The Role of Hypnotics in Continuous Positive Airway Pressure Compliance

To the Editor:

We congratulate the work of Bradshaw and colleagues on the use of hypnotics for continuous positive airway pressure (CPAP) compliance. This is the first placebo-controlled study investigating an apparent common clinical practice. There were, however, several methodologic issues that may limit the application of these results to clinical practice.

The hypnotic selected, zolpidem, has a relatively short duration of action. Since sleep apnea tends to worsen in rapid eye movement sleep, which dominates the last third of the night, the medication may be wearing off at the time when the patients are having the most difficulty. A longer-acting medication might be a more suitable choice if the goal is to increase CPAP compliance. With only 24 subjects, the study may have been underpowered. The hypnotic chosen, zolpidem, compared to placebo increases total sleep time by approximately 20 to 30 min. However, the power calculation described looked for a 1-h difference in total sleep time. Subjects were only administered 14 tablets that they could use any time over 28 days. So at least half of the time all the groups were equal since none of the subjects were taking a pill. We should not be completely surprised that the groups ended up with similar results. Nightly use of the hypnotic agent during the entire study period may have led to different results. This may be supported by the data on Table 2, which showed in the first 14 days the hypnotic group is doing better than the placebo group.

On page 1372, it states that pill counts were available for only 61 of 72 patients. This is confusing because only 48 patients should have received pills in the first place, not 72 patients. The standard-care group received a bottle filled only with cotton.

Another possible methodologic question is how was the hypnotic provided and prepared for blinding? Since zolpidem is commercially available, the pill had to be somehow masked. If the hypnotic was masked in a capsule, could this have affected the drug delivery? The manufacturer recommendations are for zolpidem to be administered preferentially on an empty stomach. However, this recommendation was not mentioned in the “Materials and Methods” section. A possible problem with hypnotic absorption is suggested by the subjects being instructed to take the drug 30 min before going to bed, which is longer than recommended by the manufacturer. A potential bias against taking a pill was established by subjects being “strongly” warned that the drug could make sleep apnea worse. That warning alone could worsen their sleep. This might help account for why the standard-care group that did not get any pills at all did better than the other two groups.

A possible reason that there was no difference found between the hypnotic and control groups is the way the CPAP was administered. Some of the subjects had the CPAP pressure picked using a split-night protocol, which may be suboptimal in some populations. In the present study, the hypnotic was offered to all patients regardless of a history of insomnia or the sleep efficiency during polysomnography. It is possible that by selecting patients with lower sleep efficiency on polysomnography, the hypnotics may be of benefit. These patients are more likely to need a little extra help sleeping with CPAP. Only male subjects were studied. Since insomnia complaints are more common in women, it is possible that using a different population the hypnotics may be of benefit. None of the patients were offered heated humidifiers; only passive humidifiers were provided. This may lower the overall compliance of the studied population. Currently, heated humidifiers are widely available. The groups did not have equal severity. The baseline apnea-hypopnea index of the group who did not receive an agent was much higher than the zolpidem group (55.9 vs 33.4). Possibly, the more severe group is more likely to have benefited from CPAP and be more motivated to use it.

Dr. Bradshaw’s group has provided an excellent first step in the critical analysis of what can be done to enhance CPAP compliance. These results however should not at present be extrapolated to general clinical practice. We among others are currently conducting a clinical trial of hypnotic use and CPAP compliance using a longer-acting hypnotic in selected patients.

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Dr. Pelayo is currently conducting a clinical trial of eszolpilone with support from Sepracor Pharmaceuticals. He has also served as an advisor and speaker’s bureau to sanofi-adventis and Takeda. Dr. Gallilmenaut has no conflict of interest to disclose.

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Sister Leena’s Sign

A Sign That May Be Useful in Differentiating Colopleural Fistula (Fecal Empyema) From Usual Empyema

To the Editor:

Colopleural fistula with secondary fecal empyema is an exceptionally rare condition. There is usually a significant delay before the presence of colopleural fistula is suspected to be the cause for empyema. In January 2006, a young woman in her 24th week of gestation was admitted to Hamad General Hospital in Qatar because of right-side, massive pleural effusion that was initially suspected to be empyema. The fluid was green, offensive, and had all the biochemical characteristics of empyema. Despite broad antimicrobial coverage and continuous chest tube drainage, the patient did not show signs of improvement. Interestingly, variable amounts of fluid ranging from few millimeters to 3 L were drained for > 3 d. The diagnosis was later confirmed to be colopleural fistula with fecal empyema in the right pleural cavity. Fortunately, the patient survived and made a good recovery after pleural decortication and resection of the part of colon containing the fistula. A nurse (L.T) who was caring for the patient made a very important observation shortly after the patient’s admission and before any of the doctors had suspected the diagnosis. None of us as doctors considered her statement seriously. However, after the possibility of colopleural fistula was raised by a senior consultant and confirmed later, I realized retrospectively that her observation was logical and could have been a key point for suspicion of the diagnosis earlier should we have considered it