



## Early View

Research letter

# Cognitive function and inhaler technique following recovery from exacerbations of COPD

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**Title:** Cognitive function and inhaler technique following recovery from exacerbations of COPD

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**Take home message:**

Cognitive impairment is highly prevalent in COPD outpatients during the post-exacerbation recovery period and is associated with poor inhaler technique.

*To the editor:*

Persons with chronic obstructive pulmonary disease (COPD) are at elevated risk for cognitive impairment. Cognitive deficits may be more common in those with very low lung function [1], in those requiring supplemental oxygen [2], and during acute exacerbation hospitalizations [3]. Cognitive impairment is also associated with poor medication adherence and inhaler technique [4]. However, cognitive function is not currently assessed as part of routine management of COPD. The effect of cognitive function on inhaler technique and COPD-related healthcare use such as hospitalizations or emergency department (ED) visits is not well known. To investigate this, we conducted a prospective observational study of cognitive function and inhaler technique among patients with COPD at high-risk of increased healthcare utilization by virtue of having a recent acute severe COPD exacerbation.

We enrolled consecutive individuals that participated in the Minneapolis Veteran Affairs (VA) COPD Case Management program which identifies all patients hospitalized or in the ED for acute exacerbations of COPD and provides nursing-led assistance in outpatient COPD management after discharge. Case management participants were enrolled during their first post-exacerbation clinic visit, which occurs approximately 2-6 weeks post-exacerbation. After obtaining informed consent, participants were screened for cognitive impairment with the Montreal Cognitive Assessment (MoCA) by a trained and certified physician (author BEH). Participants also completed the Hospital Anxiety and Depression Scale (HADS), the Rapid Estimate of Adult Literacy in Medicine – Short Form (REALM-SF), and inhaler technique was assessed using a standardized form that documents the correct steps completed for different inhaler devices (i.e. metered dose inhaler (MDI), Respimat inhaler). Assessment of inhaler technique was conducted by COPD nurses blinded to MoCA and HADS results. Incorrect inhaler technique was defined as completing  $\leq 75\%$  of steps correctly. Chart review was conducted to collect demographic variables, medical comorbidities, active medications, and lung function variables (forced vital capacity (FVC), forced expiratory volume in one second ( $FEV_1$ ), and  $FEV_1/FVC$  ratio). After 12 months of enrollment, a chart review was conducted to document use of home systemic corticosteroids and/or antibiotics for COPD exacerbations, ED visits and hospitalizations. The total number of healthcare encounters was calculated by adding the number of independent ED visits and hospitalizations for any cause. A logistic regression

model was used to evaluate the association between an abnormal MoCA score (defined using the standard clinical threshold of <26 to identify those at risk for mild cognitive impairment and dementia [5]) and inhaler technique; Poisson regression with an offset for log-days of follow up was used to evaluate associations between abnormal MoCA and health care utilization and use of home corticosteroids and/or antibiotics. Analyses were completed in R (R Core Team, 2022), version 4.2.0, and all p-values were two-sided. This study was approved by the Minneapolis VA institutional review board.

Between July 2019 and February 2020, we enrolled 47 male study participants (Table 1a), of whom 29 (62%) had a MoCA score <26 concerning for mild cognitive impairment or dementia. At enrollment, time since last exacerbation was a median of 39 days (interquartile range 29.5 – 75.0). Characteristics associated with MoCA score <26 were black race, lower educational attainment ( $\leq$ High School diploma or General Education Development Test (GED)), prescription of supplemental oxygen, and enrollment in home health services. Elevated symptoms of anxiety (HADS-A >8) were present in 33% (15/47) and elevated depressive symptoms were present in 24% (HADS-D >8; 11/47). 97.8% were prescribed an MDI (44/45; 2 participants were missing data). Compared to those with normal-range MoCA scores, those with abnormal MoCA had higher odds of incorrect MDI technique (odds ratio (OR) 5.5 [95% CI: 1.5 to 24.2]) and this remained statistically significant after adjusting for age, race, education, HADS-anxiety score, HADS-depression score, and health literacy (OR 18.9 [95% CI: 2.7 to 402.0]) (Table 1b). During 12 months of follow up (mean 348.2 +/- 57.3 days), among 34 participants there were 81 health care encounters, including 43 ED visits (of which 6 were COPD-related), and 38 hospitalizations (of which 11 were COPD-related). Five participants died during follow up. After adjustment for age, race, and education, there was no difference between those with normal and abnormal MoCA scores in rates of home corticosteroid and/or antibiotic use (among 86 events; Incidence Rate Ratio (IRR) 1.38 [95% CI: 0.86-2.28]), total health care use (IRR 0.75 [95% CI: 0.47-1.21]), hospitalizations (IRR 0.90 [95% CI: 0.45-1.85]), or ED visits (IRR 0.63 [95% CI: 0.33-1.21]) through 12 months of follow-up (Table 1b).

Cognitive impairment is highly prevalent in persons recovering from COPD exacerbations. In our cohort of outpatients with a recent hospitalization or ED visit for a COPD exacerbation, 62% screened positive

for possible mild cognitive impairment or dementia by the MoCA (<26). This is consistent with past research that has found cognitive impairment in up to 57% of COPD patients during an acute exacerbation hospitalization [3] and anywhere between 13.5% to 73% of stable outpatients depending upon the measure used [6]. To our knowledge, this is the first report of cognitive assessment in the post-exacerbation recovery period, which represents a particularly vulnerable period for re-hospitalizations, care transitions, and medication changes.

MDIs were the most prescribed type of inhaler device in this cohort. Importantly, after controlling for confounding factors, MDI technique was worse in those with impaired cognition. This is consistent with previous work showing that global cognitive abilities are associated with incorrect inhaler use [4]. Notably, incorrect inhaler technique was found in nearly half of our participants. Poor inhaler technique among COPD patients is associated with reduced treatment effectiveness, more acute exacerbations, and increased mortality as a result of unintentional nonadherence [7]. Cognitive screening of COPD patients, especially following recent COPD exacerbations, could be a simple intervention to identify those who may benefit from more rigorous inhaler monitoring and support to potentially reduce their risk of exacerbations.

There are several limitations to this study. Due to the COVID-19 pandemic, face-to-face encounters for COPD case management at our institution were discontinued and the study closed at one third of the target sample size. Due to our smaller than expected sample size, we were unable to fully explore the effect of cognition on non-MDIs such as dry powder or propellant-free devices. It is possible that technique for different styles of inhalers could be influenced differently by cognitive function. Further, the study was underpowered to draw conclusions about our prospective clinical outcomes, as evidenced by the wide 95% CIs for these analyses. In addition to the smaller-than-planned sample size, COPD patient behaviors during the early phases of the COVID-19 pandemic reduced COPD exacerbations globally [8], and this reduction in the number of outcome events further reduced study power for these clinical outcomes. Additional limitations include that cognition was only evaluated with a single assessment, the

MoCA, and this sample of veterans was exclusively men and predominately Caucasian, which limits generalizability.

Cognitive impairment is highly prevalent in COPD outpatients with recent exacerbations and is associated with poor inhaler technique. Additional studies are needed to assess the value of more widespread cognitive screening in COPD and how cognitive impairment may affect prospective COPD outcomes like hospitalizations and emergency department visits.

**Table 1a:**

Demographic and clinical characteristics of study participants at time of enrollment stratified by MoCA score (normal MoCA  $\geq 26$ ).

	Overall (n=47)	MoCA $\geq 26$ (n=18)	MoCA $< 26$ (n=29)
Age, mean (SD), y	70.7 (7.2)	69.8 (6.8)	71.2 (7.4)
Male, n (%)	47 (100)	18 (100)	29 (100)
Race, n (%)			
Black	6 (12.8)	1 (5.6)	5 (17.2)
White	40 (85.1)	17 (94.4)	23 (79.3)
Hispanic	1 (1.2)	0 (0)	1 (3.4)
Educational attainment, n (%)			
< High School	4 (8.5)	1 (5.6)	3 (10.3)
High school or GED	21 (44.7)	5 (27.8)	16 (55.2)
College or Graduate Degree	22 (46.8)	12 (66.7)	10 (34.5)
Current smoking status, n (%)	14 (29.8)	6 (33.3)	8 (27.6)
Pack years, mean (SD)	54.4 (28.3)	54 (17.1)	55 (33)
Supplemental O <sub>2</sub> use, n (%)	12 (25.5)	3 (16.7)	9 (31.0)
Home health services available, n (%)	9 (19.1)	2 (11.1)	7 (24.1)
Spirometry			
FEV <sub>1</sub> , mean (SD), L	1.8 (0.65)	1.8 (0.6)	1.8 (0.7)
FEV <sub>1</sub> % predicted (SD)	57.5 (17.6)	55.5 (16.2)	58.7 (18.6)
FEV <sub>1</sub> /FVC ratio (SD)	0.5 (0.14)	0.5 (0.1)	0.5 (0.1)
Days since last exacerbation, mean (SD), Days	57.8 (49.7)	61.0 (52.1)	55.9 (48.9)
HADS Anxiety, mean (SD)	7.1 (3.7)	6.6 (3.3)	7.4 (3.9)
HADS Depression, mean (SD)	5.6 (3.5)	4.9 (3.4)	6.0 (3.5)
REALM-SF, mean (SD)	6.3 (1.5)	6.9 (0.3)	5.9 (1.8)
Prescribed inhaler device, n (%)			
MDI	44 (97.8)	17 (100)	27 (96.4)
Respimat	22 (48.9)	9 (52.9)	13 (46.4)
Handihaler <sup>®</sup>	18 (40.0)	6 (35.3)	12 (42.9)
Twisthaler <sup>®</sup>	4 (9.1)	2 (12.5)	2 (7.1)
Incorrect* MDI inhaler technique, n (%)	21 (47.7)	4 (23.5)	17 (63.0)
Incorrect* Respimat inhaler technique, n (%)	8 (36.4)	1 (11.1)	7 (53.8)
* $< 75\%$ of steps performed correctly			
MoCA: Montreal Cognitive Assessment, SD: Standard Deviation, GED: General Educational Development Test, HADS: Hospital Anxiety and Depression Scale, REALM: Rapid Estimate of Adult Literacy in Medicine – Short Form, FEV <sub>1</sub> : Forced Expiratory Volume in 1 second, MDI: Metered Dose Inhaler			



**Table 1b:**

Unadjusted and adjusted associations between the presence of mild cognitive impairment measured by a MoCA score <26 and the outcomes of incorrect inhaler technique and health care use.

	Unadjusted	Model 1	Model 2
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Incorrect MDI Inhaler Technique	5.52 (1.50 – 24.15)	19.24 (2.90 – 395.92)	18.94 (2.65 – 401.99)
Incorrect RespiMAT Inhaler Technique	9.33 (1.20 – 200.42)	15.38 (1.25 – 634.61)	**
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Home Action Plan Use	1.29 (0.83 – 2.05)	1.38 (0.86 – 2.28)	1.22 (0.72 – 2.10)
Health Care Utilization	0.70 (0.45 – 1.09)	0.75 (0.47 – 1.21)	0.89 (0.52 – 1.51)
Emergency Department Visits	0.57 (0.31 – 1.03)	0.63 (0.33 – 1.21)	0.85 (0.41 – 1.77)
Hospitalizations	0.89 (0.47 – 1.73)	0.90 (0.45 – 1.85)	0.83 (0.37 – 1.85)
Model 1: Age, Race, Education Model 2: Age, Race, Education, HADS-Anxiety, HADS-Depression, REALM-SF (health literacy) ** Unable to calculate due to insufficient data MoCA: Montreal Cognitive Assessment, OR: Odds Ratio, CI: Confidence Interval, MDI: Metered Dose Inhaler, IRR: Incident Rate Ratio, HADS: Hospital Anxiety and Depression Scale, REALM-SF: Rapid Estimate of Adult Literacy in Medicine – Short Form			

## References:

1. Hung WW, Wisnivesky JP, Siu AL, Ross JS. Cognitive decline among patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2009;180(2):134-7.
2. Grant I, Heaton RK, McSweeney AJ, Adams KM, Timms RM. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med.* 1982;142(8):1470-6.
3. Dodd JW, Charlton RA, van den Broek MD, Jones PW. Cognitive dysfunction in patients hospitalized with acute exacerbation of COPD. *Chest.* 2013;144(1):119-27.
4. O'Connor R, Muellers K, Arvanitis M, Vicencio DP, Wolf MS, Wisnivesky JP, et al. Effects of health literacy and cognitive abilities on COPD self-management behaviors: A prospective cohort study. *Respir Med.* 2019.
5. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695-9.
6. Yohannes AM, Chen W, Moga AM, Leroi I, Connolly MJ. Cognitive Impairment in Chronic Obstructive Pulmonary Disease and Chronic Heart Failure: A Systematic Review and Meta-analysis of Observational Studies. *J Am Med Dir Assoc.* 2017;18(5):451.e1-.e11.
7. Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax.* 2009;64(11):939-43.
8. Alqahtani JS, Oyelade T, Aldhahir AM, Mendes RG, Alghamdi SM, Miravittles M, et al. Reduction in hospitalised COPD exacerbations during COVID-19: A systematic review and meta-analysis. *PLoS One.* 2021;16(8):e0255659.