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Amantadine and *L*-Carnitine Treatment of Chronic Fatigue Syndrome

Key Words
Amantadine
Carnitine
Chronic Fatigue Syndrome
Fatigue

Abstract
Carnitine is essential for mitochondrial energy production. Disturbance in mitochondrial function may contribute to or cause the fatigue seen in Chronic Fatigue Syndrome (CFS) patients. Previous investigations have reported decreased carnitine levels in CFS. Orally administered *L*-carnitine is an effective medicine in treating the fatigue seen in a number of chronic neurologic diseases. Amantadine is one of the most effective medicines for treating the fatigue seen in multiple sclerosis patients. Isolated reports suggest that it may also be effective in treating CFS patients. Formal investigations of the use of *L*-carnitine and amantadine for treating CFS have not been previously reported. We treated 30 CFS patients in a crossover design comparing *L*-carnitine and amantadine. Each medicine was given for 2 months, with a 2-week washout period between medicines. *L*-Carnitine or amantadine was alternately assigned as fist medicine. Amantadine was poorly tolerated by the CFS patients. Only 15 were able to complete 8 weeks of treatment, the others had to stop taking the medicine due to side effects. In those individuals who completed 8 weeks of treatment, there was no statistically significant difference in any of the clinical parameters that were followed. However, with *L*-carnitine we found statistically significant clinical improvement in 12 of the 18 studied parameters after 8 weeks of treatment. None of the clinical parameters showed any deterioration. The greatest improvement took place between 4 and 8 weeks of *L*-carnitine treatment. Only 1 patient was unable to complete 8 weeks of treatment due to diarrhea. *L*-Carnitine is a safe and very well tolerated medicine which improves the clinical status of CFS patients. In this study we also analyzed clinical and laboratory correlates of CFS symptomatology and improvement parameters.

Introduction

Profound muscle fatigue, precipitated by minimal physical activity, is one of the major symptoms in Chronic Fatigue Syndrome (CFS) patients [1]. In CFS there have been reports of excessive intramuscular acidification [2] and abnormal jitter with single fiber electromyography [3] suggestive of abnormal muscle membrane function. However, other investigators have not found abnormalities in muscle fatigability and excitation-contraction coupling [1, 4].

In vitro tests have shown depressed muscle mitochondrial respiration in CFS and patients have demonstrated reduced aerobic work capacity [5]. Mitochondrial palmitate oxidation has been reported to be reduced in CFS patients [6] and intracellular concentration of ATP has been demonstrated to be reduced at peak exercise in CFS patients [7]. These results suggest a mitochondrial abnormality.

Recent investigations in Great Britain have shown that 70% of CFS patients have ultrastructurally abnormal muscle mitochondria [8–10]. These mitochondria have abnormal sizes, shapes and a peculiar infolding of the inner mitochondrial membrane producing 'compartmentalization' of their internal structure. These structural abnormalities may be associated with deficits in mitochondrial energy production that may lead to fatigue.

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Carnitine is essential in mitochondrial energy metabolism. It has two principal functions: (1) to transport long-chain fatty acids into the mitochondrion for beta oxidation; (2) to help regulate the intramitochondrial ratio of acetylcoenzyme A (CoA) to free CoA [reviewed in 11]. Carnitine deficiency conditions may be primary, such as those associated with inborn errors of metabolism, or secondary, such as those associated with inadequate intake of carnitine or those that are induced by medicines. Clinical symptoms of carnitine deficiency may include: myopathy, cardiomyopathy, encephalopathy and fatigue. In a study of 38 CFS patients, serum levels of acylcarnitine were found to be statistically decreased when compared to controls [12]. Free carnitine and total carnitine levels were found not to differ statistically from controls. Also, clinical correlations were noted between increases in acylcarnitine levels and improvement in fatigue symptoms [12]. We have found decreased total carnitine, free carnitine and acylcarnitine levels in 35 CFS patients (27 females and 8 males) [13]. We have also found a statistically significant correlation between serum levels of total and free carnitine and clinical symptomatology [13]. Higher serum carnitine levels correlated with better functional capacity. These findings may be indicative of mitochondrial dysfunction that may contribute to or cause symptoms of fatigue in CFS patients.

Orally administered *L*-carnitine is an effective medicine to treat carnitine deficiency conditions (of primary and secondary causes). It is also effective in treating lethargy and fatigue seen in a variety of chronic neurologic diseases [14, 15]. An investigation of the use of *L*-carnitine in treating CFS patients has not been previously reported.

Amantadine is a very effective treatment of fatigue in patients with other chronic neurologic conditions, such as multiple sclerosis (MS) [16–18]. It has also been shown to be very effective in treating MS-associated chronic pain [15]. Amantadine can also alleviate symptoms of withdrawal, including fatigue, in patients with cocaine dependency [19].

Amantadine is an antiviral agent which acts by inhibiting penetration of the virus into the host cell. It does not appear to be virucidal and does not suppress antibody response. Amantadine may elevate dopaminergic activity [16–18]. While not a dopamine agonist, amantadine releases norepinephrine and dopamine from storage sites in the central nervous system (CNS) and retards reuptake of these neurotransmitters into neurons. Improvement of fatigue in MS patients with amantadine was acccompanied by significantly increased levels in plasma of beta-endorphin-beta-lipotropin (endogenous CNS opioids) [18]. The absence of any measureable effects of amantadine on power and endurance scores, which reflects peripheral, rather than central fatigability [20], supports the suggestion of a primarily central effect of amantadine. Although the precise mechanism of amantadine's action on the CNS is unknown, it could be a non-specific, general CNS stimulator [21].

There is one case report of a CFS patient significantly improving with amantadine [22]. One of the authors (A.P.) has succesfully treated 2 CSF patients with amantadine [unpubl. results]. An investigation of the use of amantadine for treating CFS patients has not been previously reported.

We treated 30 CFS patients in a cross-over design comparing *L*-carnitine and amantadine. Each medicine was given for 2 months, with a 2-week washout period between medicines. *L*-carnitine or amantadine was alternately chosen as the first medicine.

Both amantadine and *L*-carnitine are safe and well tolerated medicines. In a previous report of 643 patients who were treated with *L*-carnitine 2% developed diarrhea, 1% a fishy smell, 1% transient hair loss and 0.05% a skin rash [23]. The most common side effect of amantadine treatment is insomnia. This problem can be almost completely averted by giving the second dose of amantadine not later than noon. Although side effects of amantadine have been reported to include nausea, dizziness, anxiety, confusion and constipation, for the dose in our treatment program (100 mg twice a day), there are few reported adverse reactions. In a previous report of 115 MS patients treated with amantadine at this dose, only 1 patient suffered from acute confusion, whereas 4 were not able to tolerate placebo [21]. In another study of 32 MS patients treated with the same dose of amantadine, 7 were not able to tolerate amantadine, whereas 6 were unable to tolerate placebo [17].

The objective of our study was to determine whether CFS patients may be successfully treated with *L*-carnitine and with amantadine. Preliminary results of this investigation have been presented [24].

Materials and Methods

30 patients (17 females and 13 males) were evaluated for CFS. They all underwent detailed reviews of their medical history and a thorough general physical and neurologic examination. Clinical information was obtained regarding whether the onset of the illness was acute (less than 48 h), subacute (2–7 days) or chronic (greater than 7 days). All had routine blood tests performed including complete blood count, chemistry screen (including glucose, electrolytes, cal-

Table 1. CFS impairment index

Choose a number that best indicates your physical and mental condition

0 = complete disability
1 = severe impairment
2 = moderate impairment
3 = mild impairment
4 = minimal impairment
5 = no impairment

Physical parameters						
Personal care	0	1	2	3	4	5
Walking	0	1	2	3	4	5
Working	0	1	2	3	4	5
Sleeping	0	1	2	3	4	5
Coordination	0	1	2	3	4	5
Mental parameters						
Concentration	0	1	2	3	4	5
Speech	0	1	2	3	4	5
Memory	0	1	2	3	4	5
Calculation	0	1	2	3	4	5
Orientation	0	1	2	3	4	5

Physical _____ Mental _____ Total _____

Table 2. CFS Severity Index

Choose a number that best describes the severity of your illness

1 I am ill, but not disabled at all
2 I am minimally disabled
3 I am mildly disabled
4 I am moderately disabled
5 I am severely disabled
6 I am completely disabled

cium, magnesium, liver function tests and renal function tests), sedimentation rate, rheumatoid factor, ANA, T3, T4, TSH, CPK, HIV, hepatitis screen, RPR, B12, red blood cell folate and serum carnitine determinations. All patients had a urinalysis performed. All patients underwent chest X-rays and intradermal intermediate-strength PPD testing. When clinically indicated selected patients underwent Lyme disease screen, head MRI scanning and polysomnography. If patients had the necessary laboratory tests performed within the previous 6 months and were able to provide documentation of those results, the tests were not repeated. All patients underwent detailed clinical evaluations including the Fatigue Severity Scale (FSS) [24], the Beck Depression Inventory (BDI) [25], the Symptom Checklist 90-R (SCL-90-R; this consists of multiple psychologic test categories and general summary scales) [26], and the CFS Impairment Index (CFS-II) which consists of physical and mental subsets. The CFS-II is presented in table 1 and is a modification of another CFS evaluation scale [27]. In order to obtain a simpler and more general idea of overall functioning, we developed the CFS Severity Index (CFS-SI; table 2) which was also filled out by each patient. In no case was an alternate medical diagnosis made. All patients met the CDC criteria for the diagnosis of CFS [30]. Also, all of the patients met the Australian and British definitions of CFS [28, 29]. Reviewing the charts retrospectively, all patients also met the newly revised CDC criteria for CFS [31]. All patients gave signed informed consent prior to entry into this study. This study was approved by the Institutional Review Board of Mercy Hospital.

Two patients obtained abnormally elevated scores on the BDI (≥ 20) and were referred for a comprehensive psychiatric evaluation. In both cases this evaluation determined that the patients were not suffering from a primary psychiatric disease, and these patients were enrolled into the treatment program.

At the time of initial phlebotomy for laboratory testing, serum samples were immediately frozen and were courier-delivered to the Mayo Clinic laboratories for assays of total carnitine, free carnitine and acylcarnitine levels using radiolabeled enzymatic techniques [32, 33]. No patients were taking *L*-carnitine at the time of phlebotomy.

Patients were enrolled into the crossover treatment program with *L*-carnitine and amantadine. Alternate patients were assigned to be treated with *L*-carnitine or amantadine first. Thus 15 patients were treated first with *L*-carnitine and 15 with amantadine. The first phase of the medication trial was to continue for 2 months, after which time there was a 2-week washout period. After this washout period, the alternate medication was given for an additional 2 months.

During the treatment program patients were allowed to take minor analgesics (such as nonsteroidal anti-inflammatory medicines) for pain control and other medicines that they may have needed to take for other medical conditions. During the study, patients were not allowed to take any medicine that may have interfered with the evaluation of this treatment program (such as antidepressants, anxiolytics, beta-blockers, any intravenous treatments and anticonvulsants). If a patient was taking a medicine that may have interfered with the evaluation of this treatment program, that medicine was discontinued 2 weeks before starting the treatment program.

The dose of amantadine was 100 mg once in the morning for 1 month, and, if tolerated, was increased after the 1 month to 100 mg twice a day (morning and noon) [16–18, 21]. The dose of *L*-carnitine was 1 g 3 times a day.

All patients were assessed before, during and after each treatment program. During the 2 months of treatment with either medicine, the assessments were performed every 2 weeks. The efficacy of treatment was evaluated by using the above described instruments (FSS, BDI, SCL-90-R; CFS-II; CFS-SI). These scales have been used in previous investigations of fatigue in various disease processes and have been found to be reliable [34]. Patients were monitored closely for possible side effects from each medicine.

If a side effect occurred, making the continuation of a treatment program medication impossible or inadvisable, that medication was stopped, and after a 2-week washout period, the alternate medicine was started.

The treatment program was discontinued if a patient was not compliant with medicine intake or follow-up visits and evaluations. Pregnancy, should it have occurred during the treatment program, would have been grounds for discontinuation since possible teratogenic effects of *L*-carnitine and amantadine in humans are not known. Any intercurrent illness may have been grounds for discontinuation from the treatment program if the treatment program had been postponed for more than 2 months.

Medicines were provided free of charge to all patients. All clinical visits and evaluations for this study were also provided free of charge.

For statistical analysis Student's two-tailed t test, discriminant function analysis, ANOVA, Pearson's rank correlation coefficients and Spearman's nonparametric correlation coefficients were used. The statistical analysis was performed using the SPSS 4.1 program. The data is presented as the mean ± one standard deviation of the mean.

Results

Of the original 30 patients enrolled, 2 (1 female and 1 male) had to be dismissed from the study due to failure to take the assigned medicine and to come in for follow-up visits. Thus, the study data is that of 28 enrolled patients (16 females and 12 males). The age range was 18–67 years with a median of 40 years. The duration of illness ranged from 1 to 20 years with a median duration of 5.0 years. The onset of illness was acute in 23, subacute in 1 and chronic in 4. During the treatment program no significant intercurrent illnessess occurred in any of the participants. Also, no female participant became pregnant. All 28 individuals complied with directives not to take any medicines that would have interfered with the treatment program. The only supplemental medicines used were nonsteroidal anti-inflammatory medicines taken on an as needed basis.

14 patients were started on *L*-carnitine and 14 on amantadine as the first medicine. No significant differences were found between these two groups of patients for the age, sex, mode of onset, duration of disease, or carnitine levels (free, acyl and total) variables. At the time of entry into the study, of all the psychometric tests and subtests administered, the only significant difference found was in the Positive Symptoms Distress Index (PSDI) of the SCL-90-R in the *L*-carnitine-treated group (1.86 ± 0.31) versus the amantadine group (1.68 ± 0.41; $p = 0.005$). There were no significant differences found in any of the other psychometric test and subtest results between these two groups.

At the time of starting the *L*-carnitine, when we compared the 14 patients who were first treated with *L*-carnitine and the second set of 14 who were treated with *L*-carnitine as the second medicine, the only significant differences were in the Depression Index (DI) of the SCL-90-R (those treated first had a score of 1.31 ± 0.62 versus those treated second with a score of 0.80 ± 0.54; $p = 0.028$), in the Global Severity Index (GSI) of the SCL-90-R (those treated first had a score of 0.964 ± 0.395 versus those treated second with a score of 0.614 ± 0.400; $p = 0.028$) and in the Positive Symptom Total Index (PSTI) of the SCL-90-R (those treated first had a score of 45.72 ± 13.19 versus those treated second with a score of 29.29 ± 18.11; $p = 0.011$).

Clinical Correlations

In evaluating possible associations between age, sex, mode of onset of illness and duration of illness with all of the psychometric tests and subtests administered, the only statistically significant correlations exhibited were: female sex with Psychoticism Index of the SCL-90-R ($p < 0.05$); mode of onset with Phobic Anxiety Index (PAI) of the SCL-90-R ($p < 0.05$; chronic onset correlated with worse PAI scores); and mode of onset with FSS ($p < 0.05$; acute onset correlated with worse FSS scores).

In evaluating possible cross-correlations between age, sex, mode of onset of illness and duration of illness, the following statisically significant associations were found: duration and mode of onset ($p < 0.05$; longer duration of illness correlated with chronic onset); and duration with age ($p < 0.01$; longer duration of illness correlated with older age).

In evaluating possible associations between serum carnitine levels (free, acyl and total) and clinical parameters and psychometric test and subtest results, several statistically significant correlations were found. Free carnitine levels were associated with the Paranoid Ideation Index of the SCL-90-R ($p < 0.05$), with the CFS-II Physical score ($p < 0.05$; higher free carnitine levels correlated with worse results), and with the female sex ($p < 0.05$). Acylcarnitine levels were associated with CFS-II Mental score ($p < 0.05$; higher acylcarnitine levels correlated with better function), with CFS-II Total score ($p < 0.05$; higher acylcarnitine levels correlated with better function), with mode of onset ($p < 0.05$; higher acylcarnitine levels correlated with chronic onset), and with duration ($p < 0.01$; higher acylcarnitine levels correlated with longer duration of illness). Total carnitine levels were associated with mode of onset ($p < 0.01$; higher total carnitine levels correlated with chronic onset).

Amantadine

Amantadine was not well tolerated. Only 15 patients were able to complete the 8-week amantadine treatment program. 4 patients stopped taking amantadine during the 1st week, 3 during the 2nd week and 6 during the 4th week. The side effects that caused patients to stop taking this medicine are listed in table 3. Temporary discontinuation of amantadine for 2–7 days did not relieve the side effects when this medicine was reintroduced.

Table 3. Symptoms that caused patients to stop taking amantadine during the treatment program

Symptom	Patients
Insomnia	7
Increased irritability	5
Increased fatigue	3
Increased muscle pain	3
Increased mental confusion	3
Gastrointestinal symptoms (nausea, vomiting, diarrhea)	3
Increased muscle weakness	2
Increased depression	2
Increased headaches	2
Dry mouth	1
Visual blurring	1
Lymph node swelling	1
Fevers	1
Loss of appetite	1
Dizziness	1

The number of patients who stopped taking amantadine was 13 (46% of 28 enrolled patients).

Table 4. *L*-Carnitine 0–4 weeks treatment results, N = 28

	0 weeks	4 weeks	p value
SCL-90-R			
Somatization	1.33±0.58	1.21±0.59	0.211
Obsessive-Compulsive	1.34±0.69	1.21±0.79	0.183
Interpersonal Sensitivity	0.44±0.52	0.35±0.49	0.253
Depression	1.06±0.63	0.96±0.66	0.226
Anxiety	0.65±0.57	0.51±0.51	0.040[2]
Hostility	0.56±0.51	0.61±0.62	0.655
Phobic Anxiety	0.28±0.96	0.24±0.67	0.584
Paranoid Ideation	0.40±0.65	0.28±0.47	0.197
Psychoticism	0.27±0.29	0.24±0.22	0.518
GSI[1]	0.79±0.43	0.69±0.42	0.049[2]
PSDI[1]	1.87±0.31	1.80±0.45	0.259
PSTI[1]	37.5±17.7	34.9±15.8	0.188
BDI	12.9±6.1	10.1±4.7	0.003[2]
CFS-II			
Physical subset	14.3±8.7	15.9±8.5	0.007[2]
Mental subset	14.3±5.0	15.6±5.8	0.140
Total	26.6±8.9	29.5±9.5	0.004[2]
FSS	53.8±14.4	53.0±10.9	0.615
CFS-SI	4.37±1.3	4.15±1.1	0.110

[1] Summary scales of the SCL-90-R.
[2] Statistically significant.

In comparing the group of patients who were able to tolerate amantadine (n = 15) and those that were not (n = 13), there was no significant difference in age, sex, mode of onset of disease, duration of disease, or any of the psychometric tests and subtests administered. Using discriminant analysis, predictors for amantadine tolerance were the Obsessive-Compulsive Index (OCI) and the PSDI of the SCL-90-R where these two indices correctly classified 78% of amantadine tolerance cases (p = 0.012). Patients who had high OCI and high PSDI scores were the ones who were able to tolerate amantadine.

In the group of patients who were able to tolerate amantadine for 4 weeks (n = 20), the only improvements noted in any of the indices were in the Hostility Index (HI) of the SCL-90-R (before treatment: 0.545 ± 0.402; after 4 weeks: 0.345 ± 0.228; p = 0.024) and in the Positive Symptom Total Index (PSTI) of the SCL-90-R (before treatment: 37.90 ± 15.50; after 4 weeks: 30.85 ± 11.90; p = 0.034).

In the group of patients who were able to tolerate amantadine for 8 weeks (n = 15), there was no improvement seen in any of the psychometric tests and subtests comparing baseline to 8 weeks. The improvements seen at 4 weeks in the HI and PSTI of the SCL-90-R, were no longer statistically significant at 8 weeks.

L-*Carnitine*

All 28 patients were able to tolerate *L*-carnitine for 4 weeks. In 1 female patient, abdominal pain and diarrhea occurred after the 4th week causing her to stop taking this medicine before completion of the 8th week. A temporary discontinuation for 1 week of *L*-carnitine did not prevent recurrence of symptoms when the medicine was reintroduced.

The results from baseline to 4 weeks of *L*-carnitine treatment are presented in table 4. In 5 of the 18 psychometric tests and subtests there was a statistically significant improvement. It should be noted that with the results of the CFS-II an increase in scores indicates an improvement in function, whereas in all of the rest, an increase in scores indicates deteriorating function. There was no subset in which there was a deterioration in the score after 4 weeks of *L*-carnitine treatment.

The results from baseline to 8 weeks with *L*-carnitine are presented in table 5. In 12 of the 18 psychometric tests and subtests there was a statistically significant improvement. In addition, there were no tests or subtests in which deterioration was exhibited. Of note, all subtests im-

Table 5. *L*-Carnitine 0–8 weeks treatment results; N = 27

	0 weeks	8 weeks	p value
SCL-90-R			
Somatization	1.30±0.58	0.95±0.58	0.012[2]
Obsessive-Compulsive	1.32±0.69	1.05±0.75	0.036[2]
Interpersonal Sensitivity	0.44±0.53	0.29±0.42	0.073
Depression	1.07±0.64	0.76±0.59	0.006[2]
Anxiety	0.66±0.57	0.37±0.39	0.006[2]
Hostility	0.58±0.51	0.43±0.43	0.176
Phobic Anxiety	0.29±0.98	0.21±0.67	0.328
Paranoid Ideation	0.41±0.66	0.24±0.38	0.164
Psychoticism	0.27±0.29	0.23±0.28	0.512
GESI[1]	0.79±0.44	0.56±0.41	0.007[2]
PSDI[1]	1.86±0.30	1.55±0.39	0.000[2]
PSTI[1]	37.7±17.9	30.8±17.6	0.038[2]
BDI	12.8±6.1	9.4±6.3	0.022[2]
CFS-II			
Physical subset	14.7±8.7	18.0±9.9	0.000[2]
Mental subset	14.4±5.0	16.6±5.8	0.038[2]
Total	27.0±8.8	32.2±10.5	0.001[2]
FSS	53.4±14.6	50.4±12.4	0.136
CFS-SI	4.18±1.4	3.78±1.3	0.031[2]

One patient was not able to tolerate *L*-carnitine and stopped after week 4.

[1] Summary scales of the SCL-90-R.

[2] Statistically significant.

Table 6. Correlations of test and subtest results

	CFS-II-PHYS	CFS-II-TOT	PSDI
SCL-90-R			
Somatization	−0.3830*	NS	+0.4841**
Obsessive-Compulsive	NS	−0.6146**	NS
Interpersonal Sensitivity	NS	NS	+0.3885*
Depression	NS	−0.4055*	+0.4025*
Anxiety	NS	NS	+0.3815*
Hostility	NS	−0.3886*	NS
Phobic Anxiety	NS	NS	NS
Paranoid Ideation	+0.4893**	NS	NS
Psychoticism	NS	NS	NS
GSI	NS	−0.4475*	+0.4438*
PSDI	−0.3834*	−0.4215*	–
PSTI	NS	−0.3799*	NS
BDI	NS	−0.5064**	NS
CFS-II-PHYS	–	NS	−0.3834*
CFS-II-MENT	NS	+0.8772**	NS
CFS-II-TOT	NS	–	−0.4215*
FSS	−0.6664**	NS	+0.4729*
CFS-SI	NS	−0.6291**	+0.5190**

The correlations are based on the results at the time of entry into the study (n = 28). The numbers are the Pearson rank correlations (r); NS = not significant; * $p < 0.05$; ** $p < 0.01$.

proved over 8 weeks. Moreover, when comparing table 4 to table 5 results, most of the improvement seen with *L*-carnitine took place between weeks 4 and 8.

During the treatment program with *L*-carnitine, when comparing the results both at 4 and at 8 weeks, there was no significant difference between the 14 patients treated first with *L*-carnitine and the 14 treated with *L*-carnitine as the second medicine in any of the psychometric test and subtest results.

The degree of improvement with *L*-carnitine in each of the psychometric parameters studied was calculated by subtracting the baseline from the 8-week results. The degree of improvement in all of the psychometric parameters studied revealed no significant association with age, sex or mode of onset of illness. The only associations detected were between between improvement in the OCI of the SCL-90-R and acylcarnitine levels ($p < 0.05$), between improvement in the CFS-II Total score and acylcarnitine levels ($p < 0.05$), and between improvement in the Somatization Index (SI) of SCL-90-R and duration of illness ($p < 0.05$). These results indicate that those patients who had higher acylcarnitine levels improved more in the OCI and CFS-II Total scores with *L*-carnitine. These results also indicate that those who had a shorter duration of illness improved more in the SI with the use of *L*-carnitine. There were no other statistically significant associations exhibited between improvement in psychometric tests and free carnitine and total carnitine levels.

We compared the degree of improvement with the baseline psychometric results at the start of taking *L*-carnitine. The degree of improvement was significantly associated with the degree of severity for a number of tests used (Spearman nonparametric correlation coefficents): SI of the SCL-90-R ($p = 0.004$); DI of the SCL-90-R ($p = 0.001$); Anxiety Index of the SCL-90-R ($p = 0.000$); GSI of the SCL-90-R ($p = 0.001$); Positive Symptom Total of the SCL-90-R ($p = 0.006$); BDI ($p = 0.000$); FSS ($p = 0.028$). There were no other psychometric tests or subtests found which were associated with the degree of improvement.

Evaluation of Psychometric Parameters

After 8 weeks of treatment with *L*-carnitine, the most significant improvements seen were in the CFS-II Physical score, CFS-II Total score and the PSDI of the SCL-90-R (in all cases $p \leq 0.001$; table 5). These results suggest that these study parameters may be the most useful ones in evaluating CFS symptomatology and in following patients in order to assess the course of the disease and response to medicines. These parameters (at the time of entry into the study) were correlated with the other psychometric parameters and the results are presented in table 6. The other parameters that significantly ($p < 0.01$) correlated with these three include the CFS-II Mental score, the CFS-SI, the FSS, the BDI and the SI of the SCL-90-R.

Discussion

There was excellent compliance with the protocol and only 2 patients had to be discontinued from the study. No one took nonallowed medicines during the study.

Alternate assignment defined which patient would receive amantadine or *L*-carnitine first. There were no significant differences exhibited in any of the clinical and psychometric parameters studied between these two groups at the time of entry into the study. When comparing these two groups of patients after they completed 8 weeks of *L*-carnitine treatment, there were no significant differences found in any of the outcome measures studied. If we, as the investigators, had produced an expectation or bias for improvement simply from entry into the study, then one would have expected that the first medicine used would have been the more effective one. That was not the case. Thus, this result strongly suggests that there was no 'halo' effect bias present in this study [35].

Surprisingly, amantadine was poorly tolerated. Only 15 patients were able to complete the full 8-weeks of treatment, whereas 13 had to discontinue due to side effects. For those patients who were able to complete 8 weeks of amantadine, there were no statistically significant differences exhibited between baseline and 8-week results in any of the studied outcome parameters.

This finding was in sharp contrast with the results found with *L*-carnitine. This medicine was very well tolerated without any complications by 27 of the 28 patients. Only 1 patient had to stop taking this medicine due to diarrhea. After 4 weeks of treatment, all 18 outcome measures showed improvement, 5 of which had reached statistical significance. After 8 weeks, there was further improvement in all of the studied parameters: convincingly, 12 of 18 outcome measures had reached statistical significance. In no case, after 4 and 8 weeks of *L*-carnitine treatment, was there any demonstrable deterioration in function as measured by the instruments used.

Of particular significance is the observation that the degree of improvement seen with the use of *L*-carnitine was associated with the degree of severity of CFS symptoms at the time of starting this medicine. The patients who were the most ill with CFS were those that improved the most with *L*-carnitine. Of note also is the fact that depression also significantly ameliorated with the use of *L*-carnitine both as measured by the DI of the SCL-90-R and the BDI (table 5).

Most of the improvement seen with *L*-carnitine occurred between the 4th and 8th week of treatment. It is possible that a longer course of treatment may have had further beneficial effect. Also, a higher dose of *L*-carnitine may have produced a greater degree of improvement more quickly. These issues need to be adressed in future research studies.

A number of significant associations were detected during this study. These included those between duration of illness and mode of onset and age. Those individuals who had a long duration of illness, tended to be older and tended to have a chronic onset of their disease. From the psychometric tests, the only significant association found was with the FSS, in which acute onset of disease correlated with worse FSS scores.

Correlations between lower acylcarnitine levels and worse clinical CFS symptomatology has been previously reported [12]. Likewise, in a previous study, we reported decreased free and total carnitine serum levels being correlated with CFS symptomatology [13]. In the current treatment program we found decreased free carnitine levels to be associated with the female sex, an observation that is well established in normals [32, 33]. Also, we found decreased acylcarnitine levels to be associated with disease severity in two study psychometric parameters used, thus confirming previously reported results [12]. Higher acylcarnitine and total carnitine levels were also associated with longer duration of illness and with chronic onset of illness, observations that have not been previously reported.

The cause of previously reported decreased serum carnitine levels in CFS patients, and the clinical improvement seen in this study with the use of *L*-carnitine, is not known. It is possible that carnitine may not be obtained from food in sufficient amounts or carnitine synthesis in the liver may be insufficient. Also, excessive excretion by

the kidneys may be a factor. Inactivity appears not to be a possible cause of these findings since carnitine levels do not differ between controls and chronically bedridden patients [Dr. H. Kuratsune, personal communication]. Further investigations of dietary intake, carnitine metabolism and excretion in CFS patients are warranted.

This study also gave us the opportunity to evaluate the usefulness of the psychometric parameters used. Three of the parameters produced highly significant results ($p \leq 0.001$) regarding the improvement seen with *L*-carnitine over 8 weeks of treatment. These parameters are the CFS-II Physical score, the CFS-II Total score and the PSDI of the SCL-90-R. Cross-correlations between these three parameters and the other studied parameters suggest that other worthwhile instruments include the CFS-II Mental score, the CFS-SI, the FSS, the BDI, and the SI of the SCL-90-R.

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