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Mood After CPAP: Fewer Patients With Depression, but not Fewer With Anxiety

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The prevalence of depression symptoms in obstructive sleep apnea (OSA) has been variably estimated, but most studies suggest that it is considerable, especially among women [1,2]. The way OSA is related to depression is uncertain. Low or high OSA severity [3,4], hypoxemia during sleep [5], excessive sleepiness [6], have been pointed out as possible correlates of depression in OSA, but their role is highly controversial. Anxiety in OSA has been less studied than depression but, like for depression, its prevalence seems higher than in the general population [2]. So far, a large number of studies, with various experimental designs and follow-up periods, have dealt with effects of OSA treatment on mood alterations. Meta-analyses have demonstrated some positive effects of OSA treatment by continuous positive airway (CPAP) or mandibular advancement device but have highlighted heterogeneity of the studies and of their results [7,8].

The Sleep Apnea Cardiovascular Endpoints (SAVE) study is a randomised controlled trial that was planned to evaluate possible benefits of treatment of OSA by CPAP in patients with cardiovascular disease. In a well-known previous publication on patients of this trial, it was already reported that CPAP significantly improves both depression and anxiety symptoms after a mean of 3.7 years [9]. In a new study published in this issue of *EClinicalMedicine* [10], data from the same patients have been reexamined taking into account not only the change in symptoms, evaluated by the Hospital Anxiety and Depression scale (HADS) scores, but also the variation in caseness of depression and anxiety at different follow-up times. "Cases" of depressed and anxious patients were considered those who scored ≥8 at the HADS-D or HADS-A subscale, respectively, i.e. both subjects with possible (scores 8–10) and with definite (scores 11–21) mood alterations. During the follow-up, comparison between groups treated by CPAP and usual care demonstrated that both HADS-D and HADS-A scores decreased significantly with CPAP. When analysing separately patients with a score on each subscale <8 or ≥8, a significant improvement was observed only among the patients with a HADS-D score ≥8. Reduction in cases with depression was significant since the first assessment, performed at six months, and was sustained until forty-eight months. Instead, the decrease in cases with anxiety was significant with CPAP at six months but not at later assessments. The lower response of anxiety could be due to mild symptoms and to low prevalence of anxiety cases at baseline, but the similar changes in symptoms in the subgroups of less and more anxious subjects, and the similar reduction in cases of anxiety in the CPAP and usual care groups suggests a real poor efficacy of OSA treatment. Results did not differ between patients adherent and not adherent to CPAP treatment. A meta-analysis of RCTs on CPAP effects on depression and anxiety symptoms was juxtaposed to the SAVE data, and confirmed a significant benefit of CPAP on depression but not on anxiety. However, no significant effect of CPAP on depression symptoms could be demonstrated considering only studies where the control subjects had been randomised to sham CPAP.

Some results of this study deserve a special attention. A decrease in depression with CPAP treatment was demonstrated even independently of improvement in sleepiness, which suggests that mechanisms by which OSA may cause depression cannot be entirely ascribed to excessive daytime somnolence. Responses of depression and anxiety to OSA treatment were not the same, which had not emerged so clearly in other studies. Importantly, the authors demonstrate that not all improvements in symptoms of mood alterations correspond to clinically significant benefits. This inconsistency emerges from the analyses of changes in anxiety: whereas the change in symptoms, evaluated on HADS-A score as a continuous variable, was larger in the CPAP group, the decrease in the number of cases of anxious patients, evaluated on HADS-A scores as categories of anxious and non-anxious cases, did not significantly differ between groups.

Some questions remain unanswered. The study did not address the influence of OSA severity, in terms of apnea/hypopnea index, hypoxemia, or sleep disruption, on the response to treatment. Generalisability of the results to the whole OSA population is uncertain, as only patients with cardiovascular disease were studied. Although the cut-off threshold of 4 h/night used to separate patients adherent and not adherent to treatment is the most commonly used, it may not be the most

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appropriate for assessment of mood changes. Finally, lack of a difference between CPAP and sham CPAP effects, already pointed out in a previous meta-analysis [8], opposed to the significant difference between CPAP and either usual care or oral placebo, is puzzling and difficult to interpret.

With the large sample of patients, the long follow-up duration and the RCT design, this study may be considered one of the most important in its field. It supports a role of OSA as a possible determinant or aggravating factor of depression. Its findings should encourage to pursue improvement of depressed mood in OSA patients through therapy with CPAP. New studies could help to recognise which OSA patients with depression are more likely to improve their mood after OSA treatment. Furthermore, studies on samples of patients including more anxious subjects would be useful to confirm the lack of efficacy of CPAP treatment on anxiety.

Author Contribution

Oreste Marrone wrote this commentary.

Declaration of Competing Interest

The author has nothing to disclose.

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