

Online Supplement

Original Research

Exacerbations and Decreased Lung Function Predict Nebulizer Use and Uptake in COPD and Tobacco Exposed Persons With Preserved Spirometry

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Visits 1 - 4

Have you used nebulized bronchodilators in the past 3 months?

- 1) Yes
- 2) No →Skip next question
- 3) Don't know →Skip next question

Which nebulized bronchodilators have you used in the past 3 months? Yes/No (check all that apply)

- 1) formoterol (Perforomist).
- 2) arformoterol (Brovana)
- 3) albuterol and ipratropium bromide (DuoNeb)
- 4) albuterol (Proventil, Ventolin, ProAir)
- 5) ipratropium bromide (Atrovent)

Visit 5

Are you regularly using any nebulized medications

- 1) No →Skip next question
- 2) Yes

How often (daily versus as needed when having difficulties)?

- 1) Daily
- 2) As needed when having difficulties

Which medications? (Check all that apply)

- 1) Accuneb (albuterol sulfate) nebulizer
- 2) Xopenex (levalbuterol) nebulizer
- 3) Atrovent (ipratropium) nebulizer
- 4) DuoNeb (ipratropium bromide/albuterol) nebulizer
- 5) Performist (formoterol) nebulizer
- 6) Brovana (arformoterol) nebulizer
- 7) Pulmicort (budesonide) nebulizer
- 8) 3% Hypertonic saline
- 9) 7% Hypertonic saline
- 10) Other, please specify _____

Supplemental Figure 1. *Participant Survey on Nebulized Medication Use.* This figure presents questions used to assess participants' use of nebulized bronchodilators and other medications. Initial questions (Visits 1-4) identify recent use of specific bronchodilators, while questions at Visit 5 assess regular usage patterns, frequency, and specific types of nebulized medications.

Supplemental Table 1. Baseline demographics and clinical characteristics by TEPS versus COPD and Nebulizer Use Group

	TEPS		COPD	
	No Nebulizer Use (N = 682)	Nebulizer Use (N = 35)	No Nebulizer Use (N = 1,200)	Nebulizer Use (N = 230)
Age (years), mean (SD)	60.9 (9.5)	58.2 (8.3)	65.8 (7.9)	62.6 (8.3)
Male sex	48%	26%	60%	50%
Race				
White	70%	46%	84%	73%
Black	24%	49%	13%	23%
Other	6%	6%	4%	4%
Hispanic/Latino Ethnicity	6%	11%	3%	2%
ADI national rank percentile, mean (SD)	36.0 (27.6)	51.2 (29.0)	37.3 (27.8)	44.3 (28.6)
Yearly household income				
<\$15,000	22%	46%	15%	28%
\$15,000-\$34,999	16%	20%	20%	20%
\$35,000-\$49,999	11%	11%	14%	10%
\$50,000-\$74,999	15%	6%	16%	14%
\$75,000 or more	20%	9%	19%	10%
Declined to answer	16%	9%	16%	18%
BMI (kg/m²), mean (SD)	29.0 (5.0)	31.5 (5.4)	27.3 (5.1)	26.9 (5.7)
Current Smoking (ref: not smoking)	48%	43%	34%	33%
Ever diagnosed with asthma	14%	60%	20%	40%
Chronic Bronchitis by SGRQ	37%	77%	45%	57%
FEV₁ (Percent Predicted), mean (SD)	97 (13)	89 (12)	65 (22)	47 (20)
FEV₁ (L), mean (SD)	2.8 (0.7)	2.4 (0.5)	1.9 (0.8)	1.3 (0.6)
Inspiratory Capacity (L), mean (SD)	2.8 (0.7)	2.5 (0.7)	2.6 (0.8)	2.2 (0.8)
Count of Exacerbations (year before enrollment)				
None	90%	69%	79%	54%
One	7%	14%	13%	24%
Two	2%	14%	5%	10%
Three or more	1%	3%	4%	12%
CAT Score, mean (SD)	10.8 (8.0)	21.7 (7.4)	13.9 (7.5)	20.4 (7.8)
SGRQ Score, mean (SD)	23.3 (18.6)	51.4 (16.2)	33.8 (18.6)	52.1 (16.0)
MMRC Score				
0	47%	11%	27%	8%
1	40%	43%	48%	37%
2	8%	31%	16%	29%
3	4%	9%	8%	19%
4	1%	6%	2%	6%
VSAQ Score, mean (SD)	6.5 (2.9)	3.1 (2.1)	5.3 (2.6)	3.4 (1.8)
6 Minute Walk Distance (m), mean (SD)	438 (91)	344 (106)	394 (112)	320 (114)

Supplemental Table 2. Sensitivity Analysis of baseline logistic model for nebulizer use among COPD and TEPS groups.

	TEPS				COPD			
	Odds ratio	Lower end of 95% CI	Upper end of 95% CI	P-Value	Odds ratio	Lower end of 95% CI	Upper end of 95% CI	P-Value
Age (per year change)	0.948	0.888	1.013	0.115	0.948	0.927	0.969	<0.001
Male (ref. female)	1.230	0.372	4.063	0.734	1.458	1.036	2.052	0.031
Race (ref. White)								
Black	1.521	0.552	4.189	0.417	1.267	0.828	1.938	0.276
Other	0.844	0.146	4.895	0.850	1.035	0.450	2.381	0.935
BMI (per unit change)	0.989	0.906	1.079	0.805	0.992	0.962	1.022	0.587
ADI (ref. 0 to 25 th percentile)								
26 to 50 th percentile	0.858	0.271	2.720	0.795	0.832	0.544	1.271	0.394
51 st to 75 th percentile	0.922	0.284	2.992	0.893	0.788	0.507	1.225	0.290
76 th to 100 th percentile	1.409	0.411	4.832	0.586	0.808	0.482	1.356	0.420
Income (ref. <\$15,000))								
\$15,000-\$34,999	0.623	0.200	1.942	0.415	0.766	0.469	1.249	0.285
\$35,000-\$49,999	0.653	0.149	2.857	0.572	0.557	0.306	1.013	0.055
\$50,000-\$74,999	0.286	0.043	1.894	0.194	0.891	0.509	1.561	0.688
\$75,000 or more	0.720	0.138	3.767	0.697	0.606	0.326	1.124	0.112
Declined to answer	0.447	0.097	2.051	0.300	0.758	0.456	1.262	0.287
Current Smoking (ref. not smoking)	0.226	0.081	0.629	0.004	0.742	0.496	1.110	0.147
Ever diagnosed with asthma	4.399	1.838	10.531	0.001	2.067	1.462	2.923	<0.001
Chronic Bronchitis by SGRQ	2.710	1.052	6.977	0.039	1.314	0.935	1.846	0.116
FEV₁ (per liter decrease)	1.820	0.629	5.263	0.269	3.101	2.250	4.273	0.000
Exacerbations (ref. none)								
One	1.386	0.397	4.844	0.609	1.849	1.241	2.754	0.003
Two	9.586	2.300	39.952	0.002	1.488	0.822	2.695	0.189
Three or more	0.963	0.083	11.116	0.976	2.019	1.130	3.607	0.018
CAT Score (ref <10)	4.215	0.843	21.073	0.080	1.568	0.947	2.596	0.081
6MWD (per 10 m)	1.059	1.010	1.111	0.018	1.025	1.010	1.041	0.001

Supplemental Table 3: Sensitivity analysis of Hazard ratios of interval censored proportional hazards model predicting nebulizer uptake during the study period for TEPS and COPD participants.

	TEPS				COPD			
	Hazard Ratio	Lower limit of 95%CI	Upper limit of 95% CI	P-Value	Hazard ratio	Lower Limit of 95% CI	Upper Limit of 95% CI	P-Value
Age at Visit 1 (years)	0.958	0.906	1.013	0.132	0.971	0.951	0.992	0.006
Race (ref. white)								
Black	0.857	0.341	2.157	0.744	1.162	0.794	1.702	0.439
Other	2.247	0.605	8.344	0.227	0.470	0.161	1.367	0.166
BMI (per unit change)	1.021	0.945	1.104	0.598	1.018	0.991	1.046	0.201
ADI (ref. 0 to 25 th percentile)								
26 to 50 th percentile	1.013	0.355	2.890	0.980	0.976	0.656	1.453	0.907
51 st to 75 th percentile	0.853	0.294	2.473	0.769	1.324	0.881	1.990	0.177
76 th to 100 th percentile	1.556	0.548	4.419	0.406	1.010	0.643	1.587	0.966
Income (ref. <\$15,000))								
\$15,000-\$34,999	0.861	0.289	2.562	0.788	1.161	0.750	1.799	0.503
\$35,000-\$49,999	1.775	0.513	6.139	0.365	0.974	0.568	1.668	0.923
\$50,000-\$74,999	0.502	0.090	2.803	0.432	1.143	0.661	1.976	0.632
\$75,000 or more	0.963	0.111	8.394	0.973	0.684	0.363	1.287	0.239
Declined to answer	2.069	0.852	5.023	0.108	1.256	0.771	2.046	0.361
Current Smoking (ref. not smoking)	1.417	0.463	4.336	0.542	1.069	0.746	1.532	0.716
Ever diagnosed with asthma	1.095	0.478	2.509	0.829	2.043	1.514	2.757	0.000
Chronic Bronchitis by SGRQ	1.042	0.478	2.270	0.917	0.746	0.546	1.019	0.065
Exacerbations (ref. None)								
One	4.234	1.643	10.912	0.003	1.671	1.182	2.362	0.004
Two	3.608	0.910	14.309	0.068	0.975	0.587	1.621	0.923
Three or more	1.289	0.232	7.166	0.772	0.809	0.442	1.482	0.493
CAT Score >10 (ref. <10)	1.951	0.586	6.501	0.276	3.552	2.033	6.207	0.000
FEV₁ (per liter decrease)	3.029	1.195	7.682	0.020	2.039	1.563	2.659	0.000
6MWD (per 10 meter decrease)	1.019	0.966	1.076	0.486	1.010	0.996	1.024	0.171

Model adjusted for baseline (non-time varying) race; Age at Visit 1; ADI, area deprivation index quartile; income; current smoking status. Time varying covariates included: BMI, Body Mass Index; exacerbations in the last year; CAT Score, COPD assessment test score; FEV₁, forced expiratory volume in 1 second; and 6MWD, six minute walk distance.

Supplemental Table 4: Type of nebulized medication by daily versus as-needed use at Visit 5

	Overall (N=194)	Daily (N=52)	As Needed (N=142)	P-Value*
Short Acting Bronchodilators				
Albuterol	62% (120)	48% (25)	67% (95)	0.020
Levalbuterol	3% (6)	4% (2)	3% (4)	0.660
Ipratropium Bromide	8% (16)	15% (8)	6% (8)	0.039
Albuterol-Ipratropium Bromide	19% (37)	29% (15)	16% (22)	0.041
Long Acting Bronchodilators				
Formoterol	<1% (1)	2% (1)	0% (0)	0.270
Arformoterol	<1% (1)	2% (1)	0% (0)	0.270
Budesonide	2% (4)	6% (3)	<1% (1)	0.060
3% sodium chloride	1% (2)	0% (0)	1% (2)	1.000
Other (Any not defined above)	6% (12)	2% (1)	8% (11)	0.190

*Fisher's exact test

Supplemental Table 5: Hand-held inhaled medication by nebulizer use at Visit 1

	No Baseline Nebulizer Use (N=1,882)	Baseline Nebulizer Use (N=265)	Total (N=2,147)	p-value
Hand-held inhaled steroids used in the last three months at baseline				<0.001
No	1,307 (69%)	76 (29%)	1,383 (64%)	
Yes	571 (30%)	187 (71%)	758 (35%)	
Missing	4 (0%)	2 (1%)	6 (0%)	
Hand-held inhaled bronchodilators used in the last three months at baseline				<0.001
No	1,004 (53%)	21 (8%)	1,025 (48%)	
Yes	875 (46%)	243 (92%)	1,118 (52%)	
Missing	2 (0%)	1 (0%)	3 (0%)	