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Safety of Anti-Depressant in Chronic Obstructive Pulmonary Disease (SAD-COPD)

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Purpose of the Study

Purpose of the Study: In COPD and ILD (Interstitial Lung Disease) patients with perceived stress, anxiety and depression, does the addition of anti-depressant therapy improve lung function and dyspnea better than pulmonary rehab alone?

Primary Outcome: The addition of anti-depressant therapy will improve lung function and dyspnea in patients with COPD and/or ILD with perceived stress, anxiety, and depression better than pulmonary rehab alone.

Secondary Outcomes:

The addition of anti-depressant therapy will improve QOL scores in COPD and ILD patients with perceived stress, anxiety, and depression better than pulmonary rehab alone.

The addition of anti-depressant therapy will improve measures of perceived stress, anxiety, and depression in COPD and ILD patients with stress, anxiety, and depression better than pulmonary rehab alone.

Specific Aim 1:

Determine whether treatment of perceived stress, anxiety, and depression with anti-depressant therapy improves dyspnea scores, 6MW distance and QOL in patients with COPD undergoing pulmonary rehab. We will:

Patients with COPD and/or ILD undergoing pulmonary will be randomized to treatment arm (anti-depressant therapy) vs. placebo arm prior to initiating pulmonary rehab.

We will administer comprehensive surveys, including measures of anxiety and depression (HADS, AIR), perceived stress (GHQ-12), dyspnea (UCSD), and quality of life (QOL) along with performing 6-minute walk, physical exam, and pulmonary function testing at visits 1, 4, and 6.

We will also assess tolerability of treatment with SSRI (sertraline) and appropriateness of further dose increase, or need for dose decrease, in the study drug at visits 2-4, which are at 1 week intervals (+ 7 days).

We will re-administer measures of anxiety and depression (HADS, AIR) as well as dyspnea scores (UCSD) and QOL at visit 5.

Primary Hypothesis:

We hypothesize that because depression, anxiety and perceived stress are associated with decreased exercise tolerance and lower QOL, then treatment of depression, anxiety and stress with an anti-depressant will modify the clinical efficacy of pulmonary rehab in patients with COPD and/or ILD who have depression, anxiety and stress.

Background & Significance

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent disease and a major cause of morbidity and disability in those age 40 years and older (1-3). Like other chronic diseases, COPD and ILD have a significant impact on the psychological well being of those affected. It has been well documented that mental health problems, particularly depression and anxiety, are well-recognized major comorbidities in chronic lung disease (2-4) and contribute to increased mortality in these patients as well (2, 5). The prevalence of anxiety and depression is higher in patients with COPD compared to the general population (2, 6), and may even be more prevalent in COPD compared with other

chronic illnesses (7). The reported prevalence of both anxiety and depression in patients with chronic lung disease is varied, depending on the population surveyed and the tools used to assess depression and anxiety. However, it has been established that the prevalence of depression increases with severity of COPD (3, 8). Furthermore, since a high co-morbidity (up to > 50%) exits between depression and anxiety (9), it is assumed that anxiety is more prevalent as well. There is a higher likelihood of exacerbations, frequent readmissions, greater disability, and overall worse survival reported in COPD patients with depressive symptoms (2, 5,10-13). Additionally, others have shown anxiety has been linked to frequent exacerbations and readmissions as well as greater disability (14-16). Furthermore, patients with COPD who have anxiety often hyperventilate, which is associated with dynamic hyperinflation, resulting in worsening dyspnea and exercise intolerance (3, 17-18).

The impact of depression, anxiety, and even perceived stress on morbidity and mortality in patients with COPD and ILD is significant, specifically in terms of medication adherence, frequent exacerbations, overall quality of life, perceived dyspnea, and exercise intolerance. Consequently, there has been a growing interest in reducing the negative impact of these comorbidities in patients with chronic lung disease, particularly in COPD (3). Pulmonary rehab has been shown by many to be an essential therapeutic intervention for people who are symptomatic from chronic lung diseases, such as COPD and ILD (19, 20). Specifically, documented benefits from pulmonary rehab include improvement in quality of life and exercise tolerance, and a reduction in symptoms of dyspnea and fatigue (3, 21). Over the last decade, pulmonary rehab has also demonstrated reduction in symptoms of depression and anxiety in patients with moderate to severe COPD (22-24). However, there are varying results regarding whether the burden of depression and anxiety or even patients illness perceptions impact outcomes with pulmonary rehab and its effectiveness in patients with COPD (25-27). Additionally, there has been limited data looking at treating specific symptoms of perceived stress, anxiety, and depression concurrently with pulmonary rehab. Coventry et al conducted a systematic review with meta-analysis examining the comparative effects of a range of psychological and/or lifestyle interventions on depression and anxiety in COPD (28). This meta-analysis observed that the only intervention associated with significant improvements in depression and anxiety was a multicomponent pulmonary rehab, with an exercise component, relaxation techniques, and self-management education (4, 28, 29). This suggests that complex interventions that contain a combination of psychological techniques and exercise training have the greatest impact on depression and anxiety.

There is a paucity of research looking at the effects of pharmacological and non-pharmacological therapies used to treat depression and anxiety in COPD or ILD. Aside from pulmonary rehab, there are no guidelines regarding other treatment options in patients with chronic lung disease and mental health issues. There is some data looking at non-pharmacologic interventions, including relaxation therapy, cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and self-management programs for treatment of anxiety and depression (30). However, the quantity and methodological difficulties have hindered the integration of their use in formal treatment guidelines for either COPD or ILD (3).

Pharmacotherapy is used in standard clinical practice for treatment of anxiety and depression, and appears to be commonly used in patients with COPD and ILD as well as in other chronic diseases. In cardiac disease, Jiang, has looked at the effect of treating depression with an SSRI on outcomes in patients with CHF. Patients whose depression remitted had a smaller number of nonfatal cardiovascular events per patient as well as less fatal and nonfatal events combined (31, 32). Evidence for the role of anti-depressant therapy to treat mood disorders in chronic lung disease is limited. Of the available studies, most are small with large dropout rates and short follow-up period, and most have looked at the role of anti-depressants in COPD alone. SSRIs are generally considered as preferred first-line agents for treatment of depression and anxiety in patients with chronic lung disease (3). Some evidence has shown better depression scores as

well as quality of life (33, 34). Eiser et al showed significant reductions in depression scores, improved walking distance and health-related quality of life at 3-month follow-up with paroxetine. Furthermore, a systematic review by Usmani et al showed a non-significant but clinically relevant benefit with the use of SSRI for treatment of anxiety symptoms in COPD patients (35). Case reports have also shown improvement in symptoms of anxiety in COPD when treated with sertraline (36).

To date no one has looked at the role of pharmacologic treatment of perceived stress, anxiety and depression in improving outcomes with pulmonary rehab in patients with COPD and/or ILD. We suspect that perceived stress, anxiety, and depression are effect modifiers on outcomes in pulmonary rehab in COPD and ILD patients. Furthermore, we believe that pharmacologic treatment of anxiety and depression with an SSRI while participating in pulmonary rehab will improve outcomes, including improvement in walking distance, exercise tolerance, and lung function. Treatment with SSRI will also reduce perceived dyspnea scores as well. Thus, this will lead to overall improvement in quality of life.

Design & Procedures

The study is a prospective, randomized, double-blinded, placebo-controlled study to assess the effect of an SSRI on 6MW, dyspnea scores, and QOL in COPD and ILD patients undergoing pulmonary rehab. Thirty subjects that carry an ICD-9 code diagnosis of COPD and/or ILD and have evidence of depressive symptoms according to a CES-D (Center for Epidemiologic Studies Depression) score of $\geq$ 16 will be recruited from Duke Pulmonary Rehab. Once subjects have been determined to be eligible for enrollment based on inclusion criteria and consent has been signed, they will be randomly assigned to 12 weeks of double-blind treatment with SSRI or matched placebo while concurrently participating in pulmonary rehab.

Subjects will also have a physical exam, 6-minute walk test, and spirometry at Visits 1, 4, and 6. Both spirometry and the 6-minute walk test are performed clinically in both the COPD and ILD diseased patients to evaluate functional status and assess progress in pulmonary rehab, so this is not unusual for the population.

Questionnaires will be performed specifically for research evaluation of perceived stress, anxiety, and depression in this population.

Screening (Visit 0):

- Explain the study, and informed consent will be obtained.
- Perform a comprehensive medical history.
- Urine pregnancy testing for women of childbearing potential (WOCBP)**
- A comprehensive physical exam will be performed, including vital signs.
- A formal psychiatric assessment, including psychiatric or mental health history, will be performed using the Mini International Neuropsychiatric Interview (MINI).
- If there is concern for cognitive impairment, the MMSE will be used to assess whether there is clinically significant cognitive impairment due to dementia or delirium.
- If subject is determined to be eligible for enrollment, subjects will then be randomly assigned to one of the two treatment arms (either matched placebo or anti-depressant therapy/sertraline), and the study drug will be dispensed at the end of Visit 1.
- Subjects will be asked to bring the medication bottle containing the study drug with them to all scheduled visits to assess medication use and compliance by pill counting.

Visit 1 (day of enrollment into pulmonary rehab/may be same day as visit 0):

- If visit 1 does not occur on the same day as visit 0, a comprehensive physical exam will be performed (similar to Visit 0) and urine pregnancy testing for WOCBP.
- Perform Spirometry (does not need to be repeated if performed during enrollment into pulmonary rehab).
- Perform 6-Minute Walk test (does not need to be repeated if performed during enrollment into pulmonary rehab).
- Administer questionnaires, including the General Health Questionnaire (GHQ-12), Hospital Anxiety and Depression Scale (HADS), Anxiety Inventory for Respiratory Disease (AIR), UCSD dyspnea scale, and Quality of Life (QOL) scale (UCSD dyspnea scale and QOL does not need to be repeated if performed during enrollment into pulmonary rehab).
- Administer study drug.

Visits 2-3 (scheduled at 1 week intervals ± 7 days):

- Urine pregnancy test for WOCBP
- Assessment of medication compliance by pill counting.
- Assessment of tolerability for further dose titration for study drug, and if deemed appropriate, will increase dose of study drug.

Visit 4 will also include the following (scheduled at 1 week intervals ± 7 days)**: :**

- Administer questionnaires, including the HADS, and AIR, to assess symptoms of perceived stress, anxiety, and depression.
- Administer UCSD dyspnea scale and QOL scale.
- Perform Spirometry.
- Perform 6-Minute Walk test (does not need to be repeated if performed during pulmonary rehab).
- Urine pregnancy test for WOCBP
- Administer General Health Questionnaire (GHQ-12).
- Assessment of medication compliance by pill counting.
- Assessment of tolerability for further dose titration for study drug, and if deemed appropriate, will increase dose of study drug.

Of note, during the first 4 weeks of the trial, subjects will be participating in an intensive program of pulmonary rehab as per standard of care. However, during the last 8 weeks, subjects will participate in a modified-graduate program of pulmonary rehab per standard of care.

Visit 5 (scheduled at 1 month interval from visit 4 ± 7 days):

- Urine pregnancy test for WOCPB
- Administer questionnaires, including the HADS, AIR, UCSD dyspnea scale, and QOL scale.
- Assessment of medication compliance by pill counting.

Visit 6 (scheduled at 1 month interval from visit 5 ± 7 days):

- A comprehensive physical exam will be performed (similar to Visit 0).
- Urine pregnancy test for WOCPB
- Perform Spirometry.
- Perform 6-Minute Walk test.
- Assessment of medication compliance by pill counting.
- Administer questionnaires, including the General Health Questionnaire (GHQ-12), Hospital Anxiety and Depression Scale (HADS), Anxiety Inventory for Respiratory Disease (AIR), UCSD dyspnea scale, and Quality of Life (QOL) scale.

Scheduled and Missed Visits:
All visits will be scheduled based on the date of randomization (Visit 0). Visits 1-4 will be scheduled at 1 week intervals ± 7 days, and visits 5 and 6 will be scheduled at 1 month intervals ± 7 days over the 12-week treatment period. A missed appointment or visit should be followed by a telephone call to the subject.

According to the HRPP pregnancy testing policy: urine pregnancy test will be acceptable in this study. WOCPB who have active menses or who are on a medically acceptable contraceptive for 3 months, urine pregnancy test will be performed. If not, a serum pregnancy test will be done.

Study Schema:

Visit	V0	V1	V2	V3	V4	V5	V6	Phone call
Description	Pre-rehab	1st day of rehab	Week 1 +/- 7 days	Week 2 +/- 7 days	Week 3 +/- 7 days	Week 7 +/- 7 days	Week 11 +/- 7 days	f/u for missed appts
Informed consent, eligibility review	•							
Anthropometrics-Ht & Wt		•			•		•	
Vital Signs – BP, HR, RR, Sp02	•	•			•		•	
Baseline medical Hx	•							
Comprehensive Physical Exam	•	•					•	
Psych exam with MINI, MMSE	•							
Urine HCG-WOCBP	•	•	•	•	•	•	•	
6 MWT		•*			•		•*	
Spirometry		•*			•		•*	
Randomization	•							
GHQ-12		•			•		•	
HADS		•			•	•	•	
AIR		•			•	•	•	
UCSD BORG		•*			•*	•	•	
QOL		•*			•*	•	•	
IP compliance / count			•	•	•	•	•	
Assess for possible titration			•					
Administer IP		•						
Assess AE's			•	•	•	•	•	
Assess COPD exacerbations/ suicidality			•	•	•	•	•	

*If testing is being done as part of Pulmonary rehab clinical intake or close out, clinical values can be utilized.

End of Treatment Recommendations:
At the last treatment visit, subjects that continue to show anxiety or depressive symptoms will be further evaluated and the study physicians will make patient care recommendations. All subjects with depressive symptoms or significant anxiety will be referred for treatment to an outside psychiatrist or follow-up with his or her primary care physician. Treatment assignment will be disclosed at the end of the study unless a clinical emergency resulting in the subject's withdrawal from the study or that necessitates this to be disclosed earlier in the study.

At the end of the study, the outside treating physician will receive a formal letter indicating that the subject has participated in the SAD-COPD protocol and recently ended a double-blind treatment for depression and/or anxiety and the treatment assignment will be disclosed.

The principal investigator or co-investigator, will prescribe sertraline for the subsequent 30 days depending on the response to treatment as assessed on the last treatment visit completed. If the subject shows no response to the study medication (non-responder), specific instructions about tapering off the study medication will be given at the last visit completed and forwarded to the subject's physician.

For the purpose of end of treatment recommendations, treatment **responders** will be defined as a subject with score of < 8 on either the anxiety or depression component of the HADS, and a **non-responder** will be defined as a subject with a score of ≥ 8 on either the anxiety or depression component of the HADS.

Visit	V0	V1	V2	V3	V4	V5	V6	Phone call
Description	Pre-rehab	1st day of rehab	Week 1 +/- 7 days	Week 2 +/- 7 days	Week 3 +/- 7 days	Week 7 +/- 7 days	Week 11 +/- 7 days	f/u for missed appts
Informed consent, eligibility review	•							
Anthropometrics-Ht & Wt		•			•		•	
Vital Signs – BP, HR, RR, Sp02	•	•			•		•	
Baseline medical Hx	•							
Comprehensive Physical Exam	•	•					•	
Psych exam with MINI, MMSE	•							
Urine HCG-WOCBP	•	•	•	•	•	•	•	
6 MWT		•*			•		•*	
Blood draw for CRP IL6		•					•	
Spirometry		•*			•		•*	
Randomization	•							
GHQ-12		•			•		•	
HADS		•			•	•	•	
AIR		•			•	•	•	
UCSD BORG		•*			•*	•	•	
QOL		•*			•*	•	•	
IP compliance / count			•	•	•	•	•	
Assess for possible titration			•					
Administer IP		•						
Assess AE's			•	•	•	•	•	
Assess COPD exacerbations/ suicidality			•	•	•	•	•	

*If testing is being done as part of Pulmonary rehab clinical intake or close out, clinical values can be utilized.

Selection of Subjects

Potentially eligible subjects include individuals with clinically stable COPD as defined by the following criteria:

Inclusion Criteria

- Male or female with an ICD-9 code diagnosis of COPD and/or ILD and enrolling in the Duke Pulmonary Rehabilitation Center
- Age 40 years or older
- Mild, moderate, or severe major depression symptoms based on Center of Epidemiologic Studies Depression (CES-D) score $\geq$ 16.
- Able to give inform consent†
- Read and write in English

Exclusion criteria:

- Current treatment with antidepressants
- Current treatment with anti-psychotics
- Severe physical disability that would interfere with lung assessment
- History of major psychiatric illness, including bipolar disorder, psychoses, and/or severe personality disorder.
- Active suicidal ideations
- Serious cognitive problems (dementia syndrome) or cognitive impairment defined as MMSE < 22
- Recent loss of spouse within 6 weeks of study enrollment.
- History of alcohol or drug dependence in the last 6 months.
- Pregnant women or nursing mothers
- Poorly controlled concomitant conditions that pose additional procedure risk as determined by the investigator.

Study Interventions

Subjects will be randomized to receive either anti-depressant therapy (sertraline) or matched placebo to take daily along with participating in pulmonary rehab program.

Study Drug Procedures:
Storage, Dispensing, and Disposition

Duke Investigational Drug Services (IDS) will be used. The drugs will be prepared in bottles according to randomization and dispensed to the study team to provide to subjects at Duke Pulmonary Rehab facility on the day of dispensing according to the Maestro Care Order built by DOCR.

The IDS will perform the randomization of study drug versus placebo and will provide a blinded drug accountability form to the study team. All capsules of the active study drug will be 25mg each. IDS will dispense bottles of study drug or placebo each week for the first 4 weeks (visits 1-4) with each bottle containing one week worth +/- 7 days of pills. At visit 4 and 5, subjects will be provided one month supply of study drug or placebo (depending on their randomization and final determined dose) +/- 7 days. All unused drug will be returned to IDS.

Special emphasis will be placed on designing packaging and labeling that meets all of the required regulations, supports the interaction between the health care provider and the patient, and assists in meeting the clinical objectives set forth in the protocol. IDS will over-encapsulate for blinding purposes as per their SOP.

- **Storage of Study Drug**

The clinical supplies should be stored at room temperature in a restricted area, free of environmental extremes. This should be a locked storage area with access limited to the co-investigators and other authorized staff only.

- **Study Drug Accountability and Disposition**

PI, Co-Investigator, or study coordinator will be in charge of counting pills at each scheduled visit. The co-investigator must maintain adequate records of the disposition of all study drugs at each scheduled evaluation. This includes the date, quantity, and use by patient for each dose of drug dispensed. The number of bottles dispensed is dependent upon the patient's dose and next visit.

- **Unused Study Drug**

After completion of the study, all unopened and unused study drug will be destroyed on-site by IDS or per hospital policy.

Study Drug Packaging
Each enrolled subject will be assigned study drug according to their randomization. Subjects will be dose-escalated by 25 mg (or placebo capsule) during the first 4 weeks, unless the increased dose is not tolerated. All study drug capsules will contain sertraline 25mg or dextrose for placebo. Week one study drug bottles will contain 14 capsules for the subject to take 1 capsule per day for 7 days, with a +/- 7 day supply. Week 2 bottles will contain 28 capsules to account for the dose increase where subjects will take 2 capsules per day with a +/- 7 day supply. Week 3 bottles will contain 42 capsules to account for the dose increase with a +/- 7 days supply. Week 4 bottles will contain 56 capsules to account for the dose increase and a +/- 7 days supply. The remainder of study drug dispensing will be dependent on the Maestro Care order based on the subjects' tolerability. Bottles will be labeled according to IDS policy to meet the needs of the protocol and to meet North Carolina Board of Pharmacy requirements.

Study Drug Administration
The study drug should be taken by mouth once daily, preferably with the morning meal. The first dose should be taken the morning following randomization (Day 2). If necessary, the timing of the dosing may be adjusted by the co-investigator.

Stage 1 begins with randomization so significant delays in dispensing or taking of the study medication will not result in the subject receiving less than 12 weeks of treatment. Care must be taken to ensure that the subject has sufficient study drug to cover any delay in a scheduled visit. Telephone contacts should be made as clinically indicated during the trial. In particular, a missed appointment should be followed by a telephone call.

The study drug dose will be increased in 25mg increments during the first 4 weeks. However, the study drug may be decreased in 25mg increments due to intolerability at any time during the study per the PI's judgment. The target maximum dosage will be 100 mg/day. Subjects who stop treatment before the end of the study treatment should be evaluated for safety and efficacy at the final visit. Subjects who are withdrawn from the study for any reason should be followed as clinically appropriate.

The initial dose will be 25mg per day. The PI based on clinical response, will adjust study medication dosage by 25mg at visits 2-4. In the absence of dose-limiting adverse events, the dose will be further increased to 2 capsules (50mg/placebo) at the end of **Week 2,** to 3 capsules (75mg/placebo) at the end of **Week 3**, and to 4 capsules (100mg/placebo) at the end of **Week 4.**

Decision to decrease the dosage of the study medication will be based upon clinical opinion of the PI as she is a trained psychiatrist. Specifically, if the subject demonstrates evidence of significant side effects from or is unable to tolerate current dose, the dose will be decreased by 1 capsule (or 25mg). Significant side effects or intolerability will be defined as evidence of serotonin syndrome, significant agitation or tremor, worsening in anxiety or depression such that the subject is having suicidal ideation or intent.

End of treatment recommendations for treatment responders and non- responders are detailed above.

Study Drug Compliance
Study drug must be returned and counted at each scheduled visit (visits 2-6).

- If pill counts on the returned drug indicate that the subject has not taken the entire supply of prescribed study drug, the subject will be counseled on the importance of compliance and the proper way to take the study drug.
- Study medication non-compliance on the part of the subject, defined as 3 or more days of missing medications determined by admission or pill count, will result in discontinuation of the subject.
- Study medication not taken due to any reason for 14 days will result in discontinuation of the subject.

Study Drug Overdose
Treatment of possible overdose of sertraline will be dealt with by contacting the subject's primary care provider, and a treatment plan will be developed.

Study Drug Unblinding
Treatment assignments will be revealed at the end of study. The following describes exceptional circumstances that may lead to the disclosure of the double-blind treatment assignment during the study.

- Clinical Emergency during Acute Treatment Stage:

If a clinical emergency arises at any time during the study, IDS will be contacted for the subject's randomization assignment. The PI and the co-investigators will not be unblinded until either has approved unblinding in the form of a documented written request that is submitted to IDS. Then the patient's primary care provider will be contacted, and a treatment plan will be developed. In the event that the PI or the co-investigators are not available, there will be a back-up physician (Dr. Neil MacIntyre) assigned for emergency un-blinding of treatment.

Safety Measures:
Vital signs, heart, lung, and other physical exam findings will be collected at the initial visit (visit 1) and again at the final treatment visit (visit 6). COPD exacerbations or respiratory complications and suicidality will be gathered during the 12-week acute treatment phase. The event page will be used to record COPD GOLD stage and to monitor for significant events, such as:

- Deaths and cause of death
- All in-patient admissions and reasons for the admission, emergency room visits, urgent care or outpatient visit for acute respiratory reason
- Successful and unsuccessful suicide attempts

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Risk/Benefit Assessment

Study Drug: Subjects will be randomized either to receive anti-depressant therapy with a selective serotonin reuptake inhibitor (sertraline) or a matched placebo. Subjects are informed of the mechanism of action of SSRIs as well as the potential benefits, which include improvement in their mood and reduction in symptoms of depression or anxiety.

Additionally, subjects are informed of potential side effects of SSRIs, including common potential side effects like the following: feeling agitated, shaky, or anxious, feeling or being sick, indigestion or gastritis, diarrhea or constipation, loss of appetite or weight loss, dizziness, blurred vision, dry mouth, excessive sweating, insomnia or drowsiness, headaches, low sex drive, difficulty achieving orgasm during sex or masturbation, and in men, difficulty obtaining or maintaining an erection (erectile dysfunction). Much less common side effects discussed during consent, include bruising or bleeding easily (including vomiting blood or blood in your stools), confusion, problems with movement (stiffness or shaking), seeing or hearing things that are not real, being unable to pass urine.

Serotonin Syndrome: Serotonin syndrome is an uncommon but potentially serious side effect linked to SSRIs. Serotonin syndrome occurs when the levels of serotonin in your brain become too high. It is usually triggered when you take an SSRI

in combination with another medication or substance that also raises serotonins levels, such as another antidepressant or St John's Wort. Symptoms include: confusion, agitation, muscle twitching, flushing, sweating, shivering, diarrhea, fever, seizures, arrhythmias, and loss of consciousness.

Hyponatremia: Elderly people who take SSRIs may experience a severe fall in serum sodium known as hyponatremia. This may lead to a build-up of fluid inside the cells of the body, which can be potentially dangerous. This side effect can occur as SSRIs can block the effects of a hormone that helps regulate levels of sodium and fluid in the body. Elderly people are vulnerable because fluid levels become more difficult for the body to regulate.

Mild hyponatremia can cause symptoms similar to depression or side effects of SSRIs, such as feeling sick, headache, muscle pain, reduced appetite, and confusion.

More severe hyponatremia can cause the following symptoms: feeling tired, confusion or disorientation, agitation, seeing or hearing things that are not real (hallucinations), psychosis (being unable to tell the difference between reality and your imagination, and seizures.

The most serious cases of hyponatremia can cause you to stop breathing or enter a coma.

Subjects will be instructed to stop the study drug, contact someone from the research team or their regular doctor, and go to the emergency room or nearest hospital if they begin to experience any of the above serious side effects, including serotonin syndrome, hyponatremia. Subjects will be assessed for potential side effects related to the study drug at each scheduled visit.

Suicidal thoughts: Some people experience suicidal thoughts and a desire to self-harm when they first take SSRIs. At each scheduled visit, subjects will be assessed for thoughts of suicidality and/or self harm with the HADS questionnaire. Anyone exhibiting a serious suicidal intent will be immediately accompanied to an appropriate health facility such as an emergency room.

Spirometry*:* Can sometimes cause coughing; you may also experience shortness of breath, chest tightness, or light headedness.

Exercise tolerance: Subjects will undergo the 6-Minute Walk Distance test for exercise tolerance. The risks of this assessment are fatigue and falling.

Questionnaires and assessments: We will make every effort to protect privacy and keep data confidential. There is a risk of breach of privacy and confidentiality. To minimize risk, we will use only study codes to identify data and study records, and store study data and records in a secure place. All paper records will be kept secure within the research area at the Duke Asthma, Allergy, and Airway Center. All electronic data collected in this study will be stored in Excel on the divisional shared drive and secured through the following methods: access rights granted and terminated for authorized users only, secure laptops and workstations, individual ID plus password protection, routine electronic back up, network restrictions.

1. Some questionnaires inquire about anxiety and depression symptoms. If these conditions are severe enough, we will refer the subject to his or her primary care physician for evaluation and treatment. Anyone exhibiting a serious suicidal intent will be immediately accompanied to an appropriate health facility such as an emergency room.
2. Cognitive functioning for eligibility will be assessed using the MMSE. If the subject scores less than 22 on this assessment, the clinic will provide the subject a letter referring him or her for further cognitive evaluation. In addition a secondary letter to explain the MMSE results suitable to be given to all subjects has been prepared.

There is no guaranteed health benefit to subjects from involvement in this study. Subjects may have some emotional benefit to know that their participation may help other people with COPD in the future.

Data Analysis & Statistical Considerations

Multivariable regression models will be constructed to evaluate the relationship between perceived stress, anxiety, and depression with adjustments by race, gender, age, BMI and GOLD score. A multivariable regression model will be constructed to assess whether treatment of perceived stress, depression, and anxiety with antidepressant therapy (sertraline) is an effect modifier on 6MW distance and dyspnea scores in patients with COPD and/or ILD who are enrolled in pulmonary rehab.

Descriptive statistics will be used to examine the socio-demographic characteristic data. Student t-tests will be performed to assess group differences in continuous data. Categorical variables will be examined using the Pearson's Chi-Squared test. Analysis for associations between known prognostic factors for COPD outcomes, measures of disease severity and patient

reported outcomes measured in this study will rely on more complex multivariate models that include random effects terms for clinics and patients.

Data & Safety Monitoring

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research, all AE reports will be reported per the DUHS IRB policies.