Fluoxetine (at a dose of 60 mg for only 3 days) has been used to improve hypoventilation via reduction of rapid eye movement-related hypoventilation in asymptomatic obese patients, without COPD (Kopelman et al, 1992). Fluoxetine significantly increased the minimum oxygen saturation recorded (fluoxetine 81% *vs* control 73%; $P<0.05$). The total apnoea/hypopnoea index fell in six subjects with fluoxetine. In five of the six the improvement was associated with the abolition of rapid eye movement sleep. Total sleep time and quality were not affected by fluoxetine. General use is limited by side effects including sexual dysfunction, nausea, insomnia and behavioural disorders.

Acetazolamide (a carbonic anhydrase inhibitor) has been used in patients with respiratory failure resulting from lung disease as a short-term treatment when there is associated metabolic alkalosis, often caused by loop diuretic acting as a respiratory stimulant via generation of a metabolic acidosis. In a placebo-controlled study (Gulsvik et al, 2013), at a dose of 250 mg three times daily, for 5 days, it improved PaO_2 significantly by 1.41 kPa (compared to 0.81 kPa in control group). Acetazolamide is often considered an adjunct with non-invasive ventilation concurrently or in place of this as a short-term measure. It is important to monitor renal function. While these data are interesting, a review of existing studies on acetazolamide (Bales and Timpe, 2004) did not show any longer term benefits on morbidity, mortality or quality of life in COPD patients although short-term improvements in ventilator parameters and arterial blood gases have been reported.

Finally, medroxyprogesterone (30 mg twice daily) has been used as a respiratory stimulant working via progesterone receptors in the hypothalamus in patients with COPD. Short-term results are encouraging but there are no long-term data to support benefits in morbidity, mortality or quality of life in COPD (Bales and Timpe, 2004). A short-term comparative study (Wagenaar et al, 2003) between medroxyprogesterone and acetazolamide in patients with COPD favoured the latter slightly in ability to improve daytime PaO_2 and reduced time with nocturnal desaturation but with similar reductions in day and night time $PaCO_2$.

It is worth remembering the potential short-term value of medroxyprogesterone and acetazolamide that might be better tolerated (metabolic acidosis and renal failure aside with the latter) than oral theophylline. Evidence for fluoxetine is very limited in COPD, and adverse central effects are more problematic. Longer-term studies are still not available to show a clear benefit on mortality, but such drugs might be useful in COPD patients who cannot tolerate non-invasive ventilation or where there are no other therapeutic options.

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Sir,

Dr Medford has highlighted some constructive points. Pharmacological therapies which may ameliorate some of the factors contributing to hypoxaemia during sleep in patients with COPD are an alternative approach. Some medications, including theophylline, long-acting β-agonists, and long-acting anticholinergics such as ipratropium bromide or tiotropium, are accepted therapies for nocturnal hypoxia in COPD. Combined use of oxygen therapy and pharmacological therapies not only improved nocturnal hypoxia but also lowered $PaCO_2$ in previous studies.

As Dr Medford mentioned, fluoxetine has been used to improve hypoventilation via reduction of rapid eye movement-related hypoventilation in asymptomatic obese patients, without COPD (Gulsvik et al, 2013). While the racemic mixture of fluoxetine has certain advantages, its disadvantages are also obvious, with headaches, nervousness, anxiety and insomnia reported as adverse effects. Other disadvantages are its long half-life and long duration of action.

Short-term medroxyprogesterone therapy effectively improved ventilation and decreased $PaCO_2$ in patients with COPD (Saaresranta et al, 2002). Combined treatment with medroxyprogesterone acetate and acetazolamide for 2 weeks in hypercapnic patients with COPD normalized arterial blood gas values and improved nocturnal oxygen saturation and the chemical drive with a relative modest increase in minute ventilation. The combination of medroxyprogesterone acetate and acetazolamide is more beneficial than with either drug alone (Wagenaar et al, 2002). It remains to be established whether long-term combined treatment in hypercapnic patients with COPD will postpone long-term oxygen therapy or non-invasive ventilation, or even improve life expectancy. Another study reported that oral steroid therapy in stable COPD improved nocturnal oxygen desaturation and increased total sleep time. Although there are no relevant data, a similar improvement might be expected with inhaled corticosteroids (Sposato et al, 2007).

Safety is an important concern when considering pharmacological treatment for sleep-induced hypoxaemia in patients with severe COPD. Knowledge about pharmacological treatments and other interventions may direct a better prognosis that is worthy of further research.

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