of interstitial lung abnormalities to a subset of individuals with serial chest computed tomography data from the Framingham Heart Study and reported accelerated loss of FVC among individuals with radiographic progression of interstitial changes (relative to individuals without interstitial lung abnormalities or with stable interstitial lung abnormalities) (3). Within COPDGene, individuals who developed “incident PRISm” (i.e., transitioned from normal spirometry (“GOLD 0”) at phase 1 to PRISm at phase 2) also exhibited higher rates of lung function decline, albeit in both FEV1 and FVC rather than isolated declines in FVC (1). The degree to which interstitial lung abnormalities contribute to this transition has not yet been fully characterized.

Assessment of the de novo development of interstitial lung abnormalities as well as progression of existing interstitial lung abnormalities are active areas of investigation within COPDGene. Notably, a significant number of subjects with PRISm in COPDGene had anatomical abnormalities that were not limited to interstitial parenchymal changes, including chest wall and diaphragmatic deformities as well as a smaller internal transverse thoracic diameter in phase 1 (4). In addition to anatomical and parenchymal changes, functional differences, such as small airway disease (5) and gas transfer abnormalities, represent additional domains that should be explored in PRISm.

We continue to assert that the PRISm cohort is heterogeneous and is likely composed of subgroups with distinct pathobiological processes (6); interstitial lung abnormalities likely contribute to the development and progression of lung disease in a subset of subjects with PRISm. Future studies, both within and beyond COPDGene, to characterize the predictors and risks associated with distinct subgroups within PRISm are needed.

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

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Robust Methods Are Needed to Evaluate the Pharmacologic Treatment of Obstructive Sleep Apnea

To the Editor:

We read with interest the letter by Taranto-Montemurro and colleagues on the impact of atomoxetine plus oxybutynin on obstructive sleep apnea (OSA) severity (1). Although we hope there is a potential role for this new pharmacologic approach, we are concerned about methodological choices that may introduce bias into estimates of the efficacy of this treatment.

First, there is the problem of missing data. In this crossover trial, two out of 12 subjects (17%) randomized to atomoxetine–oxybutynin as the first treatment dropped out, versus zero of 10 subjects (0%) randomized to placebo first. Such dropouts are typically differential in nature, and ignoring them by using a complete-case analysis tends to overestimate the benefits of atomoxetine–oxybutynin. Methods such as mixed-effects models that use all collected data would provide a more robust estimate of the true effect of atomoxetine–oxybutynin while also allowing for the evaluation of any crossover effects (2).

Second, and of more concern, the authors focus on a post hoc analysis in which they stratified patients on the apnea–hypopnea index (AHI) while the patients were receiving a placebo (those with AHI > 10 events/h on placebo treatment). Stratification on an observed value of the study outcome is well understood to provide biased results. Performing a comparison of atomoxetine–oxybutynin versus placebo while restricting the analysis to patients with poor results on placebo would result in a positively biased estimate of the treatment effect. If the treatment were to have no effect whatsoever, one could still create the appearance of a “positive” effect by selecting only the patients with poor results on placebo—this is a variation of the commonly
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 would likely 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.

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 sleep 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% [38–43%]) 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.