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Longitudinal Management and a Decision-Aid Tool in Treatment-Resistant Sleep Apnea

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Abstract

Purpose of Review We expect an increased pressure of treating residual sleepiness in parallel with the introduction of novel wakefulness-promoting drugs to the European market. Our purpose is to review the literature on longitudinal management of treatment-resistant obstructive sleep apnea (OSA) and on this background to propose a management plan for this patient group focusing on both reduction of cardiovascular risk and relief of symptoms.

Recent Findings Most OSA literature focuses on primary diagnostics and primary or secondary treatment options in unstratified clinical populations. In this review, we focus on longitudinal management of treatment-resistant OSA described in recent, key publications. Moreover, we identified future diagnostic trends that also may be of clinical importance in this patient group. Finally, based on this background, we propose a standardized approach to secondary diagnostics and treatment decisions in treatment-resistant OSA based on a novel decision-aid tool.

Summary Limited literature was found on the longitudinal aspects of OSA treatment. Based on this background, a standardized management plan for treatment-resistant OSA and a shared decision-aid tool is proposed. The management plan focuses on both stabilization of the upper airway and relief of symptoms.

Keywords Sleep apnea · Precision medicine · Shared decision-making · Positive airway pressure · Non-adherence

Introduction

Obstructive sleep apnea (OSA) is highly prevalent and associated with an increased risk of cardiovascular disease, daytime sleepiness, and nighttime awakenings [1, 2]. Today, the most effective primary treatment option is a combination of lifestyle changes and stabilization of the upper airway by positive airway pressure (PAP) [2]. However, at least one in four patients does not accept PAP [3, 4]. Moreover, residual sleepiness is frequent both in PAP users, non-adherent patients, and patients treated with non-PAP therapies [5, 6]. Dr. Rosenberg and co-workers have recently proposed a flow chart ending with pharmacotherapy in cases with excessive daytime sleepiness [6]. We anticipate that wakefulness-promoting drugs will be marketed as viable treatment options in unstratified patient populations with residual symptoms regardless of the stability of the upper airway. Long-term effects of therapy with wakefulness-promoting drugs alone or in combination with partial stabilization of the upper airway is unknown [7].

Recently, the United States (US) Agency for Healthcare Research and Quality published a report on diagnosis and treatment of obstructive sleep apnea in adults [8]. This comprehensive report addresses central key questions on primary diagnosis and treatment. However, drug therapy aiming solely to remove sleepiness was not included in the review. Moreover, there is sparse focus on the longitudinal management of treatment-resistant OSA in the report. Accordingly, the aim of this narrative review is to present a longitudinal

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perspective on the management of treatment-resistant OSA. Furthermore, on this background, we aim to propose a management plan for this patient group focusing on both reduction of cardiovascular risk and relief of symptoms.

A Longitudinal Perspective

The Balk report raises key questions related to the diagnosis of OSA, phased testing, preoperative screening, and screening in other populations [8]. In a longitudinal perspective, the patient is already diagnosed when seeking advice for treatment failure. The diagnostic strategies per se are therefore of less interest in this perspective. However, there are some important aspects of the diagnostic process that are also relevant for longitudinal management of treatment-resistant OSA:

1. The American Academy of Sleep Medicine (AASM) is working on a revision of the International Classification of Sleep Disorders, third edition (ICSD-3) [9] and there is an ongoing discussion regarding the use of a 3% or a 4% desaturation threshold for hypopnea classification in type III devices both in the AASM and in the European Respiratory Society (ERS) [10, 11].
2. In addition to diagnostic issues raised in the Balk report, we have identified "Beyond apnea hypopnea index (AHI)" initiatives both in Europe and in the USA [12, 13, 14]. Essential for this approach are large studies using artificial intelligence such as the "Sleep Revolution" project in Europe [15].
3. Longitudinal cohort studies with cardiovascular outcomes are needed to compare diagnostic performances of both electrophysiological and serum-based biomarkers [16].
4. Introduction of level II devices that can be used in a home setting for consecutive nights. This technology is still new, but companies such as Nox medical (Sleep Diagnostics - Sleep Monitoring Devices - Nox Medical), Onera Health (Onera (onerahealth.com), Bitbrain (Advanced neurotechnology | Bitbrain), and Cerebra (Cerebra - Putting the Sleep Back Into Sleep Medicine) are developing diagnostic solutions. Moreover, several companies are developing diagnostic medical devices with untraditional designs. Among these are Sleepiz (Explore our solutions | Sleepiz.com) and Vital things https://www.vitalthings.no/.
5. The longitudinal use of only 1–2 sensors, as in a level IV device, has the potential to provide diagnostic information of clinical utility not mentioned in the Balk report [17, 18].
6. Phenotyping: This approach has developed rapidly in the last ten years both based on small physiological experiments and cluster analysis of large data sets [19, 20, 21]. Large databases promise opportunities for future artificial intelligence (AI)–based research. In Europe, the European Sleep Apnea Database (ESADA) offers data collected with a primary clinical purpose. In the USA, the National Sleep Research Resource (NSRR) also offers research possibilities for AI-based approaches. Also, the Sleep Apnea Global Interdisciplinary Consortium (SAGIC) is a promising source for future academic research.

Beyond diagnostic approaches, the most vivid discussion related to treatment in the field of sleep medicine is related to daytime symptoms. Several studies have assessed the effect of PAP treatment in patients with asymptomatic OSA and established cardiovascular disease, and the results have been disappointing [22, 23, 24, 25]. It has therefore been argued that treatment should be personalized and based on a phenotypic approach emphasizing the role of daytime sleepiness and combination therapy [26, 27].

Another proposed model for treatment decisions in OSA is the "three-dimensional model" [28]. In 2018, based on this model, a European working group presented the Baveno classification. This classification goes beyond conventional measures of OSA severity, and the multicomponent grading system combines symptoms and impact on the cardiovascular and metabolic systems [28]. The model was evaluated in 2021. Dr. Randerath and coworkers conclude that the Baveno classification "allows a better stratification of the OSA population and may be a better guidance for therapeutic decisions in OSA" [29]. However, it has also been documented that OSA patients without symptoms and established cardiometabolic signs not treated with PAP evolve to a higher Baveno class with time [30].

Finally, not all OSA patients tolerate primary treatment with PAP. Non-PAP or secondary therapies for OSA have been claimed to be less effective than PAP [31]. However, the Balk report did not find significant differences in effectiveness between PAP and mandibular advancement devices (MADs) or PAP and surgical interventions [8]. In our experience from Europe, the most frequently used secondary treatment options are MADs or tonsillectomy with or without pharyngoplasty [32]. The indication for tonsillectomy is limited to patients with hypertrophy of the tonsils defined by the Friedman classification or similar [33]. Unfortunately, there is a high proportion of patients failing to experience relief of symptoms by these, and other non-PAP therapies when administered in unstratified populations [31]. Patients in this situation can be said to be treatment resistant and in need of an integrated or tertiary treatment decision [34].

Standardized Management of Treatment-Resistant OSA

We have identified relevant literature on primary diagnostics and treatment of OSA. Gaps in the literature were found regarding longitudinal management of treatment-resistant disease. In the following, we will propose a novel strategy based on the principles of shared decision-making (SDM).

The concept of SDM was proposed more than three decades ago and has been adopted in large parts of clinical medicine [35]. However SDM is in little use in sleep medicine [36]. In SDM, information from the clinician and the patient is regarded as different but of equal importance [37]. The concept of SDM can be learned in brief training sessions [38]. Moreover, a decision-aid tool has been developed for sleep apnea [39]. Unfortunately, also this tool has gained little popularity in the sleep medicine field. In the following, we propose to explore patient perspectives along the axes of the Baveno classification [28, 29].

The Baveno classification, introduced in 2018 by an ad hoc European work group meeting in the city of Baveno, considers an *x*-axis of symptoms such as sleepiness, hypersomnia, impaired vigilance, and insomnia. *y*-axis is designed to capture signs of end-organ impact or comorbidity [28]. We will in the following discuss each axis in relation to SDM.

The Symptom Axis

In treatment-resistant OSA, the initiatives reviewed above seek to narrow the population defined by revised diagnostic criteria [10, 11]. The consequences of such efforts in a longitudinal perspective will be that future patients will be fewer and have less comorbidities and more measurable obstructive events. However, we will emphasize that it has been known for decades that obstructive events only explain a minor part of symptoms in OSA [40]. Disorders such as anxiety, depression, or somatoform pain are tenfold more strongly related to daytime sleepiness than respiratory events in a general population perspective [41]. Our literature review also identified several strategies to identify measures "beyond the AHI" that are stronger related to symptoms than the AHI. However, the clinical utility of such novel measures cannot be evaluated before predictive properties have been evaluated in longitudinal cohort studies. Accordingly, clinicians exploring patient perspectives on the symptom axis should consider to explore aspects of emotional state and personality traits.

The Cardiovascular and Cognitive Health Axis

The concept of risk prediction modeling is a complex task for clinicians. Accordingly, we searched the medical literature for validated risk prediction tools. In the field of sleep medicine, there is a strong focus on electrophysiological biomarkers derived from polysomnography or polygraphy while serum-based biomarkers and general risk calculators are mostly neglected [16]. In the cardiovascular literature, we identified validated, standardized risk prediction tools such as the SCORE2 algorithm [42]. This tool calculates a percentage scale based on the use of serum-based measurements of total and high-density lipid (HDL) cholesterol and traditional risk factors such as age, sex, smoking status, and systolic blood pressure.

We also identified an updated American Heart Association presidential advisory on cardiovascular health [43]. The article presents a clear strategy for the identification of eight domains, including sleep. The life's essential 8 score includes a broader concept of sleep beyond the AHI and other electrophysiological biomarkers. This is an advantage when exploring patient perspectives such as sleep hygiene, circadian rhythm, and positional OSA. Moreover, the life's essential 8 is designed for SDM with a possibility on focusing on single health behaviors such as diet, physical activity, and nicotine exposure in addition to sleep.

Finally, cognitive decline is related to in particular oxygen variables in OSA, and perspectives on this non-cardiovascular outcome may also be explored on this axis [44, 45].

In summary, more than one risk calculator or heuristic may be used as a fundament for SDM on the cardiovascular and cognitive health axis. However, in line with the salutogenic model originally proposed by Aron Antonovsky, we find it highly intriguing to explore patient perspectives on cardiovascular and cognitive health rather than risk [46].

Premises for Precision Medicine

The identified literature on treatment also focused mostly on primary or secondary treatment options and adherence to such strategies [8, 31]. The studies we identified on tertiary treatment focused on surgery and pharmacological treatment respectively [6, 34]. Hence, in the following, we propose a clinical approach based on a modified Baveno classification (Fig. 1) and standardized paths for tertiary treatment decisions [36, 37].

The modified Baveno classification should be discussed with the patient within the framework of SDM. Regarding cardiovascular and cognitive health, the SCORE2 is currently the most validated risk prediction tool [42]. The SCORE2 estimates the risk of having a major adverse cardiovascular event (MACE) over 10 years in percent. A percentage scale can be explored with the patient as a visual analogue scale. Moreover, the SCORE2 is dependent on information regarding age, smoking status, systolic blood pressure, and total and HDL cholesterol, and a score can easily be obtained from web-based calculators. The acceptable 10-year risk of a MACE may differ from patient to

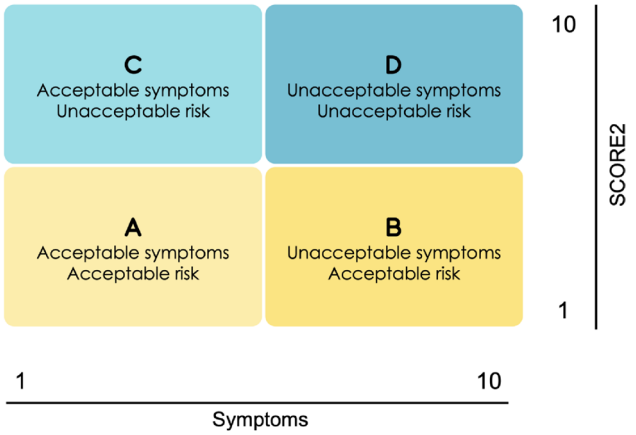

Fig. 1 Modified Baveno decision-aid tool for use in clinical practice: **A**–**D** are classified based on perceived symptoms and patient perspective of acceptable 10-year risk of cardiovascular events

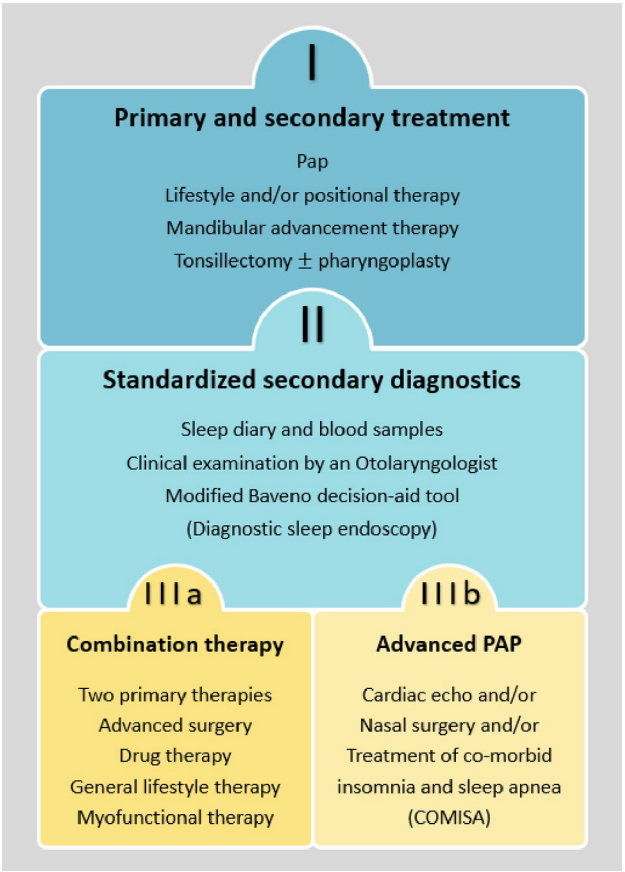

Fig. 2 Integrated model for standardized secondary diagnostics and tertiary treatment in moderate to severe sleep apnea, non-acceptable symptoms, and non-acceptable risk of major adverse cardiovascular event (MACE). COMISA, comorbid insomnia and sleep apnea

patient. When properly validated, the "life's essential 8 score" or other validated risk calculators may be used instead if preferred by individual clinicians.

On the *x*-axis of the modified Baveno decision-aid tool, we propose to replace the use of an Epworth Sleepiness Scale [47] with a visual analogue scale on symptoms in general. Symptoms in OSA are more than sleepiness, and the individual level of acceptance varies. Thus, our modified Baveno decision-aid tool introduces an opportunity for both the clinician and the patient to discuss acceptable risk and symptom load in accordance with the principles of SDM.

In addition to the minimum information needed for calculating SCORE2, a patient history and a blood sample, we recommend a more comprehensive and standardized secondary diagnostic approach before a tertiary treatment decision (Fig. 2).

First, we recommend the use of a consensus sleep diary [48, 49]. The sleep diary has the potential to identify patients with OSA that have comorbid insomnia (COMISA). COMISA has recently been identified as an independent predictor of mortality in OSA patients [50]. Moreover, a sleep diary may provide indirect information regarding patient self-efficacy [51]. If the patient cannot complete a sleep diary for two weeks, then advanced exercises or lifestyle programs are probably not suitable treatment decisions. Finally, a sleep diary also gives the OSA patient a "bird perspective" on related symptoms that may be useful in the discussion about daytime sleepiness as described above.

Secondly, we propose to perform an otorhinolaryngology examination and eventually a drug-induced sleep endoscopy (DISE). Recently published French guidelines present good guidance for when to consider DISE [52]. DISE is scored according to the pattern of collapsibility assessed by the velopharynx-oropharynx-tongue base and epiglottis (VOTE) classification [53]. The examination is resource-demanding but has been shown to be of great value when planning advanced surgical treatment such as hypoglossal nerve stimulation [54]. Moreover, the VOTE score does provide valuable information regarding the pattern of collapsibility that is crucial for surgical planning. Note that patients with severe tonsillar hypertrophy, based on clinical examination, are recommended tonsillectomy rather than DISE [52].

At last, our proposed modified Baveno decision-aid tool raises the possibility of discussing the patient's perspective on acceptance of cardiovascular and cognitive risk/health and symptoms. A recent qualitative paper identified lack of focus on the patient perspective as a limitation to shared decision-making in a sleep medicine setting [36]. Accordingly, the tool may provide a framework for the identification of patients willing to actively cope with OSA. Active coping strategies may include treatment with positional devices [55], myofunctional exercises [56], or actively modifying other health behaviors than sleep [43].

Tertiary treatment options after a standardized secondary investigation are seen in Fig. 2. We propose two

main pathways: In pathway IIIa, an otorhinolaryngologist should be consulted for combination treatment to discuss surgery, and an internal medicine specialist should be consulted if combinations with pharmacotherapy are considered. Also "two primary therapies" may be considered, such as the combination of PAP and MAD. The following procedures are classified as "Advanced surgery": Multi-level intrapharyngeal surgery [57], hypoglossal stimulation [58], and extrapharyngeal surgery [34, 59, 60]. For a review of the literature on drug therapy in OSA, we refer to Hedner and Zou or Rubino, Greenway, and co-workers [7, 61]. Finally, patients with self-efficacy to complete a sleep diary for two weeks and vocalize a clear motivation for training during SDM should be offered active treatment options. The effect of a generalized active treatment such as exercise or weight reduction or focused muscle therapy such as myofunctional therapy remains to be established. However, the side effects of such treatment approaches are minimal [31]. For more information on myofunctional therapy, we recommend a Cochrane review from 2020, recent narrative reviews by Nokes, Schimickl and co-workers, Koka, De Vito, and co-workers, and a narrative review presenting the "Sleep Revolution" project [15, 56, 62, 63].

The pathway IIIb includes echocardiography if Cheyne-Stokes respiration is identified [64]. Nasal surgery should also be considered as part of pathway IIIb if a nasal blockage prevents the use of PAP [65]. Moreover, treatment of COMISA, in sleep-onset insomnia, should be considered prior to a new attempt of PAP therapy [66].

Conclusion

Limited literature was found on longitudinal management on treatment-resistant OSA. Based on this literature, we propose a standardized secondary diagnostic protocol followed by using a shared decision-aid tool based on the Baveno classification. The management plan proposed focuses on patient perspectives on acceptable cardiovascular risk and acceptable symptoms.

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Data availability This narrative review is based on published articles. No data set is available.

Declarations

Conflict of Interest Drs. Hrubos-Strøm, Zou, and Bergqvist declare no conflict of interest related to this topic. They are funded by university or university hospital positions respectively. They are collaborating on an interregional grant application on the current topic.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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