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ABSTRACT & COMMENTARY

Can CPAP Treatment Prevent Dementia?

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips reports no financial relationships relevant to this field of study.

SYNOPSIS: Older people with sleep apnea had onset of cognitive decline at an earlier age than those without sleep apnea, and there was a tendency for those who used continuous positive airway pressure to have delayed onset of decline compared with those who did not.

SOURCE: Osorio RS, et al. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology* 2015;84:1964-1971.

This report is the result of a secondary analysis of longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI), a study designed to test whether serial MRI, PET, other biomarkers, and clinical and neuropsychological assessment can measure the progression of mild cognitive impairment and early Alzheimer's disease. For purposes of this report, the authors queried the ADNI database for patients with self-reported sleep apnea and/or treatment with continuous positive airway pressure (CPAP) and information on age at onset of mild cognitive impairment or early Alzheimer's disease. Data were analyzed with three different criteria for exclusion: first, by only excluding participants with missing data; second, by excluding participants with ambiguous classification of dementia onset or sleep apnea diagnosis; and third, by including *only* participants with incident mild cognitive impairment or Alzheimer's disease with mild cognitive impairment as documented by clinical assessment during the follow-up period.

For the first and most inclusive analysis, 63 participants were normal and diagnosed with mild cognitive impairment at follow-up (2-3 years later), 441 participants were normal and did not develop mild cognitive impairment, 40 participants had mild cognitive impairment and were diagnosed as normal at follow-up, 217 participants had mild cognitive impairment with a reported age at onset, and 6 participants had Alzheimer's dementia with a reported age at onset. Patients with sleep apnea were

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significantly younger at mild cognitive impairment onset than those without for all three analyses. In the most stringent analysis, the age difference for onset of mild cognitive impairment was 77 vs 90 years, ($P < 0.01$). There was not much difference in these findings when controlling for APO ε4, sex, education, depression, cardiovascular disease, hypertension, diabetes, age at baseline visit, and body mass index.

As an exploratory analysis, these authors also compared the small number of participants with sleep apnea on CPAP with those with untreated sleep apnea. In the more inclusive analyses, patients with obstructive sleep apnea (OSA) who were not treated with CPAP had a significantly younger age at mild cognitive impairment onset than those who used CPAP, but this difference was not statistically significant in the most stringent analysis, perhaps because of the small sample size (10 on CPAP and 18 with OSA not treated). In this study, there was no association with Alzheimer's dementia and age of cognitive impairment onset, regardless of sleep apnea diagnosis or treatment.

■COMMENTARY

Before we rush out and start everybody on CPAP to prevent dementia, let's take a look at some of the problems with this study. First, since we can't randomize people to dementia or not, this report doesn't prove causality. (The title is a bit over-reaching. It might more accurately say, "Sleep-disordered breathing is associated with earlier cognitive decline in the elderly." And, although it's unlikely, another possible interpretation of these findings is that cognitive decline causes sleep apnea.) Second, both dementia onset and sleep apnea diagnosis were based on self-report, except in the most stringent analyses, and even then, sleep apnea diagnosis was self-reported. Similarly, CPAP use/adherence was also self-reported. Thus, the reported findings could be due to any number of alternative possible explanations, including that people who get a diagnosis of OSA (and who use CPAP) may take better care of themselves in general (e.g., exercise more, smoke less) than those who don't seek medical care.

But the findings are thought-provoking and potentially important, and they build on previous work. Several prior studies have shown an association between sleepiness and cognitive decline/dementia,[2-5] and one report has linked objectively diagnosed sleep apnea with a higher risk of developing cognitive impairment among community-living women with sleep apnea.[6] Further, the authors' own work has demonstrated an association between sleep apnea and cerebrospinal fluid Alzheimer's disease biomarker changes.[7]

What is most exciting about this paper is that it is the first study to give a signal that CPAP treatment for OSA may be associated with later onset of cognitive decline. Although the current study did not find a relationship between sleep apnea, CPAP treatment, and Alzheimer's disease specifically, previous work has shown that patients with Alzheimer's disease dementia have significantly slower cognitive decline over a 3-year follow-up period when treated for sleep apnea.[8]

What does this mean for our older patients who are considering evaluation or treatment for sleep apnea? At this stage of the game, it would be inappropriate to state definitively that CPAP treatment will delay the onset of cognitive decline or dementia. However, there is growing evidence that sleepiness (from any cause) and sleep apnea are associated with earlier onset of cognitive decline, and a suggestion that CPAP treatment may delay this occurrence. And that's good news. ■

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ABSTRACT & COMMENTARY

Obesity Paradox and Diabetes

By Seema Gupta, MD, MSPH

Primary Care Physician, Charleston, WV

Dr. Gupta reports no financial relationships relevant to this field of study.

SYNOPSIS: In a prospective cohort study of overweight or obese type 2 diabetics, being overweight was associated with a lower mortality risk, but being obese was not. Overweight or obese patients suffered a higher rate of cardiac events.

SOURCE: Costanzo P, et al. The obesity paradox in type 2 diabetes mellitus: Relationship of body mass index to prognosis: A cohort study. *Ann Intern Med* 2015;162:610-618.

Obesity has reached epidemic proportions in the United States, in both adults and children. It is associated with numerous comorbidities, including type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea and sleep-disordered breathing, osteoarthritis, gout, certain cancers, and major cardiovascular diseases (CVD). In fact, more than 80% of cases of type 2 diabetes can be attributed to obesity. The association between obesity and increased risk for CVD such as heart failure, coronary heart disease, sudden cardiac death, and atrial fibrillation is well-established. However, numerous studies have documented that once CVD develops, there seems to be an obesity paradox in which patients with elevated body mass index (BMI) have a better prognosis compared with their lean counterparts.[1,2] The evidence for a similar obesity paradox among patients with diabetes has been less consistent.

To assess the association between body weight and prognosis in patients with type 2 diabetes, Costanzo et al conducted a prospective cohort study of type 2 diabetics attending an outpatient clinic in England. Researchers enrolled 10,568 patients who were followed for a median of 10.6 years. Median age was 63 years, 54% of patients were men, and more than 99% of patients had no known history of CVD. The median baseline BMI was 29.0 kg/m^2. Data on age, diabetes duration, smoking history, height, weight, and blood pressure were collected. But data on exercise and medications were not. The primary outcome of the analysis was all-cause mortality.

Researchers found that being overweight (BMI, 25-29.9 kg/m^2) was associated with a lower mortality risk, whereas obese patients (BMI > 30 kg/m^2) had a mortality risk similar to that of normal-weight persons. Patients with low body weight had the worst prognosis. However, overweight or obese patients (BMI > 25 kg/m^2) were found to have a higher rate of cardiac events (such as acute coronary syndrome and heart failure) than those of normal weight (BMI, 18.5-24.9 kg/m^2).

■COMMENTARY

Previously, many studies have attempted to examine the relationship between obesity and mortality in patients with type 2 diabetes, with varying results.[3,4] Although some have reported an increase in mortality in obese patients with type 2 diabetes, others have shown that being overweight or obese was associated with better overall survival rates, and some have even found a lack of association between BMI and mortality. The current study has several strengths, including a large sample size and long follow-up period. Adjustments were also made for other key characteristics, such as smoking, comorbid conditions, and systolic blood pressure.

However, I would not advise my diabetic patients to not lose that extra weight just yet. There may be several alternate explanations for the study findings, including that patients with lower weight may represent a higher mortality risk as they may already be sick from an etiology unrelated to diabetes. Also, neither data related to fitness nor medications were

captured or evaluated in the study. Finally, the development and treatment of type 2 diabetes may influence body weight. Therefore, to develop an informed clinical opinion, it is vital to conduct a randomized, controlled trial in which overweight and obese patients with diabetes are randomized to weight-loss and non-weight-loss groups. Only then, over time, can the risk of cardiac events and death be assessed accurately. Until that time, it would be prudent to recommend a healthy lifestyle change for obese diabetic patients, including the goal to achieve weight loss, in addition to pharmacotherapy. ■

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ABSTRACT & COMMENTARY

PCSK9: A Major New Advance in Cholesterol-lowering Therapy

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: When added to statin therapy at the maximum tolerated dose, the PCSK9 inhibitor alirocumab reduced low-density lipoprotein cholesterol levels by 62% and also reduced the rate of occurrence of cardiovascular events.

SOURCE: Robinson JG, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489-1499.

Cardiovascular disease (CVD) caused by coronary artery atherosclerosis continues to be the leading single cause of death in industrialized countries. High serum lipid levels, and especially high low-density lipoprotein cholesterol (LDL-C), have been demonstrated in numerous epidemiological studies to strongly and directly correlate with CVD risk. Moreover, large prospective clinical outcome trials have revealed that lowering LDL-C decreases cardiovascular morbidity and mortality.[1] However, despite the use of highly effective lipid-lowering therapy, such as statins and ezetimibe, a significant percentage of patients remain at high risk for CVD.

Monoclonal antibodies to pro-protein convertase subtilisin/kexin type 9 (PCSK9) have been demonstrated to reduce LDL-C levels in patients who are being treated with statins. The PCSK9 inhibitor alirocumab effectively reduces LDL-C by 40%-70% when added to background statin therapy.[2-4] Robinson et al conducted a randomized trial involving 2341 patients who were at high risk for cardiovascular events, who had LDL-C levels of ≥ 70 mg/dL and who were receiving treatments with statins at the maximum tolerated dose.[5] Either alirocumab (150 mg) or a placebo was injected every 2 weeks for 78 weeks. The primary efficacy endpoint measured was the percentage change in calculated LDL-C from baseline to week 24. Alirocumab, when added to the maximum tolerated dose of statin therapy, significantly reduced LDL-C, and a post-hoc analysis revealed evidence of a reduction in the rate of cardiovascular events.

■COMMENTARY

PCSK9 is linked to serum LDL-C levels by binding to and down-regulating LDL receptor levels on hepatocytes. The resulting reduction in receptor function results in reduced hepatic cellular uptake of LDL-C and, consequently, results in higher levels of LDL-C in serum. By contrast, if PCSK9 is inhibited or made inactive pharmacologically, the result is to cause an increase in the number of hepatocyte LDL receptors, causing an increase in LDL uptake from the circulation into the liver, resulting in lower levels of LDL-C. In the ODYSSEY LONG TERM trial,[5] performed by Robinson et al, the PCSK9 inhibitor alirocumab reduced LDL-C by 62% in high-risk patients when added to statin therapy at the maximum tolerated dose. This effect was determined to be consistent over the entire 78 weeks of therapy. The efficacy of the drug was similar across various

subgroups, including those defined according to the presence or absence of heterozygous familial hypercholesterolemia. The data from a post-hoc safety analysis revealed that the rate of major adverse cardiovascular events was 48% lower among the patients who received alirocumab than it was among those who received placebos during the 78 weeks of follow-up. These findings were similar to those of another PCSK9 inhibitor trial in which the LDL-C levels decreased by 52%-57%.[7,8] It must be recognized that the duration of follow-up therapy in the ODYSSEY LONG TERM trial was relatively short and that longer-term studies, which include careful assessment of neurocognitive drug effects and cardiovascular outcomes, are needed.

In summary, this carefully performed trial in 2341 high-risk cardiovascular patients produced results with a new drug, which could potentially offer a major advance in cholesterol-lowering therapy with a possible secondary significant reduction in cardiovascular events. In effect, PCSK9 inhibitors may be a major new addition to our cardiovascular drug armamentarium. ■

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PHARMACOLOGY UPDATE

Memantine HCl and Donepezil HCl Capsules (Namzaric™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a fixed-dose combination of memantine (MEM) and donepezil (DON) for the treatment of Alzheimer's disease. Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist, while donepezil is an acetylcholinesterase inhibitor. This fixed-combination formulation of the two drugs is marketed by Forest Pharmaceuticals as Namzaric.

INDICATIONS

MEM/DON is indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients already stabilized on MEM 10 mg twice daily or 28 mg once daily of extended-release formulation, and donepezil 10 mg or 5 mg and 10 mg, respectively.

DOSAGE

The starting dose is 28 mg/10 mg once daily in the evening.[1] The dose may be swallowed whole or sprinkled on applesauce and may be taken without

regard for meals. MEN/DON is supplied as 14 mg or 28 mg extended-release memantine HCl and donepezil HCl 10 mg.

POTENTIAL ADVANTAGES

The addition of MEM to a stable dose of an acetylcholinesterase inhibitor may improve cognitive performance.[1] The once-daily oral capsule is intended for patients currently taking memantine (10 mg twice daily or 28 mg extended-release once-daily) and donepezil 10 mg. In addition, the capsules can be opened to allow the contents to be sprinkled on food to facilitate dosing for patients who may have difficulty swallowing.[1]

POTENTIAL DISADVANTAGES

The combination as Namzaric has not been studied in a clinical trial. It is not indicated for initial therapy.

COMMENTS

The approval of this fixed combination was based on a single randomized, double-blind, 24-week study in participants with moderate-to-severe Alzheimer's disease (DSM-IV and NINCIDS-ADRDA criteria) on a stable dose of an anticholinesterase inhibitor for 3 months prior to screening.[1]

The participants (n = 677) had a Mini Mental State Examination score ≥ 3 and ≤ 14 and were randomized to memantine extended-release tablets, 28 mg or placebo. Sixty-eight percent were on donepezil.

The co-primary efficacy endpoint was the Severe Impairment Battery (SIB) and the Clinician's Interview-Based Impression of Change (CIBIC-Plus). SIB assesses key elements of cognitive performance (attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction with a range of 0-100). CIBIC-Plus assesses four domains (overall clinical status, functional [i.e., daily living], cognitive, and behavioral). Each domain is scored from 1 to 7.

At 24 weeks, the difference between MEM/AChEI was 2.6 units compared to placebo/AChEI. The responses for both groups were wide ranging but favored MEM/AChEI in terms of showing an improvement or a smaller decline. The mean difference for CIBIC-Plus was 0.3 units. Both endpoints were statistically significant.

Similar to SIB, a greater percentage of participants showed marked to minimal improvement with MEM/AChEI while placebo/AChEI showed more moderate to marked worsening. Roughly 40% showed no change with each group.

CLINICAL IMPLICATIONS

Alzheimer's disease is the most common cause of dementia. Current evidence suggests that cholinesterase inhibitors have modest overall benefit for slowing disease decline.[2] The benefit of memantine alone is less impressive.

The addition of memantine in patients stabilized on donepezil may provide benefit to some patients, at least in the short-term. A randomized, controlled, 24-week study also showed the benefit of adding memantine 20 mg to 10 mg donepezil.[3] In a much longer study, 52 weeks, the addition of 20 mg of memantine to donepezil in patients with moderate-to-severe Alzheimer's disease showed no benefit.[4]

Authors of a systemic review and a meta-analysis suggest that the clinical benefit of combination therapy is not clear.[5] Finally, an APA practice guideline for the treatment of patients with Alzheimer's disease and other dementias indicated that for cognitive symptoms, the benefits of adding memantine to cholinesterase inhibitors are, at best, slight or of unclear clinical significance.[6]

The cost of MEM/DON was not available at the time of this review. ■

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Clinical Briefs

By Louis Kuritzky, MD

Treatment of Depression: Sometimes, It's Hard to Beat Placebo

SOURCE: Papakostas GI, et al. The nature of placebo response in clinical studies of major depressive disorder. *J Clin Psychiatry* 2015;76:456-466.

In randomized, placebo-controlled medication trials for depression, meta-analyses indicate that substantial improvement occurs on placebo, averaging about 30% (range = 12-52%). Although one might expect that as rates of placebo response rise, so should active treatment response rates increase, that has been found not to be the case. Hence, when placebo-responder rates are high, the likelihood of confirming a favorable response from active treatment diminishes.

Investigation into the factors that affect placebo responses have discerned numerous potential contributors, including illness severity and chronicity, participant age, duration of the trial, and frequency of follow-up. Indeed, it has been posited that persons identified as depressed might be better categorized as "biologic" vs "environmental," with the latter group demonstrating more potent response to placebo. There has been some suggestion in the literature that clinical trials in major depression have a substantial (up to 4 weeks) run-in phase to better identify placebo responders.

Papkostas et al direct out attention to the possibility that we may have committed a statistical Type 2 error in reference to pharmacology trials in depression: we may have dismissed an intervention when indeed it was actually effective, to some degree due to an overly robust placebo response. Clinical trials in major depression may benefit from attending to issues that tend to magnify placebo response. ■

NOF Guideline on Prevention and Treatment of Osteoporosis

SOURCE: Altkorn D, Cifu AS. Screening for osteoporosis. *JAMA* 2015;313:1467-1468.

Despite widespread public awareness campaigns, osteoporosis continues to exact a heavy toll on Americans, who suffer about 1.5 million fractures/year, including 300,000 hip fractures. Population screening for osteoporosis has not been demonstrated to reduce fracture risk or mortality in a randomized trial, but extrapolation of results from interventional osteoporosis trials in men and women treated pharmacologically show impressive reductions in vertebral fractures (approximately one-third), hence the support from various agencies with interest in osteoporosis and its consequences.

The National Osteoporosis Foundation (NOF) suggests screening be routinely performed with bone mineral density (BMD) at age 65 in women and age 70 in men, as well as in men and women aged 50-69 who have risk factors (such as menopause, corticosteroid use, positive family history, prior fracture, and positive FRAX score).

In persons with low BMD, NOF guidelines suggest vertebral imaging dependent on age and other specific risk factors (e.g., low-trauma fracture during adulthood, height loss, or long-term steroid use).

Not all voices are in harmony with NOF. For instance, the U.S. Preventive Services Task Force rated osteoporosis screening in men, regardless of age, as "I": insufficient evidence to recommend for or against. No large randomized trial of BMD screening in men or women is on the horizon; hence, clinicians may have to rely on expert advice in the interim. ■

Subclinical Thyroid Dysfunction is Associated with Increased Fracture Risk

SOURCE: Blum MR, et al. Subclinical thyroid dysfunction and fracture risk: A meta-analysis. *JAMA* 2015;313:2055-2065.

Most commonly, when clinicians hear the words "subclinical thyroid dysfunction," they immediately think of subclinical hypothyroidism, even though subclinical hyperthyroidism also deserves a place of recognition because it too is associated with adverse outcomes, such as arrhythmias, especially atrial fibrillation. Subclinical disease (hypo or hyper) is defined as a thyroid-stimulating hormone (TSH) outside the reference range (above or below) with a normal T4 level and no symptoms.

Blum et al investigated databases from the United States, Europe, Australia, and Japan (n = 70,298) to elucidate the relationship between subclinical thyroid dysfunction and fractures. The association of any measureable degree of hyperfunction of the thyroid with fracture risk is fairly straightforward to explain, since frank hyperthyroidism is associated with reduced bone mineral density. Based on 762,401 person-years of follow-up, Blum et al found an increased risk of fracture in persons with subclinical hyperthyroidism, and there was a "dose/response" relationship. That is, the lowest levels of TSH (indicative of relatively greater thyroid hormone excess) were associated with greater risk for fracture. Overall, incident hip fracture was 36% more common in persons with subclinical hyperthyroidism. No relationship between subclinical hypothyroidism and fracture was found. Whether treatment of subclinical hypothyroidism will reduce risk for adverse outcomes — such as fracture or atrial fibrillation — remains to be determined. ■

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CME QUESTIONS

1. In patients with sleep apnea, mild cognitive impairment occurs:

a. at an earlier age than in those without sleep apnea.

b. exclusively in patients who cannot or will not use CPAP.

c. at the same rate as in patients without sleep apnea.

d. generally in people in their 40s.

2. Based on the study by Costanzo et al, all of the following are true in patients with type 2 diabetes *except*:

a. Being obese (BMI > 30 kg/m^2) is associated with a lower mortality risk.

b. Being overweight (BMI, 25-29.9 kg/m^2) is associated with a lower mortality risk.

c. Obese patients (BMI > 30 kg/m^2) have a mortality risk similar to that of normal-weight persons.

d. Overweight or obese patients (BMI > 25 kg/m^2) have a higher rate of cardiac events.

3. The PCSK9 inhibitor alirocumab, when added to statin therapy, which was being given at the maximum tolerated dose:

a. significantly reduced LDL cholesterol levels.

b. could not be tolerated by a significant portion of the patients.

c. had only a minimal effect on reducing the LDL cholesterol levels.

d. had a minimal effect upon the frequency of cardiovascular events.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases.
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease.
- identify cost-effective treatment regimens.
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Diabetes and Kidney Disease

Hypertension Prescriptions