

Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome

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Abstract

Objective: To test the efficacy of a graded aerobic exercise programme in the chronic fatigue syndrome.

Design: Randomised controlled trial with control treatment crossover after the first follow up examination.

Setting: Chronic fatigue clinic in a general hospital department of psychiatry.

Subjects: 66 patients with the chronic fatigue syndrome who had neither a psychiatric disorder nor appreciable sleep disturbance.

Interventions: Random allocation to 12 weeks of either graded aerobic exercise or flexibility exercises and relaxation therapy. Patients who completed the flexibility programme were invited to cross over to the exercise programme afterwards.

Main outcome measure: The self rated clinical global impression change score, "very much better" or "much better" being considered as clinically important.

Results: Four patients receiving exercise and three receiving flexibility treatment dropped out before completion. 16 of 29 patients rated themselves as better after completing exercise treatment compared with eight of 30 patients who completed flexibility treatment. Analysis by intention to treat gave similar results (17/33 *v* 9/33 patients better). Fatigue, functional capacity, and fitness were significantly better after exercise than after flexibility treatment. 12 of 22 patients who crossed over to exercise after flexibility treatment rated themselves as better after completing exercise treatment. 32 of 47 patients rated themselves as better three months after completing supervised exercise treatment. 35 of 47 patients rated themselves as better one year after completing supervised exercise treatment.

Conclusion: These findings support the use of appropriately prescribed graded aerobic exercise in the management of patients with the chronic fatigue syndrome.

Introduction

Patients with the chronic fatigue syndrome perceive greater fatigue than healthy controls taking the same exercise.^{1,2} This may be caused by physical deconditioning,¹ or sleep deprivation,³ or psychological distress,⁴ or a combination of the three. The syndrome

seems to be independent of muscle strength and fatigability, which are normal in subjects with either the chronic fatigue syndrome^{5,6} or the postinfectious fatigue syndrome.⁷ Physical deconditioning, in turn, may be caused by reduced physical activity,⁸ which may lead to adverse physical and psychological effects.^{8,9}

Exercise provides physical and psychological benefits.^{9,10} Graded aerobic exercise programmes can reduce incapacity and symptoms in many chronic and painful conditions, such as the post-polio syndrome,¹¹ chronic back pain,¹² and depressive illness.¹⁰ Fitness training improved both aerobic capacity and myalgia more than flexibility exercises in patients with the "fibrositis/fibromyalgia syndrome,"¹³ a condition which overlaps with the chronic fatigue syndrome.¹⁴ A similar training programme improved symptoms and physiological findings in an open study of patients with the "effort syndrome."¹⁵ There has been no randomised controlled trial of graded exercise treatment in patients with the chronic fatigue syndrome.⁹

We compared the physiological, symptomatic, and functional changes associated with a 12 week programme of either graded aerobic exercise or flexibility and relaxation therapy.

Patients and methods

Patients met the Oxford criteria for the chronic fatigue syndrome.¹⁶ In addition, by using the structured clinical interview for the DSM-III-R (*Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised)¹⁷ we excluded patients who also had a current psychiatric disorder or symptomatic insomnia because of the separate effects of these conditions on fatigue.^{3,4} We did not exclude patients with comorbid simple phobias.¹⁸ Physical screening and investigations were carried out or, when appropriate, full recent records were obtained from the referring doctor to ensure other disorders had been excluded.¹⁶

In a previous study of exercise therapy in a related disorder half of the subjects considered themselves moderately improved by the treatment compared with 10% of controls receiving flexibility training.¹³ By assuming similar treatment responses with $\alpha=0.05$ and a power of 0.90 we calculated that 30 subjects would be required in each treatment group.¹⁹ We recruited 66 patients to allow for 10% drop out.

In all, 167 outpatients were screened for the study. All had been referred to a chronic fatigue clinic in a

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general hospital department of psychiatry. All patients with the chronic fatigue syndrome who also had a psychiatric disorder or insomnia were offered treatment for their comorbid disorder. If treatment was successful but the patients still met criteria for the chronic fatigue syndrome they were recruited into the trial. Ninety six patients did not meet criteria for the trial. Of these patients, 74 who had a current psychiatric disorder and three who had insomnia alone usually had their fatigue alleviated by treatment for these conditions. Nine patients had organic causes for their fatigue. A further five patients were not incapacitated enough, and five others were too incapacitated to attend for outpatient treatment. Only five of 71 (7%) eligible patients refused the trial.

Sixty six patients gave valid, informed consent and entered the trial. Of these, 27 (41%) had successfully been treated for a comorbid disorder beforehand but still met criteria for the chronic fatigue syndrome. Ethical approval was obtained from the district research ethics committee.

Assessment of symptoms

The hospital anxiety and depression scale measured anxiety and depression.²⁰ Fatigue was measured with self rated visual analogue scales measuring physical, mental, and total fatigue¹⁸ and a self rated 14 item questionnaire.²¹ The Pittsburgh sleep quality index measured quality and amount of sleep.²² The 36 item short form health questionnaire (SF-36) was used specifically to measure physical functional capacity.²³

Physiological assessments

The maximal voluntary contraction of the quadriceps muscle in the dominant leg was measured, with percutaneous twitch interpolation to ensure maximal activation.²⁴ A treadmill walking test was carried out at a constant 5 km/h, the slope being increased every two minutes. All patients were encouraged to continue the test to their maximum. Expired air was analysed continuously for percentages of oxygen and carbon dioxide and minute ventilation to give the peak oxygen consumption.

Patients rated their perceived exertion, using the unmodified Borg scale, in the last 30 seconds of each treadmill stage.²⁵ Thumb prick capillary lactate concentrations were measured at rest, at a perceived exertion score of 14 (between "somewhat hard" and "hard"), and three minutes after the test. The percentage of age predicted maximum heart rate reached was calculated from the formula $210 - (\text{age} \times 0.65)$.²⁶

Treatments

All 66 patients were randomly allocated to either the exercise programme or the flexibility and relaxation programme, 33 patients being included in each group. Randomisation was achieved blindly to the psychiatrist and independently of the exercise physiologist by placing the letter E or F in 66 separate blank envelopes. These were then arranged in random order determined by random number tables and opened by an independent administrator after baseline tests as each new patient entered the study.

Exercise treatment

Patients attended weekly for 12 weeks of supervised treatment and the next week's exercise prescription. All laboratory sessions were supervised by an exercise physiologist using basic principles of exercise prescription,²⁷ which were adapted for the patient's current capacity. Home exercise was prescribed on at least five days a week, with initial sessions lasting between five and 15 minutes at an intensity of 40% of peak oxygen consumption (roughly 50% of the maximum recorded heart rate). The daily exercise prescription was increased by one or two minutes (negotiated with the patient each week) up to a maximum of 30 minutes. The intensity of exercise was then increased to a maximum of 60% of peak oxygen consumption. Patients were given ambulatory heart rate monitors to ensure that they reached but did not exceed target heart rates. The main exercise was walking, but patients were encouraged to take other modes of exercise, such as cycling and swimming. Patients were advised not to exceed prescribed exercise during a good phase. If patients complained of increased fatigue they were advised to continue at the same level of exercise for an extra week and increase when the fatigue had lessened.

Flexibility treatment

Patients attended the laboratory weekly for 12 weeks of flexibility and relaxation sessions provided by the same exercise physiologists. Each patient was taught a stretching routine and relaxation techniques. Patients were encouraged to start with sessions of 10 minutes, increasing to 30 minutes a day five days a week as more stretching exercises were added. They were specifically told to avoid doing any extra physical activities.

Patients from each group attended the laboratory at different times to avoid communication between groups. Patients kept a weekly activity diary, recording the type, duration, and response to exercise or stretching, which determined the next week's prescription.

Outcome measures

The main outcome measure was the self rated clinical global impression change score, which is a validated measure of overall change compared with study onset, with seven possible scores from "very much worse" (score 7) to "very much better" (score 1).²⁸ Secondary outcome measures included assessments of strength and fitness, symptoms, and functional capacity, as described above.

Follow up

After 12 weeks all patients were reassessed as at baseline except that the mid-exercise blood lactate concentration was measured at the same treadmill stage as before. Patients were blind to all measures at all stages. At any time two exercise physiologists participated in both testing and treatment. During the follow up week patients also attended a psychiatrist (who was blind to treatment) for a structured clinical interview for the DSM-III-R and to record their self rated clinical global impression change score. Seven subjects (four in the exercise group, three in the flexibility group) did not attend the psychiatrist at the correct time despite completing treatment; these patients assessed their clinical global impression score retrospectively and returned it by post.

Table 1 Self rated clinical global impression change scores after completing treatment

Clinical global impression change score	No (%) in exercise group (n=29)	No (%) in flexibility group (n=30)
1 (Very much better)	9 (31)	2 (7)
2 (Much better)	7 (24)	6 (20)
3 (A little better)	11 (38)	18 (60)
4 (No change)	1 (3)	3 (10)
5 (A little worse)	1 (3)	0
6 (Much worse)	0	1 (3)
7 (Very much worse)	0	0

After the follow up reassessment patients in the flexibility group could cross over to exercise treatment. Treatment and follow up were the same as for the original exercise group.

All patients were instructed to continue with regular exercise and could remain in contact with the laboratory, mainly by phone. Three months after stopping supervised exercise patients were reassessed. Roughly one year after supervised treatment stopped a letter was sent to all patients asking about their activities and asking them to record their self rated clinical global impression change score.

Statistical analysis

The clinical global impression change score was analysed categorically, a score of 1 or 2 ("very much better" or "much better") being considered clinically important versus scores of 3 to 7 ("a little better" to "very much worse"). We compared the proportions of patients rating themselves as clinically improved among those who completed treatment as well as by intention to treat analysis by means of a χ^2 test with a continuity correction. We completed follow up assessments on four of the seven patients who dropped out of treatment and included these data in the intention to treat analysis. Patients with missing data were counted as non-improvers. We compared all subsidiary outcome variables by Student's *t* or Mann-Whitney tests. The effects of the two treatments on the submaximal responses to exercise were compared by examining the group means of heart rate and perceived exertion score during the middle third (6-12 minutes inclusive) of the group maximum treadmill tests. At the three month and one year follow ups we reported the proportions of patients feeling better both after completing treatment and by intention to treat analysis.

Results

Baseline data

The 66 patients had a mean age of 37.2 (SD 10.7) years and a mean body mass index of 23.8 (4.6). Forty nine (74%) were women. The median duration of illness was 2.7 (range 0.6-19.0) years. Twenty patients were taking full dose antidepressants; 10 were taking low dose tricyclic antidepressants as hypnotics. All patients were told to continue their medication unchanged. Two thirds of patients (n=44) blamed viruses for their illness. There were no significant differences in the proportions of both groups taking antidepressants or blaming a virus for their illness.

Treatment results

Table 1 shows the main outcome of treatment. Sixteen of the 29 patients who completed exercise treatment rated themselves as "much" or "very much" better compared with eight of the 30 patients in the flexibility group ($\chi^2 = 3.85$, *df* = 1; *P* = 0.05). Only two patients (one in each group) rated themselves worse after treatment; both had developed a major depressive illness. Four patients in the exercise group and three in the flexibility group dropped out of treatment. Only two patients (one from each group) said they dropped out because the treatment made them worse. Analysis by intention to treat showed that 17 of 33 patients improved with exercise and nine of 33 improved with flexibility treatment ($\chi^2 = 4.06$, *df* = 1; *P* = 0.04).

The median peak oxygen consumption was significantly greater after exercise than after flexibility treatment (13% *v* 6% increase; table 2). The median increase in isometric strength was 26% in the exercise group and 15% in the flexibility group (Mann-Whitney *U* test = 351; *P* = 0.20). The mean heart rate during submaximal treadmill testing was 143 (SD 13) beats/min after exercise treatment versus 150 (13) beats/min after flexibility treatment (*t* = 2.06, *df* = 56; *P* = 0.04) (fig 1). The mean submaximal perceived exertion score was 14.5 (3.4) with exercise compared with 16.2 (2.8) with flexibility treatment (*t* = 2.13, *df* = 57; *P* = 0.04) (fig 2). None of these peak or submaximal measures was significantly different before treatment. Those patients in the exercise group who rated themselves as better had no significantly greater improvement in either peak oxygen consumption (*t* = 0.71,

Table 2 Physiological variables at baseline and after completing treatment

Variable	Baseline		After 12 weeks of treatment		P value
	Exercise group (n=33)	Flexibility group (n=33)	Exercise group (n=29)	Flexibility group (n=30)	
Median (interquartile range) peak oxygen consumption with exercise (ml/kg/min)	31.8 (26.8-36.8)	28.2 (23.4-33.1)	35.8 (30.8-40.7)	29.8 (24.7-34.9)	0.03
Median (interquartile range) maximum ventilation (l/min)	71.2 (52.6-89.7)	69.7 (62.0-77.5)	88.6 (66.9-107.3)	76.1 (54.0-98.2)	0.04
Mean (SD) maximum heart rate (beats/min)	170 (18)	171 (19)	174 (17)	178 (14)	0.24
Median (interquartile range) percentage of predicted maximum heart rate	91 (85-98)	93 (89-97)	95 (91-99)	95 (90-100)	0.34
Mean (SD) recovery heart rate three minutes after test (beats/min)	109 (18)	111 (17)	111 (16)	115 (15)	0.68
Mean (SD) test duration (min)	10.5 (3.7)	9.5 (3.6)	12.4 (3.5)	11.0 (3.3)	0.08
Median (interquartile range) submaximal blood lactate (mmol/l)	2.6 (1.4-3.8)	2.3 (1.4-3.4)	2.0 (1.2-2.8)	2.5 (1.6-3.4)	0.91
Mean (SD) post-test blood lactate (mmol/l)	4.9 (1.9)	5.8 (2.5)	6.2 (2.5)	6.1 (2.5)	0.95
Mean (SD) maximal quadriceps voluntary contraction (with twitch interpolation) (N)	339 (144)	340 (105)	430 (182)	378 (100)	0.18

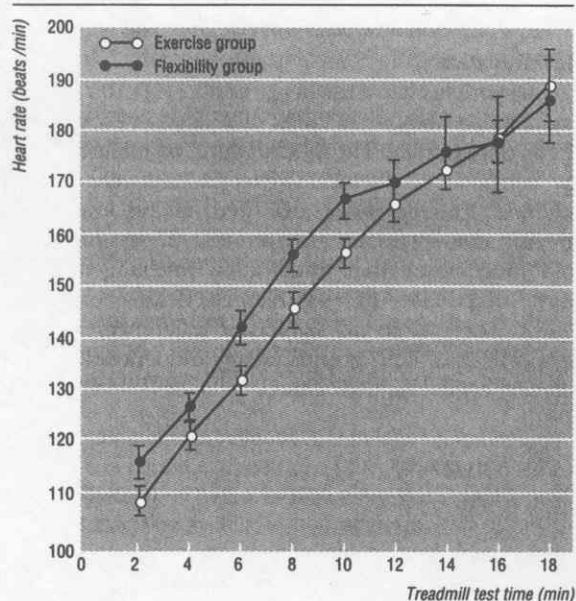


Fig 1 Mean heart rates during treadmill testing after treatment. Bars are SEM

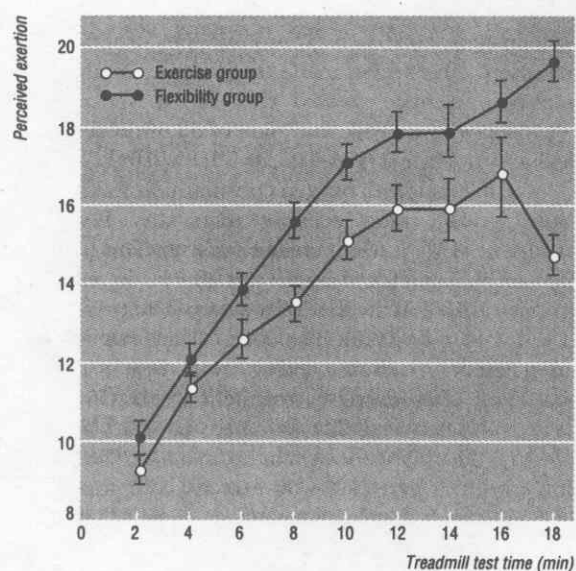


Fig 2 Mean perceived exertion scores during treadmill testing after treatment. Bars are SEM

df = 26; $P = 0.48$) or strength (Mann-Whitney U test = 71; $P = 0.24$) than the rest.

Both total and physical fatigue, total SF-36 score, physical function, and general health were significantly better after exercise than after flexibility treatment, though none of these measures had returned to normal (table 3).

Crossover subjects

Seven patients who completed the flexibility programme chose not to proceed to the exercise treatment, usually because of domestic commitments. Twenty three patients went on to exercise treatment immediately after the flexibility treatment. Twelve of 22 patients who completed the exercise programme rated themselves as better at follow up. One subject had a foot operation for an unrelated condition and dropped out. Significant improvements occurred in peak oxygen consumption ($P < 0.0001$) and physical function ($P = 0.002$) compared with baseline, which had not significantly improved after flexibility alone.

Three month follow up after exercise

Forty seven of the original 66 patients were reassessed three months after stopping supervised exercise treatment. Of the remaining 19 patients, seven dropped out of the first three months of treatment, seven did not cross from flexibility to exercise treatment, and five could not attend because of moving home or an injury unrelated to exercise. Thirty two of those who attended follow up after completing exercise treatment rated themselves as better. By intention to treat analysis 32 of 56 patients were better after exercise.

Physiological improvements recorded at first follow up were maintained or exceeded in patients who attended three months after completing exercise treatment. In particular, the mean maximal voluntary contraction force of the quadriceps muscle had increased from 339 (SD 126) Newtons (N) at baseline to 436 (161) N by six months ($P < 0.001$).

One year follow up

Fifty two (79%) patients returned questionnaires one year after stopping their supervised treatment. Thirty five of 47 (74%) patients who completed exercise treatment rated themselves as better (35 of 56 (63%) patients by intention to treat analysis). Of the seven

Table 3 Symptomatic and functional measures at baseline and after completing treatment

Variable	Baseline		After 12 weeks of treatment		P value
	Exercise group	Flexibility group	Exercise group	Flexibility group	
Mean (SD) Chalder fatigue score	28.9 (7.1)	30.5 (5.6)	20.5 (8.9)	27.4 (7.4)	0.004
Mean (SD) total fatigue score†	312 (50)	325 (45)	253 (48)	286 (67)	0.04
Mean (SD) physical fatigue score†	161 (27)	177 (16)	130 (28)	154 (34)	0.006
Mean (SD) mental fatigue score†	151 (26)	148 (34)	124 (31)	132 (39)	0.38
Mean (SD) SF-36 total score	341 (84)	336 (73)	478 (112)	420 (120)	0.05
Mean (SD) SF-36 physical function score	48.5 (22.1)	47 (18.7)	69 (18.5)	55 (21.8)	0.01
Median (interquartile range) SF-36 general health score	41 (22-48)	33 (21-40)	45 (36-66)	37 (25-52)	0.03
Median (interquartile range) depression score‡	5 (1.5-8.5)	5 (2.5-7.5)	5.5 (2.9-8.1)	4 (0.6-7.4)	0.92
Median (interquartile range) anxiety score‡	5.5 (1.5-8.5)	4 (0.5-7.5)	5.5 (3.0-8.0)	7 (3.5-10.5)	0.46
Median (interquartile range) sleep total score§	7 (5.5-8.5)	6 (4.5-7.5)	5 (3.5-6.5)	6 (4.1-7.9)	0.49

Normal or usual scores are 14 for Chalder questionnaire, 200 for total fatigue score (visual analogue scale), and 100 for physical and mental fatigue scores (visual analogue scales). 100 is maximum (full capacity) SF-36 score for physical and general health function. Score less than 8 on hospital anxiety and depression scale is considered non-pathological. Pittsburgh sleep quality index score less than 6 is considered non-pathological.

†Visual analogue scale.

‡Hospital anxiety and depression scale.

§Pittsburgh sleep quality index.

patients who had flexibility treatment alone, five replied, of whom two felt better (one of whom had done her own exercise programme). Thirty one (66%) patients who completed exercise treatment were working or studying at least part time compared with 26 (39%) of all 66 patients before treatment (95% confidence interval of difference 9% to 44%). Thirty two of 47 (68%) of these patients had continued exercising and considered themselves regularly active compared with 36 of 65 (55%) patients who said they were regularly active before becoming ill (no significant difference).

Discussion

Graded exercise treatment was more effective than relaxation and stretching exercises, suggesting that the amount of therapists' attention was not responsible for the difference in outcome. Analysis by intention to treat gave similar results, with low drop out rates and minimal adverse effects. Only five patients declined the study and five were too ill to attend as outpatients. The same result in patients who crossed over supports the original finding. The subsidiary outcome measures of fatigue and functional capacity confirmed the greater improvement with exercise. Improvement was maintained or exceeded at both three and 12 months of follow up. Almost three quarters of patients followed up felt better and had an accompanying return to pre-morbid levels of physical activity, and an increased proportion had returned to work or study. In a similar sample only 2% of subjects reported spontaneous resolution of fatigue by 18 months of follow up.²⁹ Hence it is unlikely that spontaneous improvement would have occurred without exercise in our series. Nevertheless, because of the crossover design of our study we cannot state with certainty that exercise was responsible for the continued improvement after the first follow up examination.

The 13% increase in aerobic capacity was consistent with an increase of between 5% and 10% found in healthy but sedentary people performing a similar training programme.³⁰ Surprisingly, both groups significantly increased their strength with treatment despite previous studies finding no significant difference in the strength of sufferers when compared with healthy controls.⁵⁻⁷ These improvements in strength may have been due to the increased mobility that occurred with both treatments. However, patients given flexibility treatment did not significantly improve their aerobic capacity until they crossed over to exercise treatment.

Both physiological and perceptual improvements occurred at submaximal treadmill stages after exercise treatment compared with flexibility treatment, as reported in an open study.¹⁵ This is clinically important, as submaximal activities such as walking are functionally more important than maximal activities such as running. The different changes in heart rate response to exercise were not related to antidepressants, as similar proportions of patients from both groups were taking these drugs.

The limitations of our study include the exclusion of 44% (74/167) of possible subjects because of their comorbid psychiatric disorders, though this was mitigated by the inclusion of 16% (27/167) of subjects

Key messages

- Graded exercise treatment is more effective than relaxation and flexibility treatment for patients with the chronic fatigue syndrome who do not have a psychiatric disorder or sleep disturbance
- Overall improvement is accompanied by improvements in fatigue and physical function but seems independent of the improved strength and peak aerobic capacity produced by exercise
- In this survey few patients refused or dropped out of exercise treatment and only one patient claimed to be worse after completing it
- Patients show sustained benefit one year after graded exercise treatment

who had their psychiatric disorder successfully treated before the study. Though bias may have been introduced by the lack of blindness in the exercise physiologists at reassessment, care was taken to standardise the encouragement given; submaximal results would not have been affected, and the main outcome measure was self rated to avoid this bias.

We can only speculate whether it was important to treat or exclude patients with a psychiatric disorder or sleep disturbance. The only two patients to feel worse after completing treatment had developed depressive illnesses. Though exercise may help depressive illness,¹⁰ it improved neither mood nor sleep in this or a previous study.¹³ The present evidence suggests that these factors should be treated before starting an exercise programme.^{3 4}

The only other treatment of the chronic fatigue syndrome to show promise is cognitive behaviour therapy, which improves functional capacity and symptoms more than both standard medical care and relaxation therapy.^{31 32} At first glance exercise treatment seems to work more quickly, as 52% of subjects had improved (by intention to treat analysis) after three months compared with 27% with cognitive behaviour therapy after five months.³¹ However, outcomes at final follow up were similar. The treatments cannot fairly be compared, as one cognitive behaviour therapy study recruited subjects with greater perceived physical incapacity³² and both cognitive behaviour therapy studies treated subjects with concurrent psychiatric disorders. Whether cognitive behaviour therapy is equally effective in the absence of psychiatric disorders is uncertain.^{31 32}

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