Letters to the Editor

Methylphenidate and Apathy in Alzheimer's Disease: Is Sleep Apnea a Confounding Effect?

TO THE EDITOR: We read with interest the study by Padala et al. (1), published in the February 2018 issue of the *Journal*, examining the impact of methylphenidate on apathy in patients with Alzheimer's disease. As noted by the authors, apathy is persistent and is associated with significant impairment in patients with Alzheimer's disease. It is encouraging to see that methylphenidate may result in significant improvements in this patient population.

However, we posit that one possible explanation for the efficacy of methylphenidate in this group is the likelihood that a significant proportion of patients had obstructive sleep apnea. Obstructive sleep apnea is common in the elderly, with rates of >30% described in patients older than 70 years of age (2). Obstructive sleep apnea is associated with significant cognitive impairment and daytime sleepiness, which may present as apathy (3, 4). Obstructive sleep apnea has also been shown to be a risk factor for Alzheimer's dementia (5). It is quite likely that in this sample of men with an average weight of 190 lb that a significant proportion had obstructive sleep apnea. This could have resulted in daytime sleepiness and neurocognitive effects that exacerbated their apathy.

Methylphenidate, a CNS stimulant, has been shown to improve sleepiness (6). In patients with untreated obstructive sleep apnea, the use of methylphenidate can increase alertness, which in turn could result in an improvement in apathy. This hypothesis might need further exploration, especially in light of the fact that methylphenidate resulted in a significant increase in systolic blood pressure in this study, and untreated obstructive sleep apnea can also result in hypertension (7).

REFERENCES

1. Padala PR, Padala KP, Lensing SY, et al: Methylphenidate for apathy in community-dwelling older veterans with mild Alzheimer's disease: a double-blind, randomized, placebo-controlled trial. Am J Psychiatry 2018; 175:159–168
2. Ancoli-Israel S, Klauber MR, Stepnowsky C, et al: Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med 1995; 152:1946–1949
3. Seneviratne U, Puvanendran K: Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors. Sleep Med 2004; 5:339–343
4. Bucks RS, Olaithe M, Eastwood P: Neurocognitive function in obstructive sleep apnoea: a meta-review. Respirology 2013; 18: 61–70
5. Yaffe K, Laffan AM, Harrison SL, et al: Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011; 306:613–619
6. Miyamoto T, Miyamoto M, Suga T, et al: Methylphenidate hydrochloride for excessive daytime sleepiness in a patient with myotonic dystrophy. Psychiatry Clin Neurosci 2002; 56:271–272
7. Konecny T, Kara T, Somers VK: Obstructive sleep apnea and hypertension: an update. Hypertension 2014; 63:203–209

Bhanu Prakash Kolla, M.D., M.R.C.Psych.
Meghna P. Mansukhani, M.D.

From the Department of Psychiatry and Psychology and the Center for Sleep Medicine, Mayo Clinic, Rochester, Minn.

Address correspondence to Dr. Kolla (kolla.bhanuprakash@mayo.edu).

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Addressing Possible Effects of Sleep Apnea in a Study of Methylphenidate for Apathy in Alzheimer's Disease: Response to Kolla and Mansukhani

TO THE EDITOR: We thank Drs. Kolla and Mansukhani for their commentary on our study finding that methylphenidate improves apathy in patients with Alzheimer's disease (1). The authors suggest that methylphenidate may be improving symptoms (e.g., daytime sleepiness and inattention) of obstructive sleep apnea, which presented as apathy. We agree on three points: obstructive sleep apnea is a common comorbidity in older patient populations, elevated body mass index is a risk factor for obstructive sleep apnea and apathy (2), and methylphenidate improves key symptoms of obstructive sleep apnea (3). However, while interactions between obstructive sleep apnea, apathy, and methylphenidate are plausible, it is unlikely the case in the patients we studied.

Apathy diagnosis is based on careful screening for contributions from all comorbidities, including obstructive sleep apnea. Daytime sleepiness was not common in these patients at baseline or during intervention. The patients possessed apathy syndrome rather than simply a symptom

of apathy. Apathy syndrome has cognitive, affective, and behavioral dimensions that persist longer than 4 weeks and cause significant impairment in personal, social, occupational, and other key areas of functioning (4). Motivation and goal-directed behaviors and cognitive activity are lost, and emotional blunting is found in patients with apathy (5). Daytime sleepiness and inattention are not symptoms of apathy syndrome. In fact, when diagnosing apathy syndrome during cognitive impairment, depression and other medical conditions are ruled out (4, 5).

The authors provide an important reminder that obstructive sleep apnea can be mistaken as apathy, and vice versa, in cognitively impaired older adults. Obviously, incorrect diagnosis could render treatment of either problem and of cognitive impairment less effective and could render the testing of new treatments uninterpretable. We feel strongly that management of apathy is essential to individual health. For example, preliminary studies have shown that resolution of apathy leads to improved functioning and self-care and has the potential to improve distal outcomes for comorbidities such as diabetes (6). Thus, future research into the ability for treatment of apathy and obstructive sleep apnea to empower individuals to optimally self-manage cognitive decline and other health conditions during aging will be exciting and has potential for great impact.

REFERENCES

1. Padala PR, Padala KP, Lensing SY, et al: Methylphenidate for apathy in community-dwelling older veterans with mild Alzheimer's disease: a double-blind, randomized, placebo-controlled trial. Am J Psychiatry 2018; 175:159–168
2. Padala PR, Desouza CV, Almeida S, et al: The impact of apathy on glycemic control in diabetes: a cross-sectional study. Diabetes Res Clin Pract 2008; 79:37–41
3. Lanctôt KL, Chau SA, Herrmann N, et al: Effect of methylphenidate on attention in apathetic AD patients in a randomized, placebo-controlled trial. Int Psychogeriatr 2014; 26:239–246
4. Marin RS: Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 1991; 3:243–254
5. Robert P, Onyike CU, Leentjens AF, et al: Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry 2009; 24:98–104
6. Padala PR, Padala KP, Sullivan DH, et al: Improvement of glycemic control using methylphenidate treatment of apathy: a preliminary report. J Am Geriatr Soc 2012; 60:1383–1384

Prasad R. Padala, M.D., M.S.
Richard A. Dennis, Ph.D.
Kalpana P. Padala, M.D., M.S.

From the Geriatric Research Education and Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock; and the Departments of Psychiatry and Geriatrics, University of Arkansas for Medical Sciences, Little Rock.

Address correspondence to Dr. Prasad Padala (prasad.padala@va.gov).

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The Temporal Relationship Between Alzheimer's Disease and Depressive Symptoms: Variable Matters

TO THE EDITOR: In their recent comprehensive analysis, published in the June 2018 issue of the *Journal*, Donovan et al. (1) present convincing support of the hypothesis that emerging neuropsychiatric symptoms represent an early manifestation of preclinical Alzheimer's disease. Donovan et al. appropriately viewed their analysis as a first step toward understanding the temporal relationship between Alzheimer's disease and depressive symptoms in cognitively normal older adults, with the initial aim to examine association rather than causation.

Physiological aging is accompanied by a chronic low-grade proinflammatory state, which has been named "inflammaging" (2). Inflammaging likely acts as a prodromal cofactor in the subclinical course of Alzheimer's disease (3). Neuroinflammation can also be associated with amyloid beta burden independently of inflammaging (4). In addition, several lines of evidence also associate inflammation with depressive symptoms (5). This makes the relationship between Alzheimer's disease and depressive symptoms more complex. If Alzheimer's disease causes inflammation that leads to depression, inflammation can be considered a mediating variable in the relationship between Alzheimer's disease and depressive symptoms. Alternatively, if the strength of the relationship between Alzheimer's disease and depressive symptoms is changing across levels of inflammation, then inflammation is a moderating variable. Eventually, inflammation could also be a confounding variable if it causes both Alzheimer's disease and depressive symptoms independently.

REFERENCES

1. Donovan NJ, Locascio JJ, Marshall GA, et al: Longitudinal association of amyloid beta and anxious-depressive symptoms in cognitively normal older adults. Am J Psychiatry 2018; 175:530–537
2. Franceschi C, Bonafè M, Valensin S, et al: Inflamm-aging: an evolutionary perspective on immunosenescence. Ann N Y Acad Sci 2000; 908:244–254
3. Giunta B, Fernandez F, Nikolic WV, et al: Inflammaging as a prodrome to Alzheimer's disease. J Neuroinflammation 2008; 5:51
4. Barger SW, Harmon AD: Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E. Nature 1997; 388:878–881
5. Smith KJ, Au B, Ollis L, et al: The association between C-reactive protein, Interleukin-6 and depression among older adults in the community: a systematic review and meta-analysis. Exp Gerontol 2018; 102:109–132

Didier Wion, Ph.D.

From INSERM UMR1205, Brain Tech Lab, Université Grenoble Alpes, La Tronche, France.

Address correspondence to Dr. Wion (didier.wion@univ-grenoble-alpes.fr).

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