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Review Article

Obstructive Sleep Apnea Endophenotypes

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Sleep Sci

Abstract

Obstructive sleep apnea (OSA) is a common disorder with major neurocognitive and cardiometabolic consequences. It is now recognized as a heterogeneous disease with multiple different underlying mechanisms (endotypes) as well as variable clinical expression of disease (phenotypes). The importance of this variability is emphasized since one variable in isolation typically explains only a fraction of the variance in OSA occurrence. This review provides an update of what is known regarding OSA heterogeneity. The importance of OSA endotypes is discussed in the context of how mechanism might affect disease management and/or design of subsequent randomized trials. Further research is recommended to provide further validation of OSA endophenotypes and how this information may influence clinical management in the future.

Keywords
- sleep
- lung
- hypoxemia
- arousal

Obstructive sleep apnea (OSA) is known to affect almost a billion people worldwide based on recent estimates.[1] Even using a strict definition of an apnea-hypopnea index (AHI) >15 events/hr, the estimates suggest that roughly half a billion people worldwide are afflicted. The HypnoLaus study from Switzerland showed that, in a community sample, 23% of women and 50% of women had an AHI >15 events per hour.[2] Although one may question the importance of disease identified in the community not coming to clinical fruition, the AHI predicted diabetes mellitus, hypertension, and depression. Thus, these patients cannot be ignored given the important observed associations.

Although OSA is now accepted to be highly prevalent, the disease is clearly heterogeneous.[3] There are multiple underlying mechanisms of OSA (endotypes) as well as variable clinical expression of the disease (phenotypes).[4] A new concept is emerging that the mechanism underlying OSA may be a determinant of clinical expression of disease.

Obstructive sleep apnea pathogenesis is thought to involve a complex interplay of anatomical predisposition, pharyngeal dilator muscle control, ventilatory control instability (elevated loop gain), and low arousal threshold.[5–9] People with OSA are anatomically predisposed to pharyngeal collapse based on biomechanical properties compared to matched controls.[10–13] The pharyngeal anatomy can be assessed using drug-induced sleep endoscopy, although its utility in this context has been controversial. Through compensatory mechanisms present during wakefulness, the upper airway muscles have increased activity allowing the maintenance of pharyngeal patency.[14] However, with the onset of sleep, there is a fall in dilator muscle activity yielding collapse in those who are anatomically predisposed. Elevated loop gain refers to instability in the ventilatory control system whereby oscillations in the output from the central pattern generator (CPG) can occur, such that activation of the upper airway muscles is low during periods of low output from the CPG.[15–20] A low arousal threshold refers to a propensity to wake up that can predispose to repetitive apnea.[21,22] Respiratory stimuli can accumulate during sleep, allowing activation of the pharyngeal dilator muscles; however, premature arousal leads to repetitive apnea if there is inadequate duration or magnitude of stimuli to activate the pharyngeal dilator muscles.[23,24] The upper airway dilator muscles are necessary and sufficient to stabilize breathing based on evidence of high activity occurring during spontaneous periods of stable breathing.[25,26] Some individuals have multiple underlying mechanisms adding to the complexity of OSA pathogenesis.[27,28]

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Obstructive sleep apnea endotypes are clearly important for a number of reasons. First, OSA endotype may guide therapy. For example, the subset of patients with anatomical compromise at the level of the velopharynx may be the subgroup who benefits from uvulopalatopharyngoplasty (UPPP).[29,30] Similarly, genioglossus advancement and hypoglossal nerve stimulation may be particularly helpful for patients with retroglossal anatomical compromise. Patients with instability in ventilatory control may benefit from agents such as oxygen or acetazolamide, which can lower loop gain and stability breathing.[31,32] Mandibular advancement devices appear to be particularly effective for OSA patients with moderate pharyngeal collapsibility and weaker pharyngeal dilator muscle compensation as well as lower loop gain and higher arousal threshold. Secondly, the risk factors for OSA may be explained by endotypes. For example, patients with neuromuscular disease or various myopathies are at risk of OSA, likely due to impairment in pharyngeal dilator muscle function. Third, the endotypes of OSA may predict clinical phenotypes. For example, OSA in older adults is thought to be related to pharyngeal mechanics while OSA in younger adults may be more a function of elevated loop gain.[33–36] Given that data strongly suggest that OSA in older adults has fewer consequences than OSA in matched younger individuals, a concept is emerging that the consequences underlying OSA in older adults may explain the minimal observed complications in these individuals.[37,38] Fourth, OSA endotypes may explain treatment responses. Individuals with elevated loop gain are at high risk of treatment emergent central apnea upon initiation of continuous positive airway pressure (CPAP).[39] Patients undergoing UPPP are at high risk of surgical failure if they have elevated loop gain given that surgical intervention has minimal direct impact on breathing control per se.[40,41] Obstructive sleep apnea endotypes could potentially be used to stratify surgical risk as underlying mechanisms may explain why some patients have robust surgical response whereas other patients have minimal response to surgery. Thus, OSA endotypes are important for various clinically important reasons (see ►**Fig. 1**).

With regards to OSA phenotypes, considerable heterogeneity has been reported. Ye et al.[42] reported various OSA clusters in which some OSA patients were asymptomatic, some had fragmented sleep, while others had excessive daytime sleepiness. Of note, the group with severe sleepiness appears to be at cardiovascular risk, whereas the other groups may be at lower risk for these complications.[43,44] The approach of conducting randomized trials of OSA to prevent cardiovascular disease has largely failed to show major benefits to apnea therapy, perhaps because fewer than half of OSA patients are at major cardiovascular risk.[45–47] Thus, the failure of the one-size-fits-all approach may be a result of underlying heterogeneity in OSA endophenotypes.

After considering the heterogeneity of OSA, multiple potential explanations exist for the equivocal results from clinical trials in showing hard outcome benefit:

1) Given that only a subset of OSA patients may be at cardiovascular risk, the failure of CPAP trials to show cardiovascular benefit may reflect a need to identify *a priori* high-risk patients or those most likely to benefit from intervention. Various approaches have been suggested, such as enrolling the most symptomatic patients, those with the greatest hypoxic burden or various biomarkers including microRNAs (miR-210), which may help to characterize high risk patients.[48–52]
2) Recent studies have shown that patients who adhere to PAP therapy show hard outcome benefits in individual patient meta-analyses.[52] These findings suggest that improved adherence may be required to demonstrate the cardiovascular benefits to CPAP. In addition, the large sample size available for this meta-analysis suggests the possibility that statistical power may have been an issue in some of the randomized trials. On the other hand, analyses based on adherence are subject to the healthy user effect, whereby PAP therapy may be a marker of a highly motivated patient with good health literacy rather than a direct effect of PAP per se.[53]
3) Some recent studies have shown potential deleterious effects of high levels of CPAP, including the release of angiopoietin 2, which is a marker seen in lung injury.[54,55] Whether CPAP is leading to low level lung injury over time is unproven, but the possibility that CPAP has risks as well as benefits may be one explanation for why longer-term studies have shown mixed results.

Future priorities for research in this context are multiple, but a few examples are offered here:

a) Increased validation regarding the various techniques to estimate endotypic traits will be required.[56] The gold standard physiological techniques to define arousal threshold and loop gain as well as upper airway muscle function are quite cumbersome and, thus, unlikable to be scalable or accessible to most clinicians.[57–59] A number of sources of variance are present with techniques to characterize OSA pathogenesis, including biological and methodological variability.[59,60] Given that OSA varies night to night and with body position as well as with sleep stage, one would not predict the underlying mechanisms to be static. However, further data regarding the reproducibility and validity of various signal processing techniques would help to address skepticism regarding these methods.[60,61]
b) Further work regarding the biomarkers of OSA may help to identify robust surrogate outcome measures for future clinical trials. The ideal biomarker would be: easily obtainable and have good sensitivity and specificity for disease; predictive of disease complications; responsive to therapy, and be involved in an important causal pathway.[62,63] Although no ideal biomarker exists, several candidates have been reported, which may require further study.[64] In theory, a trial could be designed to show improvements in a surrogate outcome measure if there was confidence that such changes would predict improvements in hard outcomes.

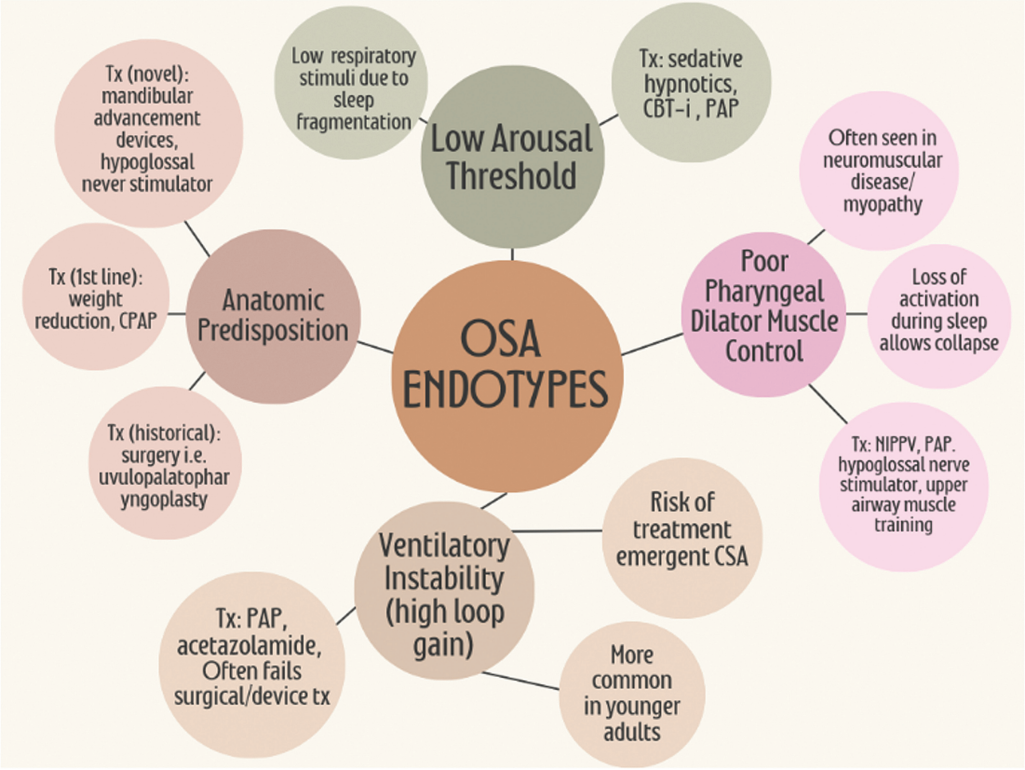

Fig. 1 A figure illustrating the various mechanisms underlying obstructive sleep apnea (OSA) as well as key clinical pearls regarding potential manipulation of each of these traits. There are complex interactions between the various traits that are not fully depicted in this figure.

Abbreviations: CBTI, cognitive behavioral therapy for insomnia; CSA, central sleep apnea; NIPPV, non-invasive positive pressure ventilation; OSA, obstructive sleep apnea; PAP, positive airway pressure.

c) The recent insights into OSA endophenotypic heterogeneity have led to novel approaches for interventional studies.[65] In theory, therapeutic interventions could be determined based on underlying mechanisms (e.g., oxygen or acetazolamide for patients with unstable ventilatory control or sedative/hypnotics for patients with low arousal threshold).[66] Given the robust benefits of CPAP for some patients, sophisticated trials could be designed, such as rescue strategies for CPAP failures. Comparative effectiveness studies could also be designed to allow identification of optimal therapy, which may differ for patients based on their personal preferences or underlying physiology.[67,68]

In summary, considerable progress has been made in understanding OSA heterogeneity. Such findings may already be clinically directive and could help to guide future research studies. Only by further efforts with basic, clinical, and translational research are new therapeutic approaches and strategies likely to emerge.

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Conflict of Interests
The authors have no conflict of interests to declare.

References
1 Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019;7(08): 687–698
2 Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3(04):310–318
3 Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014;383(9918):736–747
4 Malhotra A, Mesarwi O, Pepin JL, Owens RL. Endotypes and phenotypes in obstructive sleep apnea. Curr Opin Pulm Med 2020;26(06):609–614
5 Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. Am J Respir Crit Care Med 2003;168(06):645–658
6 Younes M. Pharyngeal anatomy and severity of obstructive apnea. Am J Respir Crit Care Med 2004;170(06):716
7 Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 2004;169(05):623–633
8 Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev 2010;90(01):47–112
9 Badr MS. Pathogenesis of obstructive sleep apnea. Prog Cardiovasc Dis 1999;41(05):323–330
10 Isono S, Feroah TR, Hajduk EA, Brant R, Whitelaw WA, Remmers JE. Interaction of cross-sectional area, driving pressure, and airflow of passive velopharynx. J Appl Physiol 1997;83(03):851–859

11 Isono S, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol 1997;82(04):1319–1326
12 Schwab RJ. Upper airway imaging. Clin Chest Med 1998;19(01): 33–54
13 Schwab RJ. Imaging for the snoring and sleep apnea patient. Dent Clin North Am 2001;45(04):759–796
14 Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). J Clin Invest 1992;89 (05):1571–1579
15 Khoo MC. Determinants of ventilatory instability and variability. Respir Physiol 2000;122(2-3):167–182
16 Khoo M. Theoretical models of periodic breathing. In: Bradley T, Floras J, eds. Sleep apnea implications in cardiovascular and cerebrovascular disease. 146. New York: Marcel Dekker; 2000: 355–384
17 Khoo MC. Using loop gain to assess ventilatory control in obstructive sleep apnea. Am J Respir Crit Care Med 2001;163(05): 1044–1045
18 Hlastala MP, Berger AJ. Chemical Control of Breathing. Physiology of Respiration. 2nd ed. New York: Oxford University Press;; 2001. p. 151, 5.
19 Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2001;163(05):1181–1190
20 Wellman A, Malhotra A, Jordan AS, Schory K, Gautam S, White DP. Chemical control stability in the elderly. J Physiol 2007;581(Pt 1):291–298
21 Berry RB, Gleeson K. Respiratory arousal from sleep: mechanisms and significance. Sleep 1997;20(08):654–675
22 Gleeson K, Zwillich CW, White DP. The influence of increasing ventilatory effort on arousal from sleep. Am Rev Respir Dis 1990; 142(02):295–300
23 Stanchina M, Malhotra A, Fogel RB, et al. Genioglossus muscle responsiveness to chemical and mechanical loading during NREM sleep. Am J Respir Crit Care Med 2002;165:945–949
24 Malhotra A, Deacon N, Powell F, Katz ES. Adaptive responses using obstructive sleep apnea as the paradigm. Physiology (Bethesda) 2014;29(03):153–155
25 Jordan AS, Wellman A, Heinzer RC, et al. Mechanisms used to restore ventilation after partial upper airway collapse during sleep in humans. Thorax 2007;62(10):861–867
26 Jordan AS, White DP, Lo YL, et al. Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. Sleep 2009;32(03):361–368
27 Edwards BA, Sands SA, Eckert DJ, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. J Physiol 2012;590(05):1199–1211
28 Edwards BA, Sands SA, Owens RL, et al. The Combination of Supplemental Oxygen and a Hypnotic Markedly Improves Obstructive Sleep Apnea in Patients with a Mild to Moderate Upper Airway Collapsibility. Sleep 2016;39(11):1973–1983
29 Kezirian EJ, Malhotra A, Goldberg AN, White DP. Changes in obstructive sleep apnea severity, biomarkers, and quality of life after multilevel surgery. Laryngoscope 2010;120(07):1481–1488
30 Kezirian EJ, Simmons M, Schwab RJ, et al. Making Sense of the Noise: Toward Rational Treatment for Obstructive Sleep Apnea. Am J Respir Crit Care Med 2020;202(11):1503–1508
31 Sands SA, Edwards BA, Terrill PI, et al. Identifying obstructive sleep apnoea patients responsive to supplemental oxygen therapy. Eur Respir J 2018;52(03):1800674
32 Edwards BA, Connolly JG, Campana LM, et al. Acetazolamide attenuates the ventilatory response to arousal in patients with obstructive sleep apnea. Sleep 2013;36(02):281–285
33 Edwards BA, O'Driscoll DM, Ali A, Jordan AS, Trinder J, Malhotra A. Aging and sleep: physiology and pathophysiology. Semin Respir Crit Care Med 2010;31(05):618–633
34 Edwards BA, Wellman A, Sands SA, et al. Obstructive sleep apnea in older adults is a distinctly different physiological phenotype. Sleep 2014;37(07):1227–1236
35 Kobayashi M, Namba K, Tsuiki S, Matsuo A, Sugiura T, Inoue Y. Clinical characteristics in two subgroups of obstructive sleep apnea syndrome in the elderly: comparison between cases with elderly and middle-age onset. Chest 2010;137(06):1310–1315
36 Ancoli-Israel S. Sleep problems in older adults: putting myths to bed. Geriatrics 1997;52(01):20–30
37 Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 2010;182(02):269–277
38 Lavie P, Herer P, Lavie L. Mortality risk factors in sleep apnoea: a matched case-control study. J Sleep Res 2007;16(01):128–134
39 Stanchina M, Robinson K, Corrao W, Donat W, Sands S, Malhotra A. Clinical Use of Loop Gain Measures to Determine Continuous Positive Airway Pressure Efficacy in Patients with Complex Sleep Apnea. A Pilot Study. Ann Am Thorac Soc 2015;12(09):1351–1357
40 Li Y, Ye J, Han D, et al. Physiology-Based Modeling May Predict Surgical Treatment Outcome for Obstructive Sleep Apnea. J Clin Sleep Med 2017;13(09):1029–1037
41 Li Y, Ye J, Han D, et al. The Effect of Upper Airway Surgery on Loop Gain in Obstructive Sleep Apnea. J Clin Sleep Med 2019;15(06): 907–913
42 Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. Eur Respir J 2014;44 (06):1600–1607
43 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 (04):493–506
44 Mazzotti DR, Lim DC, Sutherland K, et al. Opportunities for utilizing polysomnography signals to characterize obstructive sleep apnea subtypes and severity. Physiol Meas 2018;39(09):09TR01
45 McEvoy RD, Antic NA, Heeley E, et al; SAVE Investigators and Coordinators. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med 2016;375(10):919–931
46 Sánchez-de-la-Torre M, Khalyfa A, Sánchez-de-la-Torre A, et al; Spanish Sleep Network. Precision Medicine in Patients With Resistant Hypertension and Obstructive Sleep Apnea: Blood Pressure Response to Continuous Positive Airway Pressure Treatment. J Am Coll Cardiol 2015;66(09):1023–1032
47 Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, 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(04):359–367
48 Azarbarzin A, Sands SA, Taranto-Montemurro L, Redline S, Wellman A. Hypoxic burden captures sleep apnoea-specific nocturnal hypoxaemia. Eur Heart J 2019;40(35):2989–2990
49 Azarbarzin A, Sands SA, Taranto-Montemurro L, et al. The Sleep Apnea-Specific Hypoxic Burden Predicts Incident Heart Failure. Chest 2020;158(02):739–750
50 Azarbarzin A, Sands SA, White DP, Redline S, Wellman A. The hypoxic burden: a novel sleep apnoea severity metric and a predictor of cardiovascular mortality-Reply to 'The hypoxic burden: also known as the desaturation severity parameter'. Eur Heart J 2019;40(35):2994–2995
51 Shang F, Wang SC, Gongol B, et al. Obstructive Sleep Apnea-induced Endothelial Dysfunction is Mediated by miR-210. Am J Respir Crit Care Med 2022
52 Sánchez-de-la-Torre M, Gracia-Lavedan E, Benitez ID, et al. Adherence to CPAP Treatment and the Risk of Recurrent Cardiovascular Events: A Meta-Analysis. JAMA 2023;330(13):1255–1265
53 Platt AB, Kuna ST, Field SH, et al. Adherence to sleep apnea therapy and use of lipid-lowering drugs: a study of the healthy-user effect. Chest 2010;137(01):102–108

54 Karmpaliotis D, Kosmidou I, Ingenito EP, et al. Angiogenic growth factors in the pathophysiology of a murine model of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2002;283(03): L585–L595
55 Gottlieb DJ, Lederer DJ, Kim JS, et al. Effect of positive airway pressure therapy of obstructive sleep apnea on circulating Angiopoietin-2. Sleep Med 2022;96:119–121
56 Sands SA, Edwards BA, Terrill PI, et al. Phenotyping Pharyngeal Pathophysiology using Polysomnography in Patients with Obstructive Sleep Apnea. Am J Respir Crit Care Med 2018;197(09): 1187–1197
57 Edwards BA, Eckert DJ, McSharry DG, et al. Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2014;190(11):1293–1300
58 Orr JE, Sands SA, Edwards BA, et al. Measuring Loop Gain via Home Sleep Testing in Patients with Obstructive Sleep Apnea. Am J Respir Crit Care Med 2018;197(10):1353–1355
59 Tolbert TM, Schoenholz RL, Parekh A, et al. Night-to-night reliability and agreement of obstructive sleep apnea pathophysiologic mechanisms estimated with phenotyping using polysomnography in cognitively normal elderly participants. Sleep 2023;46(08):zsad058
60 Younes M, Schwab R. Con: can physiological risk factors for obstructive sleep apnea be determined by analysis of data obtained from routine polysomnography? Sleep 2023;46(05): zsac158
61 Sands SA, Edwards BA. Pro: can physiological risk factors for obstructive sleep apnea be determined by analysis of data obtained from routine polysomnography? Sleep 2023;46(05): zsac310
62 Montesi SB, Bajwa EK, Malhotra A. Biomarkers of sleep apnea. Chest 2012;142(01):239–245
63 Shih JL, Malhotra A. Could vitamins be helpful to patients with sleep apnea? Chest 2011;139(02):237–238
64 Malhotra A, Ayappa I, Ayas N, et al. Metrics of sleep apnea severity: beyond the apnea-hypopnea index. Sleep 2021;44 (07):zsab030. Doi: 10.1093/sleep/zsab030
65 Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implications. J Appl Physiol 2014;116(03):325–336
66 Eckert DJ, Owens RL, Kehlmann GB, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clin Sci (Lond) 2011;120(12):505–514
67 Patel SR, Althouse AD. Robust Methods Are Needed to Evaluate the Pharmacologic Treatment of Obstructive Sleep Apnea. Am J Respir Crit Care Med 2019;199(10):1294–1295
68 Carson SS, Goss CH, Patel SR, et al; American Thoracic Society Comparative Effectiveness Research Working Group. An official American Thoracic Society research statement: comparative effectiveness research in pulmonary, critical care, and sleep medicine. Am J Respir Crit Care Med 2013;188(10):1253–1261

