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PATERNS OF FATIGUE IN CHRONIC OBSTRUCTIVE  
PULMONARY DISEASE

by

Lawrence Henry Chyall

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

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in the

GRADUATE DIVISION

of the

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## **Acknowledgments and Dedication**

This thesis is submitted with thanks and acknowledgment to my committee, Drs. Virginia Carrieri-Kohlman, DorAnne Donesky, and Kathryn Lee for their patient help and encouragement. I also offer deep thanks and appreciation to Kevin Biggerstaff. His unending love and support turned the dream of this thesis and the education that preceded it into a reality. No large project, including a career change, can be possible without the help of one's family friends. With great thanks I acknowledge the decades' long support and love of Gary and Joan Chyall, Leonard Chyall, Howard Greils, Jan Birnbaum, Linda Giglio, Sara Miles, and John Golenski.

Dedicated to my mother, Joan Chyall, RN.

Покровъ

## **Abstract**

### **Purpose**

To describe the patterns of fatigue and the symptom/well being and physical/physiological correlates of fatigue over one year in patients with COPD.

### **Patients and Methods**

Secondary analysis of data from a prospective, randomized, single-blind study to evaluate the effect of three different doses of supervised exercise in a dyspnea self-management program in patients with stable chronic obstructive pulmonary disease (N = 103; age  $66 \pm 8$ , females 57; FEV<sub>1</sub>  $44.8\% \pm 14\%$  predicted).

### **Results**

Mean fatigue was stable at the measurement times during the course of the study. Four patterns of fatigue were identified “stable” (n=29), “improving/stable” (n=28), “worsening/stable” (n=18) and “labile” (n=4). Fatigue was moderately correlated with dyspnea, depressive and anxious symptoms, and reduced quality of life. Fatigue was mildly correlated with reduced exercise performance.

### **Conclusions**

Mean fatigue is not a sufficient measure of fatigue over time in patients with chronic obstructive pulmonary disease. Subgroup analysis may be necessary to understand fatigue in this population.

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## Introduction

Fatigue is a common and debilitating symptom in patients with chronic obstructive pulmonary disease (COPD).<sup>4-6</sup> Patients with COPD often experience a greater amount of fatigue than healthy persons<sup>7</sup> and fatigue has been shown to be closely associated with dyspnea.<sup>5</sup> It has been reported that patients often cannot separate the two symptoms because they are so closely aligned in time, intensity, and frequency.<sup>5</sup> The combination of fatigue and dyspnea may be an important factor in the “cycle of decline” experienced by many patients with COPD in which symptom avoidance leads to reduced activities, resulting in further deconditioning and increased symptoms.<sup>4,10,11</sup> Additionally, fatigue has been shown to negatively impact the quality of life of people with chronic lung disease.<sup>8</sup> A more thorough understanding of fatigue and the symptoms associated with it will help clinicians and researchers to assess and develop both medical and self-help therapies for this pervasive symptom. This is especially important given that the number of people with COPD is an increasing cause of substantial morbidity and mortality in both developed and developing nations.<sup>14</sup>

Like dyspnea and pain, fatigue is a subjective sensation that is best measured by patient self-report.<sup>15</sup> A consensus, however, on the definition of fatigue has not yet been developed.<sup>16</sup> For the purpose of this secondary analysis, fatigue is defined as “the awareness of a decreased capacity of physical and/or mental activity.”<sup>17</sup> Although there have been descriptions of fatigue and the factors correlated with it at one point in time, to date the symptom has not been followed for the long term. Therefore, the purpose of this secondary analysis was to describe the patterns of fatigue and the symptom/well being and physical/physiological correlates of fatigue over one year in patients with COPD.

## Review of Literature

Previous research by others has shown an association between fatigue and other symptoms, disease severity, decreased functional performance, and decreased quality of life in patients with COPD (Figure 1). Researchers have reported moderate to strong associations between dyspnea and fatigue with Pearson correlation coefficients ranging from  $r = .34$  to  $r = .76$ .<sup>1-4,7-9,13</sup> It is noteworthy that Janson-Bjerklie, Carrieri, and Hudes found that patients may describe their dyspnea in terms of fatigue and thus the two symptoms are not distinguishable by all patients.<sup>5</sup> Although patients with COPD rank dyspnea as their most distressing symptom,<sup>5</sup> patients with cancer report that fatigue is their most distressing symptom, greater than pain and nausea.<sup>18-20</sup> Thus, the rank of fatigue as an unpleasant symptom may be dependent on the disease state(s) of the patient.

Patients with COPD report symptoms of mood disturbance often heighten fatigue. An association between anxiety and fatigue was reported by Borge and colleagues ( $r = .45$ )<sup>3</sup> and Kapella and colleagues ( $r = .61$ ).<sup>2</sup> Depression commonly accompanies fatigue in patients with COPD. Four studies have reported a correlation between depression and fatigue with Pearson coefficients ranging from  $r = .44$  to  $r = .59$ .<sup>2,3,7,8</sup> These findings are consistent with those from researchers studying fatigue in other diseases including non-Hodgkins lymphoma and testicular cancer.<sup>21,22</sup> An association between pain and fatigue ( $r = .48$ ) in patients with COPD has been described,<sup>3</sup> as it has in patients with breast cancer.<sup>23</sup> Sleep disturbance is known to be associated with fatigue in several diseases including cancer and Acquired Immune Deficiency Syndrome (AIDS).<sup>24</sup>

<sup>26</sup> Investigators have described a correlation between the two symptoms in COPD ( $r = .24$  to  $r = .58$ ).<sup>2,3,9</sup>

Given fatigue's positive association with other debilitating symptoms, it is not surprising that fatigue has been observed to have a negative impact on the functional performance of patients with COPD. Breslin and colleagues found that fatigue was associated with reduced six-minute walk distance (6MD) ( $r = .53$  to  $r = .55$ ).<sup>8</sup> Reduced time out of doors has been reported to be associated with fatigue ( $r = .43$ ) as has reduced quality of life ( $r = .46$  to  $r = .61$ ).<sup>2,7</sup> Fatigue has also been associated with COPD exacerbation ( $r = .27$ ).<sup>7</sup> Fatigue may, therefore, play an important part in the functional performance and quality of life in patients with COPD.

The association between fatigue and disease severity in patients with COPD is less clear. Three authors have reported a correlation ( $r = -.20$  to  $r = -.62$ ) between fatigue and percent predicted forced expiratory volume over one second (FEV<sub>1</sub>%).<sup>8,9,12</sup> Others have described smaller, non-significant correlations.<sup>3,7</sup> GOLD stage and arterial blood oxygen saturation have not been found to be significantly associated with fatigue.<sup>7</sup>

## **Methods**

The methods for the parent study from which this data was taken have been reported extensively<sup>27,28</sup> and will only be briefly described here.

### **Design**

This study uses data from a one-year randomized clinical trial of a dyspnea self-management program that included the components of education, nurse coaching, and three levels of exercise. Patients with COPD and limitations in their daily activities due to dyspnea completed baseline testing including treadmill exercise and measurement of pulmonary function. Study participants were randomly assigned to one of three treatment

groups: a dyspnea self-management program alone (DM,  $n = 36$ ), DM with four nurse-coached exercise sessions during the first two months (DM-Exposure,  $n = 33$ ), or DM with 24 nurse-coached exercise sessions during the first two months of the year (DM-Training,  $n = 34$ ). The dyspnea self-management program included an exercise prescription to walk four times per week for a minimum of 20 minutes, six hours of individualized education and support, and bi-weekly telephone calls from the treatment nurse. Outcomes were measured every two months for one year. In order to reduce study participant burden, not all outcomes were tested at each session. For this secondary analysis, measures of fatigue from the baseline, two, four, eight, and 12 month visits were correlated with the other variables of interest.

### **Sample**

A convenience sample of 115 participants, recruited from medical practices, and Better Breathers Clubs, met the inclusion criteria of age greater than 40 years, a diagnosis of COPD, clinically stable for at least one month, persistent moderate to severe airflow obstruction after inhaling two puffs of albuterol, absence of pulmonary rehabilitation or exercise training for at least one year, and absence of other diseases that would interfere with exercise. Four participants from each treatment group left the study before the two-month evaluation leaving a sample of 103 participants.

### **Measurements**

#### **Fatigue**

Fatigue was measured using the Chronic Respiratory Questionnaire Fatigue subscale (CRQ-F) by interview. The CRQ is a well-validated and reliable disease-specific instrument widely used to assess quality of life in patients with COPD.<sup>1</sup> It includes four

scales: fatigue, dyspnea, emotion, and mastery (feeling of control over the disease and its effects) with higher scores indicating a higher level of functioning. Thus, higher scores on the fatigue and dyspnea dimensions indicate lower levels of fatigue and dyspnea. It asks patients to rate their fatigue over the previous two weeks using a seven point scale. Evidence for convergent validity of the CRQ-F was found during this analysis by correlation with the Profile of Mood States Fatigue-Inertia (POMS-F/I) subscale at the baseline, two, four, eight, and 12-month time points ( $r = -.750$  to  $r = -.799$ ). There was evidence for divergent validity with fatigue being correlated with the SF-36 Vitality subscale at the same time points ( $r = -.796$  to  $r = -.866$ ).

### **Symptom/Well-being Measures.**

Dyspnea was measured with the Chronic Respiratory Questionnaire Dyspnea subscale (CRQ-D)<sup>1</sup> and the UCSD shortness of breath questionnaire (UCSD).<sup>29</sup>

Depressive symptoms were measured using the Center for Epidemiological Studies Depression scale (CESD).<sup>30</sup> Participants' experience of pain was measured using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Bodily Pain scale (SF-36 BP) and overall functional health and well being was measured with the composite physical health summary measure component of the SF-36 (SF-36 Physical).<sup>31,32</sup>

### **Physiological/Physical Measures.**

#### *Severity of Illness*

Spirometry was completed at baseline, including measurement of forced expiratory volume in one second (FEV<sub>1</sub>) and the percent predicted value (FEV<sub>1</sub>%). An arterial blood sample was collected at baseline and arterial blood gases, including the

partial pressure of arterial blood oxygen (PaO<sub>2</sub>) and the partial pressure of arterial blood carbon dioxide (PaCO<sub>2</sub>), were obtained. The participants also completed a single-breath diffusion capacity for carbon monoxide (D<sub>L</sub>CO)

The BODE index was calculated for each participant.<sup>33</sup> It is a composite marker of COPD severity and a validated predictor of mortality in patients with COPD<sup>10</sup> calculated from the participants predicted FEV<sub>1</sub>, six-minute walk distance (6MW), modified Medical Research Council (MRC) dyspnea grade,<sup>34</sup> and body mass index.

### ***Exercise performance.***

At baseline, two, four, eight, and 12 months, two consecutive six-minute walks (6MW) were conducted with a 30 minute interval between the walks.<sup>35</sup> If the walk distances did not agree within 10%, then a third walk was performed. An incremental treadmill test (ITT) was performed according to methods previous described in the parent study at baseline, six, and 12 months.

## **Results**

### **Sample**

As previously reported in the parent study, there was no significant difference in fatigue as measured by the CRQ-F between the treatment groups at any of the measurement times.<sup>28</sup> Therefore, for this secondary analysis, the three treatment groups were collapsed into a single group for the purpose of describing the patterns of fatigue and the symptom/well being and physical/physiological correlates of fatigue over time in patients with COPD.

Scores on the Chronic Respiratory Questionnaire Fatigue subscale (CRQ-F), the primary outcome of this analysis, were missing at one or more time points on 24

participants due to death ( $n = 3$ ), voluntary withdrawal from the study ( $n = 7$ ), or other reasons ( $n = 14$ ). There was no difference in treatment group assignment based on whether participants had at least one missing CRQ-F score or not. Participants with complete data ( $n = 79$ ), did however, have statistically significant differences in pulmonary function, exercise performance, and quality of life than the entire sample ( $n = 103$ ) (Table 1).

### **Patterns of Fatigue**

There were no significant changes in mean fatigue scores during the study period (Figure 2). Mean CRQ-F ranged from 15.2 points ( $SD = 4.8$ ) to 17.3 points ( $SD = 4.7$ ). Mean POMS Fatigue-Inertia scores ranged from 6.0 points ( $SD = 4.3$ ) to 7.5 points ( $SD = 5.0$ ).

Four patterns of fatigue were identified by analyzing individual CRQ-F scores . All participants with complete data ( $n=79$ ) were assigned into 1 of 4 mutually exclusive groups:

1. Stable ( $n=29$ ). CRQ-F subscale scores at two, four, eight, and 12 months were within 5 points of the baseline measure (5 points = one standard deviation of the sample mean) (Figure 2a).
2. Improving/Stable ( $n=28$ ). One or more CRQ-F subscale scores at two, four, eight, and 12 months were 5 points or more greater than the baseline measure. No scores were 5 points or more less than the baseline score (Figure 2b).
3. Worsening/Stable ( $n=18$ ). One or more CRQ-F subscale scores at two, four, eight, and 12 months were 5 points or more less than baseline measure. No scores were 5 points or more greater than the baseline score (Figure 2c).

4. Labile (n=4). One or more CRQ-F subscale scores at two, four, eight, and 12 months were 5 points or more greater than baseline measure, and one or more CRQ-F subscale scores at two, four, eight, and twelve months were at least 5 points less than baseline measure.

Participants in the Improving/Stable category had a greater baseline level of fatigue, [ $F(3,74) = 7.56, p < .001$ ], than the other groups. The Worsening/Stable group had a greater baseline level of physical well being than the other groups [ $F(3,74) = 5.72, p < .001$ ]. Other differences between groups were not statistically significant (Table 2).

### **Correlates of Fatigue Over Time**

#### **Symptom/Well Being Measures**

A moderate correlation between CRQ-F and CRQ-Dyspnea subscale was observed at baseline, 2, 4, and 12 months (Table 3), however, the correlation at 8 months was smaller and not statistically significant. CRQ-F was correlated with dyspnea measured by the UCSD shortness of breath questionnaire at all visits. Mild to moderate correlations between the CRQ-F and both the POMS Tension/Anxiety subscale and CESD depression scale were observed at all time points. The CRQ-F and the SF36 Pain subscale were mildly correlated at baseline, two, four, and eight months, but not significantly correlated at 12 months.

#### **Physiological/Physical Outcomes.**

Exercise performance was mild to moderately correlated with fatigue at some time points (Table 2). CRQ-F scores were correlated with the 6MW distance and ITT at the baseline and 12 month visits (the ITT was not performed at 2, 6, and 8 months). Weaker and non-significant correlations between CRQ-F and 6MW were observed at 2,



6, and 8 months. Fatigue was not significantly associated with age ( $r = -.09$ ), gender ( $t(101) = -1.93, p = .047$ ), FEV<sub>1</sub>% ( $r = -.10$ ), PaO<sub>2</sub> ( $r = -.09$ ), PaCO<sub>2</sub> ( $r = .10$ ), DLCO % ( $r = 0.1$ ), or BODE index ( $r = -.18$ ).

## Discussion

This secondary analysis showed that there are individual differences and unique patterns in the amount of fatigue over time in patients with COPD, even though mean fatigue remained stable at the measurement times. Significant correlations between fatigue and measures of symptoms, mood, and functional performance over time ranged from mild to moderate. Fatigue was not associated with measures of disease severity, however participants who experienced a least one period of worsened fatigue had a greater baseline level of physical functioning than participants with the other patterns. Participants who experienced at least one period of improved fatigue reported less fatigue at baseline.

Mean CRQ-F scores did not vary significantly between groups at any time point, even while they were participating in the dyspnea self-management program with education about strategies for dyspnea and an exercise prescription provided to all treatment groups. CRQ-F scores were not associated with gender. It is noteworthy that the mean POMS-F/I scores ranged from 6.0 ( $SD = 4.3$ ) to 7.5 ( $SD = 5.0$ ) in this sample of people with moderate to severe COPD. Kapella and colleagues report mean POMS-F/I scores of 11.5 ( $SD = 6.4$ ) for men and 11.6 ( $SD = 6.5$ ). While we also found no difference in fatigue based on gender, our sample reports less fatigue overall than the sample reported by Kapella and colleagues. That sample had mean CRQ-D scores of 3.1 ( $SD = 1.1$ ) for men and 2.9 ( $SD = 1.1$ ) for women and thus reported considerably more dyspnea than the participants in our study. This discrepancy in the intensity of fatigue and

shortness of breath is not readily explained by age or disease severity – both samples had similar age and FEV<sub>1</sub> % predicted profiles.

The mean fatigue scores over time do not, however, create a full picture of the fatigue experience for individuals. Of the 79 participants with complete data, 50 had at least one fatigue score that was a least one standard deviation above or below the participant's baseline score, indicating a period of improving or worsening fatigue. Other investigators have observed that fatigue increases at exacerbation and returns to baseline by 6 weeks post exacerbation.<sup>7</sup> It is possible that the improving and/or worsening fatigue scores reported may have been associated with exacerbations. Thus, patterns of fatigue shown may be related to exacerbation or other temporary changes in physiological health. Exacerbations were not measured in this study and a fuller understanding of this phenomenon is needed.

Participants with improved fatigue were more likely than the other people in the fatigue patterns to have had greater fatigue initially. It is possible that these individuals entered the study during recovery from a fatigue producing illness and that their only remaining symptom was fatigue. Thus, as the study progressed, their fatigue improved.

Those participants who reported at least one episode of worsened fatigue scored significantly higher on the SF-36 Physical Health component than the other groups. Although not statistically significant, this group also reported less dyspnea, had a longer mean time on the incremental treadmill test, and a longer six-minute walk. It is possible that the Worsening/Stable fatigue category represents a group of people not usually bothered by symptoms who push themselves to continue about their usual activities

despite increased symptoms. This may necessitate a period of physical recovery and the symptom of fatigue may be a protective mechanism to ensure adequate rest.

Our findings support the findings of other investigators with similar chronically ill patients with COPD that increased fatigue is related to increased dyspnea, depression, anxiety, and pain (Table 3). They also provide additional evidence for the symptom cluster of dyspnea, pain, and fatigue in patients with COPD that has been found with patients with COPD and cancer.

The correlations between fatigue and other symptoms were not, however, entirely stable over time in this sample of patients with COPD. The time at which fatigue and symptoms were measured may have affected the correlation. This may be responsible for the range of correlation coefficients reported by others.

Instrumentation might also be responsible for the difference in the relationships between fatigue and six-minute walk and FEV<sub>1</sub> % in this study versus those of others.<sup>2,8,12</sup> Breslin and colleagues,<sup>8</sup> Breukink and colleagues,<sup>12</sup> and Kapella and colleagues<sup>2</sup> used multi-dimensional instruments, e.g, the Multifimensional Fatigue Inventory, and the Lee Fatigue Scale to measure fatigue that may be more sensitive to the physical dimension of fatigue than the CRQ-F. The CRQ-F did, however, show a strong correlation to the POMS fatigue /inertia subscale. This suggests that the CRQ-F may be as sensitive and valid useful as the widely used POMS fatigue/inertia subscale. The uniform adoption of a fatigue instrument by researchers would enable the cross comparison of fatigue study samples. The CRQ-Dn the subscale that measures dyspnea with activities has been effectively adopted by many researchers to measure dyspnea; having a similar widely used instrument may be useful for fatigue research.

The significant limitations of this analysis include the use of a monodimensional fatigue measure and the absence of a sleep impairment measure. Fatigue is thought to have several dimensions<sup>16</sup> and the CRQ-F may not capture all of them. A valid multi-dimensional instrument may be necessary in fatigue research despite any additional participant burden a longer instrument might impose. Sleep is known to impact fatigue and must be controlled. The use of a simple sleep measure may have provided more insight into fatigue in this research.

This secondary analysis described four unique patterns of fatigue patterns of fatigue over time in patients with COPD: stable, improving/stable, worsening/stable, and labile. It confirmed the findings of others - that fatigue is correlated with dyspnea, depressive and anxious symptoms, exercise performance, and quality of life. These correlations may not be stable over time.

**Table 1.**  
Baseline Participant Characteristics <sup>28</sup>

Variable	All Participants (n=103)	Complete Data (n=79)
Gender (F/M)	57/46	43/33
Age (years)	66.9±7.4	66.3±7.6
<b><i>Symptom/Well Being Measures</i></b>		
CRQ-F (0-28, ↑ less fatigue)	15.2±4.8	15.7±4.7
CRQ-D (0-35, ↑ less dyspnea)	16.3±4.8	16.7±4.7
UCSD (0-120, ↑ more dyspnea)	53.3±1.7	51.5±1.9
CESD (1-40, ↑ more depressive symptoms)	13.5± 8.9	12.8± 8.7
POMS T/A (0-20 ↑ more anxiety)	7.2±3.2	4.4±3.2
SF-36 Bodily Pain (0-100, ↑ less pain)	71.5±26	71.4±26
SF-36 Physical (0-100, ↑ higher functioning)*	34.6±17.5	40±18.4
<b><i>Physiological/Physical Measures</i></b>		
FEV <sub>1</sub> % *	44.8±14.7	46.9±14.2
PaO <sub>2</sub> (n = 99)	74.2± 9.3	74.9±9.6
PaCO <sub>2</sub> (n = 99)	39.4± 4.8	40.0± 4.7
D <sub>L</sub> CO %	65.0±20	67.5±21
BODE	3.1±1.8	2.8±1.8
6MW Distance (feet)*	1398.8±351.3	1438.1±259.5
ITT Duration (minutes)*	9.1±4.1	9.6±4.2

± Mean standard deviation

\* Significant difference ( $p < .05$ ) between participants with complete data compared with participants missing CRQ-Fatigue

**6MW** Six-minute walk distance, feet

**BODE** BODE index

**CESD** Center for Epidemiological Studies Depression questionnaire

**CRQ-D** Chronic Respiratory Questionnaire Dyspnea subscale

**CRQ-F** Chronic Respiratory Questionnaire Fatigue subscale

**D<sub>L</sub>CO %** Diffusion capacity for carbon monoxide, percent predicted

**FEV<sub>1</sub> %** Forced expiratory volume over one second, percent predicted

**ITT** Incremental Treadmill Test, time in minutes

**PaCO<sub>2</sub>** Partial pressure of arterial carbon dioxide, resting, room air

**PaO<sub>2</sub>** Partial pressure of arterial oxygen, resting, room air

**POMS T/A** Profile of Mood States Tension/Anxiety subscale

*SF-36 Bodily Pain Medical Outcomes Study 36-Item Short Form Health Survey Bodily Pain scale*  
*SF-36 Physical Medical Outcomes Study 36-Item Short Form Health Survey Physical Health component*  
*UCSD University of California San Diego Shortness of Breath questionnaire*

**Table 2.**

Characteristics of fatigue categories

Variable	Stable	Improving/ Stable	Worsening/ Stable	Labile
<i>n</i>	29	28	18	4
Gender (F/M)	14/15	18/10	12/6	2/4
Age (years)	66.6 ± 7.9	67.4 ± 6.3	66.1 ± 8.7	65.7 ± 6.7
<b>Symptom/Well Being Measures</b>				
CRQ-F (0-28, ↑ less fatigue)	16.8 ± 4.2	<b>13.0 ± 4.3*</b>	18.9 ± 4.3	14.3 ± 2.5
CRQ-D (0-35, ↑ less dyspnea)	16.3 ± 4.9	16.0 ± 4.6	18.9 ± 4.6	18.0 ± 4.4
UCSD (0-120, ↑ more dyspnea)	53.6 ± 16.6	54.0 ± 16.9	44.8 ± 18.0	43.7 ± 16.9
CESD (1-40, ↑ more depressed)	12.2 ± 9.3	13.8 ± 7.9	11.9 ± 9.4	11.0 ± 9.8
POMS T/A (0-20 ↑ more anxiety)	4.2 ± 2.8	4.6 ± 3.8	4.8 ± 3.0	2.0 ± 1.0
SF-36 Bodily Pain (0-100, ↑ less pain)	72.3 ± 23.0	68.0 ± 29.4	70.6 ± 26.5	87.3 ± 21.9
SF-36 Physical (0-100, ↑ higher functioning)*	33.4 ± 14.0	31.1 ± 18.1	<b>50.9 ± 19.1*</b>	50.0 ± 25.0
<b>Physiological/Physical Measures</b>				
FEV <sub>1</sub> % *	45.9 ± 13.4	47.7 ± 17.2	46.5 ± 12.4	42.7 ± 3.2
PaO <sub>2</sub> ( <i>n</i> = 99)	39.0 ± 5.3	38.3 ± 4.8	39.8 ± 3.3	40.7 ± 1.6
PaCO <sub>2</sub> ( <i>n</i> = 99)	76.6 ± 9.9	73.3 ± 10.0	76.2 ± 7.3	67.5 ± 11.4
D <sub>L</sub> CO %	67.7 ± 22.4	67.5 ± 20.0	66.1 ± 23.9	72.0 ± 6
BODE	1.7 ± 0.82	1.5 ± 1.0	1.8 ± 1.0	2.0 ± 0
6MW Distance (feet)*	1440 ± 270	1343 ± 376	1545 ± 213	1375 ± 79
ITT Duration (minutes)*	9.9 ± 3.1	8.5 ± 4.7	10.8 ± 3.9	9.8 ± 7.7

\* Significant difference (*p* < .05) between treatment groups

± Mean standard deviation

**6MW** Six-minute walk distance, feet

**BODE** BODE index

**CESD** Center for Epidemiological Studies Depression questionnaire

**CRQ-D** Chronic Respiratory Questionnaire Dyspnea subscale

**CRQ-F** Chronic Respiratory Questionnaire Fatigue subscale

**D<sub>L</sub>CO %** Diffusion capacity for carbon monoxide, percent predicted

**FEV<sub>1</sub> %** Forced expiratory volume over one second, percent predicted

**ITT** Incremental Treadmill Test, time in minutes

**PaCO<sub>2</sub>** Partial pressure of arterial carbon dioxide, resting, room air

**PaO<sub>2</sub>** Partial pressure of arterial oxygen, resting, room air

**POMS T/A** Profile of Mood States Tension/Anxiety subscale

**SF-36 Bodily Pain** Medical Outcomes Study 36-Item Short Form Health Survey Bodily Pain scale

**SF-36 Physical** Medical Outcomes Study 36-Item Short Form Health Survey Physical Health component

**UCSD** University of California San Diego Shortness of Breath questionnaire

**Table 3**

Pearson Correlations Between CRQ-Fatigue Subscale and Symptom, Mood, and Physiological Measures Over Time

Correlation	Time	
	Baseline	12 months
<i>Symptom/Well Being Measures</i>		
CRQ-D	.314**	.441**
UCSD	-.390**	-.461**
CESD	-.445**	-.528**
POMS T/A	-.332**	-.479**
SF36-Phys	.318**	.324**
<i>Physiological/Physical Measures</i>		
FEV <sub>1</sub> %	-.100	.113
6MW	.330**	.230*
ITT	.267**	.265*

\* significant at the .05 level, \*\* significant at the .001 level (two-tailed)

**6MW** Six-minute walk distance, feet

**CESD** Center for Epidemiological Studies Depression questionnaire

**CRQ-F** Chronic Respiratory Questionnaire Fatigue subscale

**FEV<sub>1</sub> %** Forced expiratory volume over one second, percent predicted

**ITT** Incremental Treadmill Test, time in minutes

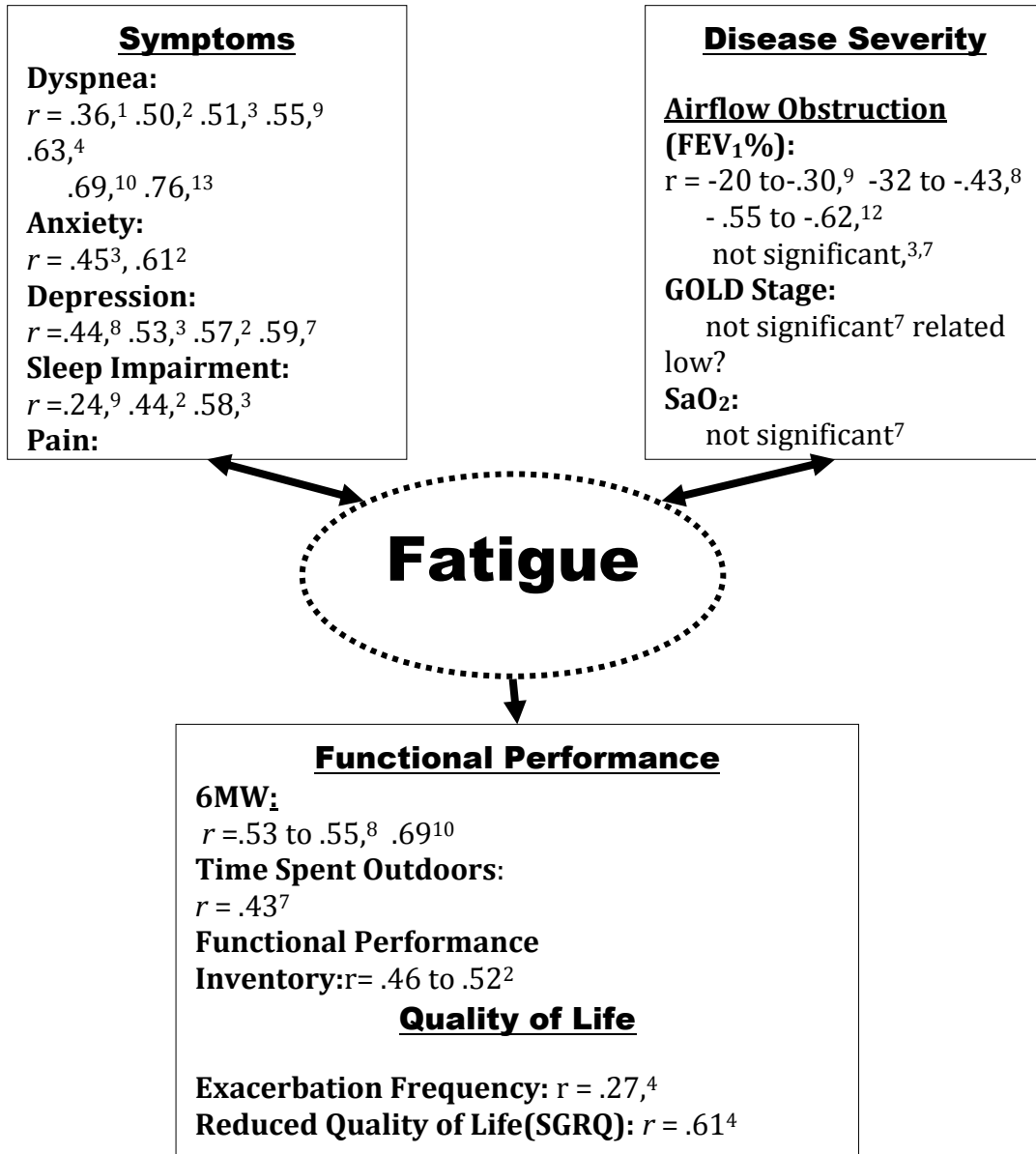
**POMS T/A** Profile of Mood States Tension/Anxiety subscale

**SF-36 Physical** Medical Outcomes Study 36-Item Short Form Health Survey Physical Health component

**UCSD** University of California San Diego Shortness of Breath questionnaire

**Figure 1**

Literature review of the association between fatigue and symptoms, disease severity, functional performance, and quality of life in patients with COPD.



*6MW = Six Minute Walk distance*

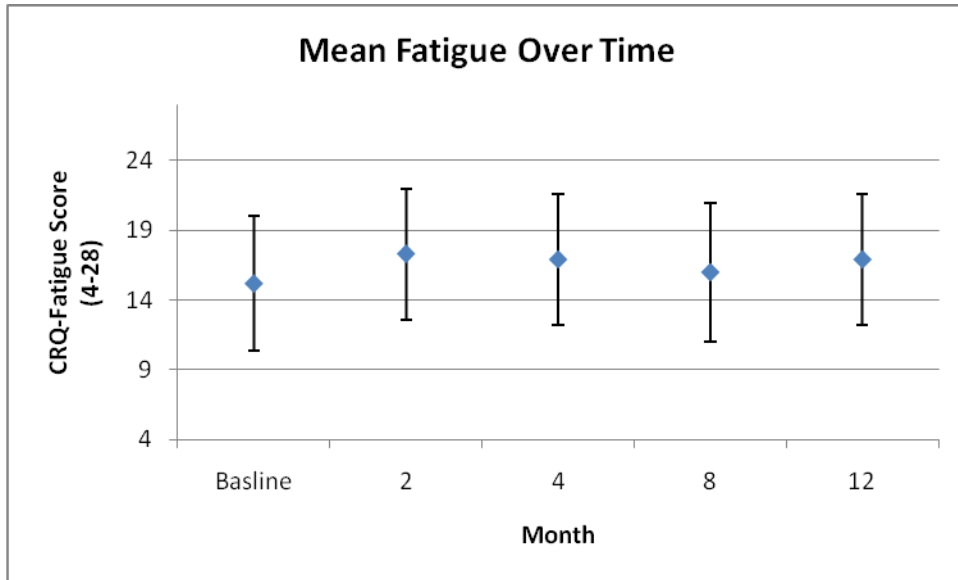
*FEV<sub>1</sub>% = Percent predicted forced expiratory volume over one second*

*GOLD = Global Initiative for Obstructive Lung Disease*

*SGRQ = Saint George Respiratory Questionnaire*



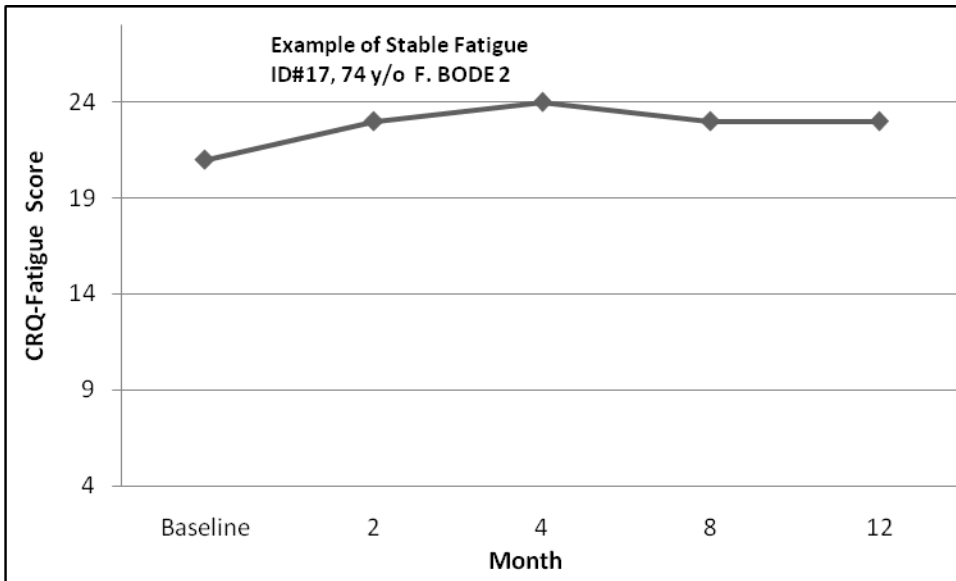
**Figure 2**  
Mean fatigue over time.



**n = 103, Anova  $p > .05$**

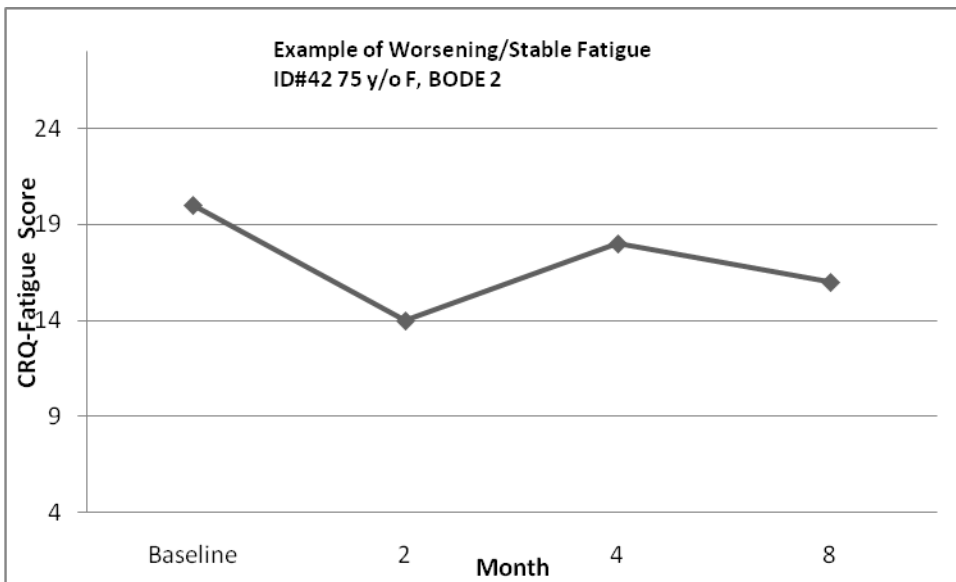
**Figure 3a**

Example of stable fatigue over time.



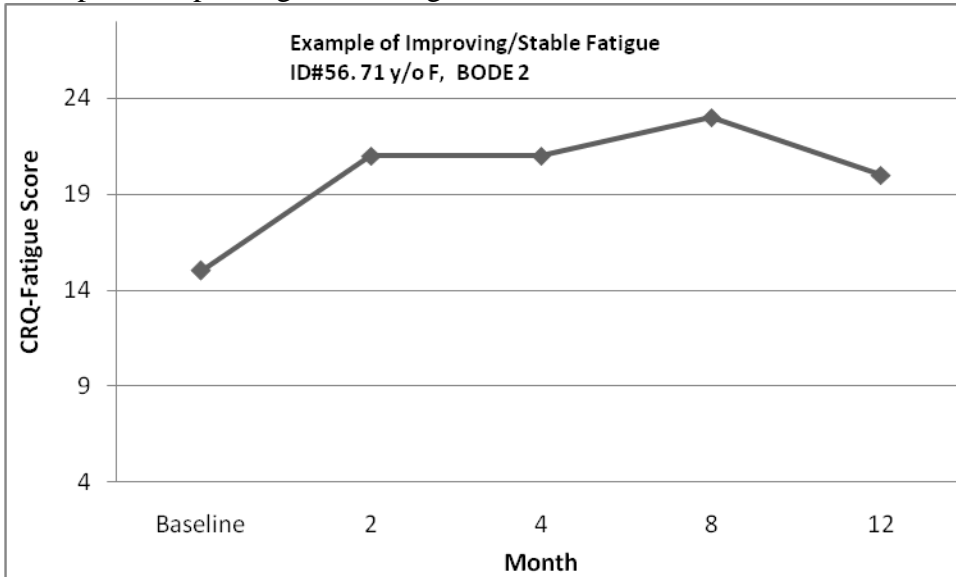
**Figure 3b**

Example of worsening/stable fatigue over time.



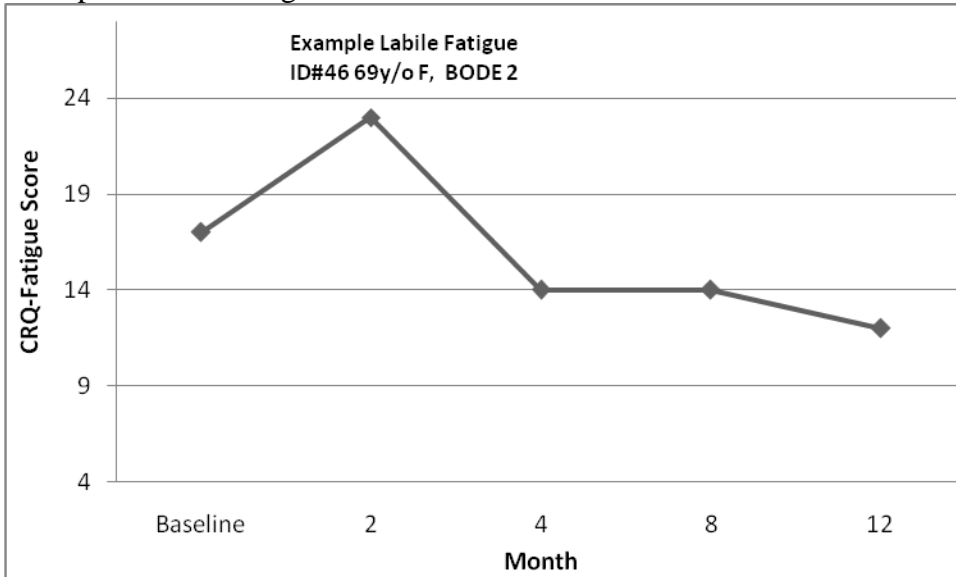
**Figure 3c**

Example of improving/stable fatigue over time



**Figure 3d**

Example of labile fatigue over time



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