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Selective serotonin reuptake inhibitors and lung function in the Multi-Ethnic Study of Atherosclerosis Lung Study

Hilary F. Armstrong, PhD,
Columbia University Medical Center, New York

David Lederer, MD,
Columbia University Medical Center, New York

Gina S. Lovasi, PhD, MPH,
Drexel Dornsife School of Public Health, Philadelphia

Grant Hiura, MPH,
Columbia University Medical Center, New York

Corey E. Ventetuolo, MD, MS,
Brown University, Providence

R Graham Barr, MD, DrPH
Columbia University Medical Center, New York

Abstract

Objective: Depression in patients with Chronic Obstructive Pulmonary Disease (COPD) has been shown to be chronic and potentially increase the burden of symptoms. Selective serotonin reuptake inhibitors (SSRIs) have anti-inflammatory and serotonergic effects that may improve lung function. We hypothesized that participants taking SSRIs have better lung function than those not taking SSRIs. The dataset was the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. Use of SSRIs was assessed by medication inventory; spirometry was conducted following standard guidelines; dyspnea ratings were self-reported.

Results: Contrary to our hypothesis, FEV1 was lower, and odds of dyspnea were higher among participants taking SSRIs as compared with those not taking an antidepressant; these differences persisted even with control for potential confounders including depressive symptoms. We found no evidence of a beneficial association between SSRI use and lung function or dyspnea in a large US-based cohort.

SUMMARY

Corresponding author: Hilary F. Armstrong, hilary.armstrong86@gmail.com.

Authors' contributions- HA analyzed the data, designed, interpreted, and drafted manuscript; DL designed and drafted manuscript, GSL designed, interpreted and drafted manuscript, GH analyzed and interpreted data, CEV designed and drafted manuscript, RGB designed, interpreted and drafted manuscript.

Ethics approval- The institutional review boards of all collaborating institutions and the National Heart Lung and Blood Institute (National Institutes of Health, Bethesda, MD, USA) approved the protocols for MESA and all procedures described herein. All participants provided written informed consent

Competing interests- None

Code availability- available upon request

- Using the MESA dataset, we analyzed whether SSRIs are associated with improved lung function compared to those not prescribed SSRIs
- There was no association with SSRIs and lung function
- This investigation was among the first to assess the impact of antidepressants on lung function using epidemiologic methods and use a large, high-quality study

Keywords

Selective serotonin reuptake inhibitors; depression; lung function; FEVI; dyspnea; COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is classified as an inflammatory group of diseases that cause airflow obstruction, respiratory muscle weakness, and exacerbations that result in reduced lung function [1]. Prior longitudinal studies have shown that depression in patients with COPD is chronic and inadequately treated, which may increase the burden of symptoms for these patients [2]. Even in those without COPD, higher inflammatory markers are associated with lower lung function [3], suggesting an association between lung function and inflammation predating the clinical development of obstructive disease. Reducing inflammation may be beneficial for subclinical disease, in addition to those with clinically defined obstructive disease.

Some antidepressants, namely selective serotonin reuptake inhibitors (SSRIs), may have off-label uses in treating COPD symptoms. SSRIs are anti-inflammatory and act upon serotonin, which is integral to central breathing control [4, 5]. Several prior studies have suggested an association of SSRI use with better lung health [6, 7] but all have been small and with limited adjustment for potential confounders. Most recently, fluvoxamine has been hypothesized to help patients with COVID-19 due to its anti-inflammatory effects [8]. The purpose of this study is to investigate whether those using prescription SSRIs have better concurrent lung function and dyspnea ratings than those not using SSRIs in a large US cohort.

Methods

This study uses data from the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study (NCT00843271). MESA is a multi-center, population-based, longitudinal study of 6,814 men and women free of clinical cardiovascular disease at ages 45–84 years at baseline (in 2000–02) across six sites in the United States [9]. The MESA Lung Study is an ancillary study of MESA to test the endothelial hypothesis of COPD and emphysema that recruited 3,965 MESA participants in 2004–06 [10]. The current analysis uses cross sectional data from Exam 4 (Sept 2005 to May 2007). Analyses were duplicated using data from Exam 5 (Apr 2010 to Dec 2011) to check for robustness.

The institutional review boards of all collaborating institutions and the National Heart Lung and Blood Institute (National Institutes of Health, Bethesda, MD, USA) approved the

protocols for MESA and all procedures described herein. All participants provided written informed consent.

Outcome variables

Spirometry, including FEV1, was measured in accordance with American Thoracic Society/European Respiratory Society guidelines [11, 12] on a dry-rolling-sealed spirometer (Occupational Marketing, Inc., Houston, TX) as previously described [12]. Trained interviewers assessed dyspnea at both exams. Dyspnea is defined as a positive answer to one of the following questions: “When walking on level ground, do you get more breathless than people your own age?” or “Do you ever have to stop walking due to breathlessness?” Dyspnea was coded dichotomously (yes (1)/no (0)) in logistic regression analyses.

Exposure

Medications were assessed by medication inventory, in which participants were asked to bring in their current medications, which were recorded. The exposure of interest was use of SSRIs and, for secondary analyses, other antidepressants. Antidepressants were categorized according to the Anatomical Therapeutic Chemical classification system (SSRIs, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors) [13]. We coded this variable as an indicator variable (yes (1)/no (0)) to indicate whether a participant self-reported use of the drug or not at the time of the visit.

Statistical analysis

Analyses were conducted in SAS 9.4 (Cary, NC). We excluded participants if they a) did not have exposure (medication) information available, b) were on more than one antidepressant or c) were missing data on any confounder included in the model. FEV1 was analyzed using multiple linear regression, dyspnea was analyzed using logistic regression. Results are shown as unadjusted, adjusted model 1 [adjusted for age, sex, race/ethnicity, height, weight, smoking status, pack-years, and depressive symptoms (using the Centers for Epidemiologic Studies Depression (CES-D) scale [14])], and adjusted model 2 (variables from model 1 + serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants).

As inhaled corticosteroids and bronchodilators are the current medications for low lung function, we performed an additional sensitivity analysis that included an indicator variable for common medications that affect lung function in the model.

Results

The MESA Lung sample consisted of 3,542 participants (Table 1). We excluded 11 participants from further analysis since they were on more than one antidepressant. The mean age of the sample was 66±10 years, 51% were female, 35% White, 16% Asian, 26% Black, and 23% Hispanic. Approximately 9% were current smokers and 39% were former smokers, with an average of 22 pack-years. The mean ± standard deviation of FEV1 was 2387±732mL; dyspnea was reported in 15% of the cohort. The average CES-D score was 8, with 14% classified as depressed according to the CES-D scale (CES-D>16).

There were 178 participants on SSRIs, 42 on serotonin norepinephrine reuptake inhibitors, and 38 on tricyclic antidepressants. The mean age was roughly similar across antidepressant groups, with those on tricyclic antidepressants being slightly older. The SSRI group had the highest proportion of current smokers and the lowest FEV1% at baseline. This group also had the largest proportion of participants who were depressed.

Forced expiratory volume in one second

The unadjusted and adjusted findings from the linear regression models between SSRIs and FEV1 for Exam 4 are in Table 2. At both exams, findings indicate an inverse relationship between SSRIs and FEV1. 95% confidence intervals excluded a strong association in the direction hypothesized.

Dyspnea

Results from the logistic regression models assessing the relationship between SSRIs and dyspnea are in Table 3. SSRIs were associated with an increased odds of dyspnea in both the unadjusted and adjusted models. 95% confidence intervals excluded a strong association in the direction hypothesized.

Sensitivity analysis

Adding lung function medications to the models decreased the effect sizes slightly, but the direction and results remained consistent.

Discussion

We hypothesized that SSRIs might be associated with better lung function through their anti-inflammatory and serotonergic effects. The results did not support our hypothesis; indeed, the associations found were in the opposite direction. Using a large population-based prospective dataset, we found that SSRIs were inversely associated with FEV1 and dyspnea, after controlling for confounders. Furthermore, this association persisted after further controlling for serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants. This indicates that a better understanding of the effects of anti-depressants on lung function may be warranted.

Prior research on the associations of antidepressants and lung function have been in small studies [6, 7]. Momtaz et al. studied two groups of age- and sex-matched severe COPD participants (n=50), one of which received fluoxetine, an SSRI [6]. After 3 months on the antidepressant, the treatment group increased their FEV1 from 1.10±0.49 to 1.20±0.44 liters ($p=0.01$); the group that did not receive antidepressant had no change in FEV1. In a study by Perna et al., six participants were treated with citalopram, an SSRI, and after 1 month, their FEV1 significantly increased from 0.91±0.17 to 1.12±0.15 liters ($p<0.05$) [7].

Although we controlled for depression in this study using the CES-D, we have no measure of the severity of depression prior to being on an antidepressant. Even in individuals who were on antidepressants, the depression scores were still elevated, and a significant proportion had scores indicating depression. Since depression is linked to increased levels

of inflammation [15], it is possible that the increased inflammation seen in depression overrides the potential anti-inflammatory effects of SSRIs. Therefore, we may be seeing an increase in inflammation from depression leading to a decrease in lung function rather than the SSRIs causing a decrease in lung function. Supporting this are results from two randomized, placebo-controlled studies by Brown et al. involving patients with asthma and major depressive disorder. The authors found there was no change in the dyspnea scale after treatment with SSRIs [16, 17]; however, participants who were able to achieve a depression remission had greater reductions in dyspnea than those that did not. Further studies may assess inflammation as a mediator between antidepressant and lung function.

There are several strengths to this study. This investigation was among the first to assess the impact of antidepressants on lung function using epidemiologic methods and use a large, high-quality study. Prior studies have been limited to small sample sizes and often did not consider potential confounding; this study included measures of demographics, depressive symptoms and smoking status.

Limitations

Limitations of the current study include the non-randomized, cross-sectional design and lack of information on antidepressant dose. Confounding by indication is a possibility, but due to the cross-sectional design, we are unable to assess temporality. We do not know the true reason for antidepressant prescription as they can be prescribed for conditions other than depression, such as anxiety and neurogenic pain, and we have no data on the adherence and dose of the antidepressants. Lastly, there were few participants in severe or very severe stages of COPD; it is therefore unknown if they would benefit from antidepressants.

Conclusion

In conclusion, although small, poorly controlled studies have shown an association between SSRIs and better lung endpoints, we were unable to replicate these findings in a large observational cohort.

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Availability of data and materials-

The datasets generated and/or analyzed during the current study are available in the MESA Lung repository, https://www.mesa-nhlbi.org/

List of abbreviations

CES-D	Centers for Epidemiologic studies depression
COPD	Chronic obstructive pulmonary disease
FEV1	forced expiratory volume in one second
MESA	Multi-Ethic Study of Atherosclerosis
SSRI	Selective serotonin reuptake inhibitor

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Table 1.

Description of cohort at MESA Exam 4

Sample characteristics	No antidepressant N=3273		SSRI N=178		SNRI N=42		TCA N=38		Total N=3542	
	N or mean ± SD	%	N or mean ± SD	%	N or mean ± SD	%	N or mean ± SD	%	N or mean ± SD	%
Age, years, mean±SD	66±10		66±10		64±10		70±10		66±10	
Gender										
Male	1651	51	65	37	9	21	13	34	1748	49
Female	1617	49	113	64	33	79	25	66	1794	51
Race/Ethnicity										
White	1086	33	113	64	30	71	16	42	1254	35
Asian	559	17	4	2	3	7	1	3	567	16
Black	876	27	19	11	4	10	7	18	907	26
Hispanic	752	23	42	24	5	12	14	36	814	23
Height, cm, mean±SD	166±10		165±9		167±9		164±7		166±10	
Weight, lb, mean±SD	171±39		173±38		190±43		175±46		172±39	
BMI, kg/m^2, mean±SD	28±5		29±6		31±6		29±7		28±5	
Health Insurance										
None	181	6	5	3	2	5	1	3	189	5
Medicaid	268	8	16	9	5	12	7	18	297	8
Medicare	325	10	10	6	3	7	3	8	341	10
HMO	2147	66	128	72	30	71	19	50	2331	66
VA/Other	352	11	19	11	2	5	8	21	384	11
Cigarette smoking status										
Never-smokers	1720	53	80	45	17	42	16	42	1835	52
Former smokers	1257	39	69	39	20	49	17	45	1371	39
Current smokers	286	9	29	16	4	10	5	13	325	9
Smoking history pack-years[#]	22±25		27±36		18±15		34±36		22±26	
FEV_1, mL, mean±SD	2394±736		2305±711		2375±555		2301±637		2387±732	
FEV_1 % predicted, mean±SD	94±18		90±18		91±12		97±16		94±18	

Sample characteristics	No antidepressant N=3273		SSRI N=178		SNRI N=42		TCA N=38		Total N=3542	
	N or mean ± SD	%	N or mean ± SD	%	N or mean ± SD	%	N or mean ± SD	%	N or mean ± SD	%
COPD Stage										
None	2551	78	139	78	31	74	29	76	2757	78
Mild	420	13	17	10	6	14	6	16	449	13
Moderate	265	8	19	11	5	12	3	8	295	8
Severe	32	1	2	1	0	0	0	0	35	1
Very Severe	5	.15	1	.60	0	0	0	0	6	.1
Dyspnea	465	14	42	24	14	33	14	37	541	15
CES-D										
Score, mean±SD	7±7		13±11		11±11		10±8		8±8	
Depressed (CES-D>16)	413	13	54	30	10	24	8	21	489	14
Corticosteroid use										
Yes	135	4	17	10	2	5	5	13	159	5
No	3138	96	161	91	40	95	33	87	3383	96

SSRI: selective serotonin reuptake inhibitors, TCA: tricyclic antidepressants, SNRI: serotonin-norepinephrine reuptake inhibitors; cm: centimeters; kg: kilogram; m: meter; CES-D: Center for Epidemiological Studies-Depression

[#]among ever-smokers. All numbers reported as number and percentage unless otherwise stated. Shaded variables or values were not applicable for mean±SD when reporting percentage.

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Table 2.

Forced expiratory volume in one second (FEV1) at MESA Exam 4: unadjusted and adjusted models

	A. Unadjusted model			B. Adjusted model 1			C. Adjusted model 2		
	β	**95% CI**	**p-value**	***β***	**95% CI**	**p-value**	***β***	**95% CI**	**p-value**
SSRI	−88.6	−196.2 to 19.0	0.11	−63.0	−128.0 to 2.1	0.06	−66.0	−131.2 to −0.8	0.048*
SNRI							−511	−182.1 to 79.9	0.44
TCA							72.2	−51.5 to 195.9	0.25
Cigarette smoking status									
Never-smokers				Ref	Ref	Ref	Ref	Ref	Ref
Former smokers				1.4	−33.7 to 36.6	0.94	1.6	−33.6 to 36.8	0.93
Current smokers				−116.0	−172.8 to −59.3	<.0001*	−115.9	−172.7 to −59.1	<.0001*
Smoking pack-years				−3.8	−4.6 to −3.0	<.0001*	−3.8	−4.6 to −3.0	<.0001*
CES-D Score				−1.8	−3.7 to 0.04	0.06	−1.8	−3.7 to 0.04	0.06

CES-D: Center for Epidemiological Studies-Depression, SNRI: serotonin-norepinephrine reuptake inhibitors, SSRI: selective serotonin reuptake inhibitors, TCA: tricyclic antidepressants. Shaded variables or values were not included in the model. Beta shows the mean difference. Adjusted model 1: cigarette smoking status (Never, former, and current smokers), smoking pack years, CES-D score, age, sex, race/ethnicity, height and weight. Adjusted model 2: model 1 + serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants

Table 3.

Dyspnea at MESA Exam 4: unadjusted and adjusted models

	A. Unadjusted model			B. Adjusted model 1			C. Adjusted model 2		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
SSRI	1.99	1.41 to 2.80	<.0001*	1.18	0.80 to 1.74	0.40	1.15	0.78 to 1.70	0.48
SNRI							1.51	0.72 to 3.18	0.28
TCA							2.66	1.40 to 5.04	0.003*
Cigarette smoking status									
Never-smokers				Ref	Ref	Ref	Ref	Ref	Ref
Former smokers				0.99	0.78 to 1.27	0.15	0.99	0.77 to 1.26	0.14
Current smokers				1.40	0.96 to 2.03	0.052	1.38	0.95 to 2.01	0.06
Smoking pack-years				1.01	1.00 to 1.01	0.002*	1.01	1.00 to 1.01	0.002*
CES-D Score				1.07	1.06 to 1.08	<.0001*	1.07	1.06 to 1.08	<.0001*

CES-D: Center for Epidemiological Studies-Depression, SNRI: serotonin-norepinephrine reuptake inhibitors, SSRI: selective serotonin reuptake inhibitors, TCA: tricyclic antidepressants. Adjusted model 1: age, sex, race/ethnicity/ height, weight, cigarette smoking status (never, former, and current smokers), smoking pack-years, and CES-D score. Adjusted model 2: model 1 + serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants