We believe that additional mechanisms of action of desipramine in OSAS need to be investigated, particularly in the case of a longer time design protocol. First, it has been reported in animal models and cell lines that desipramine may have antiinflammatory properties and can decrease lymphocytes, tumor necrosis factor (TNF)- α , and the activity of transcription factor nuclear factor (NF)- κ B (3). Lymphocytes, TNF- α , and NF- κ B are potential targets of desipramine in OSAS because (1) a lymphocyte infiltration that encompasses both the mucosal and muscular layers has been shown in the upper airway mucosa of patients with OSAS (4), and (2) circulating NF- κ B-dependent genes, such as TNF- α and IL-8, have been reported to be increased in patients with OSAS and related to comorbid conditions (5, 6). Second, the noradrenergic stimulation induced by desipramine may not only reduce pharyngeal muscle hypotonia during non-REM sleep but also increase wake time after sleep onset and decrease the REM sleep duration, which may altogether reduce the global apnea-hypopnea index (AHI). Accordingly, the authors showed in both studies (1, 2) the REM-suppressing effect of desipramine compared with placebo. Unfortunately, the effect of desipramine was only studied in an acute design on non-REM AHI or global AHI, without report of changes in REM AHI events that may drive part of the results obtained.

In conclusion, we hope that future trials investigating the interest of desipramine in patients with OSAS with a protocol duration longer than one night will include both peripheral approaches (i.e., persistent upper airway collapsibility and antiinflammatory effect) and central approaches (i.e., monoamine neurotransmission and REM sleep changes). Evidence-based medicine supports that the roles of both the inflammatory pathway and REM sleep are important in the pathogenesis of OSAS and their consequences on cardiovascular morbidity and mortality, given a hypothetical influence of desipramine on this pathway. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Dany Jaffuel, M.D., Ph.D.
Jean-Pierre Mallet, M.D.
Centre Hospitalier Régional Universitaire Montpellier
Montpellier, France

Yves Dauvilliers, M.D., Ph.D.
Institut National de la Santé et de la Recherche Médicale U1061
Montpellier, France

Arnaud Bourdin, M.D., Ph.D.
Centre Hospitalier Régional Universitaire Montpellier
Montpellier, France

and
PhyMedExp, University of Montpellier, Institut National de la Santé et de la Recherche Médicale U1046, Centre National pour la Recherche Scientifique Unité Mixte de Recherche 9214
Montpellier, France

References

1. Taranto-Montemurro L, Edwards BA, Sands SA, Marques M, Eckert DJ, White DP, Wellman A. Desipramine increases genioglossus activity and reduces upper airway collapsibility during non-REM sleep in healthy subjects. *Am J Respir Crit Care Med* 2016;194:878–885.
2. Taranto-Montemurro L, Sands SA, Edwards BA, Azarbarzin A, Marques M, de Melo C, Eckert DJ, White DP, Wellman A. Desipramine improves

upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. *Eur Respir J* 2016;48:1340–1350.

3. Roumestan C, Michel A, Bichon F, Portet K, Detoc M, Henriquet C, Jaffuel D, Mathieu M. Anti-inflammatory properties of desipramine and fluoxetine. *Respir Res* 2007;8:35.
4. Boyd JH, Petrof BJ, Hamid Q, Fraser R, Kimoff RJ. Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;170:541–546.
5. Ryan S, Taylor CT, McNicholas WT. Predictors of elevated nuclear factor-kappaB-dependent genes in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2006;174:824–830.
6. de Lima FF, Mazzotti DR, Tufik S, Bittencourt L. The role inflammatory response genes in obstructive sleep apnea syndrome: a review. *Sleep Breath* 2016;20:331–338.

Copyright © 2017 by the American Thoracic Society

Reply

From the Authors:

We thank Dr. Jaffuel and colleagues for their interest in our articles on the effects of desipramine on genioglossus activity, airway collapsibility, and obstructive sleep apnea (OSA) severity (1, 2). Given the evidence that inflammatory markers are elevated in OSA and reduced after continuous positive airway pressure (CPAP) treatment (3), and that desipramine showed antiinflammatory properties in animal models of allergic asthma and septic shock (4), we agree with the authors of the letter that these properties may have a long-term beneficial role in the treatment of OSA.

Our small trials represent an important first step to find a pharmacological treatment for OSA by stimulating upper airway muscles. Desipramine has a high affinity for the norepinephrine transporter and a moderate affinity for serotonin and dopamine transporters. The increase in these monoamines in the central nervous system may be responsible for the noted reduction or abolition of REM sleep in the subjects we studied (5). The effect of this reduction in REM may be beneficial for the overall apnea-hypopnea index (AHI), as REM sleep is often associated with a higher frequency of apneas and more severe oxygen desaturation (6).

In our study of patients with OSA (2), 200 mg of desipramine taken before sleep completely eliminated REM sleep in seven subjects compared with placebo. Four subjects had REM sleep only while on CPAP, and, for this reason, an REM AHI could not be measured. Only three subjects demonstrated REM sleep off CPAP on both nights for a time period between 20 and 35 minutes: AHI during REM sleep was markedly reduced in two of these subjects (43 to 8 and 30 to 0 events/h sleep), whereas it was unchanged in one subject (21 to 18 events/h sleep).

Supported by Fan Hongbing, President of OMPA Corporation, Kaifeng, China; National Institutes of Health grants R01 HL102321 and P01 NIH HL095491; Harvard Catalyst Clinical Research Center grant UL1 RR 025758-01; American Heart Association grant 17POST33410436 (L.T.-M.); National Health and Medical Research Council of Australia's CJ Martin Overseas Biomedical Fellowship 1035115 (B.A.E.); and American Heart Association grant 15SDG25890059 (S.A.S.).

Originally Published in Press as DOI: 10.1164/rccm.201701-0172LE on February 10, 2017

These data are insufficient to draw any conclusion regarding the effect of desipramine on REM sleep, but the substantial reduction in disordered breathing during REM sleep in two subjects suggests a possible effect of desipramine on upper airway muscle activity during REM sleep. This warrants further investigation in future trials.

As pointed out by Dr. Jaffuel and colleagues, we aimed to assess the effects of a one-night trial with a high dose of desipramine on both clinical (i.e., AHI) and physiological outcomes (genioglossus activity/responsiveness and upper airway collapsibility). Pilot trials such as this can help to evolve a strategy for pharmacological treatment for OSA but are far from conclusive.

On the basis of our findings we hope that longer-term trials will be performed in patients with OSA with specific phenotypes. Lower doses of the drug might also reduce unwanted side effects, such as suppression of REM sleep and a reduction in arousal threshold, while hopefully preserving upper airway muscle activation and other potential beneficial effects, such as systemic antiinflammatory properties. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Luigi Taranto-Montemurro, M.D.
Scott A. Sands, Ph.D.
*Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts*

Bradley A. Edwards, Ph.D.
*Monash University
Melbourne, Victoria, Australia*

Danny J. Eckert, Ph.D.
*Neuroscience Research Australia (NeuRA)
Randwick, Sydney, Australia*
and
*University of New South Wales
Randwick, Sydney, Australia*

David P. White, M.D.
Andrew Wellman, M.D., Ph.D.
*Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts*

References

1. Taranto-Montemurro L, Edwards BA, Sands SA, Marques M, Eckert DJ, White DP, Wellman A. Desipramine increases genioglossus activity and reduces upper airway collapsibility during non-REM sleep in healthy subjects. *Am J Respir Crit Care Med* 2016;194:878–885.
2. Taranto-Montemurro L, Sands SA, Edwards BA, Azarbarzin A, Marques M, de Melo C, Eckert DJ, White DP, Wellman A. Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. *Eur Respir J* 2016;48:1340–1350.
3. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? *Thorax* 2009;64:631–636.
4. Roumestan C, Michel A, Bichon F, Portet K, Detoc M, Henriquet C, Jaffuel D, Mathieu M. Anti-inflammatory properties of desipramine and fluoxetine. *Respir Res* 2007;8:35.
5. Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. *Hum Psychopharmacol* 2005;20:533–559.
6. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. *J Clin Sleep Med* 2009;5:519–524.

Copyright © 2017 by the American Thoracic Society