-UP STUDY

Illness course in chronic fatigue syndromes

A 5 years follow-up study

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ABSTRACT

Background

A six months randomized clinical trial (cognitive behavioural treatment, medications) showed positive effects in patients with chronic fatigue syndrome (CFS) and neurasthenia.

Aims

To examine the long-term effect of treatment interventions and the illness course.

Method

Patients with CFS and neurasthenia (n=70) were examined 6 months, 1 year, and 5 years after treatment.

Results

After 5 years there was a substantial reduction in fatigue symptoms ($p=0.004$), clinical global severity ($p<0.001$) and in depression scores, which were correlated significantly with reduction in fatigue symptoms ($r=0.46$; $p=0.001$). Good prognosis related to low initial fatigue scores, poor prognosis to severity of fatigue at the initial phase of illness, sudden onset, and slow improvement during the first year. Patients qualifying for the Centre of Disease Control CFS diagnosis had less improvement, more debilitating and consistent symptoms of fatigue and the poorest prognosis.

Conclusion

The initial treatment had less importance for the long-term course in CFS than the severity and characteristic of the illness itself. Diagnoses tended to shift from CFS towards the less serious condition of neurasthenia.

Declaration of interest

None

INTRODUCTION:

Chronic fatigue syndrome (CFS) is an incapacitating illness characterized by excessive fatigue following minimal exertions, accompanied by a range of symptoms such as muscle pain and weakness, cognitive disturbances, sensory irritability and sleep disturbance (1, 2). The severity of the illness varies between individuals and within individuals over time. Diagnostic criteria and case definitions vary between the diagnosis of neurasthenia and case definitions of CFS. The case definitions of CFS differ in their emphasis on precipitating factors and symptoms like fatigue, general malaise and cognitive impairment.

A commonly used case definition in Europe for CFS is the British/ Oxford case definition, CFS-Oxford (3). Internationally the 1994- Centre of Disease Control (CDC) case definition, CFS-CDC (4) have become the standard case definition. The specificity and ambiguities of the CDC-case definition has been questioned (5, 6), and a reclassification of CFS has been called for (7). The older term Neurasthenia (8) is still being used throughout the world (9, 10) as a clinical useful entity for fatigue illnesses. Also, the term myalgic encephalopathy (ME) has been increasingly popular during the last decade, although controversial with unclear differentiation to CFS (11, 12), in spite of efforts to reach consensus (13-16). Patient organizations have advocated a strict and exclusive definition of CFS/ME, based on an understanding of the illness as a clear somatic disease, precipitated by an infection, and with immune and neuroendocrine dysfunction (17). Such exclusive delineation of the illness has not been supported by scientific studies meeting scientific standards (11). The ICD-10 distinct classification of postviral chronic fatigue/ benign myalgic encephalomyelitis in the diseases of the nervous system (G93.3) and neurasthenia in mental disorders (F48.0) were based on almost identical descriptions of the clinical conditions (9). Since WHO did not allow for dual classification of the same disorder, the illnesses of CFS/ME and neurasthenia have since emerged as separate entities. Diagnoses and labels will often mirror attributions and could influence therapies and illness perception (18).

The many different diagnoses, labels and case definitions may represent overlapping expressions of a continuous spectrum of fatigue illnesses (19). In general population studies, neurasthenia and CFS seem to be inconsistent entities, with fluctuating symptoms and patterns of intermittent remissions and relapses (20, 21). In studies of referred patients with CFS, a full recovery from untreated CFS is rare (11). However, there is increasing evidence for the effectiveness of cognitive behavioural and graded exercise therapies on improvement

of fatigue symptoms (22, 23). Studies of how the outcome and prognosis of CFS vary with the different case definitions of CFS are few, but indicate that CFS-CDC patients have poorer prognosis than other fatigue illnesses (24).

In the original randomised controlled trial we studied the treatment effects of a comprehensive cognitive treatment program, mirtazapine/ placebo medication and a combination of these in patients with chronic fatigue syndrome (CFS) and neurasthenia (25). We found a general improvement in the total patient population through a 6 months treatment program, with significant differences in improvement depending on the specific treatment interventions. The findings indicated that an individually adjusted comprehensive cognitive treatment program combined with mirtazapine medication had significantly better effect on fatigue symptoms and clinical severity of fatigue, compared to combinations of mirtazapine or placebo alone. After the end of this systematic treatment program, we followed the same patient group (n=70) over five years, without any new systematic intervention.

The aim of the follow-up study was twofold. One was to examine the long-term effect of the treatment interventions and to examine if the initial treatment effects found in the RCT were sustained. Secondly we wanted to study the illness course and diagnostic stability in CFS, based on different case definitions.

Material:

72 patients with chronic fatigue were recruited from general practitioners to a specialist psychosomatic clinic, and fulfilled a 24 week treatment program (see (25) for details). 13 of the 72 patients had a premature discontinuation; for these patients data from last observation carried forward (LOCF) were used in end-of-treatment analysis. All patients (n=72) were invited to follow-up investigations; 70 patients (97 %) met for follow-up studies at 6 months and 1 year; 58 patients (81 %) responded at 5 years follow-up (2007) by completing questionnaires, 56 (78 %) completed interviews and diagnostic evaluation (fig. 1).

(Insert fig 1 about here)

At baseline, the patients were characterized by high female: male ratio (59:13), they were of middle age, had high scores of fatigue symptoms and clinical severity, and had severe physical functional impairment and moderate scores of depression (table 1). Speed of onset of

fatigue illness was categorized into sudden onset (less than 6 months of onset) and slow onset (more than 6 months). Self-reported infections immediately prior to onset of fatigue symptoms were registered.

Insert table 1 about here.

All patients (n=72) fulfilled ICD-10 criteria for neurasthenia (F48.0), 65/72 fulfilled the case definition for CFS-Oxford and 29/72 fulfilled the case definition for CFS-CDC. For analysis purposes, the study population was classified into three exclusive categories: CFS-CDC (n=29); CFS-Oxford (non- CDC; n=36) and neurasthenia (non- CFS; n=7). At 5 years follow-up, 24/ 29 patients fulfilling CDS-CDC case definitions at baseline attended, 28/36 patients fulfilling CFS-Oxford case definitions at baseline attended and 3/7 patients who fulfilled criteria for neurasthenia at baseline attended.

Method:

Patients met for interviews and completed questionnaires at 6 months, 1 year and 5 years after the end of the treatment program, with no systematic treatment in the follow-up period. Symptoms, functional impairment, clinical severity and improvement were evaluated by self-report questionnaires, structured interviews and clinical assessment (BS). The diagnoses of neurasthenia and Chronic Fatigue Syndrome, by Oxford- and CDC-case definitions, were confirmed by a trained psychiatrist (BS), using structured clinical interview (SCAN) (26) and CFS case checklists.

Outcome measures:

Primary outcome measurements were fatigue symptoms and clinical global improvement, assessed by self-report and by a trained clinician. Secondary outcomes were health-related quality of life, depression and general health complaints.

Instruments:

Fatigue:

The Fatigue scale (27) is a self-rating scale developed to measure severity of fatigue. Principal components analyses have indicated a two-factor solution (physical and mental fatigue) (28).

The scale consists of 11-items, being rated 0-3 in severity. The scale has been found to be reliable and valid in chronic fatigue syndrome, showing a high degree of internal consistency..

Clinical Global Impression:

Clinical Global Impressions (CGI) (29) –dimensions of Severity of Illness (CGI-S) and Improvement (CGI-I) were used; rated on a 7-point scale. Severity of illness is rated within last week; global improvement is rated since admission to the study. CGI-Severity was assessed by clinical assessment, CGI-Improvement was based on patient self-reports.

QoL (Quality of life): SF-36 = Short Form 36 items Life quality:

Health related quality of life was measured by the generic health status measure SF-36 for health situations during the last 4 weeks (30) . SF-36 is a generic QoL scale consisting of 36 items describing eight dimensions (31), aggregated to one physical and one mental health component (32). Adjusted SF-36 scores were calculated. The mean is 50, and a deviation of ten points from the mean represents one standard deviation.

Mental health/ depression:

Depression was assessed by Hamilton Depression Scale (HAMD), rating symptoms of depression by a 21-item rating scale (33, 34), indicating the level of depression. The usual cut-off-level of HAMD is 11/12 in depression, but this has been questioned when used in chronic fatigue syndrome, suggesting a cutoff of 13/14 (35).

General health status. General health was assessed by subjective health complaints, measured by the Subjective Health Complaint Inventory (SHC)(36, 37), consisting of 29 items, rated 0-3, on subjective somatic and psychological complaints experienced during the last 30 days, describing five dimensions of complaints, aggregated to one total score (SHC-total = severity · duration). The questionnaire has been tested and has satisfactory validity and reliability (37).

Statistical methods

Analyses were done with a mixed model for normally distributed continuous data for the outcome measures; using PROC MIXED in SAS version 9.1 for MS-Windows. To account for the repeated measures for the individuals, individual were entered in a mixed model for repeated measures, with an autoregressive (AR1) covariance structure. Other variables were entered as fixed effects. Descriptive statistics and other analyses were done using SPSS version 14.01.

Ethics

The study was approved by the Regional Ethic Committee and the Norwegian Data Inspectorate. The trial was registered with the Norwegian Social Science Data Services (NSD) prior to any patient inclusion. All participants had received written information about the trial and had given formal consent about participation, including new formal consent about the follow-up study.

Results:

The initial clinical difference between the treatment groups (medication/ placebo/ CBT) (25) from the original RCT was not sustained during the 5 years follow-up period, neither at 6 months ($p=0.62$), 1 year ($p=0.81$) or 5 years ($p=0.93$) follow-up. We found no statistically significant differences on any outcome measure between the treatment groups. However, the total patient group showed a gradual improvement from baseline to 5 years follow-up in self-reported fatigue symptoms ($p=0.004$) and a gradual reduction in clinician-assessed clinical severity (CGI, $p<0.001$), independent of the previous interventions.

The total patient group reported depression scores at baseline that indicated mild levels of depression. 51 % of patients had depression scores on HAMD above suggested cutoff for depression in CFS (HAMD 14) at baseline. There were no statistically significant differences in depression score between patients with neurasthenia (mean \bar{x} 16.3, SE 0.9), CFS-Oxford (mean \bar{x} 13.9, SE 0.7) and CFS-CDC (mean \bar{x} 14.8, SE 0.7) ($p=0.29$).

There were significant reductions in depression scores in the total group during the follow-up period ($p<0.001$ in an unadjusted model, paired T-test, $p<0.001$), with no significant difference between subgroups of patients with CFS-CDC, CFS-Oxford or neurasthenia ($p=0.894$). At 5 years follow-up, only 5.5 % of patients had HAMD scores above cutoff for depression (HAMD=14), representing a significant reduction from baseline (McNemar test, $p<0.001$). There was a significant association between reduction in fatigue symptoms and reduction in depression score from baseline to 5 years follow-up, calculated as the difference between the scores at 5 years and at baseline ($r=0.46$; $p=0.001$).

Self-reported global improvement (CGI-I; $p=0.025$) and clinician-assessed improvement (CGI-S; $p=0.005$) were significantly greater among the patients using antidepressant medication at 5 years follow-up, compared to the patients who did not use antidepressants. Dosage or duration of medication was not recorded.

Based on the different case definitions of neurasthenia, CFS-Oxford and CFS-CDC, we found significant differences from baseline through the 5 years follow-up period in the different subgroups. At baseline, patients with CFS-Oxford and CFS-CDS differed significantly on symptom severity (Fatigue scale and CGI- severity) (table 2). CFS-CDC patients reported more severe fatigue symptoms and more impaired physical quality of life (SF-36) than CFS-Oxford patients. Patients with neurasthenia differed significantly from CFS-CDC on CGI-severity and health related quality of life (SF-36, physical component), showing less impairment. There were also significant differences in the numbers of patients with sudden onset of illness (< 6 months) and reported frequency of infection shortly prior to onset of fatigue condition in the subgroups (table 2). CFS-CDC patients reported a more sudden onset of fatigue, the duration of illness was shorter and there were more frequent reports of a precipitating infection.

(insert table 2 about here).

At the completion of the 6 months treatment interventions, patients with neurasthenia reported significantly greater improvement in fatigue symptoms (mean 7.7 on Fatigue Scale; SE=3.4) than patients with CFS-Oxford (mean 1.3, SE .91) and CFS-CDC (mean 2.1, SE=.82), (p=0.021). The difference in improvement in clinical global severity (CGI) was not significant between groups (p=0.65). Self-reported fatigue symptoms and clinical assessed severity of fatigue differed significantly between the subgroups of neurasthenia and CFS- groups (p=0.002 on Fatigue scale; p=0.023 on CGI-severity), but not between CFS- Oxford and CFS-CDC.

During the 5 years follow-up period there were significant differences between the diagnostic subgroups on fatigue and on health-related QoL SF-36), physical component (table 4). The improvement in patients with neurasthenia and CFS-Oxford was significantly better than in patients with CFS-CDC (table 3). Patients with CFS-Oxford reported significantly better improvement than patients with CFS-CDC at 6 months (p<0.001), at 1 year (p=0.013) and at 5 years follow-up (p=0.026). The CFS-CDC patients had a poorer prognosis, showed no improvement by clinical assessment of severity (CGI-S) between 6 months and 5 years follow-up, and reported significant impairment in SF-36, physical component, between 1 year and 5 years follow-up (p=0.031).

(insert table 3 about here)

At 5 years follow-up, 47 % of the total patient group showed a substantial clinical improvement of more than 6 points reduction from baseline on the Fatigue scale; 28 % showed an improvement of more than 10 points reduction, while 15 % showed no change or even higher scores on the Fatigue scale. There were statistically significant differences in improvement of fatigue between the diagnostic subgroups at 5 years follow-up. The CFS-CDC-patients had a significantly more severe condition, both by self-report of fatigue symptoms and on assessment of clinical global severity (CGI-S), compared to CFS-Oxford and neurasthenia (table 3).

Patients with sudden onset of fatigue illness (< 6 months) reported significantly more impaired physical functioning ($p < 0.001$) and were assessed to have a more severe condition ($p = 0.049$) than patients with slow onset (> 6 months), irrespective of diagnostic subgroup. Patients with slow onset had a less severe illness condition by clinical assessment, but reported significantly lower scores on mental/ emotional components of SF-36 than the patients with sudden onset of fatigue illness ($p = 0.028$). There was a significant association between poor improvement in fatigue symptoms and level of total subjective health complaints (SHC-total, $p = 0.0021$).

From baseline to 5 years follow-up there was a shift of diagnosis towards milder conditions of neurasthenia/ chronic fatigue illness or no fatigue illness. Half of the patients with a fatigue diagnosis at baseline did not fulfil the same diagnostic criteria at 5 years follow-up. Nearly all of these patients showed improvement, only 2 patients had diagnosis changed from CFS-Oxford to CFS-CDC, and none from neurasthenia to CFS (table 4).

(Insert table 4 about here)

Discussion

The interpretation of the findings from this follow-up study is complicated, as it examines both the specific long-term effects of different interventions and the illness course in subgroups of fatigue patients classified by different case definitions. The illness course over 5

years could be influenced by the initial treatment program, possibly with specific effects for the different patient groups. Our study design and sample size make it impossible to evaluate this. All patients received some kind of active treatment, at least 12 weeks of cognitive behavioural treatment (CBT), body awareness therapy and individual exercise. Previous CBT studies on CFS assume that the increased activity and functional improvement are due to the cognitive reorientation, altered illness perception and less fear of activity (2). Our findings confirmed this change in illness perception in the total patient group (25). Such cognitive changes of illness perception are thought to be quite robust, making it probable that the effect of CBT treatment influences the further course of the illness (38).

In the total group of patients (all three subgroups combined) we found a clinical significant improvement from baseline in fatigue symptoms in nearly half of the patients at the 5 years follow-up. This is less than found in general population studies of CFS patients (21), but a little more than reported in most follow-up studies of CFS patients referred to specialist care (22). The improvement reported at 5 years follow-up was not associated with the specific treatment interventions patients had received 5 years earlier, suggesting that the improvement may be independent of the treatment received. However, the improvement in fatigue symptoms was significantly associated with initial severity and subgroups of different CFS case definitions, both during the intervention period and during the follow-up-period. The least severely affected patients improved the most; the most severe patients improved the least, or reported impairment of the fatigue illness.

The improvement within the total patient group corresponded with shifts in diagnoses during the 5 years follow-up period. There was a general movement from the more severe case definitions of CFS-CDC through CFS-Oxford to the diagnosis of neurasthenia or no fatigue diagnosis. This is in line with earlier research (21) and supports the association between case definitions, symptoms and clinical severity. Patients with CFS-CDC showed the most serious condition, by self-report and clinical assessment, both at baseline and through the 5 years period, representing the poorest prognosis. CFS-CDC had a more rapid speed of onset, higher frequency of reported precipitating infection, as well as greater global severity, lower level of physical functioning, and a higher level of total subjective health complaints compared to the other groups. A reduction in self-reported fatigue symptoms was not followed by a corresponding improvement in global severity; this was unchanged through the follow-up period. Physical functioning showed significant impairment from 1 year to 5 years.

Our findings support the assumption that CFS-CDC represents a distinct illness entity within the fatigue diagnoses, characterized more by global severity, functional impairment and subjective health complaints than fatigue symptoms alone. However, this was not consistent for the whole group with CFS-CDS, some of these patients improved substantially. The case definition of CFS-CDC still seems to represent ambiguities, as discussed by other researchers (5, 7). More specific case definitions or subtypes of fatigue illnesses may be needed in order to predict specific outcome and prognosis.

On the other hand, the splitting into more subtypes is not supported by the shift in diagnosis from CFS to neurasthenia. This finding suggests that both the illness and the case definitions may represent a continuum of fatigue rather than specific subgroups. This could be taken as an argument for keeping inclusion criteria and case definitions for chronic fatigue syndrome wide. The discussions about neurasthenia and the decision to keep neurasthenia as a useful illness entity within ICD-10 are reflecting this (9, 10, 39, 40).

Our data did not support an association between level of fatigue and depressive symptoms, although half of the patients reported depressive symptoms above cutoff level for clinical depression. This is consistent with the mild impairment on the mental/ emotional component of SF-36, which contrasts with the extremely low levels on physical dimensions. It is in line with previous studies and reviews, questioning the association between CFS and depression (41), but is also consistent with other reports of high prevalence of depression in CFS (42). The association between improvement in fatigue symptoms and improvement in depression score was significant. Whether this association is expressing an ease of mood secondary to fatigue relief, or the other way around, remains unsettled.

Improvement in self-reported and clinician-assessed fatigue severity in patients using antidepressant medication at 5 years follow-up could indicate that some patients benefit from antidepressant medication on fatigue symptoms, irrespective of depressive symptoms. This could be caused by complex effects on the global fatigue illness, including treating comorbid depression or anxiety symptoms, inhibition of ascending pain pathways or inhibition of prefrontal cortical areas that are responsible for "attention" to noxious stimuli (43, 44). A similar effect on fatigue symptoms have been found in other studies (45).

Our findings confirmed that most patients with chronic fatigue syndrome have a substantial improvement over some years, while many patients still suffer a severe illness course. The strongest predictor for a good prognosis seemed to be improvement in early phases of the illness. Improvement of fatigue and improvement of mood seemed significantly associated.

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Fig 1:

Flow chart:

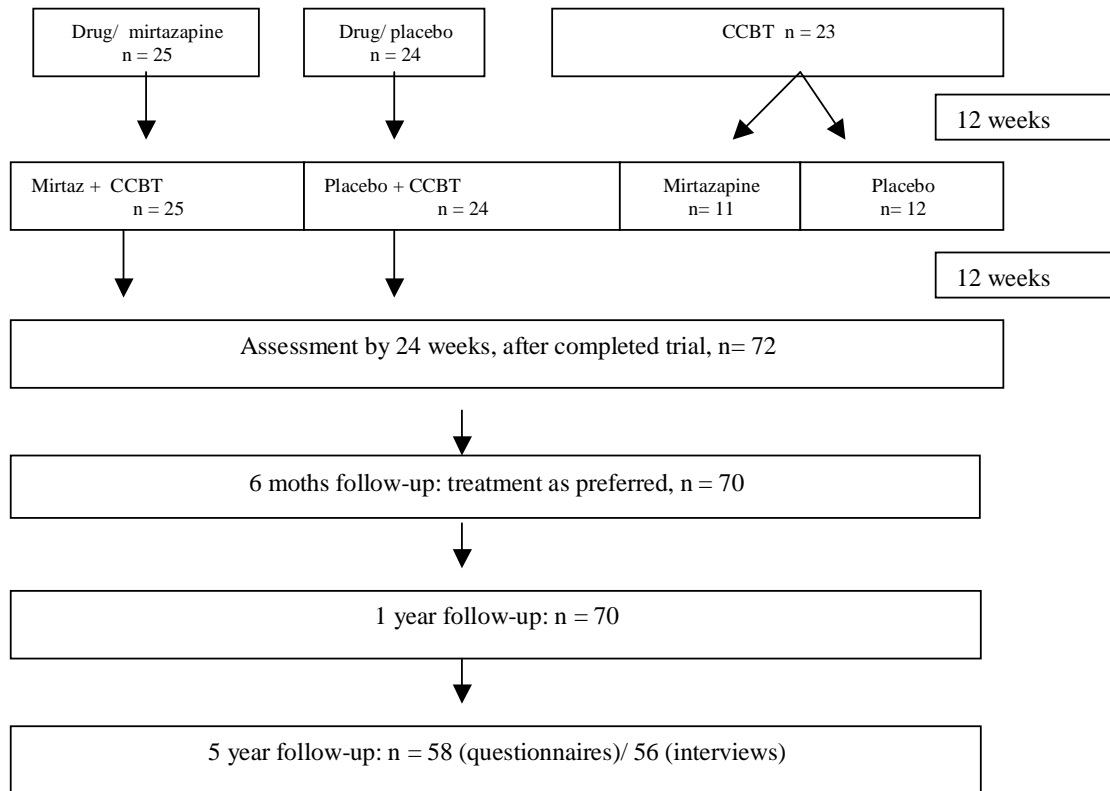


Table 1:
Characteristics at baseline (n=72)

	<i>Mean</i>	<i>SD</i>
Age	46	8,8
Fatigue Scale	25,0	4,5
CGI	4,99	0,75
SHC tot	25,5	10,4
SF-36 physical	28.94	11.31
SF-36 mental	39.37	13.06
HAMD-21	14,5	3,9

Table 2:**Analysis of differences in chronic fatigue- subgroups at baseline:****CFS- CDC, CFS-Oxford (non-CDC) and neurasthenia (non-CFS)**

	CFS – CDC n = 29	CFS- Oxford n= 36	Neurasthenia n = 7	p-value
Male/Female	6/23	4/32	3/4	
Age	43.5 (8.7)	46.5 (9.0)	46.9 (7.4)	.36*
SHC tot	27.4 (10.2)	24.5 (10.3)	23.3 (11.8)	.44*
HAMD-21	14.8 (3.8)	13.9 (4.2)	16.3 (2.4)	.289*
Duration of illness (yrs)	3.5 (2.7)	6.2 (5.1)	3.8 (3.1)	.025*
Sudden onset*	10/29 (34%)	3/35 (9 %)	0/7 (0%)	.000 **
Infection*	9/28 (32 %)	1/33 (3 %)	0/7 (0%)	.003 **
% cases (n=72)	29/ 72 (40 %)	36/ 72 (50 %)	7/72 (10 %)	

* Analysis of variance (ANOVA), ** chi-square test

Table 3

Predicted values for CGI-S (severity), Fatigue scale and SF-36 from baseline to the 5 years follow-up,
classified by fatigue diagnosis at baseline (based on a mixed model in SAS version 9.1 for MS-Windows).

	CGI-S		Fatigue scale		SF-36- physical		SF-36-mental		
	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	
Baseline		0.024*		0.049*		0.002*		0.53*	
	CFS-CDC	5.41 (0.20)	Ref	27.07 (1.06)	Ref	22.39 (2.24)	Ref	41.3 (2.5)	Ref
	CFS-Oxford non-cdc	4.74 (0.18)	0.017	23.58 (0.95)	0.019	29.98 (1.93)	0.14	39.2 (2.1)	0.53
	Neurasthenia	4.43 (0.40)	0.036	23.43 (2.16)	0.139	40.24 (4.29)	<0.001	35.4 (4.7)	0.27
6 months follow-up			0.008*		<0.001*				
	CFS-CDC	4.21 (0.20)	Ref	25.21 (1.06)	Ref				
	CFS-Oxford non-cdc	3.35 (0.19)	0.004	19.23 (1.01)	<0.001				
	Neurasthenia	3.20 (0.45)	0.047	19.80 (2.40)	0.047				
1 year			0.003*		0.036*		< 0.001*	0.013*	
	CFS-CDC	4.07 (0.20)	Ref	23.17 (1.06)	Ref	25.03 (2.17)	Ref	44.32 (2.4)	Ref
	CFS-Oxford non-cdc	3.06 (0.19)	<0.001	19.28 (1.03)	0.013	30.39 (1.92)	0.071	43.2 (2.1)	0.73
	Neurasthenia	3.37 (0.43)	0.149	19.64 (2.31)	0.174	44.84 (4.29)	<0.001	28.3 (2.5)	0.0043
5 years			<0.001*		0.060*		<0.001*	0.31*	
	CFS-CDC	4.22 (0.22)	Ref	21.54 (1.13)	Ref	21.42 (2.15)	Ref	49.7 (2.4)	Ref
	CFS-Oxford non-cdc	2.93 (0.20)	<0.001	17.97 (1.02)	0.026	30.98 (1.92)	0.002	42.0 (4.7)	0.34
	Neurasthenia	2.96 (0.50)	0.029	17.46 (2.48)	0.144	38.41 (4.29)	0.001	42.0 (4.4)	0.15

* = test for homogeneity

Table 4:
Diagnoses at baseline v. diagnoses at 5 years follow-up

		Diagnose 5 yrs				<i>Total</i>
		<i>No fatigue diagnose</i>	<i>Neurasthenia, non CFS</i>	<i>CFS-Oxford, non-CDC</i>	<i>CFS-CDC</i>	
Diagnose baseline	Neurasthenia, non-CFS	0	4	0	0	4
	CFS-Oxford, non-CDC	6	18	2	2	28
	CFS-CDC	3	7	4	10	24
<i>Total</i>		9	29	6	12	56