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Residual Sleepiness Despite Effective CPAP Therapy: A Case Report

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Abstract Residual excessive daytime sleepiness may persist despite effective treatment of obstructive sleep apnea with continuous positive airway pressure. We report a woman first evaluated at age 73 with moderate obstructive sleep apnea who continued to experience persistent daytime sleepiness and frequent naps despite excellent treatment adherence. Serial device downloads demonstrated average nightly use of nearly nine hours and residual apnea-hypopnea index values of 0.9 and 0.5 events/hour. Modafinil was discontinued because of neuropsychiatric adverse effects, with suicidal ideation documented during treatment, and solriamfetol 75 mg was discontinued because of gastrointestinal upset and worsening gastroesophageal reflux. An individualized off-label trial of bupropion 75 mg was subsequently attempted but was discontinued after severe migraine, gastrointestinal upset, anorexia, racing thoughts, marked activation, and significant insomnia occurred on two treatment attempts. Evaluation for a central disorder of hypersomnolence was discussed but not completed. This case highlights the challenges of managing residual sleepiness despite objectively effective positive airway pressure therapy when multiple pharmacologic options are limited by poor tolerability.

Keywords: *obstructive sleep apnea, residual excessive daytime sleepiness, continuous positive airway pressure, solriamfetol, modafinil, bupropion, medication intolerance*

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1. Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder in which excessive daytime sleepiness (EDS) can substantially impair daytime functioning. Although continuous positive airway pressure (CPAP) effectively controls obstructive respiratory events and improves sleepiness in many patients, a subset continues to experience clinically meaningful EDS despite optimized treatment [1,2]. Persistent sleepiness should therefore prompt confirmation of treatment efficacy and evaluation for other contributing factors rather than being attributed automatically to inadequately treated OSA.

Evaluation of residual EDS should include confirmation of adequate PAP adherence and respiratory-event control, assessment of sleep duration and sleep quality, and consideration of medical, psychiatric, circadian, medication-related, and other sleep-related contributors [3]. When clinically indicated, central disorders of hypersomnolence should also remain in the differential diagnosis. Pharmacologic therapy may be considered when clinically significant sleepiness persists after potentially reversible contributors and inadequate OSA treatment have been addressed.

Wake-promoting therapy may be limited by adverse effects and individual tolerability. Solriamfetol has demonstrated efficacy for residual EDS associated with OSA and acts through inhibition of dopamine and norepinephrine reuptake [4,5]. Bupropion also influences dopaminergic and noradrenergic neurotransmission but is pharmacologically distinct and is not an established treatment for residual EDS associated with OSA [6]. This case illustrates the challenges of managing persistent residual sleepiness in an older patient with objectively controlled OSA when established wake-promoting therapies are poorly tolerated and individualized treatment strategies are required.

2. Case Presentation

A 73-year-old woman with obesity, gastroesophageal reflux disease, asthma, arthritis, chronic back pain, headaches, and a history of prior Epstein-Barr virus (EBV) infection was evaluated in sleep medicine for obstructive sleep apnea (OSA). A prior diagnostic polysomnogram demonstrated moderate OSA, with an apnea-hypopnea index (AHI) of 19 events/hour and a minimum oxygen saturation of 74%. Respiratory events were more pronounced during rapid eye movement (REM) sleep and in the supine position. A subsequent positive airway pressure titration demonstrated effective control of

respiratory events with continuous positive airway pressure (CPAP) at 8 cm H2O, which was prescribed for ongoing therapy.

At the initial sleep medicine evaluation, she reported consistent CPAP use with some improvement in overall sleep quality and resolution of previously noted snoring and witnessed apneas. Despite these benefits, she continued to experience excessive daytime sleepiness and fatigue. Her typical sleep schedule was from approximately 11:00 PM to midnight until 9:00 to 10:00 AM, with a sleep latency of approximately 15 minutes and two to four nocturnal awakenings without difficulty returning to sleep. She reported napping four to five days per week for 90 to 120 minutes and had an Epworth Sleepiness Scale (ESS) score of 11/24 [7]. She denied cataplexy, sleep paralysis, hypnagogic or hypnopompic hallucinations, parasomnias, sleep-related movement symptoms, and insomnia.

At subsequent follow-up, she continued to report persistent daytime sleepiness and fatigue despite ongoing CPAP therapy. Objective device data demonstrated excellent adherence, with an average nightly use of 8 hours 50 minutes, use for at least four hours on 100% of recorded nights, a residual AHI of 0.9 events/hour, and a 95th percentile leak of 13.4 L/min while using CPAP at 8 cm H2O. Modafinil 100 mg daily had been discontinued because of neuropsychiatric adverse effects, with suicidal ideation documented during treatment. Despite objectively effective control of sleep-disordered breathing during the documented PAP interval, her excessive daytime sleepiness persisted.

Over subsequent follow-up, she continued to report daytime sleepiness and fatigue despite ongoing subjective benefit from CPAP, including somewhat more refreshing sleep and reduced sleep fragmentation. At age 76, a new back injury required her to sleep upright and was associated with sleep-onset insomnia, introducing an additional potential contributor to impaired sleep quality. However, her excessive daytime sleepiness had been documented for several years before the injury. PAP download data during this period continued to demonstrate excellent adherence and respiratory-event control, with an average nightly use of 8 hours 57 minutes, use for at least four hours on 100% of recorded nights, a residual AHI of 0.5 events/hour, and a 95th percentile leak of 14.5 L/min on CPAP at 8 cm H2O. Despite these findings, she continued to report unrefreshing sleep, daytime fatigue, and persistent sleepiness.

At a later follow-up, her ESS score was 9/24, and residual daytime sleepiness persisted despite continued PAP use. Given her prior intolerance to modafinil, a trial of solriamfetol 75 mg daily was initiated. She subsequently discontinued solriamfetol because of gastrointestinal upset and worsening gastroesophageal reflux symptoms. At the next evaluation, her ESS score was 11/24. Because excessive daytime sleepiness persisted despite objectively well-controlled OSA, further evaluation with a multiple sleep latency test for a possible central disorder of hypersomnolence was discussed. Rather than proceeding immediately with additional diagnostic testing, she elected to pursue another pharmacologic trial and was started on bupropion 75 mg daily.

At an interim telephone follow-up, she had taken only two doses of bupropion 75 mg and reported no adverse effects; however, the limited exposure precluded assessment of clinical efficacy. With continued treatment, she subsequently developed severe migraine, gastrointestinal upset, anorexia, racing thoughts, marked activation, and significant insomnia, prompting discontinuation. A second trial of bupropion produced a similar adverse-effect pattern and was again discontinued. The reproducibility of these symptoms across two treatment attempts was consistent with significant individual intolerance, although the clinical course did not establish a specific pharmacologic mechanism.

At the most recent follow-up, she had been off wake-promoting medications for approximately one week and continued to require daily naps because of persistent daytime sleepiness. Further treatment with modafinil and solriamfetol was deferred because of prior intolerance. Morning L-tyrosine 500 mg was planned, although no treatment outcome was available. Prior EBV serologic testing was consistent with past infection and did not suggest an active infectious process.

Table 1. Longitudinal Clinical Course and Management of Residual Excessive Daytime Sleepiness

Clinical Stage	OSA and PAP Status	ESS	Intervention or Diagnostic Consideration	Outcome
Initial evaluation, age 73	Moderate OSA; diagnostic AHI 19 events/hour, minimum SpO2 74%; CPAP 8 cm H2O prescribed after effective titration	11/24	Persistent daytime sleepiness evaluated despite PAP use	Frequent prolonged naps and residual sleepiness persisted
Subsequent follow-up	Average PAP use 8 h 50 min/night; 100% of nights >=4 h; residual AHI 0.9 events/hour	Not recorded	Modafinil 100 mg daily	Discontinued because of neuropsychiatric adverse effects, with suicidal ideation documented during treatment
Later follow-up, age 76	Average PAP use 8 h 57 min/night; 100% of nights >=4 h; residual AHI 0.5 events/hour	Not recorded	Continued CPAP; later back injury associated with sleep-onset insomnia	Residual daytime sleepiness persisted despite objectively effective PAP therapy
Later pharmacologic management	OSA remained well controlled on PAP	9/24, later 11/24	Solriamfetol 75 mg daily; MSLT discussed for possible central hypersomnolence disorder	Solriamfetol discontinued because of gastrointestinal upset and worsening reflux; MSLT was not completed
Subsequent treatment	Continued PAP therapy	Not recorded	Individualized off-label bupropion 75 mg trial and rechallenge	Severe migraine, gastrointestinal upset, anorexia, racing thoughts, marked activation, and significant insomnia on two treatment attempts; bupropion discontinued
Most recent follow-up	Continued treatment of OSA with CPAP	Not recorded	Off wake-promoting medication	Persistent daytime sleepiness with continued daily naps

3. Discussion

Residual excessive daytime sleepiness may persist in some patients with obstructive sleep apnea despite effective treatment of sleep-disordered breathing [1,2]. In this patient, persistent sleepiness was documented despite excellent CPAP adherence, nearly nine hours of nightly use, and residual AHI values of 0.9 and 0.5 events/hour on separate device downloads. These findings make inadequate PAP use or substantial residual respiratory events unlikely explanations for her symptoms and support the distinction between effectively treated OSA and persistent residual EDS [3]. Her symptoms also persisted longitudinally, rather than occurring only during a transient period of poor sleep or medical illness.

Evaluation of residual EDS should include assessment of sleep opportunity, sleep quality, medications, medical and psychiatric comorbidities, circadian factors, and other sleep disorders [1,3]. This patient initially reported a relatively generous sleep opportunity, frequent prolonged naps, and no difficulty initiating or maintaining sleep. She denied cataplexy, sleep paralysis, and hypnagogic or hypnopompic hallucinations. A later back injury caused sleep-onset insomnia and required upright sleeping, but her excessive daytime sleepiness had been documented for several years before this event. Because symptoms persisted despite well-controlled OSA, a multiple sleep latency test was discussed to evaluate for a possible central disorder of hypersomnolence. Testing was not completed; therefore, narcolepsy, idiopathic hypersomnia, or another central hypersomnolence disorder could neither be confirmed nor excluded based on the available data.

Wake-promoting medications may be considered when clinically significant sleepiness persists despite adequately treated OSA, although adverse effects and individual tolerability may limit their use [8]. Modafinil was discontinued because of neuropsychiatric adverse effects, with suicidal ideation documented during treatment. Solriamfetol 75 mg daily was subsequently discontinued because of gastrointestinal upset and worsening gastroesophageal reflux symptoms. Solriamfetol inhibits dopamine and norepinephrine reuptake and has demonstrated efficacy for EDS associated with OSA [4,5]. In the TONES 3 trial, adverse effects included headache, nausea, decreased appetite, and anxiety [4]. In this patient, intolerance to both modafinil and solriamfetol substantially narrowed established pharmacologic options.

Bupropion was subsequently considered as an individualized off-label treatment attempt. Although bupropion also influences dopaminergic and noradrenergic neurotransmission through reuptake inhibition, it is pharmacologically distinct from solriamfetol and is not an established treatment for residual EDS associated with OSA [5,6]. After minimal initial exposure without adverse effects, continued treatment was associated with severe migraine, gastrointestinal upset, anorexia, racing thoughts, marked activation, and significant insomnia. A second treatment attempt produced a similar adverse-effect pattern and again required discontinuation. Headache, nausea, agitation, and insomnia are recognized adverse effects of bupropion [6,9]. Recurrence of a similar symptom complex after re-exposure supports significant individual intolerance but does not establish a specific pharmacologic mechanism or prove causality for each symptom. This experience illustrates that partial overlap in catecholaminergic pharmacology does not necessarily predict equivalent clinical response or tolerability.

Several limitations should be considered. Objective daytime sleepiness testing was not completed, ESS scores varied during follow-up, and the later back injury introduced an additional sleep-related confounder. Medical comorbidities could also have contributed to fatigue. Prior EBV serology was consistent with past infection and did not establish an infectious cause of the persistent sleepiness. Bupropion was an individualized off-label treatment attempt rather than an established therapy for residual EDS, and no efficacy assessment of the subsequently planned L-tyrosine trial was available. As a single case, the observed medication responses cannot establish pharmacologic causality or be generalized to other patients. Nevertheless, this case demonstrates that residual daytime sleepiness may remain clinically important despite objectively effective CPAP therapy and that management can become challenging when established wake-promoting treatments are poorly tolerated. Careful reassessment of contributing factors and individualized treatment selection remain important in these patients.

4. Conclusion

Residual excessive daytime sleepiness may persist despite objectively effective CPAP therapy and requires evaluation for alternative or contributing causes. Pharmacologic management can be limited by substantial individual differences in tolerability, even among agents with overlapping catecholaminergic mechanisms. This case highlights the importance of continued reassessment and individualized treatment when residual sleepiness persists and conventional wake-promoting therapies are poorly tolerated.

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Statement of Competing Interests

The author has no competing interests.

Patient Consent for Publication

Verbal consent was obtained from the patient for publication of deidentified clinical information in a medical journal case report.

List of Abbreviations

AHI: apnea-hypopnea index; CPAP: continuous positive airway pressure; EBV: Epstein-Barr virus; EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; OSA: obstructive sleep apnea; PAP: positive airway pressure; REM: rapid eye movement.

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