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Original

Predictors of Change Following Participation in Non-Pharmacologic Interventions for CFS

Leonard A. Jason[1*], Susan Torres-Harding[2], Molly Brown[1], Matthew Sorenson[1], Julie Donalek[1], Karina Corradi[1]
Kevin Maher[3] and Mary Ann Fletcher[4]

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Abstract

The purpose of this study was to evaluate predictors of change in physical function in individuals diagnosed with chronic fatigue syndrome (CFS) following participation in nurse delivered, non-pharmacologic interventions. Participants diagnosed with CFS were randomly assigned to one of four, 6-month interventions including cognitive behavior therapy, cognitive therapy, anaerobic exercise, or a relaxation control group. Baseline measures including immune function, actigraphy, time logs, sleep status, and past psychiatric diagnosis significantly differentiated those participants who demonstrated positive change over time from those who did not. Understanding how patient subgroups differentially respond to non-pharmacologic interventions might provide insights into the pathophysiology of this illness.

Keywords: Subgroups, Immunologic markers, Actigraphy, CFS, Non-pharmacologic, Treatments

Chronic fatigue syndrome (CFS) is an incapacitating illness affecting approximately 800,000 Americans [1], with estimated annual total direct and indirect costs in the United States of between $19.5 and $25 billion [2]. Underlying mechanisms of CFS remain poorly understood. The symptoms of CFS may well represent heterogeneous subgroups [3] making it difficult to identify commonalities in people with this diagnosis. The benefit of classifying individuals with CFS into diagnostic categories is that it facilitates selection of treatment methods, prediction of response to treatment and communication among clinicians and researchers [3]. In addition, as the current journal covers topics related to viral and bacterial infection, as well as public health, it is particularly relevant and important to identify distinctly different patterns of lymphocyte subset distributions that might predict response to therapy.

Evidence for multiple immunological abnormalities in CFS have frequently been reported in the literature [4]. Inconsistencies in the results of these studies may be due to deficiencies in laboratory methodologies and variations in methodological parameters such as sampling time, shipping conditions, transit times, and processing methods [4], as well as the absence of appropriate control groups for defining “normal” ranges [5]. Despite these methodological challenges, some immunological findings have been demonstrated across studies when comparing individuals with CFS with healthy controls. Several theorists have proposed that people with CFS appear to have two basic problems with immune function: a) poor cellular function, with low natural killer cell cytotoxicity and frequent immunoglobulin deficiencies (most often IgG1 and IgG3), and b) elevations of activated T lymphocytes, including cytotoxic T cells, and elevations of circulating cytokines [6-8]. Natelson et al [9] found increases in cytokines (IL-8 in some patients and IL-10 in others), and these findings support the hypothesis that in some patients with CFS, symptoms may be due to immune dysfunction within the central nervous system. Siegel et al. [10] recently found that patients with CFS who had low levels of natural killer cell activity did worse on a variety of cognitive and other measures.

A better understanding of this syndrome’s etiology and pathophysiology will ultimately lead to improved treatment approaches for CFS. If there are distinct subgroups, then treatments might need to be tailored to the differential needs

[1] DePaul University
[2] Roosevelt University
[3] Labcorp & University of Miami
[4] University of Miami
* Corresponding author:
Center for Community Research, DePaul University, 990 W. Fullerton Ave., Chicago, Il.60614.

of patients with CFS. Cho et al. [11] reviewed all controlled trials with patients with CFS, and found a relatively low, pooled placebo response of 19.6%. Relaxation or standard medical care had a low placebo response (14%), oral placebos had a medium placebo response (16.5%), and injected placebos had a high placebo response (24%). These data are open to interpretation, but the low rate of spontaneous remission among patients with CFS is certainly one possible explanation.

Despite improvements found in some non-pharmacological behavioral interventions [12-14], several have been less successful. A recent cognitive behavior therapy (CBT) trial by Bazelmans et al. [15] actually found higher functional improvements for the waiting list control condition. Whitehead and Campion [16] worked with general practitioners, attempted to train them to deliver CBT, but were unsuccessful for many reasons. Similar disappointing results were obtained by Huibers et al. [17]. Edmonds et al. [18] reviewed 5 randomized controlled trials using exercise and concluded that, although some patients might benefit from non-pharmacologic interventions, these treatments are less acceptable to patients than other approaches such as rest and pacing. They concluded that further randomized studies are needed to determine whether patients who respond to these interventions maintain their gains over time.

Only a few studies have compared CBT and exercise-based interventions. For example, Ridsdale et al. [19] randomized a diverse group of fatigued patients to graded exercise or CBT. At an 8-month follow-up, there were no significant differences between the two conditions. Donta et al. [20] randomly assigned over 1,000 veterans with multi-symptom illnesses to one of two groups: CBT plus exercise alone or CBT alone and usual care. There were no significant differences in the proportion of veterans who reported an improvement in physical functioning at a one year follow-up.

In contrast to exercise, it is suggested that cognitive-based therapy might modify the way stressful circumstances are appraised and diminish the way negative emotional responses influence immune dysregulation. In a study utilizing a cognitively oriented coping skills intervention, Friedberg and Krupp [21] found a trend ($p < .06$) towards reduced depression scores and a significant reduction in maladaptive illness beliefs. In one of the few comparative studies, Ridsdale et al. [22] found counseling was as effective as CBT with fatigue patients. It is unclear which type of non-pharmacologic intervention is most effective for patients with CFS.

Several studies suggest that subgroups of patients with CFS react differently to exercise than healthy controls. For example, while exercise increases the pain threshold by releasing endogenous opioids and growth factors, individuals with CFS have reductions in pain threshold in healthy controls after modest exercise [23]. Sorensen et al. [24] found that patients with CFS showed increases in complement protein C4a at 6 hours after an exercise challenge. Symptom scores at 24 hours after exercise were significantly correlated with the C4a increase noted at 6 hours after exercise. In research reviewed earlier by Peckerman et al. [25], it was suggested that there might be left ventricular dysfunction in the heart of some patients with CFS and that lower cardiac output could make it difficult for patients to exercise. Lane et al. [26] did find a subset of patients with CFS who were positive for enterovirus sequences. Further, this subset of patients also experienced an abnormal lactate response to exercise. Bazelmans et al. [15] recently reported on a group CBT trial, and found that those who improved the most had fewer complaints at baseline. Cleare [27] found that those responders to CBT (43% of the sample at end of treatment) had baseline urine cortisol levels close to normal whereas those who did not respond had baseline levels below normal. This indicates that those who were most impaired on hypothalamic-pituitary-adrenal (HPA) functioning might have been the least able to improve with graded activity interventions. Clearly, a better understanding of subtypes is needed to determine why only certain patients benefit from these non-pharmacologic interventions.

Jason et al. [28] recently reported on the findings of a comparison study of four interventions (CBT, cognitive therapy, anaerobic exercise, and relaxation) for patients with CFS. While all four groups improved over time, the changes were relatively modest and few patients were cured of this illness. These results are similar to conclusions from other investigators, particularly those who have collected longer term follow-up data. For example, when Deale et al. [29] collected five-year follow-up data on a previous study, only 23% of patients provided with CBT reported that they had completely recovered. Similar erosion occurred in the Sharpe et al. [14] investigation [30]. In Van Hoof's [31] critique of Prins et al.'s CBT trial, moreover, the treatment effects were no longer present after three years. Understanding how patient subgroups differentially respond to non-pharmacologic interventions might provide insights into the pathophysiology of this illness. In this exploratory study, we examined baseline measures involving immune functioning, actigraphy, time logs, sleep status, and past psychiatric diagnosis for those who improved and those who did not improve following exposure to the non-pharmacologic interventions described by Jason et al. [28].

METHOD

Participant Recruitment. Participants were recruited from a variety of sources, including physician referrals. Information about the non-pharmacologic treatment trial study was disseminated to health care provider colleagues through mailings, phone communication, and invited grand rounds. In addition, study announcements for new participants were placed in local newspapers and recruitment offers were made at local CFS support group meetings and newsletters. These efforts were continued throughout the study period until the target enrollment numbers were achieved. One hundred and fourteen individuals were recruited and enrolled in the study.

Of the 114 individuals, 46% were referred by physicians, 34% were recruited by media (newspapers, TV, radio, etc.), and 20% stemmed from other sources (e.g., heard about the study from a friend, family member, person in the study, etc.). There were no significant demographic differences for patients recruited from these varying sources. Twenty-four additional individuals who were screened were excluded due to a variety of reasons (i.e., lifelong fatigue, less than 4 Fukuda symptoms, BMI>45, melancholic depression or bipolar depression, alcohol or substance abuse disorder, autoimmune thyroiditis, cancer, lupus, rheumatoid arthritis).

Initial Screening. All participants were required to be at least 18 years old, not pregnant, able to read and speak English, and considered to be physically capable of attending the scheduled sessions. Those who were bedridden, housebound, or who used wheelchairs were excluded due to the practical difficulties of keeping therapy appointments. Referrals to local physicians who treat CFS and to support groups were offered to these individuals. After providing and explaining the consent form and responding to questions, the second author screened consenting prospective participants using a structured questionnaire.

The CFS Questionnaire. The screening scale initially validated by Jason et al. [32] was recently revised by Hawk et al. [33]. This scale is used to collect demographic, health status, medication usage, and symptom data, and it uses the definitional symptoms of CFS. Hawk et al. [33] administered the questionnaire to three groups (i.e. those with CFS, major depressive disorder, and healthy controls). The revised instrument, which was used in the present study, affords good test-retest reliability as well as good sensitivity and specificity.

The CFS Questionnaire was designed to assess the diagnostic criteria for CFS as specified by Fukuda et al. [34]. For each symptom, participants were asked to indicate if the symptom had been present for 6 months or longer, if the symptom began before the onset of their fatigue or health problems, and how often (never, seldom, often/usually, or always) the symptom is experienced. Participants were also asked to rate the severity of each symptom they endorsed on a scale of 0 to 100, where 0 = no problem and 100 = the worst problem possible. This is a numerical rating scale, which has been shown to be a consistently valid measure of symptom intensity, particularly for pain intensity [35]. To measure the Fukuda et al. [34] case definition symptoms, items were designed to measure the severity of the eight minor symptoms (i.e., impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep, and post-exertion malaise) as specified by the Fukuda et al. case definition.

Next, a semi-structured psychiatric interview, the Structured Clinical Interview for DSM-IV (SCID) [36] was administered. Axis I was used to establish psychiatric diagnoses. The professionally administered SCID allows for clinical judgment in the assignment of symptoms to psychiatric or medical categories, a crucial distinction in the assessment of symptoms that overlap between CFS and psychiatric disorders, such as fatigue, concentration difficulty, and sleep disturbance [37]. A psychodiagnostic study [38] validated the use of the SCID in a sample of CFS patients. Because CFS is a diagnosis of exclusion, prospective participants were screened for identifiable psychiatric and medical conditions that may explain CFS-like symptoms. These measures were completed at DePaul University and took approximately two hours. After the initial interview was completed, the information was reviewed to ensure that the patients met all eligibility requirements. If an individual was deemed eligible for the study, a medical appointment was made. Conversely, if an individual was not eligible, referral for counseling was provided.

Medical Assessment of CFS. A board-certified internist who frequently treats patients with CFS performed the medical screening. The evaluation included an in-depth medical and neurological history, as well as general and neurological physical examinations. The evaluation also included a structured instrument, a modified version of the CFS questionnaire [39]. This instrument assesses the signs, symptoms, and medical history to rule out other disorders. Relevant medical information was gathered to exclude other possible medical causes of chronic fatigue, including history of exposure to tuberculosis, AIDS, and non-AIDS sexually transmitted diseases. Information on prescribed and illicit drug use was also assessed and recorded. Finally, the complete history of all symptoms related to CFS was gathered.

Laboratory tests in the battery were the minimum necessary to rule out other illnesses [34]. Laboratory tests in-

cluded a chemistry screen (which assesses liver, renal, and thyroid functioning), complete blood count with differential and platelet count, erythrocyte sedimentation rate, arthritic profile (which includes rheumatoid factor and antinuclear antibody), hepatitis B, Lyme Disease screen, HIV screen and urinalysis. A tuberculin skin test was also performed. The project physician performed a detailed medical examination to detect evidence of diffuse adenopathy, hepatosplenomegaly, synovitis, neuropathy, myopathy, cardiac or pulmonary dysfunction. The examining physician identified patients whose symptoms were better explained by other illness and counseled them regarding appropriate treatment. At the time of the medical examination, a blood sample was also drawn for further immunological assay. Those participants found by the examining physician to have CFS and to to be free of exclusionary disorders were then provided with a battery of other tests.

Flow Cytometry. Helper/inducer (CD3+CD4+) T-cell, cytotoxic (CD3+CD8+) T-cell, B-cell (CD19+), and natural killer (CD3-CD56+) cell counts were determined using four -color flow cytometry. One hundred microliters of heparinized whole blood was incubated for 15 minutes at room temperature with optimal concentrations of fluorochrome conjugated antibodies. CD45 (Fluorescein [FITC]), CD14 (Phycoerythrin RD1), CD3-(Phycoerythrin CY5 [PC 5]), CD8 (Phycoerythrin-Texas Red [ECD]), CD45RA (FITC), CD62L (Phycoerythrin, PE), CD2 (FITC), CD26 (PE), CD4 (ECD) CD 8 (PC 5) and isotype controls, in 4 color combinations, for 15 min at 25 ℃. Samples were then fixed and lysed with Optilyse-C reagent, followed by analysis on an XL-MCL flow cytometer. All reagents and instrumentation were from Beckman Coulter Corporation, Hialeah, Florida. Analyses were performed by collecting 2500 events in the lymphocyte region. All determinations were corrected for purity by dividing by the percent CD45+CD 14- events in the lymphocyte gate. Absolute count for each of the subsets was calculated by multiplying the percent positive for each marker by the lymphocyte count determined from the automated complete blood count (CBC). CBC was performed on a Coulter MAX-M (Coulter Corporation, Hialeah, FL). Accuracy and precision of analyses were optimized through the adherence to the CDC's recommendations for flow cytometric analyses [40]. Lymphocyte, monocyte and granulocyte populations were determined using light scatter and back gating on fluorescence for the CD 45 bright and CD14 negative population. The isotype controls were the reference for negative events. Spectral compensation was established daily. Quality control included the optimization for lymphocyte recovery, purity of the gate of analysis, and lymphosum.

Data obtained include basic lymphocyte subsets. For example, data were provided on B cells (CD19+) % p range (classified into normal/low versus high), B cells (CD19+) % pos, B cells (CD19+) cells /uL (with higher scores indicating expanded humoral B cell immunity). Data also included Total CD8 % which is the total number of CD8 positive cells, with lower counts indicating lower anti-viral immune responses (lower Th1). In addition, CD2+ % were provided. CD2 is an umbrella marker, which contains within it the T-cells and the NK (natural killer) cells (% of T cells plus % of NK cells = % of CD2 cells). T cell (CD3+) uL range was also examined. The number of T cells is approximately the sum of both helper and cytotoxic T cells, with scores in the low/normal being better. Finally, the total number of CD56 cells (including CD3+ and CD3-) were inspected, with higher scores suggesting a more cellular type (Th1) response.

Medical Outcomes Study-Short Form-36. (MOS-SF-36). The MOS-SF-36, a 36 item broadly-based self-report measure of functional status related to health, identifies eight health concepts as perceived by the individual. A higher score indicates better health or a lower impact of health on functioning. Test construction studies for the SF-36 [41, 42] have shown adequate internal consistency, significant discriminate validity among subscales, and substantial differences between patient and non-patient populations in the pattern of scores. The SF-36 has also indicated sufficient psychometric properties as a measure of functional status in a CFS population [43]. A behavioral treatment study of CFS patients showed that the MOS-SF-36 is sensitive to treatment changes [12]. The MOS Physical Functioning Scale was utilized in the present investigation as in several previous non-pharmacologic trials [44].

Sleep Disturbance. Sleep disturbances were assessed using the Pittsburg Sleep Quality Index, which was developed to measure sleep quality in psychiatric research [45]. This Index measures sleep disruptions and sleep quality. There are nineteen questions on a 0-3 scale that generate several "component" scores on daytime dysfunction, with higher scores indicating worse sleep quality. Three items from this scale were identified as central to CFS and were utilized in this study, i.e. trouble staying awake while driving, eating meals, or engaging in social activities (0=not during the last month; 1=less than once a month; 2=once or twice a month; 3=three or more times a week).

Actigraph. Participants wore an actigraph for a one-week period at baseline and at the end of treatment. An actigraph is a small, lightweight, cost-efficient activity monitor that can be worn on the waist. It has a long battery life and can continuously collect data over the 24-hour period for 22 days before its memory reaches capacity [46]. Unlike most activity monitoring devices, the actigraph is capable of

recording movement intensity. The actigraph transduces activity using an accelerometer. An 8-bit analog-to-digital converter quantifies these measurements into 128 levels of positive acceleration and 128 levels of negative acceleration 10 times each second. Integration over the resulting sampling time of 0.1 s in combination with other details provided by Tryon and Williams [46] would result in measurement units of 1.664 milli-g/activity activity count. For simplicity, analog-to-digital (A/D) counts are retained as activity units. The average of 600 absolute A/D values is stored in memory at the end of every minute. Participants wore the actigraph on their waist at all times except when bathing or sleeping. Participants were divided into two categories at baseline: low/moderate activity and high activity.

The ACTRE. The ACTRE is a daily self-administered log of physical activity. Respondents log their daily activities every half-hour over the course of two days. Respondents rate the intensity of their activity (e.g., sedentary or active) and classify the nature of their activity into categories for every recorded half-hour of activity. In a validation study of the ACTRE, Gerber and Furst [47] demonstrated that the ACTRE has adequate psychometric properties as a measure of activity and functional status in a population with a chronic disabling condition. The ACTRE is significantly correlated with other measures of fatigue [47]. Two items were of particular interest: sleep (time at which participant goes to bed) and work (paid or volunteer activities in or out of the home, school work, writing papers, attending classes, studying, or similar activities). In effect, clinicians and researchers are able to obtain a composite that represents a comprehensive profile of functioning as well as areas of dysfunction [47].

Perceived and Expended Energy. Participants were asked to rate daily perceived energy and expended energy on a 100-point scale (0=no energy; 100=abundant energy) corresponding to times of complete wellness. Perceived energy referred to the participant's estimation of his or her own available energy resources (estimated over the entire day for daily ratings, and at the time of rating for hourly ratings). Expended energy was defined as the participant's estimation of the total amount of energy expended (estimated over the entire day for daily ratings, and at the time of rating for hourly ratings). Expended energy can be greater than perceived energy, particularly when the participant pushes himself or herself over his/her energy limits. These indices were used to refer to whether or not the participants remained within the boundaries of their available energy.

Treatment Protocols Two nurse-clinicians previously trained in each of the protocols, administered thirteen forty-five minute sessions of cognitive behavior therapy, anaerobic graded exercise, anaerobic activity alone, cognitive coping skills, or relaxation once every two weeks (See [28] for more details). Approaches to reduce attrition included the use of mail and telephone reminders of all appointments, flexibility regarding working around vacations and medical and other crises, reimbursement for transportation costs, and participant honoraria. Participants attended an average of 10.0 sessions out of a possible 13 sessions, with a range from 1-13. The average dropout rate of 25% was not significantly different per condition. These dropout rates are more than acceptable among clinical trials with CFS [44]. For example, among CBT and ACT trials with CFS patients, dropout rates of 28% [13], 29% [48], 34% [22], 34% [19], and 39% [49] have been reported. In a study of CFS among Gulf War Veterans using CBT and GA, only 30% of participants adhered to the treatment protocol [20].

RESULTS

Sample

A total of 28 or 29 participants were randomly assigned to each of the four conditions. There were no significant socio-demographic differences among these groups at baseline. Of the 114 participants, 16.7% are male and 83.3% are female. The average age at baseline was 43.8 years. By ethnicity, 87.7% are Caucasian, 4.4% are African-American, 4.4% are Latino, and 3.5% are Asian-American. By marital status, 49.1% are married/ cohabitating, 33.3% are single, and 17.6% are either divorced or separated. In terms of work status at the baseline, 24.6% were on disability, 23.7% were unemployed, 20.2% were working part-time, 19.3% were working full-time, 6.1% were retired, 4.4% were part-time students, 0.9% were full time students, and 0.9% were working part-time and on disability. In terms of education, 47.4% had earned a standard college degree, 21.8% had a graduate or professional degree, 21.1% had partial college, and 9.7% had a high school/GED degree or less.

Outcome Variable

The SF-36 physical functioning scale has been used in several treatment studies to assess changes over time (e.g., [12]), and was chosen for this study. In the normal population, a score of less than or equal to 70 is the criteria for the lower 25th percentile. King and Jason [50] compared a group diagnosed with CFS and a group diagnosed with major depressive disorder. Participants with CFS had an average score of 44, whereas individuals with major depressive disorder had an average score of 70. In comparing baseline and 12 month follow-up data, 42% of the sample had not improved or improved only a few points (changes from 5 to -35) while 58% of the sample had made greater positive changes on this measure of physical disability (changes

from 10 to 55). This cutoff point (changes of 5 to -35 versus changed from 10 to 55) was used to separate the sample into those who did not improve versus those who did improve on the physical functioning scale. Of the sample of 114 participants, baseline and follow-up data on this variable were available for 86 participants. This baseline physical functioning variable was not significantly related to number of sessions attended, dropout rates, illness duration, gender, ethnicity or work status. Physical functioning rates for those who improved versus those who did not were not significantly different at baseline [Ms=50.4 versus 43.9; F (1,84)=1.50, p= .224] but were significantly different at the 12-month follow-up time [Ms=42.2 versus 66.0; F(1,84)= 17.66, p< .000]. Those in the improved group changed from 43.9 to 66.0 whereas those who did not improve showed declining scores from 50.4 to 42.2. In summary, there were two outcome groups, one of which remained at stable or declining levels on the physical functioning scale, and another group that showed significant positive change over time.

Immune functioning

Overall, those who did not improve demonstrated alterations in lymphocyte subset distributions that suggested that their immune systems had experienced prior immune stimulation and expansion of T and B cell subsets, relative to the improving group. Those who improved versus those who did not had significantly lower baseline Total B cells (CD19+) % pos (Ms=12.7 versus 16.3; F(1,84)=7.16, p= .009) and Total B cells (CD19+)/uL (Ms=263.4 versus 364.2; F(1,84)=8.15, p = .005). In addition, those with low/normal Total B cells (CD19+) % pos range versus those with high scores at baseline had a significantly higher percentage of individuals who improved (Ms=65% versus 29%; X^2 (1, N=86)=7.19, p = .007). In addition, those with low/normal scores on baseline T cells (CD3+)/uL versus those with high scores had significantly more patients within the improved versus non-improved groups (Ms=67% versus 41%; X^2 (1, N=86)=5.05, p = .025).

Alterations were also found for other immunologic indices. Higher scores were present among those who improved versus those who did not on the following baseline measures: Total CD8 % pos (Ms=26.7 versus 23.8; F(1,84) =3.80.15, p= .055), Total CD2 % pos (Ms=84.2 versus 80.9; F(1,84)=5.26, p= .024), and CD56 positive cells 1 (Ms= 10.2 versus 7.6; F(1,84)=6.12, p= .016).

Actigraphy

When low or moderately active individuals at baseline were compared to those who were highly active, more significant positive change occurred for those in the low or moderate active groups (Ms=63% versus 29%; X^2 (1, N= 86)=5.82, p = .016).

Time logs

Individuals who improved over time spent significantly less time at baseline sleeping (Ms=34% versus 39%; F(1,79)=12.46, p= .001) and reported significantly more half hours working (Ms=11 versus 6; F(1,79)=6.44, p= .013) at baseline. In addition, those who improved spent 12.6% of their time on self care and those who did not improve spent 17.1% of their time on self care at baseline (F (1,77)=8.19, p = .005).

Sleep status

Those who improved had significantly less daytime dysfunction at baseline (Ms=1.6 versus 2.1; F(1,84)=6.33, p = .014). Those in the improved group were less likely to indicate that during the past month, they had trouble staying awake while driving, eating meals, or engaging in social activities at baseline (Ms= .7 versus 1.4; F(1,84)=7.80, p= .006).

Psychiatric status

Current psychiatric status at baseline was not related to recovery. However, those that improved versus those that did not were significantly more likely to have had a past psychiatric diagnosis (74% versus 48%; X^2 (1, N=86)=5.47, p= .019).

Perceived versus expended energy

Those who improved versus those who did not had significantly more baseline perceived energy (Ms=46.2 versus 37.0; F(1,85)=4.45, p= .038) and expended significantly less energy at baseline (72.6 versus 85.1; F(1,85)=4.72, p= .033).

DISCUSSION

This study provides some preliminary and speculative data about possible markers for improvement on the physical functioning score of the SF-36 following participation in non-pharmacologic CFS treatment. At baseline, those who improved versus those who did not had significantly lower baseline percent and number of B cells (CD19+) and significantly more participants with low/normal percentages of B cells (CD19+) and low/normal scores on baseline T cells (CD3+)/uL. Higher baseline scores were found for those who improved versus those who did not for Total CD8 % pos, Total CD2 % pos, and CD56 positive cells. These findings suggest that those who did not improve and those who did had distinctly different patterns of lymphocyte subset distributions that predicted response to therapy. Past research has shown that CFS is associated with a shift toward a Type 2 immune response [51], and in the present study, those with this pattern tended not to improve. Other corroborating findings of this study indicate that those who improved versus those who did not were better able to stay awake and continue doing some type of work, and had more

perceived energy at baseline.

Antoni et al. [52] found that patients with low natural killer cell activity (NKCA) and a state of overactivation of lymphocyte subsets (e.g., CD2+CD26+ % activation markers) had the greatest fatigue intensity and greatest fatigue-related impairments in emotional and mental functioning. These findings support the dominance of Type 2 cytokines over the Type 1 cytokines in patients with CFS. Hanson et al. [53], using neural-network classifiers, also identified this shift to the dominance of Type 2 cytokines over the Type 1 cytokines. In the present study, those who had higher Total B cell (CD19+) scores and other markers were less likely to improve, and those with decreased T and B cells and elevated NK % numbers were most likely to improve. Although cytokine analyses were not performed in this study, the distribution of lymphocyte subsets at baseline suggests that those who did not improve had an elevated humoral immune response (Type 2/B Cell).

In contrast, those who improved had a more cellular immune response as indicated by the relatively expanded cytotoxic subsets (CD8, CD56/Type 1). In other words, those with a dominance of the Type 2 over the Type 1 immune response, as indicated by the patterns of lymphocyte subset distributions among those with CFS, did not improve over time. Previous studies of cytokine and lymphocyte subset distributions in CFS have indicated varying results. Such inter-study differences have been attributed to methodological discrepancies [4]. The current study further supports the contention that clinically distinct subsets of patients exist within the current definition of CFS. Such differences, which may explain some of the previous discrepant conclusions, highlight the need to define clinical subsets in CFS. Understanding how non-pharmacological interventions differentially affect patient subgroups might provide insights into the pathophysiology of this illness [54].

Those who were better able to stay awake and continue doing some type of work, as indicated by the time log data, had better outcomes. It is again possible that individuals who are more impaired might need to sleep and might also have less available energy reserves to become involved in work. The energy data also suggest that those who were found at baseline to have more perceived energy and expended less energy, were those who improved the most. The actigraph data also suggested that those who were not at the highest activity level tended to achieve the best improvement over time. These findings support the work of Jason et al. [55] on activity management. Jason recommended that patients with CFS should pace their activity according to their available energy resources. In this approach, the phrase, “staying within the envelope,” is used to designate a comfortable range of energy expenditure in which an individual avoids both over-exertion and under-exertion, thus maintaining an optimal level of activity over time. Application of the Envelope Theory does not include a unilateral endorsement of either increase or decrease in activity for individuals with CFS. Some people need to be encouraged to increase their activity, if they have the appropriate amount of perceived energy to do so. However, there are also individuals with CFS who need to be encouraged to do less in order to decrease the discrepancy between perceived and expended energy. The key is to not over-expend energy supplies or consistently go outside the “envelope” of available energy. Once this has been accomplished, it would then be possible to slowly increase activity. This approach focuses on improving the ability of those with CFS to manage this illness. Tailored interventions are needed for the unique needs of different subgroups. Proper application of this theory further demonstrates the need to understand the differential needs of subtypes of patients with CFS.

Masuda et al. [56] found that individuals with a viral onset without psychiatric comorbidity had a greater reduction in physical symptoms following multidisciplinary treatment for CFS than those with viral onset and psychiatric comorbidity. In the present study, it is unclear why those with past psychiatric diagnoses tended to do better than those without past diagnoses. Perhaps, in contrast to the Masuda findings related to the presence of concurrent psychopathology, the history of a psychiatric condition and recovery from it provided patients a sense of enhanced self-efficacy for their involvement in the present non-pharmacologic trials.

Attempting to predict trajectories for patient groups seems a promising approach. As an example, in a comparison of intervention responses in individuals experiencing fibromyalgia (FM), an illness with some connections to CFS, Turk et al. [57] classified FM patients into one of the three profiles: dysfunctional (DYS: high levels of pain, functional limitation, and affective distress), interpersonally distressed (ID: similar to DYS but further characterized by low levels of support from their significant other), and adaptive coper (AC: low levels of pain, distress, and disability). Turk et al. [58] found that patients within these subgroups responded differently to a standard rehabilitation treatment protocol. Patients in the DYS group improved in most areas, whereas the ID patients failed to respond to the treatment. There was little change in the AC patients. This type of work involving the identification of clinically significant subgroups is the logical next step in furthering CFS research.

Some individuals may be at higher risk of developing particular factors related to CFS, such as chronic activation, due to genetic vulnerabilities or to constitutional issues. There may be multiple pathways leading to the cause and

maintenance of the neurobiological dysregulation and other symptoms experienced by individuals with CFS. Depending upon the individual and subtype, these may include unique biological, genetic, neurological, psychological, and socio-environmental contributions. Subgrouping is the key to understanding how CFS begins, how it is maintained, how medical and psychological variables influence its course, and in the best case, how it can be treated and cured and even eventually prevented [3].

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