known phenomenon of regression to the mean (3). Because the AHI is known to vary from night to night (4), restricting an analysis to subjects with the highest AHI on one night of placebo treatment results in a subgroup whose AHI likely would be lower if the subjects were simply treated with placebo for a second night. If the analysis is restricted to a subgroup of patients whose AHI on placebo is an overestimate of their true mean AHI, the effect of atomoxetine–oxybutynin in lowering the AHI compared with placebo will also be overestimated. Regression to the mean can explain why those with the highest AHI on placebo showed not only the greatest difference (atomoxetine–oxybutynin – placebo) in AHI but also the greatest differences in variables that are correlated with the AHI, such as arousal index, sleep efficiency, and sleep quality.

An alternative approach that would provide an unbiased estimate of the true effect of atomoxetine–oxybutynin would be to stratify results on the AHI determined before enrollment rather than on the AHI observed on placebo. The inclusion criteria for this study reported on clinicaltrials.gov include an AHI of >15 events/h, so presumably the authors have an AHI assessment before randomization. Surprisingly, this AHI is not reported in the article and is not used for stratification purposes. This would enable a more valid assessment of whether the response to pharmacologic therapy is greater in patients with more severe OSA.

Patients and clinicians eagerly await a pharmacologic treatment for OSA that will be better tolerated than currently available therapies. Despite the hunger for a magic cure, it is important to preserve methodological rigor to ensure that treatments are actually as effective as we say they are.

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Sanjay R. Patel, M.D., M.S.*
Andrew D. Althouse, Ph.D.
University of Pittsburgh
Pittsburgh, Pennsylvania

ORCID IDs: 0000-0002-9142-5172 (S.R.P.); 0000-0002-8654-5014 (A.D.A.).

*Corresponding author (e-mail: patelsr2@upmc.edu).

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**Reply to Patel and Althouse**

From the Authors:

We are grateful for the opportunity to comment on the opinion expressed by Dr. Patel and Dr. Althouse. The authors raise concerns regarding methodological choices that they considered may have overestimated the efficacy of the combination of atomoxetine and oxybutynin (ato–oxy) on obstructive sleep apnea (OSA) severity (1). Patel and Althouse noted that two patients were excluded from our primary analysis because they dropped out after completing the ato–oxy arm, leaving no placebo data. As suggested by the authors, we reanalyzed our data using a mixed-effects model approach including all 22 patients enrolled. Treatment with ato–oxy versus placebo was assessed adjusting for period and randomization sequence (fixed effects), with ‘patient’ as a random offset. To handle skewed apnea–hypopnea index (AHI) data (evident in model residuals), we used square-root transformation. In this reanalysis (Table 1), the estimated mean reduction in AHI with ato–oxy versus placebo was 23 (20–26) events/h (P = 2 × 10−11, equivalent to a 76% [64–85%] reduction from placebo; mean [95% confidence interval]). This effect is similar to, if not slightly stronger than, the median (interquartile range) reduction reported in the article (16 [7–35] events/h, 63% [88–43%]) for the 20 patients who completed both nights. We also caution readers that mixed-effects model analysis per se cannot replace the missing placebo dropout data and eliminate bias. Notably, repeating the above reanalysis assuming a zero drug effect in the two dropouts (using ato–oxy treatment values for missing placebo values) yielded similar results (reduction in AHI = 20 [12–28] events/h, P = 6 × 10−10; 72% [58–83%] reduction). Overall, a strong effect of ato–oxy versus placebo on the AHI was evident.

The authors also expressed concerns about the post hoc analysis describing the 15 of 20 patients who exhibited OSA (AHI >10 events/h) on placebo, which was performed given the unexpected inclusion of several patients without OSA on placebo. We are not as confident as the letter authors that the regression-to-the-mean phenomenon will explain away the greater improvements in AHI and emergent improvements in sleep variables in the higher AHI subgroups. Recent independent AHI data were available from our other research studies for 10 out of 15 patients in this subgroup, and suggested no artificial elevation in placebo AHI via regression-to-the-mean selection bias (the median [interquartile range] difference in AHI between placebo and independent AHI was −1 [−5 to 12] events/h, P = 0.85). We also note that four out of five patients with AHI <10 on placebo also had AHI <10 on treatment. If these values were artificially reduced on placebo, then either 1) the drug was therefore effective at lowering AHI in this group (unlikely), or 2) the patients truly did not have OSA while in the study (likely), thus justifying exclusion for post hoc exploratory purposes.

Admittedly, these concerns about the post hoc analysis would not be present if baseline night data had been available for all of the patients. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

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patients (OSA diagnosis was based on prior sleep studies dating back to 2009, which were conducted externally, used heterogeneous criteria and equipment, and thus were unsuitable for scientific use). Yet, the criticism is out of context. Our laboratory has been running numerous small-sample, proof-of-principle, randomized-controlled physiology studies with a pragmatic two-night design (desipramine, tiagabine, trazodone, and 4-aminopyridine), largely with negative results (2–6). Fortunately, these studies were completed rapidly enough to allow us to test ato–oxy. An increase in methodological rigor through additional study nights to answer secondary questions comes at a cost: in our case, the addition of a third study (baseline) under consistent conditions would have increased the patient burden and delayed completion dates, ultimately delaying much-needed progress for the patient community, with arguably minimal benefits.

Overall, the concerns raised by Patel and Althouse do not diminish our enthusiasm for these findings, which provide an exciting precursor to phase II/III trials and will hopefully support a pharmacological therapy for OSA in the not-too-distant future.

Table 1. Mixed-Effects Model for the Effect of Atomoxetine and Oxybutynin versus Placebo on the Apnea–Hypopnea Index (Events/h)

| Variable   | Mean (95% CI)        | P Value |
|------------|----------------------|---------|
| Constant   | 30 (22 to 41)        | $2 \times 10^{-15}$ |
| Ato–oxy    | $-23 (-26 to -20)$   | $2 \times 10^{-11}$ |
| Sequence   | 2 (-15 to 25)        | 0.8     |
| Period     | $-3 (-9 to 4)$       | 0.4     |

Definition of abbreviations: Ato–oxy = effect of treatment (combination of atomoxetine and oxybutynin) versus placebo; CI = confidence interval. Square root–transformed results were back-transformed for presentation. Randomization sequences (drug-then-placebo and placebo-then-drug) were denoted by −0.5 and +0.5, and periods (night 1 and night 2) were denoted by −0.5 and +0.5, such that “constant” represents the expected placebo apnea-hypopnea index under average sequence and period conditions.

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Luigi Taranto-Montemurro, M.D.*
Scott A. Sands, Ph.D.
Ali Azarbarzin, Ph.D.
Andrew Wellman, M.D., Ph.D.
Brigham and Women’s Hospital and Harvard Medical School
Boston, Massachusetts

*Corresponding author (e-mail: ltarantomontemurro@bwh.harvard.edu).

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