CNS Drugs (2026) 40:597–600
https://doi.org/10.1007/s40263-025-01253-w

RESEARCH LETTER

Pitolisant Improves Depressive Symptoms in CPAP-Treated Patients with Obstructive Sleep Apnea and Severe Residual Sleepiness: First 12-Month Clinical Experience

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Received: 3 August 2025 / Accepted: 27 November 2025 / Published online: 16 December 2025

Obstructive sleep apnea (OSA) is a chronic condition affecting almost one billion people worldwide associated with relevant morbidity and mortality. Continuous positive airway pressure (CPAP) is a highly effective treatment, improving symptoms and rapidly resolving daytime sleepiness, in most patients. However, because of mechanisms largely unknown, residual excessive daytime sleepiness (rEDS) persists in a limited number of patients adequately treated with CPAP [1]. In these patients, rEDS compromises safety, work performance, and the overall quality of life (QoL). Depressive symptoms and poor quality of sleep are also common factors further degrading daily functioning. Clinically, rEDS is defined as an Epworth Sleepiness Scale (ESS) score > 10. For these patients, the ERS/European Sleep Research Society guidelines recommend evaluating pharmacotherapy to promote wakefulness only after confirmation of CPAP adherence and a residual apnea/hypopnea index < 5/h [2]. In recent years, wake-promoting agents have been studied for patients with OSA and rEDS; however, although four drugs are available, only solriamfetol and pitolisant have been approved by the European Medicines Agency [3]. While solriamfetol may increase blood pressure, pitolisant has a better safety profile as it is associated with a neutral hemodynamic profile [3]. In a network meta-analysis comparing efficacy, safety, and benefit/risk of alerting agents for rEDS in OSA, pitolisant, solriamfetol, and modafinil had comparable efficacy for maintaining wakefulness. However, pitolisant had a better safety profile and benefit-risk ratio compared with solriamfetol and modafinil [4].

Pitolisant is a selective H_3-receptor inverse agonist that reduced rEDS over a period of 12 weeks as shown by two randomized trials (HAROSA-I and II) in either CPAP-treated or untreated patients with OSA [5, 6]. In an extension study, the drug retained its wake-promoting efficacy up to 12 months [7]. Currently, only these registration studies are available in the literature for pitolisant in adults with OSA and no real-world data have been published to our knowledge after its implementation in clinical practice in Europe. After pitolisant became available for patients with OSA in Italy and after our OSA Unit was entitled to prescribe it, we designed a pilot prospective study, in order to evaluate over the long term, the effect of the treatment on parameters of QoL including depression symptoms, sleep quality, and fatigue. This was explicitly designed as a pilot study, with no a priori sample-size calculation; its goal was to obtain a preliminary estimate of treatment magnitude and variability. The study was approved by the local ethics committee and signed consent was obtained for all participants.

We enrolled adults with severe OSA (diagnosed with full polysomnography) on stable CPAP ≥ 3 months (usage > 6 h/night; residual apnea/hypopnea index < 5/h; mask leaks < 25 L/min), ESS score > 10 who tolerated a full dose after titration. Exclusion criteria were narcolepsy, restless-legs syndrome or periodic leg movements, medical conditions and drugs known to cause EDS. Patients with neurological and psychiatric disorders on pharmacological treatment were excluded. Although pitolisant is not contraindicated in patients with severe depression, "caution" is recommended when treating these patients because of the risk of suicide. In our study, two patients had severe depression, scoring >19 at PHQ-9. They were first referred to a psychiatrist to establish whether pharmacological treatment for depression was a priority. In both cases, it was advised to initiate

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pitolisant before considering antidepressant drugs, and to check if symptoms improved. For patients who scored 15–19 (moderately severe symptoms), pitolisant was initiated after alerting the patient to the need for a psychiatric consultation if improvement of symptoms did not occur after treatment. Dose titration followed the scheme: 4.5 mg (week 1), 9 mg (week 2), and 18 mg from week 4. We administered the following self-evaluation questionnaires at baseline and after 1, 3, 6, and 12 months: ESS, Patient Health Questionnaire-9 (PHQ-9) evaluating symptoms of depression, Pittsburgh Sleep Quality Index (PSQI), and Pichot Fatigue evaluating perceived fatigue. Clinical parameters were also assessed at each visit. We compared each score at baseline versus the 12th month using paired t tests and calculated the effect size with Cohen *d*.

A total of ten patients with severe OSA completed the study (Table 1). According to the basal mean ESS score (18.6 ± 2.5), these patients had severe rEDS. The ESS score gradually improved in all patients and after 12 months from treatment initiation fell by a mean of 10.8 points, with a very large effect size ($d = 2.84$) (Table 2). The mean PHQ-9 score was 15.1 ± 5.1 at baseline (range 5–21), indicating moderately severe depressive symptoms, and decreased by 6.7 points after 12 months shifting the mean cohort score to mild symptoms ($d = 1.33$). A reduction in sleepiness occurred early in most patients, with a mean drop of 6 points in the ESS after 3 months, although this change did not reach statistical significance. After 6 months, there was a concomitant significant reduction in both scores that reached a minimum value on the 12th month (Table 2). The PSQI and Pichot Fatigue scores showed a numeric reduction over time without reaching statistical significance. None of the patients completing the study complained of any side effect.

Table 1 Demographic and clinical data of the study group

	Patients, $n = 10$
Male sex, %	70
Age, years	59.9 ± 9.3
BMI, kg/m^2	31.2 ± 4.5
History of cardiovascular disease, *n*	1
History of metabolic disease, *n*	3
AHI basal	38.4 ± 12.1
AHI during CPAP	3.2 ± 1.7
Duration of CPAP treatment, years	3.6 ± 4.2

Data are presented as mean ± standard deviation unless otherwise stated

AHI apnea-hypopnea index, *BMI* body mass index, *CPAP* continuous positive airway pressure

This study provides the first real-world evidence on patient-reported outcomes related to treatment with pitolisant in OSA. It is noteworthy that our patients had more severe sleepiness compared with those included in the HAROSA I and II trials (ESS 18.7 vs 14.9 and 15.7, respectively). After a 12-month treatment, we achieved a mean ESS score (7.8) similar to the score shown in the pooled cohorts from HAROSA 1 and II trials after 1 year of pitolisant treatment [7]. Thus, pitolisant produced a more marked improvement in sleepiness in our small cohort. In a real-world study, pitolisant confirmed a wakefulness gain (ESS score − 10.8) far above the minimal clinically important difference (≥ 2–3) indicating that severely sleepy patients derive an outsized benefit [5]. As this is a first experience with pitolisant in OSA, focusing on its safety profile is an essential aspect. In the HAROSA I trial, treatment-related adverse effects were not significantly different in the study group and in the placebo group, consisting mainly of headache, insomnia, and diarrhea [5, 6]. Our patients experienced none of these symptoms throughout the treatment period, but of course this may be because of the small sample size. We also encouraged patients to monitor regularly their blood pressure, but no problem occurred.

The novel finding of this study is the effect of pitolisant on depressive symptoms evaluated by the PHQ-9 questionnaire that were not previously addressed in HAROSA I or II. Although depressive mood is common in patients with OSA, it generally improves during CPAP treatment [8].

Table 2 Changes in scores of self-reported questionnaires

	Baseline	6th month	12th month	Δ Value	*p* Holm[a]	Cohen *d*[b]
ESS	18.6 ± 2.5	10.11 ± 4.8	7.8 ± 4.7	− 10.7 ± 3.9*	< 0.001	2.84
PHQ-9	15.1 ± 5.1	10.78 ± 3.8	8.3 ± 4.1	− 6.7 ± 4.1*	0.008	1.33
PSQI	11.0 ± 3.4	10.78 ± 4.4	8.8 ± 3.6	− 2.1 ± 4.3	0.38	0.61
Pichot Fatigue	17.6 ± 9.8	14.13 ± 5.5	13.7 ± 5.4	−3.8 ± 7.4	0.58	0.40

Data are presented as mean ± standard deviation unless otherwise stated

ESS Epworth Sleepiness Scale, normal range 0–9, *PHQ-9* Patient Health Questionnaire-9, normal range 0–4, *Pichot Fatigue* Pichot Fatigue Scale normal range 9–21, *PSQI* Pittsburgh Sleep Quality Index, normal range 0–4, *Δ Value* baseline to 12th month

[a]Two-tailed paired *t* tests; Holm–Bonferroni adjustment for the four outcomes

[b]Effect size calculated with baseline standard deviation (pre-treatment). The asterisk indicates that data are statistically significant

In this study, we found a PHQ-9 of 15.1 (normal values < 5), confirming the observation that rEDS is associated with high depression scale scores [8]. We have previously reported on a population of CPAP-treated not sleepy patients from our OSA Unit, a mean PHQ-9 score of 8.3, indicating only mild symptoms [9]. Interestingly, after 1 year of treatment with pitolisant also in these patients with rEDS, the score was 8.3, thus comparable to those patients with no rEDS. Indeed, the large reduction in the PHQ-9 score that we observed supports the link between restored alertness and mood change, reinforcing the potential of pitolisant to enhance multiple QoL domains and not vigilance alone. Noteworthy, an improvement occurred also in patients with severe depression who were otherwise candidates for treatment with antidepressant drugs.

Sleep quality is another important determinant of QoL that was not explicitly addressed by the HAROSA I trial, although in the Leeds questionnaire the item "quality of sleep" was present and improved after 6, but not 12 months [5, 7]. We have previously shown that sleep quality in patients with OSA, although using CPAP, still remains suboptimal (mean PSQI score 6.4, normal value < 5). In this study, a mean PSQI score of 11 reveals an extremely poor sleep quality that remained unchanged after 1 year of treatment. Indeed, we cannot exclude that this finding could be due to the small sample size; however, it is possible that the disturbed sleep trait may persist in these patients without worsening. Noteworthy, although in a previous report modafinil significantly improved the sleep pattern and PSQI score in OSA on CPAP, in a recent national real-world study on 83 patients treated with solriamfetol, 91% of them reported no change in night-time sleep quality [3, 10].

In conclusion, preliminary data from this study suggest that in addition to CPAP treatment, pitolisant has great potential to improve important determinants of QoL such as depressive symptoms that are common and severe in patients with rEDS, while some other features, including the quality of sleep, remain uncertain. In addition, in the real world, at a dosage that is much lower than that used for narcolepsy, pitolisant was able to improve extremely severe rEDS in OSA, normalizing the ESS score. We believe that these data provide a solid base for designing further powered comparative studies.

Funding Open access funding provided by Università degli Studi di Catania within the CRUI-CARE Agreement. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of interest Domenico Caratozzolo, Giuseppe Muscato, Pierpaolo Rizzo, Cristina Gangemi, Adriana Scionti, Salvo Mancuso, Carlo Vancheri, and Lucia Spicuzza have have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, with the exception that this study was retrospectively registered. The ethics approval number is 212-21-12-2023. This study was retrospectively registered at DRKS-Deutsches Register Klinischer Studien (German Clinical Trials Register) number DRKS00038339.

Consent to participate Informed signed consent to participate in the study was obtained for each participant.

Consent for publication Consent to publish data was obtained for each participant.

Availability of data and material Data and details on each patient included in the study will be provided upon request.

Code availability Not applicable.

Author contributions DC and LS designed the study. DC, GM, SM, PR, and AS collected the data. DC, LS and GM analyzed the data. DC drafted the manuscript. CV and LS revised it critically. All authors were involved in revising the manuscript. All authors have read and approved the final submitted manuscript and agree to be accountable for the work.

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