

Patient Related Outcome and Therapy Effects in Stimulation Treatment of Sleep-Related Breathing Disorders



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ABSTRACT

Several neurostimulation devices exist for the treatment of various sleep-related breathing diseases. Most data for hypoglossal nerve stimulation (HNS) in the therapy of obstructive sleep apnea (OSA) derive the HNS with respiratory sensing. Herewith, daytime sleepiness measured with the Epworth Sleepiness Scale (ESS) was improved in several publications by 5 points with a stability shown for up to several years. Sleep related quality of life, documented with the Functional Outcomes of Sleep Questionnaire, increased by 2 points. Many cohorts showed a mean usage of 5 to 6 hours per night. Under the consideration of shorter follow-up intervals and smaller group sizes, the ESS improved by 4 under unilateral continuous HNS and by 3 under bilateral HNS. Transvenous stimulation of the phrenic nerve is approved for the treatment in central sleep apnea. In a pivotal trial with 5-year follow-up data, an ESS reduction is documented by 3 points. There is one publication describing a usage of more than 5 hours. The daytime enoral neuromuscular electrical therapy improved ESS (2 points) and sleep-related quality of life of snoring patients and their bed partner. The daytime training for the effects during the night adherence is given with 83 %.

For all described devices, there are running or announced studies and/or registry trials that consider the patient related outcome.

Contents

| | | | | | |
|-------|--|----|-----|--|----|
| 1 | Introduction and basics | S2 | 2.3 | Transvenous stimulation of the phrenic nerve for central sleep apnea and Cheyne-Stokes respiration | S6 |
| 1.1 | Sleep-related breathing disorders and snoring | S2 | 2.4 | Enoral stimulation training for snoring and mild sleep apnea | S6 |
| 1.2 | Psychometric test instruments for measurement of the patient-related outcome in sleep-related diseases | S3 | 3 | Usage of therapy | S6 |
| 1.3 | Stimulation therapy for sleep-related breathing disorders | S3 | 3.1 | Sleep duration in Germany | S6 |
| 1.3.1 | Stimulation of the hypoglossal nerve for obstructive sleep apnea | S3 | 3.2 | Stimulation of the hypoglossal nerve for obstructive sleep apnea | S7 |
| 1.3.2 | Transvenous stimulation of the phrenic nerve for central sleep apnea or Cheyne-Stokes respiration | S3 | 3.3 | Transvenous stimulation of the phrenic nerve for central sleep apnea and Cheyne-Stokes respiration | S7 |
| 1.3.3 | Enoral stimulation training for snoring and mild sleep apnea | S4 | 3.4 | Enoral stimulation training for snoring and mild sleep apnea | S7 |
| 2 | Patient-related outcome: measurements and results | S5 | 4 | Significance of long-term cohorts and registry trials | S7 |
| 2.1 | Current significance of patient-related outcome in reimbursement | S5 | 5 | Outlook | S8 |
| 2.2 | Stimulation of the hypoglossal nerve for obstructive sleep apnea | S5 | 6 | Conclusion | S8 |
| | | | 7 | References | S8 |

1. Introduction and basics

1.1 Sleep-related breathing disorders and snoring

Most different data exist regarding the prevalence of sleep-related breathing disorders (SRBD) depending importantly on the population with its age and sex structures and on the applied diagnostic measures [1]. In cases of obesity, especially in male patients, and higher ages, the diagnosis is more frequently made especially with sensitive polysomnographic methods of a sleep lab instead of outpatient measurement devices. Since anatomical and pathological narrowness of the upper airways may lead to SRBD, the disease is highly relevant for the discipline of oto-rhino-laryngology. In the global context, the prevalence amounts to more than 50% in several countries [2]. Personal experience reveals that nearly always an interested audience asks questions in private or public discussions. The incidence of snoring is even more difficult to assess because the level of suffering of the patients or their bed partners plays a significant role [3, 4]. The risk factors for (pathological) snoring are nearly congruent with SRBD, also because both disorders can sometimes occur together.

Main diagnostic criterium for the presence or absence of SRBD is the apnea-hypopnea index (AHI). Apnea is defined as the cessation of breathing for at least 10 seconds while a clear impairment for more than 10 seconds together with arousal and/or drop of oxygen saturation of four percentage points is called hypopnea. The definition of hypopnea has become less strict recently so that this may lead to a changed prevalence as well as indication for therapeutic measures [5]. Since it could be proven that hypopnea with desaturation is associated with an increased cardiovascular risk, other parameters such as the oxygen desaturation index (ODI) are included. Other classic data are minimum oxygen saturation values, which is prone to artifacts, and the sleep duration with less than 90% oxygen saturation. However, the latter is less relevant in the context of preexisting pulmonary diseases or obesity-related hypoventilation.

The AHI may be measured with different technical devices. Supervised polysomnography (PSG) performed in a sleep lab has been considered as method of reference for many decades [1]. Due to the limited availability of PSG, different polygraphy systems have been developed that provide reliable results after adequate validation. Since they can be performed without higher cabling efforts and in the home environment, they are very suitable for second line therapy patients who feel uncomfortable in the narrow situations of a sleep lab. For many years now, systems could be established that measure oxygen saturation signals together with the peripheral arterial tonus. Beside the significance for first and follow-up diagnostics of SRBD, there is no need for applications in the face and they can register more than one night. This is very important for sleep apnea patients with anxiety disorders and for the problem of night-to-night variability, especially in cases of SRBD related with supine position or REM sleep [6].

The decision to treat SRBD is determined by several factors: severity, clinical symptoms, additional diseases, profession as well as physical conspicuities of the upper airway including dental status and obesity (mostly body mass index, BMI). Furthermore, the experience with single therapeutic measures and the discipline of the

diagnosing institution determine the next treatment steps. An intensive discussion of the different treatment options can be found in the literature on this topic. Considering some important treatment options and the patient-reported outcome (PRO), it becomes obvious that the focus is increasingly placed on the patient-related aspects beside the classic outcome parameters like the AHI. Due to the validation of these psychometric instruments, they are now main effect parameters and no longer surrogate parameters.

Positive airway pressure (PAP) therapy in its different appearances is a very effective treatment option. Breathing disorders and PRO can be well improved independently from the severity and the patients' age [7] but the therapeutic effects are subject to a certain dose-related curve and depend on the usage [8]. According to well-structured review articles, treatment with mandibular protrusion splints in cases of mild to moderate obstructive sleep apnea (OSA) is not inferior to PAP therapy with regard to daytime sleepiness and quality of life [9], however, in clinical routine the candidates for this type of treatment are preselected according to the severity, obesity, dental status, and reimbursement modalities. Significant improvement of the daytime sleepiness could be shown with high evidence for multi-level surgery and uvulopalatoplasty with tonsillectomy in the second line situation [10–12] so that reliable results are also available for surgical procedures. Data of recent systematic reviews suggest good effects on daytime sleepiness after weight loss and changed lifestyle habits [13].

In cases of mainly central sleep apnea or Cheyne-Stokes respiration, PAP procedures with preset inspiratory and expiratory support are applied, e. g., adaptive servoventilation. If a specific disease is underlying, in most cases cardiac failure, treatment according to the respective guidelines has priority. Generally, however, the occurrence of central sleep apnea combined with high-grade heart failure is a clear contraindication of adaptive servoventilation. This information resulted from the randomized controlled SERVE-HF trial [14]. Transnasal oxygen application for central sleep apnea and high-grade heart failure is only recommended in the context of studies [15].

Regarding snoring, the recommendations for the diagnostic and therapeutic processes were recently prepared to be published as S3 guideline [3, 4]. In this context, snoring was defined as independent phenomenon without possibly simultaneous occurrence of OSA. Several recommendations are based on an expert consensus because explicit trials on the reduction of snoring are not available, e. g., about weight loss or avoidance of supine position. In contrast, significant data exist on mandibular protrusion splints and single surgical measures like radiofrequency treatment of the soft palate and uvulopalatopharyngoplasty. Some recommendations are subject to requirements, as for example surgery of the nose can only be performed in cases of nasal obstruction.

The purpose of this article is to illustrate the therapy effects of electrical stimulation procedures in cases of SRBD and snoring taking into account the patients' perspective. This information based on the patients' history and follow-up consultations can now be compared more easily due to the increasing number of questionnaire-supported measurement tools. The significance of the patients' perspective regarding the stress caused by SRBD and snoring comes more and more to the fore when new therapeutic pro-

cedures are established and the cost justification is discussed with German healthcare institutions like the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA). The reader shall know frequently applied test procedures and assess them based on different exemplary treatment methods of SRBD with stimulation techniques.

1.2 Psychometric test instruments for measurement of the patient-related outcome in sleep-related diseases

Numerous psychometric measurement tools are applied in the treatment of SRBD. Stimulation therapies focus mainly on the daytime sleepiness, quality of sleep, and disease-related or health-related quality of life in the PRO [16].

The **Epworth Sleepiness Scale (ESS)** by Johns could be established as undisputed method for assessing the subjective daytime sleepiness since its first description in 1991 [17]. The patient is asked to answer eight items rating the probability of falling asleep during the past weeks with four possible grades from 0 – 3. The score of these eight ratings gives hints to an inconspicuous, excessive, or pathological daytime sleepiness. For German speaking countries, standard values exist so that a score as of 10 is considered as conspicuous [18]. The questionnaire is characterized by the clarity of the short questions on everyday situations and the comprehensive use of most different questions on sleep medicine so that the ESS is nearly always applied in larger therapy trials on SRBD.

The **Functional Outcomes of Sleep Questionnaire (FOSQ)** has been applied in the last years in the context of numerous trials on stimulation therapy in order to assess the sleep-related quality of life. This questionnaire includes 30 items that are subdivided into 5 subcategories like level of activity or vigilance [19]. Based on the five possible answers, a weighted overall score between 5.0 and 10.0 is calculated. A high score represents a high sleep-related quality of life. Scores below 17.9 reflect an impaired subjective quality of life [8]. In particular, the application of several questionnaires may distort the results due to the increasing tiredness of the candidates. One option may be to use the shorter FOSQ-10.

The **Pittsburgh Sleep Quality Index (PSQI)** describes the sleep-related quality of life and differentiates between “good” and “poor” sleep in the self-perception of the past four weeks [20]. A score between 0 and 21 is calculated from the answers to 19 items while a higher score indicates a higher quality of life. In contrast to the FOSQ, the PSQI focuses less on daytime effects but it covers more concretely sleep disorders such as insomnia with regard to sleep latency and duration as well as the use of sleeping drugs.

The seven items with their five possible answers of the **Insomnia Severity Index (ISI)** include questions on different aspects of insomnia like problems with initiating and maintaining sleep or early waking up [21, 22]. In addition, the self- and third-party perception of the sleeping disorder is considered so that the overall score results in four different categories of mild, moderate, or severe sleeping disorder or an insomnia that is not clinically relevant. Beside the existing categories, no limit value could be established up to now, however, average values between six and seven were found in German validation trials for different comparison collectives [23].

1.3 Stimulation therapy for sleep-related breathing disorders

1.3.1 Stimulation of the hypoglossal nerve for obstructive sleep apnea

Stimulation of the hypoglossal nerve (HNS) has been applied in cases of obstructive sleep apnea since the 1990ies, mainly the STAR trial of 2014 [24] led to the increased clinical application and to intensive scientific interest [25, 26]. Currently, several implants of different manufacturers are available in Germany that vary with regard to the indication, technical details, and therapy adaptation as well as the evidence level: HNS with respiratory sensing (Inspire Medical Company) and unilateral continuous hypoglossal nerve stimulation (LivaNova Company; formerly ImThera Medical) as well as the bilateral stimulation (Nyxoah S.A.) [26, 27] (see ► **Table 1**). All therapy options are reserved to second line situations after PAP therapy [28]. With regard to the limit values of obesity in BMI, single trials vary, or limit values are not defined in the Conformité Européenne (CE) label [26]; however, with increasing BMI the complete concentric collapse in sleep endoscopy is frequently found as exclusion criterion [29] (► **Table 1**).

HNS implantations are activated only after healing phases of several weeks and then adjusted under clinical and polysomnographic control. In selected cases, PSG is even not required [30]. As an example, the setting and therapy control is depicted in ► **Fig. 1**. It is recommended to check the therapy outcome, intensity of usage, and side effects in yearly intervals [26, 31].

1.3.2 Transvenous stimulation of the phrenic nerve for central sleep apnea or Cheyne-Stokes respiration

Breathing Transvenous stimulation of the phrenic nerve (remede, Respicardia Company) is applied in patients suffering from central sleep apnea and Cheyne-Stokes respiration. In contrast to HNS therapy, there is no therapy control by remote because initially a more regular daytime rhythm was expected in mostly limitedly active heart failure patients. Therapy starts when the following conditions are present:

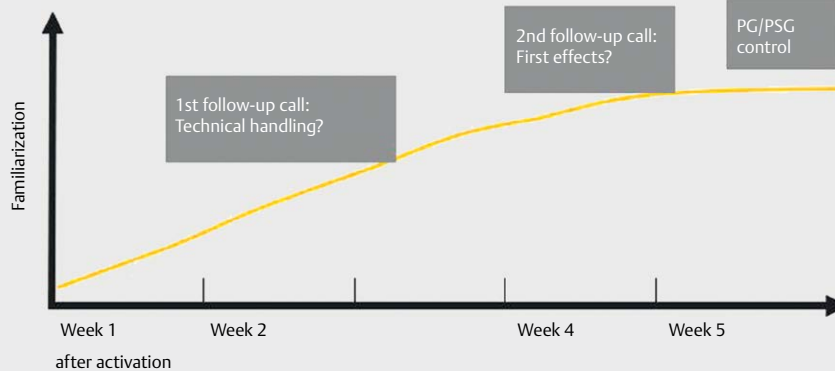
1. Within the individually programmable time frame (e. g., 10:00 pm to 6:00 am)
2. The patient has assumed his sleeping position (the impulse generator contains an adjustable inclination sensor)
3. By means of actinography, a constant position is recognized as rest situation.

Stimulation is interrupted via programmable time variables when the patient turns or gets up to visit the toilet.

Interventional cardiologists insert an impulse generator, an impulse probe as well as optionally a sensory probe. On the level of the pericardium, the pericardiophrenic vein runs in parallel to the phrenic nerve over a longer distance. A subclavicular access allows insertion of a stimulation probe into this vein under radiological control. Its correct position is verified by diaphragmatic movements during test currents. It is optional to insert a spiral sensor into the azygos vein via the same access on the contralateral side. This probe registers breathing efforts of the thorax by recognizing wall movements. After healing of about one month, the first activation and programming of the conditions is performed to determine the impulse release. For the adaptation period, a gradual impulse increase

► **Table 1** Comparison of hypoglossal nerve stimulation procedures regarding technical details and indication.

| | Inspire Medical | LivaNova (formerly ImThera) | Nyxoah |
|--|---|---|--|
| Assessment of respiratory activity | Breath synchronous | Independent from breathing | Independent from breathing |
| Power release | At the end of expiration | Permanently toning via alternating activation | Phasic, coordinated with breathing in PSG |
| Stimulation site | Unilateral at protrusion fibers | Unilateral at the hypoglossal nerve stem | Bilateral at the hypoglossal nerve branches |
| Supply | Fully implanted, battery | Fully implanted, accumulator | Partially implanted, accumulator via induction |
| MRI conditional | Limited (among others, head and extremities possible up to 1.5 Tesla) | No | 1.5 and 3.0 Tesla possible without limitation of extremities |
| Drug induced sleep endoscopy necessary | Yes, to exclude completely concentric soft palate collapse | No | Yes, to exclude completely concentric soft palate collapse |



► **Fig. 1** Description of accompanied therapy familiarization in cases of breathing-controlled hypoglossus stimulation. .

is individually programmed while several re-programming steps are necessary in the first months in order to adapt to the patients' experiences and sleep habits. Polysomnographic adjustment is helpful but not mandatory. The therapy effects are controlled clinically and by polygraphy.

1.3.3 Enoral stimulation training for snoring and mild sleep apnea

For nearly 20 years, randomized controlled trials on electric stimulation have been available showing a reduction of snoring after trainings of 20 minutes twice per day over eight weeks [32] or in other study designs with ECG electrodes [33, 34]. Based on feasibility trials [35] prospective cohort studies followed for the eXcite OSA® system (formerly Snoozeal, Signifier Medical Limited) [36, 37]. The washable mouthpiece that has two contacts under and on the tongue, each, is inserted by means of a control unit with handle. This unit is controlled by an app (► **Fig. 2**). The training program is performed over 20 minutes during daytime and includes bipolar low frequency currents (up to 20 Hz) with an impulse intensity of max. 15 mV. Bursts of six seconds alternate with rest phases of four seconds.



► **Fig. 2** Therapy device consisting of mouthpiece and control unit.

This therapy device was applied in trials that are available up to now when OSA with more than 15 per hour in the AHI and an obesity of more than 35 kg/m² were excluded. Significant airway obstructions due to e. g., nasal pathologies or tonsillar hyperplasia were exclusion criteria as well as surgery in the oral area for snoring.

After six and twelve months as well as in yearly intervals, the effect on daytime sleepiness and sleep-related breathing disorders is controlled by means of poly(somno)graphy and the control of therapy usage is recommended [31].

2 Patient-related outcome: measurements and results

2.1 Current significance of patient-related outcome in reimbursement

Among others, the treatment guidelines of the G-BA refer to statements of the Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; IQWiG) when a certain treatment measure ought to be reimbursed. Interestingly, the IQWiG report on mandibular protrusion splints for OSA does not consider classic sleep-medical parameters for outcome evaluation like the AHI or ODI as patient-relevant aspects; they are only considered to have the level of surrogate parameters [9]. Therefore, the methodically strict report only takes into account the results mentioned in the literature that have been evaluated based on validated test instruments such as ESS or FOSQ.

This example for an approach to method assessment for the treatment of OSA emphasizes the significance of PRO that have been assessed with reliable psychometric methods. Referring to exclusively polygraphic or polysomnographic OSA parameters contributes only partially to the evaluation of a therapy procedure in the reimbursement process in Germany.

2.2 Stimulation of the hypoglossal nerve for obstructive sleep apnea

Publications are mainly available for **respiration controlled HNS**. On one hand, there are the cohort studies entitled STAR [24, 38–40] and the German Postmarket study [31, 41–43] as well as the registry study called ADHERE [44, 45] including the prospective comparative study [46] initiated and supported by the manufacturer of Inspire Medical Company. On the other hand, there are independent cohort trials of larger implantation centers with sometimes several years of follow-up examinations [47–51] and the randomized controlled therapy withdrawal study of EFFECT [52].

Regarding daytime sleepiness, the ESS was reduced within the first 12 months from initially 11 to 6 in the STAR trial [24], the German Postmarket study [41, 42], and in the analysis of two US American centers with short follow-up durations [49] and to 7 points in the analysis of more than 1,000 patients of the ADHERE registry [44], respectively. Thus, the difference in most publications amounts to about 5 points in the ESS up to 6.5 [47]. In a substudy of the ADHERE registry as comparison with patients who wait for coverage of the costs, the ESS could also be reduced by 5 points under HNS therapy, while the therapy candidates in the waiting arm showed an increase by 1.8 points [46]. In the continuing evaluations of the ADHERE registry, these improvements could be revealed in the comparison of the patient groups with a BMI below 32 and with a BMI between 32 and 35 kg/m², independently from obesity [45]. Recently, the German randomized therapy withdrawal trial entitled EFFECT was published reporting about a difference of 4.6 points under therapy compared to sham in a cohort of 89

study participants [52]. In summary, this reduction of nearly always 5 ESS points seems to be seen also in older patients, as it could be described in an evaluation of veterans of the US American military [51]. 53 patients with an average age of 63 years achieved an improvement from 11 to 6 points. A matched analysis of geriatric patients older than 64 years compared to younger people did not reveal significant differences regarding an improvement of the daytime sleepiness although the comorbidity rates of the older patients were higher [53]. In some cohorts, an ESS reduction under HNS therapy does not correlate with objective OSA parameters like the AHI and ODI [43, 50] so that also formal non-responders should be motivated to use the device in cases of clinical improvement [54]. These good results turned out to be stable in the long-term perspective which became obvious in the 3- and 5-year data of the STAR cohort with an ESS decreasing from 11 to 7.0 and 6.9, respectively [38, 40]. From initially 60 study participants of the German Postmarket trial, the data of 41 and 38 patients are available after 2 and 3 years, respectively, showing a stable ESS reduction from 13 points at the beginning to 4 and 6 [31]. Another cohort evaluation revealed in the follow-up that 68 of a total of 132 patients who had been treated for at least 3 years achieved a reduction from 14 to 7 points in the ESS. However, if clinically relevant insomnia is complained at the same time, the reduction amounts to only 3.5 points [50].

Beside the ESS, several of the above-mentioned cohort studies also perform the FOSQ regarding the sleep-related quality of life. The initial values of the STAR and German Postmarket trials were similar with slightly over 14 points as were also the improvements to 17.3 after one year [24, 41, 42] remaining stable with 17.4 and 18.0 after 3 and 5 years, respectively [38, 40]. This difference of nearly 2 points could be elaborated in the randomized controlled withdrawal trial entitled EFFECT [52]. In the prospective comparison between the therapy group and the HNS candidates in the waiting arm, the sub-trial of the ADHERE registry used the short version of the FOSQ, i. e., the FOSQ-10 [46]. The difference at the end of the trial under therapy was obvious with a mean of 18 with and 12 without therapy. A long-term cohort with 132 patients showed that the improvement in 64 investigated patients with 2 years or less after implantation amounted to 3.1 points in the FOSQ compared to 4.4 when HNS therapy had been active for at least 3 years [50]. This analysis also revealed the influence of insomnia complaints because without them the FOSQ value improved by 4.5 and otherwise only by 1.5 points. These aspects must be borne in mind when consulting patients regarding their expectations of the PRO because the AHI and ODI reduction is not different in both groups.

Beside the ESS and the FOSQ, only few publications are available for breath synchronous HNS that use validated questionnaires. Hereby the ISI for insomnia complaints must be mentioned. In the already described cohort of older veterans, half of them had conspicuous scores with an average of 16 points [51]. Another follow-up cohort with 132 patients revealed moderate to severe impairment due to synchronous insomnia in 34 individuals [50]. The median value amounted to 18.5 points. Compared with the other patients, the 34 insomnia patients had about the same age, sex distribution, and OSA severity, however, they had statistically higher initial ESS and FOSQ scores. This makes clear that insomnia aspects have to be considered in second line situations and in these cases

possibly closer care should be recommended in order to foster the usage of HNS therapy also for only low-grade improvement of the daytime sleepiness and quality of life despite comparable OSA control.

For unilateral continuous HNS, data of 6- and 12-months follow-up are available. After six months, the initial ESS could be reduced from 12.0 to 8.3 points in 46 participants while 35% were considered as therapy responders regarding AHI reduction [55]. The data after 12 months showed an average improvement of the ESS from 10.8 to 7.9 points in 13 patients with a significantly higher rate of therapy responders of 76.9% [56]. For December 2022, the end of the randomized THN3 trial is expected [ClinicalTrials.gov identifier: NCT02263859] that assesses as secondary endpoints the daytime sleepiness and the quality of life by means of ESS and FOSQ-10, among others.

Concerning bilateral HNS, a multicenter trial with initially 27 participants could show in finally 22 patients an improved daytime sleepiness in the ESS with a reduction from 11.0 to 8.0 points after six months and an increased sleep-related quality of life in the FOSQ-10 from 15.3 to 17.2 points [57]. Currently two trials are running while the DREAM trial [ClinicalTrials.gov Identifier: NCT03868618] is based on security aspects as well as AHI and ODI effects in its application. In contrast, the BETTER SLEEP trial [ClinicalTrials.gov Identifier: NCT03763682] includes among other endpoints the ESS and the FOSQ-10 in the study concept which comprises 3 years and explicitly compares the results of patients with and without complete concentric collapse in the drug-induced sleep endoscopy.

2.3 Transvenous stimulation of the phrenic nerve for central sleep apnea and Cheyne-Stokes respiration

Data regarding transvenous stimulation of the phrenic nerve are mainly based on the pilot study with 57 [58] and the subsequent key trial with initially 151 included participants [59] as well as subsequent trials on long-term results after for example 5 years [60]. Overall, it must be taken into account when evaluating the ESS scores on daytime sleepiness that the percentage of heart failure patients is high in both cohorts with NYHA \geq II in 70 and 60%, respectively. In general, the about 1,300 participants of the SERVE-HF trial on central sleep apnea who randomly underwent adaptive servoventilation for optimized treatment of the heart failure experienced an improvement of the ESS to 7.0 and 7.1, respectively [14].

The results of the pilot study revealed a reduction of the ESS from 8.0 to 6.1 points after 6 months [58]. In the key trial, both study arms received implantation but the devices in the randomized control group were activated with a 3-month delay [59]. Hereby, an improvement from initially 10.2 and 9.5 points, respectively, was observed by -3.6 in the treatment arm compared to +0.1 in the ESS of the control arm ($p < 0.0001$). This reduction to a median of 9 or a reduction by 3 points could be maintained in the 5-year follow-up of 53 patients [60]. In the long-term follow-up, 62% of the patients revealed an improvement of at least 3 points. Also, the subanalysis of the exclusively 96 heart failure patients with an initial score of 8.9 points showed this ESS reduction of about 3 after 12 months [61]. Currently, the first European study center of

the ReST registry in Lübeck, Germany [ClinicalTrials.gov Identifier: NCT03884660] is working actively on this project. In this prospective registry that is limited to 500 patients, also heart-failure-related QoL tests such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) are applied beside the ESS on daytime sleepiness.

2.4 Enoral stimulation training for snoring and mild sleep apnea

Interestingly, for the enoral stimulation training of eXciteOSA (Signifier Medical Technologies Company) data are available concerning daytime sleepiness as well as sleep-related quality of life of snoring patients and the bedpartners. In the feasibility trial with the final analysis of 13 patients, only the ESS of the entire cohort was mentioned with 7.4 points before study onset when focusing on the reduction of snoring [35]. In the prospective trial of a treatment center [36], the daytime sleepiness of the snoring patients decreased from 8.4 to 6.1 points ($p < 0.001$) while the reduction for the bedpartners remained without statistical significance (ESS reduction from 5.8 to 5.0; $p = 0.21$). In contrast, both achieved a significant improvement of the quality of life in the PSQI from 7.0 to 5.9 ($p = 0.004$) and from 7.3 to 6.3 ($p = 0.03$), respectively. The following prospective multicenter trial [37] including 115 patients of whom 56% were patients affected with mild OSA and 44% snorers with an AHI of less than 5 per hour. They revealed again a significant increase of the sleep-related quality of life in both groups: Snorers undergoing therapy reduced the PSQI from 7.2 to 5.8 points ($p < 0.001$) and the bedpartners from 6.9 to 5.9 ($p < 0.02$). In analogy to the previous paper [36], the daytime sleepiness was also improved in snorers (from 8.4 to 5.8; $p < 0.01$) while the change for the bedpartner did not achieve any statistical relevance (from 6.2 to 5.7 points; $p = 0.22$). A high initial ESS score correlated well with positive therapy response regarding objectifiable loudness of snoring sounds. In the future, further patient-relevant effects may be expected from a market launch trial with 200 patients [ClinicalTrials.gov Identifier: NCT04392765] because hereby again the ESS and the PSQI will be applied in addition to the EQ-5D.

3 Usage of therapy

3.1 Sleep duration in Germany

Data on the duration of sleep of the adult population may vary significantly depending on the cohort and scientific method. For orientation, the following recent, mainly German data are mentioned here. The Robert Koch Institute initiated a trial for monitoring the healthcare of adults in Germany (Studie zur Gesundheit Erwachsener in Deutschland; DEGS) with 8,100 adults who were asked about their self-perceived effective duration of sleep during the previous four weeks [62]. 81.6% of the participants reported a duration between 6 and 8 hours, only 12.3% mentioned 5 hours or less, and 6.1% more than 9 hours. A recent paper registered the sleep duration of nearly 400 adults with an average age of 45.0 ± 14.2 years and a percentage of 50.9% females [63]. Hereby, a mean duration of sleep of about 6.5 hours appeared depending among other factors from the status of fulltime or parttime jobs, the sex, and the day of the week.

Based on the duration of use of about 4,200 PAP device data of a medical product manufacturer, usage data could be retrieved retrospectively for the German healthcare system [64]. The average duration of usage amounted to 6.4 hours while 91.8% used their PAP device for more than 4 hours. In other international cohorts like the SAVE trial with more than 2,700 participants, the average duration of usage amounted to 3.3 hours per night [65].

3.2 Stimulation of the hypoglossal nerve for obstructive sleep apnea

The usage of the breathing-controlled HNS can be read out telemetrically directly from the IPG or transmitted indirectly via the remote-control unit into a cloud-based system of the manufacturer. The last-mentioned method has the advantage that for each single night the sleep times as well as the use of the interruption function and the impulse intensity may be documented. In many German hospitals, the application is not possible due to data protection matters or to problems with storage systems of the hospital's own information technology. Therefore, the data from previous publications are retrieved from telemetric read-outs that work as overall usage registration in order to additionally present calculated use per week. Possibly, the significance is thus poorer compared to night-specific remote-control read-out because the non-use immediately prior to reading does not become obvious if the therapy was applied regularly over many months before.

In most publications, the usage amounts to about 5.6 hours like for example in the recent analysis of 1,800 patients of the ADHERE registry or the German Postmarket trial [42, 45]. For the last-mentioned study, the usage data of 2 and 3 years are available amounting to 6.1 and 6.3 hours, respectively [31]. There are single publications of clinic cohorts reporting about higher durations with 6.6 hours after 12 months [47] or three years [66]. An evaluation of two institutions with 102 patients revealed a good correlation between the objective usage and the data from the patients' perspective ($r = 0.485$; $p < 0.001$) [67]. The objective usage amounted to 5.7 hours while 55.7% used the therapy device for more than 6 hours and 77.4% for more than 4 hours per night. Several parameters have an impact on the usage. In the evaluation of more than 1,000 participants of the ADHERE registry, women tend to use the device more intensively (5.9 versus 5.5 hours; $p = 0.18$) [44]. Hereby, it must be taken into consideration that other publications report about longer sleep durations for females in Germany [63]. The use of the HNS was better with a BMI below 32 kg/m^2 compared to the group with a BMI between 32 and 35 kg/m^2 ($p = 0.028$) [45]. In this context, the factor of obesity may play a role for therapy response even if the AHI reduction was not different. A study comparing patients over 65 years with younger ones who were matched regarding AHI and BMI revealed that the older patients had a significantly better therapy usage with 6.7 hours after 6 and 12 months while the younger ones used the therapy less intensively with 5.8 and 5.0 hour, respectively [53]. Patients with clinically relevant insomnia complaints used the device for 5.2 hours compared to those without insomnia with 6.1 hours [50].

For unilateral continuous HNS, no analyses regarding usage are available [27].

The current version of bilateral HNS does not allow objectifiable analyses of the usage so that only questionnaire-based results exist for 22 patients after 6 months [57]. 91% of the participants reported a usage of more than 5 days and 77% stated that they used the device for more than 5 hours.

3.3 Transvenous stimulation of the phrenic nerve for central sleep apnea and Cheyne-Stokes respiration

In contrast to breathing-controlled HNS, the frequency of usage cannot be deliberately controlled by the patients because the treatment depends on the individually programmed conditions, like pre-defined times, patient activity below actinography thresholds, assumption of a certain body position for sleeping. In this way, the therapy is interrupted for example in cases of heart failure patients visiting the toilet or sleeping times outside programmed times, e. g., in the afternoon, are neither treated nor registered as usage.

In the pilot study with 6-month perspective [58], the therapy was active during 5.4 of 5.8 hours of potential sleeping time with the mentioned preconditions. The following publications as well as the 5-year follow-up of the key study [59, 60], however, do not provide results on therapy times.

3.4 Enoral stimulation training for snoring and mild sleep apnea

For enoral stimulation training, adherence data cannot be given because the training lasting for 20 minutes is performed twice [35] or once [36, 37] during daytime in the awake state. It may be assessed by means of a smartphone app if the training is performed regularly during daytime. It could be found that the training compliance amounted to an average of 83 [37] and 83.3% [36], respectively, while the spectrum for the last-mentioned cohort amounts to 59.5 to 95.2%.

4 Significance of long-term cohorts and registry trials

Several neurostimulation procedures have left the level of feasibility trials and comparative values are available for new procedures. Beside the classic OSA parameters like AHI and ODI, many registries and long-term follow-up analyses consider patient-related outcomes such as daytime sleepiness, usage, and quality of life. Regarding effects on certain OSA-associated diseases such as heart attack or cardiac arrhythmia, the 6- or 12-month perspective is too short, and a three-digit cohort size is too small. Therefore, follow-up intervals of several years are required. The analyses of meanwhile four-digit registry cohorts such as ADHERE for breathing-controlled HNS with reference to cardiovascular events before implantation and in the first year of therapy are highly anticipated. Furthermore, a structured report about technical conspicuities and complications of an implant is requested so that experiences of single institutions may be better classified. In particular in an interdisciplinary treatment concept consisting of ENT-surgical implantation and sleep-medical therapy set-up as well as follow-up, well-regulated responsibilities are required in order to manage occurring problems and to provide a contact person for the patients [26].

5 Outlook

Based on the structured studies on neurostimulation of the previous 10 years, also the evidence level for non-stimulation procedures in sleep surgery could be enhanced and the assessment of PRO was standardized. In the future, increased research activity in the sense of personalized medicine may be expected for several procedures taking into account other (sleep-related) diseases. The negative impact of untreated sleep apnea on the cardiovascular and the metabolic systems as well as the risk of traffic accidents in cases of microsleep will be placed in the focus because the high initial expenses of implantation will have to be justified in comparison to the absence of treatment or standard procedures [68]. Validated psychometric procedures such as disease-specific QoL questionnaires will represent a fixed standard.

Concerning the technical development, the telemetric availability will have to be enhanced beside miniaturization and in this context also justified (data) security aspects of the patients and the participating hospitals and private practices will have to be considered in a world of increasing cyber attacks also on healthcare institutions. In this context, a computer-based remote-control analysis might be an option in order to illustrate more reliably the aspects of microsleep in cases of traffic accidents under therapy for example regarding medicolegal questions. Furthermore, it must be expected that the partly limited MRI suitability of certain field strengths or body regions will be improved; single manufacturers already have a whole-body approval for their devices. In analogy to refined set-up options of PAP therapy of many years ago, a multitude of patients would benefit from detailed technical configurations. Hereby the ramp function must be mentioned so that the impulse does not start abruptly or a sensor allowing to set an impulse intensity that is specific for the supine position.

First results on the application of neurostimulation of other neural structures have been published. If the stimulation of the superior laryngeal nerve [69] or of the ansa cervicalis [70] alone allow stabilization of the upper airway, is highly anticipated. Electromyographic results on the palatine tensor muscle [71] seem to indicate further target structures for the development of neurostimulation.

6 Conclusion

Meanwhile several procedures of neurostimulation are available for different sleep-related diseases and snoring. Their effectiveness could be proven in reliable trials with regard to patient-related outcome on daytime sleepiness, sleep-related quality of life, and usage. Registries including four-digit numbers of participants confirm study data in real world application. For several therapy options, long-term data from different cohort are available.

Therefore, clear recommendations may be given to patients as well as convincing arguments to cost bearers.

Conflict of interest

Armin Steffen is working as consultant for Inspire Medical, Respicardia and Merz Pharmaceutical. He received travel cost refund and remuneration for lectures by Intersect.

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