−1.08 to −0.13) (1). The authors do not outline the results of their pooled analysis in detail (such as with a Forrest plot) and explain that such detail will be independently published later.

Nici and colleagues (1) neglect to specify for the reader that out of the 12 trials included in their meta-analysis on opioids for dyspnea in COPD, only 3 reported statistically significant positive results for opioids over placebo, and the remaining 9 were negative. Furthermore, one of the three positive trials involved individuals with COPD, not secondary to tobacco smoke exposure but instead secondary to mustard gas (2); thus, this study is associated with bias. Along with the overall pooled estimate, it would have been helpful for Nici and colleagues (1) to concurrently present such important details, to provide readers with a more comprehensive and balanced view of their meta-analysis. When considering the results of a meta-analysis, it is instructive to know if a positive signal is being driven by a majority of studies included, versus a small number, and if the latter case, whether such studies might be associated with bias.

The authors also overlook acknowledging two other recently published meta-analyses on the topic of opioids for dyspnea in COPD (3, 4), using nearly the same evidence base yet reporting strikingly different findings. Considering 10 out of 12 trials that Nici and colleagues (1) did, Ekström and colleagues (3) in 2015 reported a markedly lower SMD in dyspnea scores for opioids over placebo (−0.35; 95% CI, −0.53 to −0.17). Subsequently, in 2016, a meta-analysis was published by Barnes and colleagues (4), and when considering studies involving only individuals with COPD, this group reported an SMD in dyspnea scores similar to that of Ekström and colleagues (5), but not statistically significant (SMD −0.49 [95% CI, −1.08 to 0.10] for trials where dyspnea scores were compared with baseline, and SMD −0.21 [95% CI, −0.45 to 0.04] for trials where dyspnea scores were compared with the pretreatment period). The SMD estimates from the aforementioned two meta-analyses show, at best, a small improvement in dyspnea intensity with opioids and fall below the threshold that Nici and colleagues (1) set as clinically meaningful (SMD >0.50). It is challenging to reconcile the SMD estimate of Nici and colleagues (1) with that of Ekström and colleagues (3) and Barnes and colleagues (4), without more details being provided by the former authors.

Finally, Nici and colleagues' (1) literature search terminated in July 2019. However, since then, two more randomized controlled trials have been published that evaluated opioids for dyspnea in advanced COPD (5, 6). Both trials reported negative results, and the study by Currow and colleagues (5) is the largest and, arguably, best-quality trial on the topic conducted to date. Therefore, Nici and colleagues' (1) recommendation regarding opioids for dyspnea in COPD does not incorporate the most up-to-date, best-quality evidence on the topic.

On such an important and controversial topic as using opioids to treat refractory dyspnea in COPD, in a guideline document, it behooves Nici and colleagues (1) to provide readers much more detail about their meta-analysis, including what, why, and how data got pooled. ■

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Reply to Vozoris

From the Authors:

We appreciate the opportunity to clarify Dr. Vozoris's questions concerning the American Thoracic Society (ATS) clinical practice guideline (CPG) on the pharmacological treatment of chronic obstructive pulmonary disease (COPD) (1). Dr. Vozoris's questions relate to the specific clinical question addressed in the ATS guideline concerning the use of opioids for COPD. Dr. Vozoris specifically highlights concerns related to the lack of specific details of the meta-analysis used to assess the benefits and risks of the impact of opioids on dyspnea.

Although there was not enough space in the ATS CPG to detail every systematic review relevant to the clinical questions addressed, we acknowledge that there have been previous systematic reviews and meta-analyses on opioids. Our meta-analysis differed from the meta-analysis by Eckström and colleagues and by Barnes and colleagues in that our search resulted in one additional study not included in the

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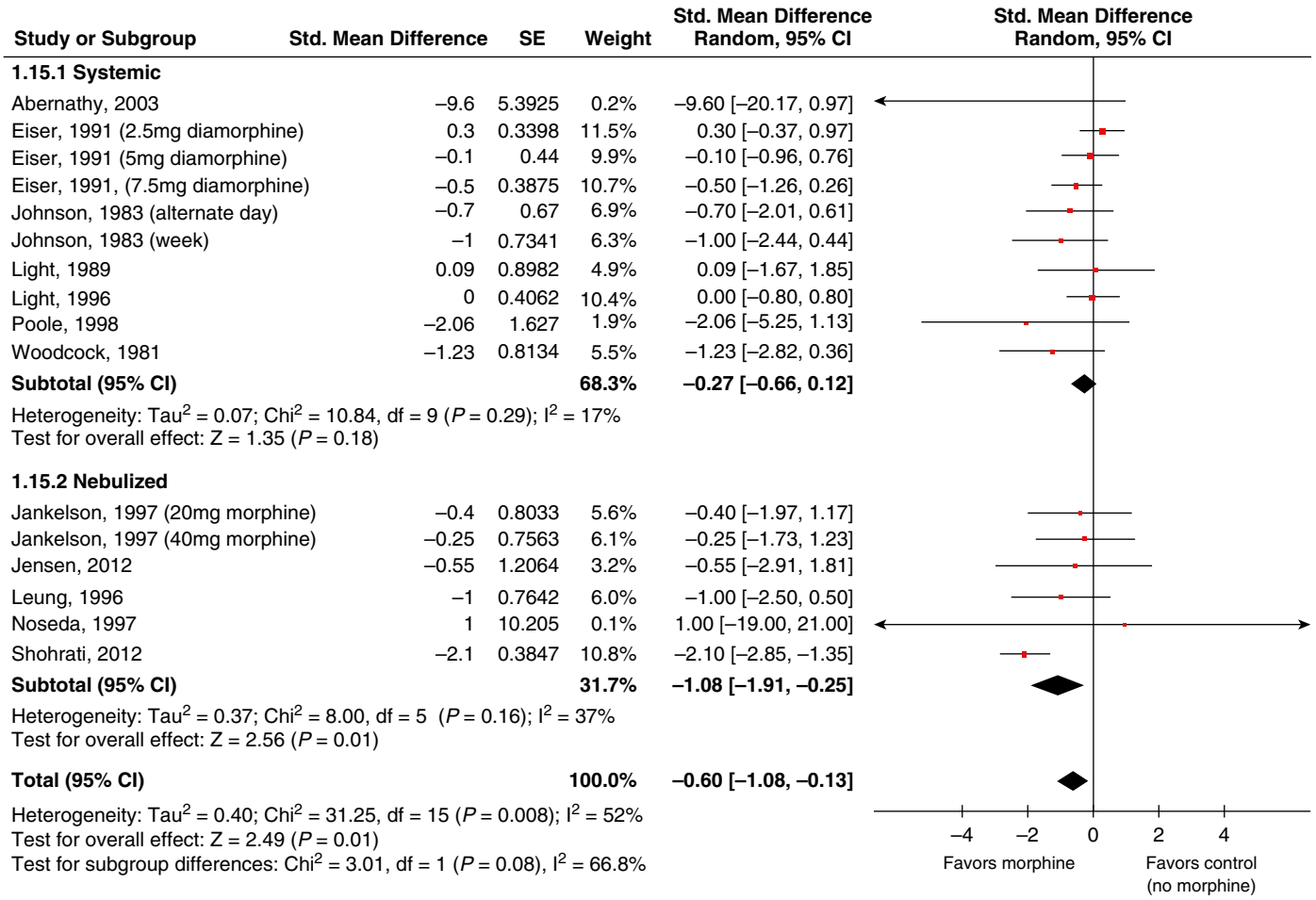

Figure 1. Forest plots for opioids in the treatment of dyspnea in patients with chronic obstructive pulmonary disease. CI = confidence interval; Std. = standardized.

meta-analysis by Eckström and colleagues and five studies that were not included in the meta-analysis by Barnes and colleagues (2, 3). Thus, our analysis included additional data not pooled in the aforementioned meta-analyses. The individual trials included in our meta-analysis used different dyspnea assessment scores, including the visual analog scale for dyspnea, diary cards, Medical Research Council scale, Chronic Respiratory Disease Questionnaire dyspnea subscale, and Borg scale, so the standardized mean difference (SMD) was used to pool the data. We used the statistical program Revman 5.3 to analyze pooled data for the eligible studies using Mantel-Haenszel random effects and inverse variance meta-analytical approaches for continuous data associated with the dyspnea outcome, whereas Barnes and colleagues used fixed-effect modeling. The differences in the individual studies included in each meta-analysis, and the differences in methods used to standardize and analyze the study data contributed to differences in the results of our meta-analysis compared with previously published systematic reviews.

To aid in the identification of the contribution of each study to the pooled results, we include the forest plot detailing our meta-analysis of the effect of opioid use on dyspnea in patients with COPD (Figure 1). The forest plot shows the pooled SMD and reduced dyspnea in patients randomized to receive opioid therapy compared with the control group (SMD, −0.60; 95% confidence interval [CI], −1.08 to −0.13; $P = 0.01$; I^2 of 52%).

Importantly, the pooled estimates reported in the meta-analysis by Ekström and colleagues (SMD, −0.35; 95% CI, −0.53 to −0.17) indicate a statistically significant improvement in dyspnea, and the magnitude and direction of effect of the findings of the meta-analysis by Barnes and colleagues are also similar to what we reported (SMD, −0.49; 95% CI, −1.08 to 0.10). Thus, we disagree that the pooled estimates reported in the previously published meta-analysis are significantly different than the findings from our meta-analysis.

Dr. Vozoris is also concerned that the trial by Shohrati and colleagues included patients who developed COPD from mustard gas inhalation, and that this introduces bias into the meta-analysis. We disagree with this opinion. ATS, European Respiratory Society, and Global Initiative for Obstructive Lung Disease all state that COPD can be due to inhalation of noxious particles or gases (4, 5). People can develop COPD from exposure to tobacco smoke, farm dusts, cocaine, and, in the case of the study by Shohrati and colleagues, mustard gas. We disagree that the etiology of COPD would lead to a higher bias rating of the study.

Finally, Dr. Vozoris is concerned that the meta-analysis for our CPG did not include two randomized controlled trials that were published in January 2020 and March 2020 (6, 7). We concur that those studies present useful quality data on the topic; however, to construct a CPG by an academic, professional society, there needs to be time between the conclusion of the literature search, the conduct of the systematic review, the meta-analysis, and the subsequent expert panel weighing of the evidence with subsequent write-up of the CPG. This is then followed by submission of the CPG to the professional society and finally peer review by the professional society and the publishing journal. Our CPG was submitted for consideration for approval and publication to the ATS Board of Directors in December 2019, whereas the two articles cited by Dr. Vozoris were both published in 2020, after our CPG was written and finalized. ■

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Weight Loss and Upper Airway Anatomy in Patients with Obstructive Sleep Apnea

To the Editor:

In their study, Wang and colleagues determined the effect of weight loss on upper airway anatomy in patients with obesity and obstructive sleep apnea (OSA) (1). Weight loss was significantly associated with reduction in the volumes of several upper airway soft tissues, including tongue fat. Furthermore, Pearson's rho of 0.62 showed that reduction in tongue fat volume was strongly correlated with reduction in the apnea–hypopnea index (AHI). Improved AHI with weight loss might be mediated by reduction in tongue fat volume. However, I have two concerns about the relationship between OSA and obesity.

First, Sutherland and colleagues conducted an intervention to assess the change in upper airway size and regional facial and abdominal fat with weight loss and their associations with OSA improvement (2). In combination with significant reductions in weight of 7.8 kg and AHI of 15.9 events/h, velopharyngeal airway volume significantly increased from the baseline, whereas facial and parapharyngeal fat volumes were significantly reduced. In addition, a reduction in upper airway length was significantly associated with improvement in AHI, and 31% of the variance in AHI improvement could be explained by changes in upper airway length and visceral abdominal fat. They also specified that both upper airway length and visceral abdominal fat contributed to an improvement in AHI. In contrast, Wang and colleagues conducted mediation analyses, and abdominal fat volumes did not reach the level of significance in terms of the relationship between percentage change in weight and AHI (1). Therefore, the level of obesity, sex, age, and ethnicities should also be comprehensively evaluated to verify the association between weight loss and OSA.

Second, Pillar and colleagues also focused on the role of pharyngeal anatomy on OSA and recognized that there were bidirectional relationships between OSA and obesity (3). Continuous positive airway pressure (CPAP) treatment increased the level of obesity, which was not accompanied by any adverse

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