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Editorial

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Comparative outcomes in obstructive sleep apnea therapy: mean disease alleviation as a more appropriate measure—it's about time

Olivier M. Vanderveken[1,2,*] and Frédéric Gagnadoux[3,4]

[1]Department of Otorhinolaryngology, Head and Neck Surgery, Antwerp University Hospital, Edegem, Belgium,
[2]Department of Otorhinolaryngology, Head and Neck Surgery, Translational Neurosciences, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium,
[3]Department of Respiratory and Sleep Medicine, Angers University Hospital, Angers, France and
[4]INSERM, CNRS, MITOVASC, Equipe CarME, SFR ICAT, University of Angers, Angers, France

*Corresponding author. Olivier M. Vanderveken, MD, PhD, Full Professor and Chair, ENT-HNS Department, Antwerp University Hospital, Drie Eikenstraat 655, 2650 Edegem, Belgium. Email: olivier.vanderveken@uantwerp.be.

In the literature on obstructive sleep apnea (OSA), focus has been for the most part on the effect or *efficacy* of the treatment and more specifically the *efficacy* defined as the apnea–hypopnea index (AHI) size reduction under treatment compared to the AHI at baseline. However, it has been shown that the benefit of OSA therapy on health outcomes is not well translated by the change in AHI, the universal clinical metric of OSA severity. By distilling OSA into this single metric, the AHI, other potentially impactful disease characteristics are disregarded [1]. It has been hypothesized that the overreliance on this single metric might be part of the explanation for the inconsistent findings and negative results of cardiovascular outcomes when treating OSA [1–4]. Recent data from population- and clinic-based cohorts have shown that phenotypic traits such as excessive daytime sleepiness or comorbid insomnia, and promising biomarkers of OSA such as specific hypoxic impacts or autonomic nervous system dysfunction might, better than AHI, predict adverse health outcomes, and treatment response in OSA [5–10]. On the other hand, by not taking into account adherence to the therapy versus sleep duration, it can appear that an OSA treatment is highly efficacious, potentially giving an important and significant decrease in AHI, for example during a titration night. Not infrequently, however, this will not be equal to the actual OSA alleviation in a daily routine for some of the patients with a specific OSA therapy. So, in any case, there is a need for a better assessment of the *efficacy* of OSA therapies.

The true clinical *effectiveness* of a therapy for OSA, however, will be given not only by the *efficacy* of this given treatment: the daily *adherence* to the therapy should also be considered [11]. *Adherence* in terms of overnight usage of a therapy can be relatively low with continuous positive airway pressure (CPAP) [2, 12, 13], with a recent French database analysis indicating up to half of the patients starting CPAP discontinuing this therapy within the first 3 years [13]. This low CPAP adherence needs to be taken into account when assessing treatment effectiveness while real-life clinical data clearly demonstrate a dose-response relationship between daily CPAP use and incident major adverse cardiovascular events in OSA patients [14].

The metric mean disease alleviation (MDA) refers to the principle of integrating both *efficacy* and *adherence* when reporting the true therapeutic effect and is given by the product of the *efficacy* and the *adherence* [11]. When MDA calculation is applied to comparative research in OSA, this approach enables a potential answer to equal *effectiveness* as compared to using only the effect size of the treatments [12, 15]. For instance, when a study that compared CPAP with custom-made mandibular advancement device (MAD) treatment showed that the 24-hour mean arterial pressure was not inferior on MAD treatment compared to CPAP, MDA values led to the assumption that the greater *efficacy* of CPAP was being offset by the inferior *adherence* to CPAP therapy relative to a higher overnight usage of MAD [12]. These findings support the increasing application of MDA calculation in OSA research.

In their landmark study published in this issue of the Journal *SLEEP* Every *and colleagues (SLEEP 2023 in press)* used MDA to compare treatment *effectiveness* between CPAP and multilevel upper airway surgery for OSA [16]. In their data analysis, surgical therapeutic *effectiveness* in terms of MDA remained superior to the *effectiveness* of CPAP in all unmatched and matched analyses [16]. The results of this large retrospective study suggest an at least comparable *effectiveness* of CPAP and multilevel surgery for OSA [16]. With 69 percent of CPAP usage during sleep, the mean CPAP adherence was relatively high in the reported study compared to other series [2, 12, 13, 16, 17]. This might be at least partly explained by the exclusion of patients who did not have objective use data or failed/refused CPAP. With 67 percent of average surgical treatment *efficacy*, expressed as percent reduction in AHI, the authors argue that the success in this multilevel surgery cohort was well above the commonly used surgical success definition

and that this supports their selection methods and multilevel surgery therapies used in this study [16, 18, 19].

The authors need to be congratulated for the graphics clearly indicating the discrepancy between the *effectiveness* and *efficacy* of the CPAP group representing the impact of adherence on CPAP *effectiveness* [16]. On the other hand, with 100 percent adherence in the surgical group, there cannot be a discrepancy between *effectiveness* and *efficacy* in surgery outcomes [16, 20]. The use of cardinality matching for covariate matching while accounting for a relatively sample size is another strength of the study.

The study is, however, not without limitations including its retrospective design and the fact that sleep duration was determined during the single-night baseline polysomnography (PSG). Most notably, the authors measured treatment efficacy in the CPAP group using CPAP-derived AHI rather than full-night PSG. This should be kept in mind as a significant limitation of the study. Although the use of CPAP adherence tracking system has been recommended for treatment follow-up in routine practice [21], CPAP-derived AHI is a different metric than AHI determined by PSG. Manufacturer definitions for apnea and hypopnea are not only different from those recommended for PSG scoring, but also different between manufacturers [22].

Comparing different treatment options for OSA is a challenge when measuring PSG parameters because of variable *adherence* to therapy, in particular referring to the relatively low overnight usage of CPAP. In line with previous reports, the present study *(SLEEP 2023 in press)* demonstrates the importance of *adherence* in OSA treatment outcomes, with comparable overall net clinical *effectiveness* in non-CPAP treatments such as multilevel surgery, hypoglossal nerve stimulation and MAD treatment versus CPAP groups [12, 15, 16]. The results support the hypothesis that surgery for OSA can be at least as effective as CPAP. Yet, this is another study that suggests it is time to move away from "one size fits all" and "CPAP first for all OSA patients". We do advocate the use of MDA with objective adherence measurement in future research projects that aim at comparing different OSA treatment options. Ideally, novel biomarkers of OSA severity [5–10] should also be implemented in these future trials.

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References

1. Won CHJ. When will we ditch the AHI? *J Clin Sleep Med*. 2020;**16**:1001–1003. doi: 10.5664/jcsm.8594
2. McEvoy RD, *et al.*; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;**375**:919–931. doi: 10.1056/NEJMoa1606599
3. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with non-sleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med*. 2016;**194**:613–620. doi: 10.1164/rccm.201601-0088oc
4. Sánchez-de-la-Torre M, *et al.*; Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med*. 2020;**8**:359–367. doi: 10.1016/S2213-2600(19)30271-1
5. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med*. 2019;**200**:493–506. doi: 10.1164/rccm.201808-1509OC
6. Labarca G, *et al.* Sleep apnea physiological burdens and cardiovascular morbidity and mortality. *Am J Respir Crit Care Med*. 2023. doi: 10.1164/rccm.202209-1808OC.
7. Azarbarzin A, *et al.* The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J*. 2019;**40**:1149–1157. doi: 10.1093/eurheartj/ehy624
8. Azarbarzin A, *et al.* Cardiovascular benefit of continuous positive airway pressure in adults with coronary artery disease and obstructive sleep apnea without excessive sleepiness. *Am J Respir Crit Care Med*. 2022;**206**:767–774. doi: 10.1164/rccm.202111-2608OC
9. Solelhac G, *et al.* Pulse wave amplitude drops index: a biomarker of cardiovascular risk in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2023;**207**:1620–1632. doi: 10.1164/rccm.202206-1223OC
10. Trzepizur W, *et al.* Sleep apnea-specific hypoxic burden, symptom subtypes, and risk of cardiovascular events and all-cause mortality. *Am J Respir Crit Care Med*. 2022;**205**:108–117. doi: 10.1164/rccm.202105-1274OC
11. Vanderveken OM, Dieltjens M, Wouters K, De Backer WA, Van de Heyning PH, Braem MJ. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. *Thorax*. 2013;**68**:91–96. doi: 10.1136/thoraxjnl-2012-201900
12. Phillips CL, *et al.* Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med*. 2013;**187**:879–887. doi: 10.1164/rccm.201212-2223OC
13. Pépin JL, Bailly S, Rinder P, Adler D, Szeftel D, Malhotra A, Cistulli PA, Benjafield A, Lavergne F, Josseran A, Tamisier R, Hornus P; On Behalf Of The medXcloud Group. CPAP therapy termination rates by osa phenotype: a french nationwide database analysis. *J Clin Med*. 2021;**10**:936. doi: 10.3390/jcm10050936
14. Gervès-Pinquié C, *et al.* Positive airway pressure adherence, mortality, and cardiovascular events in patients with sleep apnea. *Am J Respir Crit Care Med*. 2022;**206**:1393–1404. doi: 10.1164/rccm.202202-0366OC
15. Heiser C, Steffen A, Strollo PJ, Jr, Giaie-Miniet C, Vanderveken OM, Hofauer B. Hypoglossal nerve stimulation versus positive airway pressure therapy for obstructive sleep apnea. *Sleep Breath*. 2023;**27**:693–701. doi: 10.1007/s11325-022-02663-6
16. Every JD, Mackay SG, Sideris AW, Do TQ, Jones A, Weaver EM. Mean disease alleviation between surgery and CPAP in matched

adults with obstructive sleep apnea. *Sleep.* 2023. zsad176. doi:10.1093/sleep/zsad176
17. Kushida CA, *et al*. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Longterm Efficacy Study (APPLES). *Sleep.* 2012;**35**:1593–1602. doi: 10.5665/sleep.2226
18. MacKay SG, Lewis R, McEvoy D, Joosten S, Holt NR. Surgical management of obstructive sleep apnoea: a position statement of the Australasian Sleep Association. *Respirology.* 2020;**25**:1292–1308. doi: 10.1111/resp.13967
19. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep.* 1996;**19**:156–177. doi: 10.1093/sleep/19.2.156
20. Ravesloot MJ, de Vries N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. *Sleep.* 2011;**34**:105–110. doi: 10.1093/sleep/34.1.105
21. Schwab RJ, *et al.*; ATS Subcommittee on CPAP Adherence Tracking Systems. An official American Thoracic Society statement: continuous positive airway pressure adherence tracking systems. The optimal monitoring strategies and outcome measures in adults. *Am J Respir Crit Care Med.* 2013;**188**:613–620. doi:10.1164/rccm.201307-1282ST
22. Bertelli F, *et al*. Apnoea-hypopnoea indices determined via continuous positive airway pressure (AHI-CPAPflow) versus those determined by polysomnography (AHI-PSGgold): a protocol for a systematic review and meta-analysis. *BMJ Open.* 2021;**11**:e044499. doi:10.1136/bmjopen-2020-044499