

Open-label study of s-citalopram therapy of chronic fatigue syndrome and co-morbid major depressive disorder

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Abstract

Objective: Chronic fatigue syndrome (CFS) is a debilitating disorder with prominent symptoms of malaise, fatigue, myalgia, arthralgia, and impaired concentration. The symptoms of CFS may often overlap those of Major Depressive Disorder (MDD). Treatment of CFS has generally been disappointing. We hypothesized that s-citalopram therapy may improve the symptoms of both disorders in CFS patients with co-morbid depression.

Methods: 16 patients received s-citalopram 10 mg to 20 mg daily for up to 12 weeks. Outcome measures of CFS included the Chalder Fatigue Questionnaire (CFQ), the multi-dimensional Fatigue Impact Scale (FIS), the CFS symptom rating (CFS-SR) 100 mm visual analogue scale, and the clinical global impressions severity (CGI/S) and change (CGI/C) ratings. Secondary outcomes of MDD included the Hamilton Depression Rating (HAM-D), Beck Depression Inventory (BDI), and the CGI/S and CGI/C ratings of MDD.

Results: We observed reductions in the mean CFQ score ($p < 0.0005$), FIS score ($p < 0.0005$), and CGI/S ($p < 0.0005$) and CGI/C ($p < 0.0005$) ratings over time. There was a significant improvement in 5 of the 8 CFS-SR symptoms: post-exertion malaise ($p = 0.001$), headaches ($p < 0.0005$), un-refreshing sleep ($p < 0.0005$), and impaired memory and concentration ($p < 0.0005$). There was also a reduction in mean HAM-D ($p < 0.0005$), BDI ($p < 0.0005$), CGI/S ($p = 0.001$) and CGI/C ($p < 0.0005$) ratings of MDD.

Limitations: The sample size was limited and the study design was not double-blind or placebo controlled.

Conclusion: We observed a significant reduction in both CFS and co-morbid MDD symptom severity ratings, and improvement in 5 of 8 core somatic symptoms of CFS during s-citalopram therapy.

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Keywords: Chronic fatigue syndrome (CFS); Fatigue; Major Depressive Disorder; s-citalopram; Selective serotonin reuptake inhibitor (SSRI)

1. Introduction

Fatigue may be a prominent feature of Chronic Fatigue Syndrome (CFS) and of Major Depressive Disorder (MDD). While much is known about the pathophysiology and treatment of MDD, less is known about the causes and treatment of CFS (Cleare

et al., 1995; Cleare, 2003; Gerrity et al., 2004; Papanicolaou et al., 2004). CFS, like MDD, is a disorder characterized by symptoms of physical malaise, fatigue, muscle aches, and other somatic and neuropsychological symptoms (Fukuda et al., 1994; Kennedy et al., 2004; Jason et al., 1995; Jason et al., 1999). Known also as ‘chronic fatigue immune dysfunction syndrome’ and ‘myalgic encephalomyelitis’, CFS is increasingly diagnosed in the general population (Jason et al., 1995; Skapinakis et al., 2004; Patten et al., 2005; Ranjith, 2005). It may represent a sub-syndromal form of MDD or may be co-morbid and overlap with MDD (Brunello et al., 1999; Morriss et al., 1999; Henningsen et al., 2004). A recent community-based epidemiologic survey (Jason et al., 1995) estimated the prevalence of CFS to be 422 cases per 100,000 adults, or about 0.8–1 million cases in the US. However, because of the substantial diagnostic overlap with MDD (Brunello et al., 1999; Morriss et al.,

Abbreviations: BDI, Beck Depression Inventory; CDC, Center for Disease Control; CFQ, Chalder Fatigue Questionnaire; CFS, Chronic fatigue syndrome; FIS, Fatigue Impact Scale; HAM-D, Hamilton Depression Rating; MDD, Major Depressive Disorder; SSRIs, Selective serotonin reuptake inhibitors; TCAs, Tricyclic antidepressants.

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1999; Henningsen et al., 2004), this figure may be substantially higher (Jason et al., 1995; Gerrity et al., 2004; Skapinakis et al., 2004). Like MDD, there is a higher prevalence of CFS among women, some ethnic groups, and in individuals of lower socio-economic classes (Jason et al., 1995). Thus, patients with CFS may represent a sizable population that has largely gone undiagnosed and untreated.

The diagnosis of CFS has been based upon the following symptom criteria set forth by the Center for Disease Control (CDC) (Fukuda et al., 1994; Kennedy et al., 2004): (1) unexplained, persistent or relapsing fatigue for ≥ 6 months that is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and (2) the presence of ≥ 4 of the following 8 symptoms which are persistent for ≥ 6 months including (i) post-exertion malaise lasting ≥ 24 h, (ii) sore throat, (iii) tender cervical or axillary lymph nodes, (iv) muscle pain, (v) multi-joint pain without swelling or redness, (vi) headaches, (vii) un-refreshing sleep, and (viii) impairment of short-term memory or concentration.

The treatment of CFS has been empirical and largely based upon the prevailing etiologic hypothesis (Cleare et al., 1995; Cleare, 2003; Gerrity et al., 2004; Papanicolaou et al., 2004; Sullivan et al., 2005). For example, various antiviral therapies, immunosuppression therapies, or steroid drugs have been used to treat putative viral or immunological cause of CFS (Whiting et al., 2001; Solomon and Reeves, 2004). Similarly, antidepressant drug therapy has been used to treat CFS based upon symptom and pathophysiologic overlap of CFS and MDD (Lynch et al., 1991; Bakheit et al., 1992; Goodnick and Sandoval, 1998; Dinan et al., 1997; Sharpe et al., 1997; Scott, 1999; Neeck, 2000; Alnigenis and Barland, 2001; Lynch, 2001).

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been used to treat CFS with variable results depending upon the target symptoms examined, the dose and duration of treatment, and the length of time the comorbid MDD has been present (Lynch et al., 1991; Goodnick and Sandoval, 1998; Lynch, 2001; Blondel-Hill and Shafran, 1993; Deale et al., 1998; Hartz et al., 2003). In addition, other antidepressant drug classes including mixed reuptake inhibitors (Lynch and Seth, 1996; Taylor and Rowbotham, 1996; Hickie, 1999; Ansari, 2000; Dryson, 2000; Gallagher, 2000; Hayes et al., 1992; Iyengar et al., 2002), monoamine oxidase inhibitors (MAOIs) (Natelson et al., 1996; Hickie et al., 1998; Hickie et al., 2000), and atypical antidepressants (Hickie, 1999; Spath et al., 2000; Kiser et al., 2001) have been used to treat CFS with variable results.

While several studies have found SSRI therapy to be well tolerated in CFS patients, the efficacy of SSRI therapy in this disorder has been variable (Lynch et al., 1991; Goodnick and Sandoval, 1998; O'Malley et al., 1999; Arnold et al., 2000; Lynch, 2001; Hartz et al., 2003). Given the putative role of the serotonergic system in CFS (Dinan et al., 1997) and the selective affinity of *s*-citalopram for the serotonin transporter (Klein et al., 2006), we speculated that *s*-citalopram may be suitable for treating CFS. The present study examines the safety

and effect of *s*-citalopram in reducing CFS symptoms in patients with co-morbid CFS and MDD.

2. Methods

2.1. Patient selection

Outpatients ≥ 18 years old with a diagnosis of CFS according to the International Research Case Definition (Fukuda et al., 1994; Kennedy et al., 2004) and a DSM IV Axis I co-morbid diagnosis of MDD (American Psychiatric Association, 2000), were enrolled into the trial. All patients had a baseline 17-item Hamilton Depression Rating (HAM-D 17) (Hamilton, 1960) score ≥ 16 . Patients with a co-morbid DSM IV Axis I diagnosis other than MDD (e.g., generalized anxiety disorder) were not specifically excluded from the trial if the condition did not constitute the primary Axis I disorder. Patients were excluded from the study if they had a history of mania, schizophrenia, psychosis; were actively suicidal or required hospitalization; had current alcohol or substance abuse or alcohol or substance dependence in the preceding 3 months; were non-responsive to prior *s*-citalopram therapy; had prior sensitivity to citalopram or *s*-citalopram; were pregnant or nursing; had an uncontrolled medical condition (e.g., hypertension, diabetes, Lyme's disease); or, had a serum thyrotropin level ≥ 5 μ Iu/ml. Other exclusion criteria were the presence of clinically significant cardiac disease, malignancy, central nervous system disorder (e.g., Parkinson's disease, dementia), hepatic or renal disease, or the use of chemotherapy, over-the-counter antidepressant preparations (e.g., St. John's Wort), tranquilizers, barbiturates, or other sedative or hypnotic medications.

2.2. Evaluation procedures

Before enrolling in the trial, each patient provided signed informed consent in accordance with the ethical standards set forth by the Institutional Review Board (IRB) of the University of Pennsylvania. The clinical trial was conducted using the Principles of Good Clinical Practice Guidelines, with oversight monitoring by the Office of Human Research of the University of Pennsylvania, and by an independent data and safety monitoring board.

A medical and psychiatric history was obtained using the Structured Diagnostic Interview for DSM IV (SCID) (First et al., 2001). All patients met CDC criteria (Fukuda et al., 1994; Kennedy et al., 2004) for definite or probable CFS. All patients had a physical examination including vital signs and weight, a complete blood count, blood chemistry profile (including serum electrolytes, glucose, hepatic enzymes, urea nitrogen, creatinine, and thyroid panel), a pregnancy test (in women of child-bearing potential), urinalysis, urine screen for drugs of abuse, and a 12-lead electrocardiogram. A listing of prior psychotropic drug treatment and a listing of concomitant medication was obtained.

Primary outcome measures included the Chalder Fatigue Scale (CFQ) (Chalder et al., 1993); the multi-dimensional

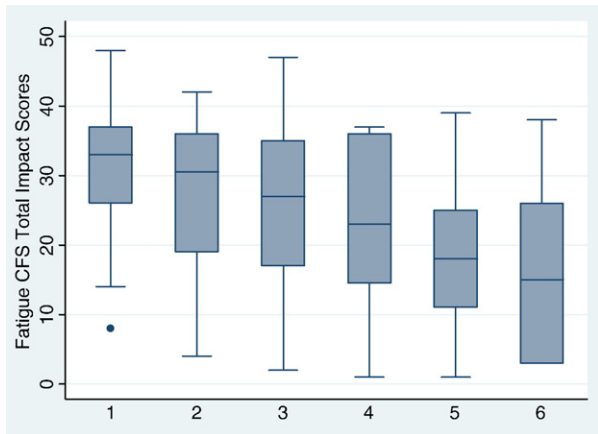


Fig. 1. Total Chalder Fatigue Questionnaire (CFQ) score over time.

Fatigue Impact Scale (FIS) (Fisk et al., 1994); the CFS Symptom Rating (CFS-SR) (Jason et al., 1999) which includes the following symptoms: 1) post-exertion malaise; 2) sore throat; 3) tender lymph nodes; 4) muscle pain; 5) multiple joint pain without swelling or redness; 6) headaches; 7) un-refreshing sleep; and 8) impairment in short term memory or concentration; and, the clinical global impressions severity (CGI/S) and change (CGI/C) ratings for CFS (Guy, 1976). Secondary clinical outcome measures include the 28-item HAM-D with the embedded HAM-D 17 and the 17-item HAM-D ‘atypical’ symptom profile (HAM-D 17-R) rating (Reimherr et al., 1998), the Beck Depression Inventory (BDI) (Beck et al., 1961) and the CGI/S and CGI/C rating for MDD (Guy, 1976).

2.3. Treatment procedure

Patients taking ineffective or partially effective antidepressant therapy prior to enrolling in the trial had this medication discontinued for at least 7 days (14 days for MAOIs) before starting *s*-citalopram therapy. None of the patients were taking fluoxetine, a mood stabilizer, or an atypical anti-psychotic agent within 3 months of enrollment in the study. Patients with $\leq 25\%$ reduction in HAM-D 17 score between screen and baseline study visits, and who maintained a minimum baseline HAM-D 17 score ≥ 16 , received *s*-citalopram therapy at 10 mg daily. Patients, who had $< 50\%$ reduction in total HAM-D 17 score after 2 weeks of *s*-citalopram therapy, increased their *s*-citalopram dose to 20 mg daily (as tolerated) for an additional 10 weeks of therapy. The *s*-citalopram dose could be reduced to 10 mg daily for adverse events. Patients who were intolerant of *s*-citalopram 10 mg daily were discontinued from the trial.

Efficacy and safety measures were obtained at screen and baseline and after 2, 4, 8, and 12 weeks of treatment (or at the time of discontinuing treatment). (Note — in Figs. 1 and 2 these measurement occasions are labeled as visits 1, 2, 3, 4, 5, and 6). All efficacy and safety measures were obtained by a study doctor or research nurse who completed inter-rater reliability training. Concomitant treatment with zolpidem 5–20 mg or zaleplon 5–20 mg was permitted for symptomatic treatment of severe insomnia.

Fourteen patients took at least one concomitant medication. The most common reason for taking concomitant medication was: (i) general health (4 patients), (ii) asthma (3 patients), (iii) diabetes mellitus (2 patients), (iv) hypercholesterolemia (2 patients), (v) hypertension (2 patients), and (vi) insomnia (2 patients). The most commonly used concomitant medication was: (i) multivitamins (4 patients), (ii) albuterol (4 patients), (iii) zolpidem (2 patients), (iv) aspirin (2 patients), and (v) acetaminophen (2 patients).

2.4. Statistical procedures

All analyses were conducted using Stata 9.0 with 2-sided tests of hypotheses. A p -value < 0.05 was considered to be statistically significant. However, adjustments were also made for multiple comparisons in the primary analyses, as described below. Initial analyses were descriptive and included calculation of means, medians, and standard deviation (SD) for continuous variables, and as frequencies for categorical variables. Preliminary analyses of efficacy were performed using the quasi-least squares (QLS) approach that is based on generalized estimating equations (GEE) to describe treatment change over time. This procedure specifies a correlation matrix to describe the pattern of association between the repeated observations on each patient. In comparison with GEE, QLS allows for easier implementation of the Markov correlation structure that is appropriate for longitudinal data that are unequally spaced in time (Chaganty and Shults, 1999). According to the Markov structure, the correlation between two measurements y_{ij} and y_{ik} collected on subject i at times t_{ij} and t_{ik} equals $\alpha^{|t_{ij}-t_{ik}|}$. The Markov structure is plausible because it is often reasonable to assume that two measurements on a subject will be less similar, and therefore less highly correlated, if they are collected farther apart in time. To assess the fit of the Markov structure and other working correlation structures that included the identity structure, we used the Rotnitzky–Jewell criteria (Rotnitzky and Jewell, 1990) as described in Wang and Carey (2003) and implemented in Shults et al. (2006). If the Markov structure (or another structure) was reasonable, as indicated by the Rotnitzky–Jewell criteria, an excellent fit would be indicated

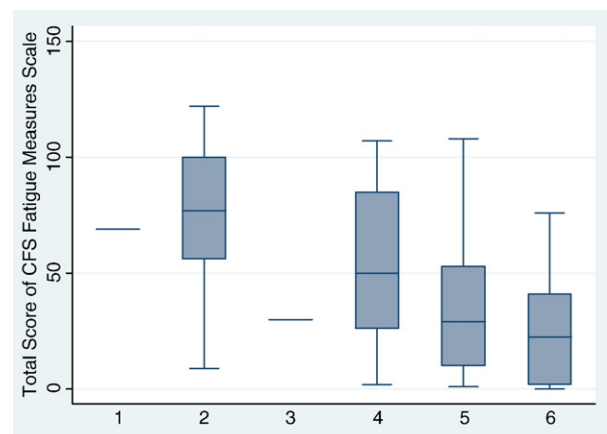


Fig. 2. Fatigue Impact Scale (FIS) score over time.

by values close to 1, 1, 0 for the statistics obtained using this approach. The estimated intra-subject correlation of measurements was relatively high for all outcomes. The QLS regression models for each outcome included time (in weeks) as a covariate. If the regression parameter associated with time was negative and differed significantly from zero, this indicated a significant decline over time in the outcome under consideration. Table 1 displays twelve times the estimated regression coefficient for time (in weeks), with 95% confidence interval and p -value for the test of the hypothesis that this regression coefficient is zero. This represents the expected change in each outcome measure between baseline and the end of the study (12 weeks post-baseline). For each outcome variable, we also constructed box-plots of outcome versus measurement occasion. Figs. 1 and 2 are the box-plots plots for CFQ and FIS scores, respectively. Box plots for other outcome measures are not shown. To adjust for multiple measurements, we included a Bonferroni adjustment to the p -values for each outcome variable. The adjustment was to assess significance at a $0.05 \div 18 = 0.0028$ significance level. The Bonferroni adjustment is conservative because it assumes the tests were independent, which is unlikely for the highly correlated outcome measures of this study. An additional adjustment could also be based on the approach of Shults and Morrow (2002) and Shults et al. (2006) that considers all outcomes on a subject simultaneously, while also adjusting for the intra-outcome correlation of measurements. The results of this study were interpreted cautiously due to the extremely limited sample size.

3. Results

3.1. Patient demographics

Eighteen patients (7 women; 11 men) were enrolled into the study. They had a mean (SD) age of 46 (17.3) years and an age range of 21 to 78 years. Fifteen (83.4%) were Caucasian and 3 (16.7%) were African American. The mean age at the time of CFS onset was 39.4 (18.4) years (range 15 to 68 years), and the mean duration of CFS symptoms was 44.3 (69.6) months (range 5 to 264 months). The mean age at the time of MDD onset was 34.1 (20.0) years (range 12 to 68 years), and the mean current MDD episode duration was 33.2 (38.0) months (range 2 to 144 months). The mean number of prior MDD episodes was 1.28 (1.84) with a range of 0 to 5. The mean age of onset of CFS symptom did not differ significantly from the mean age of onset of MDD symptoms ($p=0.25$, paired t -test). Seventeen of 18 patients (94.5%) reported a possible or definite family history of affective disorder (e.g., 17 depression, 2 bipolar disorder), while 4 (22.3%) had a possible or definite family history of anxiety disorder, and 9 (50%) had a possible or definite family history of substance abuse or dependence. One patient (5.6%) had a family history of anorexia nervosa, and 2 (11.2%) had a family history of suicide.

Two patients (11.2%) were screen failures and did not receive s-citalopram therapy: one who withdrew consent to participate in the study, and one who tested positive for drugs of abuse. Sixteen patients received s-citalopram therapy and had

at least one outcome evaluation. Five patients (31.3%) discontinued treatment prior to study completion for lack of efficacy.

3.2. Efficacy measures

QLS analysis identified a significant reduction in the mean total CFQ scores over time ($p<0.0005$) (Fig. 1). GEE analysis found a significant reduction in the total FIS scores over time ($p<0.0005$) (Fig. 2).

Table 1 displays the estimated change in study outcome measures over the course of the study, with 95% confidence intervals and p -values for the test that the regression coefficient for change is zero. Using the Bonferroni adjusted p -value <0.0028 , there was a significant change over time in 5 of the eight CFS symptom variables as measured using the self-rated 100 mm visual analog scale (VAS). There was a significant reduction in severity of post-exertion malaise ($p=0.001$), headache symptoms ($p<0.0005$), un-refreshing sleep ($p<0.0005$), and impaired memory and concentration ($p<0.0005$). In contrast, there was no significant change over time in the symptoms of lymph node tenderness, sore throat, or multiple joint pain. There was a significant reduction on both the CGI/S and CGI/C measures of CFS ($p<0.0005$).

GEE analysis found a significant reduction in HAM-D 17, HAM-D 17-R, and HAM-D 28 scores over time ($p<0.0005$), as well as a significant decrease in BDI scores ($p<0.0005$) and in the CGI/S ($p=0.001$) and CGI/C ($p<0.0005$) scores for depressive symptoms.

Table 1
Estimated change (12 weeks minus baseline) in study outcome measures

Outcome measure	Change since baseline	95% confidence interval (CI) ^a	p -value
FIS	-48.23	(-64.81,-31.65)	<0.0005
CFQ	-13.24	(-19.33,-7.16)	<0.0005
CGI/S for CFS	-1.75	(-2.21,-1.29)	<0.0005
CGI/C for CFS	-1.81	(-2.36,-1.27)	<0.0005
Post-exertion malaise	-27.23	(-44.02,-10.43)	0.001
Sore throat	-14.72	(-25.02,-4.42)	0.005
Tender lymph nodes	-19.43	(-75.42, 35.51)	0.45
Muscle pain	-30.84	(-48.55,-13.13)	0.001
Multiple joint pain	-16.27	(-30.30,-2.05)	0.025
Headache symptoms	-39.20	(-55.73,-22.68)	<0.0005
Un-refreshing sleep	-31.68	(-43.56,-19.81)	<0.0005
Impaired memory	-29.51	(-42.25,-16.77)	<0.0005
HAM-D 17	-12.34	(-15.64,-9.04)	<0.0005
HAM-D 17-R	-10.41	(-13.33,-7.49)	<0.0005
HAM-D 28	-14.68	(-18.85,-10.51)	<0.0005
BDI	-16.18	(-22.70,-9.65)	<0.0005
CGI/S for MDD	-1.81	(-2.39,-1.22)	<0.0005
CGI/C for MDD	-2.18	(-2.79,-1.57)	<0.0005

^a 95% CI for change between baseline and 12 weeks post baseline (12 weeks minus baseline).

3.3. Safety measures

The most frequently occurring adverse events were daytime tiredness, gastrointestinal upset, jitteriness, diminished libido, insomnia, and agitation. The majority of adverse events were rated as ‘mild’ or ‘moderate’ in severity. There were no meaningful changes in vital signs, physical findings, or laboratory tests during treatment.

4. Discussion

There is a substantial clinical overlap between the symptoms of CFS and MDD (Amsterdam et al., 1986; Jason et al., 1995; Brunello et al., 1999; Morriss et al., 1999; Henningsen et al., 2004; Patten et al., 2005). Both disorders are characterized by low drive, lethargy, lassitude, sleep disturbance, and impaired concentration and memory. Brunello et al. (1999) have suggested that CFS may be most similar to DSM IV dysthymic disorder. However, while antidepressant therapy appears to be effective for 65% of patients with dysthymic disorder (Brunello et al., 1999), antidepressant efficacy of CFS appears to be more variable. Gruber et al. (1996) reviewed evidence-based data on the efficacy of antidepressant therapy of CFS, fibromyalgia, migraine syndrome, irritable bowel syndrome, and atypical facial pain syndrome. Although many of the studies reviewed had differences in design and methodology, the majority appeared to show some benefit of antidepressant therapy — regardless of the drug class employed. While some studies found TCAs to be of benefit for un-refreshing sleep, myalgia, and fatigue symptoms (Lynch et al., 1991; Blondel-Hill and Shafran, 1993; Goodnick and Sandoval, 1998; Deale et al., 1998; Lynch, 2001), the presence of anticholinergic side effects generally precluded the wide-spread use of TCAs in CFS. In an open-label trial, White and Cleary (1997) studied the safety and efficacy of moclobemide in 49 patients with CFS with or without co-morbid depression. Moclobemide was administered up to 600 mg daily for 4 weeks. They found a small, but statistically significant, reduction in the symptoms of fatigue, depressed mood, and somatic pains. Patients with co-morbid CFS and depression showed the best benefit. In a subsequent double-blind, placebo-controlled trial of moclobemide, Hickie et al. (2000) observed a 51% reduction in CFS symptoms (compared to 31% with placebo) that were felt to be independent of changes in mood. Natelson et al. (1996) performed a double-blind, placebo-controlled trial of phenelzine in non-depressed patients with CFS. Patients in the placebo condition received placebo for 6 consecutive weeks. Those in the phenelzine condition were treated in three 2-week segments: placebo, phenelzine 15 mg every other day, and then phenelzine 15 mg daily. There was a modest, but significant, pattern of CFS symptom improvement during phenelzine versus placebo therapy. In a subsequent study, Natelson et al. (1998) treated 25 CFS patients with the selective MAO B inhibitor, selegiline. Using a 19-item CFS symptom and functional status questionnaire, a modest improvement was seen in the domains of tension/anxiety, vigor, and sexual relations.

Some evidence suggests that mixed serotonin and noradrenalin reuptake inhibitors (SNRIs) may be beneficial in

some fatigue and pain syndromes (Taylor and Rowbotham, 1996; Hickie, 1999; Ansari, 2000; Dryson, 2000; Hayes et al., 1992; Iyengar et al., 2002). Some investigators have hypothesized a beneficial effect that may result from the combined action of these agents on important pain centers and neuronal pathways within the diencephalon and spinal cord (Ruoff, 1996). Using wrist activity monitoring, these investigators have reported an increased daytime activity during SSRI treatment in MDD patients (Stanley et al., 1999). Similar studies have not been performed in patients with co-morbid symptoms of CFS.

SSRIs have received more attention for the treatment of CFS. While SSRIs have been shown to be better tolerated in patients with CFS, their efficacy has been variable (Lynch et al., 1991; Goodnick and Sandoval, 1998; O'Malley et al., 1999; Arnold et al., 2000; Lynch, 2001). Two double-blind, placebo-controlled trials with fluoxetine found conflicting results (Vercoulen et al., 1996; Wearden et al., 1998). Wearden et al. (1998) demonstrated antidepressant benefit for the depressive symptoms of CFS, while Vercoulen et al. (1996) could not find any difference in outcome between depressed and non-depressed CFS patients treated with fluoxetine. A more recent study of citalopram in CFS showed modest benefit on pain, depressed mood, and sense of well-being in women with fibromyalgia (Anderberg et al., 2000). Similarly, Arnold et al. (2002) reported significant benefit from fluoxetine on the fatigue symptoms of fibromyalgia. Finally, in an 8-week, double-blind trial, Hartz et al. (2003) studied the efficacy of citalopram in patients with idiopathic chronic fatigue (ICF), and observed a greater reduction in fatigue, myalgia, and headaches symptoms compared placebo therapy. It should be noted, however, that Hartz et al. (2003) did not specifically examine patients with CFS, a condition that may be less responsive to SSRI therapy.

The present observations with *s*-citalopram comport with the findings of Hartz et al. (2003) who used citalopram. However, we found no significant change over time in the CFS symptoms of lymph node tenderness, sore throat, or multiple joint pain. Thus, while *s*-citalopram appeared to improve some CFS symptoms that overlapped with MDD (e.g., post-exertion malaise, un-refreshing sleep, myalgia, and impaired concentration), it had less effect on those CFS symptoms suggestive of an infectious or neuro-immunologic etiology.

Several limitations of our study need to be considered in interpreting the current findings. For example, this study had a limited sample size, and had a limited (12-week) treatment duration. It was not placebo-controlled and was not powered to detect statistically significant changes in specific CFS symptoms. Given the substantial overlap of CFS and MDD symptoms, it is possible that the benefit observed for the CFS symptoms was primarily related to the antidepressant effect of *s*-citalopram, rather than to a specific anti-CFS efficacy. Moreover, the open-label study design may have led to observer bias which could have influenced the findings. Improvements in CFS symptoms may also have resulted from other, non-specific, factors such as placebo effect, spontaneous remission, regression toward the mean, or a reductions in co-morbid depressive

symptoms. Moreover, because CFS patients without co-morbid MDD were not included in the trial, no firm conclusions can be drawn about the specific anti-CFS efficacy of *s*-citalopram. Finally, the design of the present study did not permit us to specifically examine the independent benefit of SSRI therapy on CFS and MDD symptoms due to the overlap in these disorders. Future studies of SSRI therapy in CFS patients without co-morbid MDD will be needed to resolve this issue.

5. Conclusion

We examined the safety and efficacy of *s*-citalopram therapy in patients with co-morbid symptoms of CFS and depression. While we observed a significant reduction in several measures of CFS, the interpretation of the present findings must be tempered by shortcomings in the study design and methodology. Larger scale studies of patients with CFS without co-morbid MDD will be needed to determine the efficacy and safety of SSRI therapy for CFS.

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