Aclidinium bromide improves symptoms and sleep quality in COPD: a pilot study

To the Editor:

In patients with chronic obstructive pulmonary disease (COPD), nighttime and early-morning symptoms are associated with an increased rate of exacerbation, hospital admission and reduced survival [1, 2]. Furthermore, patients with COPD frequently have poor sleep quality [3] and reduced physical activity [4, 5]. We hypothesised that nighttime airflow obstruction in patients with COPD is associated with impaired sleep quality, leading to early-morning symptoms and reduced physical activity.

Inhaled once-daily long-acting muscarinic antagonists (LAMAs) have demonstrated modest beneficial effects on sleep quality [6, 7]. The LAMA aclidinium bromide in a dosage of 400 µg given twice daily has been shown to provide clinically meaningful improvements in bronchodilation over 24 h; however, its effect on sleep quality and physical activity has not yet been assessed. We conducted a pilot study to assess the effect of aclidinium on lung function, sleep quality, COPD symptoms and physical activity in patients with stable moderate to severe COPD.

This was a 21-day, randomised, double-blind, placebo-controlled, two-period crossover pilot study conducted in two centres in Germany. Eligible patients were aged ≥ 40 years, current or former smokers (≥ 10 packs per year) with moderate to severe COPD (post-bronchodilator forced expiratory volume in 1 s (FEV₁) $\geq 40\%$ and $< 80\%$ predicted and FEV₁/forced vital capacity ratio $< 70\%$). Key exclusion criteria included: history or current diagnosis of asthma; apnoea–hypopnoea index ≥ 15 h⁻¹ at screening; respiratory infection, COPD exacerbation or significant cardiovascular conditions. All patients provided written informed consent and study protocols and amendments were approved by a local ethics committee.

Following a 7-day run-in period, patients were randomised to two subsequent 3-week treatment periods in which they received aclidinium bromide 400 µg or placebo dosage (every 12 h: morning, 08:00–10:00; evening, 20:00–22:00) with a 10–14-day washout period between treatments. All study treatments were administered *via* GenuairTM/Pressair[®] dry powder inhaler. Inhaled salbutamol (100 µg per puff) was permitted as relief medication. Inhaled corticosteroids, oral or parenteral corticosteroids (equivalent to ≤ 10 mg per day of prednisone or 20 mg every other day) and oral sustained-release theophyllines were permitted as maintenance medication if treatment was stable ≥ 4 weeks pre-screening.

COPD symptoms were assessed (by using early-morning, evening and nighttime questionnaires completed at all visits), in addition to nighttime awakenings and early morning and evening activity limitation [8]. Serial 24-h FEV₁ was evaluated by spirometry at baseline and at the end of each treatment period (week 3) [9]. Polysomnography (PSG), including measurements of oxygen desaturation index (ODI), rapid eye movement sleep (REM), total sleep time (TST) and sleep efficiency, was conducted at baseline and at the end of each treatment period, with measurements scored in a central laboratory (University Hospital Regensburg, Germany) in accordance with the American Academy of Sleep Medicine guidance [10]. Health status was assessed by using the COPD Assessment Test (CAT) at all visits. Physical activity (assessed by patients wearing a SenseWear Pro3[®] armband, BodyMedia Inc., Pittsburgh, PA, USA) was recorded over 7 days before the first and last visits of each treatment period [5, 11]. Adverse events and serious adverse events were recorded throughout the study.

As this was a pilot study, no formal sample size calculation was performed. The per-protocol population (all patients in the safety population who had no major protocol deviations) was used to analyse all efficacy measures.

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Aclidinium statistically improved symptoms, and sleep and physical activity in moderate COPD <http://ow.ly/2chV30adLbW>

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We investigated 30 patients with COPD (mean $\pm$ SD age 64.4 $\pm$ 7.0, 50% male, 63.3% current smokers). The mean $\pm$ SD post-bronchodilator FEV₁ was 1.5 $\pm$ 0.4 L; most patients (66.7%) had moderate COPD and the mean $\pm$ SD CAT score was 13.9 $\pm$ 4.9; 86% of patients had a CAT score >10.

Following 3 weeks of treatment, patients receiving acclidinium demonstrated statistically significant improvements in FEV₁ versus placebo ($p<0.05$) (figure 1a). Acclidinium increased peak and trough FEV₁

FIGURE 1 a) Least squares (LS) mean (se) forced expiratory volume in 1 s (FEV₁) at week 3; b) LS mean change from baseline at week 3 in overall symptom severity score in the morning, evening and nighttime; c) LS mean change in rating of limitation of activities during the morning and evening; d) LS mean change in moderate physical activity; e) LS mean change in oxygen desaturation index h⁻¹ of total sleep time (TST); f) LS mean change in rapid eye movement sleep; g) LS mean change in TST; h) LS mean change in sleep efficiency. *: $p<0.05$. Error bars represent 95% confidence intervals. Baseline mean overall symptom severity scores were as follows: morning, 0.99; evening, 0.93; nighttime, 0.57. Baseline rating of limitation of activities was as follows: morning, 0.66; evening, 0.81.

from baseline by 175 mL ($p=0.0004$) and 100 mL ($p=0.0323$) *versus* placebo, respectively. There were statistically significant changes from baseline in overall symptoms with acclidinium observed during the evening, with improvements observed that did not reach statistical significance during the early morning and nighttime (fig. 1b). Furthermore, there were significant reductions from baseline in symptoms limiting early-morning activities (-0.17 ; standard error [SE] ± 0.06 ; $p=0.0068$) and evening activities (-0.21 ; SE ± 0.07 ; $p=0.0062$) (fig. 1c) *versus* placebo. Although the change from baseline in mean CAT total score was not significantly different between treatments groups, patients receiving acclidinium achieved an additional 18 min per day moderate activity *versus* those receiving the placebo (fig. 1d). Additionally, there was a general trend towards improvement in sleep and ventilation parameters with acclidinium *versus* placebo. Indeed, significantly greater improvements from baseline in ODI (-2.54 h^{-1} TST; $p=0.0286$) (figure 1e) and REM sleep stage (2.53%, $p=0.0331$) (figure 1f) were identified in patients treated with acclidinium *versus* placebo, whilst TST and sleep efficiency showed improvements that did not reach statistical significance (fig. 1g and h). Finally, all reported adverse events were mild or moderate in intensity (none were considered related to the study drug); no patients withdrew from the study and there were no serious adverse events.

This is the first study to use PSG to examine the effect of the LAMA acclidinium bromide 400 µg dosage on sleep profile in addition to lung function, physical activity and symptoms in patients with moderate to severe COPD and without concomitant sleep apnoea. Our study suggests that treatment with acclidinium not only improves lung function and symptoms, but might also improve sleep quality. It provides further evidence of improvements in physical activity seen previously [11] in patients with COPD.

Recently, several studies have reported that in patients with COPD, nighttime and early-morning symptoms are associated with poorer health status, impaired daily activities and increased risk of exacerbation than in patients without these symptoms [12, 13]. McSHARRY *et al.* [14] performed a PSG assessment of patients with COPD and found that sleep efficiency was low (66%) and REM sleep was diminished (12.7%) in comparison with historical normative populations. To date, however, few studies have used PSG to investigate the effects of bronchodilators on sleep quality. MARTIN *et al.* [6] compared ipratropium bromide with placebo and showed that the effect sizes on TST and REM sleep were similar to those observed in the present study. In contrast, McNICHOLAS *et al.* [7] compared tiotropium bromide with placebo but were unable to demonstrate a change in TST and other parameters of sleep quality. Importantly, in our study there was a significant reduction of the ODI and a trend towards improvements in mean oxygen saturation during REM sleep *versus* placebo. This compares favourably with previous studies of LAMAs that have demonstrated significant improvements in mean nocturnal oxygen saturation [6, 7]. RYAN *et al.* [15] also demonstrated an improvement in oxygen saturation following treatment with salmeterol, but there was no significant change in sleep quality.

There were trends towards improvements in physical activity for patients receiving acclidinium *versus* placebo; however, these did not reach statistical significance. In a similar 3 week study of 112 patients receiving acclidinium 400 µg dosage [11], significant improvements in physical activity end-points were observed that were comparable with the range of improvements seen in our study, which suggests that the lack of statistical significance seen here may be due to the small number of patients.

While larger studies of a longer duration are required to confirm our findings, being able to see improvements within 3 weeks in a small number of patients is very encouraging. Indeed, based on the results from this pilot study, we speculate that improvements in nighttime lung function may be associated with improved sleep quality and this may be an important feature linking bronchodilation to improvement in symptoms and physical activity.

Helgo Magnussen¹, Michael Arzt², Stefan Andreas^{3,4}, Tanja Plate⁵, Anna Ribera⁶, Beatriz Seoane⁶, Henrik Watz¹ and Anne-Marie Kirsten¹

¹Pulmonary Research Institute at LungenClinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany. ²Centre of Sleep Medicine, Dept of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany. ³Lungenfachklinik Immenhausen, Immenhausen, Germany. ⁴Cardiology and Pneumology, Universitätsmedizin Göttingen, Göttingen, Germany. ⁵AstraZeneca GmbH, Hamburg, Germany. ⁶AstraZeneca Plc, Barcelona, Spain.

Correspondence: Helgo Magnussen, Pulmonary Research Institute at LungenClinic Grosshansdorf, Wöhrendamm 80, 22927 Grosshansdorf, Germany. E-mail: magnussen@pulmoresearch.de

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