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Review

A Narrative Review of the Clinical Trials in Sleep-Related Breathing Disorders from 2022 to Present

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Abstract

Sleep-related breathing disorders (SRBD) comprise obstructive sleep apnea (OSA), central sleep apnea (CSA), obesity-hypoventilation syndrome (OHS), as well as isolated sleep-related hypoxemia (ISRH), according to the recent International Classification of Sleep Disorders 3. During the last decades, there have been cumulative research reports indicating an association between the SRBD and increased cardiometabolic illness and death, as well as decreased quality of life. Notwithstanding, the results have been inconclusive, and the evidence level was not high regarding the effect of treatment for the SRBD on adverse outcomes. In the current work, we aim to give a comprehensive review of the clinical trials published from January 2022 to August 31, 2023. We highlight the heterogeneity of cardiometabolic disorders among adults with SRBD and particularly emphasize OSA management, drug therapy for OSA, positive airway pressure (PAP) therapy and cardiovascular outcomes, other effects of PAP in pregnancy and neurocognitive function, as well as the effects of surgical treatment and oral appliances. We also underline future directions in OSA management, telemonitoring, and drug-induced sleep endoscopy in managing the SRBD, especially OSA. We ascertain that more studies are needed within the CSA, OHS, and ISRH research fields.

KEYWORDS: Sleep-related breathing disorders, obstructive sleep apnea, cardiovascular, drug therapy, telemedicine
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INTRODUCTION

The current narrative review aims to summarize the recent research articles regarding the clinical trials within the sleep-related breathing disorders (SRBD) research field from January 2022 to August 31, 2023. According to the International Classification of Sleep Disorders (ICSD) 3, SRBD comprise obstructive sleep apnea (OSA; defined as an apnea–hypopnea index [AHI] ≥15 events/h), central sleep apnea with Cheyne–Stokes respiration (CSA-CSR), obesity hypoventilation syndrome (OHS), as well as isolated sleep-related hypoxemia (ISRH) (nocturnal oxyhemoglobin saturation [SpO_2] <88% for ≥5 minutes).[1] In the current report, we particularly emphasize OSA management, drug treatment for OSA, continuous positive airway pressure (CPAP) and cardiovascular outcomes, other effects of PAP in pregnancy and neurocognitive function, as well as the effects of surgical treatment and oral appliances. We also highlight future directions in OSA management, telemonitoring, and drug-induced sleep endoscopy (DISE) in managing the SRBD.

EFFECT OF TOTAL SLEEP OR RAPID EYE MOVEMENT SLEEP DEPRIVATION AND OBSTRUCTIVE SLEEP APNEA ON MALE REPRODUCTIVE FUNCTION

In a randomized trial by Alvarenga et al (NCT01884454),[2] the effects of sleep deprivation and OSA on male reproductive function have been evaluated in a 3-arm parallel study. A predefined OSA group as well as a group of healthy volunteers was randomized to total or rapid eye movement (REM) sleep deprivation. Circulating levels of total and free testosterone and high-density lipoproteins, as well as proportions of healthy sperm cells and sperm concentrations, were lower in participants with OSA compared to those in volunteers. Circulating levels of thyroid-stimulating hormone and insulin were higher, and homeostatic model assessment of insulin resistance levels was increased in healthy volunteers with total or REM sleep deprivation. Although spermiograms did not present any alterations, a reduction in total testosterone after total sleep deprivation was observed. Thus, OSA and sleep deprivation may be important factors that should be taken into consideration in the assessment of adults with impaired reproductive functions.

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EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON OVERACTIVE BLADDER IN WOMEN

Ertas et al[3] (NCT05250245) have examined the impact of CPAP therapy in 60 female OSA patients with overactive bladder (OAB) with and without tolterodine treatment for 3 months. Despite significant favorable improvements in both arms, a more pronounced improvement was observed in the combined treatment group in regard to mean incontinence questionnaire-urinary incontinence short form scores and mean OAB awareness-8-item tool scores compared to the CPAP-only group.

COGNITIVE BEHAVIORAL THERAPY AND CONTINUOUS POSITIVE AIRWAY PRESSURE FOR COMORBID INSOMNIA AND SLEEP APNEA

Tu et al[4] (NCT01785303) have investigated the effect of cognitive behavioral therapy for insomnia (CBT-I) and CPAP for comorbid insomnia and sleep apnea (COMISA) on sleep as well as daytime functioning. In the study examining 118 patients with COMISA, one group of patients received CBT-I followed by CPAP, and another group was allocated to self-monitoring followed by CBT-I in addition to CPAP, another group was randomized to self-monitoring followed by CPAP alone. Cognitive behavioral therapy for insomnia was better than CPAP and self-monitoring regarding the reduction in diary-measured sleep onset latency and wake after sleep onset and improving sleep efficiency, in addition to refining the scores of the Functional Outcome of Sleep Questionnaire and Flinders Fatigue Scale compared to results with self-monitoring. Thus, CBT-I concurrent with CPAP seems to be an efficient treatment modality for patients with COMISA.

AUTO-CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT IN PREGNANCY

Kalkhoff et al[5] conducted a randomized control trial (RCT) (NCT02755831) of a targeted auto-CPAP for pregnant women at risk of OSA. Patients were randomized to a sleep study screening group receiving auto-CPAP (n = 100) or a control group (n = 93) followed with standard care. In addition to 2 sleep studies performed during pregnancy in the first group, all participants underwent a sleep study 3 months after the delivery. Auto-CPAP treatment was initiated in appropriate patients (n = 6) in the first group with AHI ≥5 events per hour detected in the sleep tests during pregnancy (n = 24). The study has revealed similar outcomes in both groups regarding adverse pregnancy outcomes (46% of the screened group vs. 43% of the control group; $P = .77$) including hypertension, preterm birth, stillbirth, low birth weight, diabetes mellitus, as well as average hospital expenses. The secondary outcomes were the severity of OSA and hospital expenses. The AHI has increased during the pregnancy and reached the highest levels at 3 months following delivery ($P < .001$). Positive airway pressure compliance was poor (2%-43%). Even if no meaningful differences are detected between the groups regarding the outcomes of the study, probably due to the small sample size and low power, this special patient population with increasing occurrence and AHI throughout the pregnancy and postpartum period requires special consideration.

Continuous Positive Airway Pressure and Cardiovascular Outcomes

Recent RCTs, the Randomized Intervention with CPAP in coronary artery disease and obstructive sleep apnea (RICCADSA) trial (NCT 00519597),[6] the Sleep Apnea Cardiovascular Endpoints (SAVE) study (NCT 00738179),[7] and the Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome (ISAACC) study (NCT 01335087),[8] failed to show any reduction in major cardiovascular and cerebrovascular events (MACCEs) in intention-to-treat analyses. Several arguments have been suggested for the neutral results, comprising low adherence to CPAP therapy in those studies and those individuals with excessive daytime sleepiness were not included.[9] Other explanations of these null findings have also been attributed to the failure to consider OSA as a heterogeneous disorder that consists of multiple phenotypes.[10] In one of the post hoc investigations of the RICCADSA trial, Azarbarzin and colleagues reported that patients with higher elevated heart rate response (ΔHR) to respiratory events show greater cardiovascular benefits from CPAP treatment (NCT 00519597 for the main RCT).[11] The CPAP-related reduction in risk increased progressively with increasing pretreatment ΔHR. In another secondary investigation of the RICCADSA study, Eulenburg and colleagues compared the cardiovascular outcomes in sleepy vs. nonsleepy coronary artery disease (CAD) patients with OSA (NCT 00519597).[12] The researchers reported that adverse cardiovascular outcomes did not differ by the severity of excessive daytime sleepiness (EDS) for patients with CAD and OSA who were untreated or nonadherent to treatment. However, CPAP use for at least 4 hours per night was associated with less adverse outcomes in patients without EDS.[12]

Obstructive sleep apnea is associated with atrial fibrillation (AF). Catheter ablation with pulmonary vein isolation (PVI) has been used more and more to reduce symptoms of AF as well as the need for antiarrhythmic medication. In a recent RCT, Hunt and colleagues evaluated the impact of CPAP on the recurrence and burden of AF after PVI in adults with OSA (NCT 02727192).[13] A home sleep apnea test (HSAT) was conducted in all participants. Patients with paroxysmal AF and OSA were randomized to CPAP (n = 37) or no-CPAP (n = 46). There was no meaningful reduction in the risk of AF recurrence after PVI; the rate of AF recurrence was 57% in both groups.[13]

Postoperative atrial fibrillation (POAF) occurs in up to 50% of patients with CAD after coronary artery bypass grafting (CABG). In another post hoc investigation of the RICCADSA trial, 147 patients with CABG at baseline who underwent HSAT in 73 days after the surgical treatment were included (NCT 2000519597).[14] POAF was observed among 33% of the cases, and there was a significant risk increase for POAF across the AHI categories with the highest odds ratio (OR) for severe OSA (OR 6.8, 95% CI, 1.3-35.5; $P = .023$) compared to no-OSA, independent of age, sex, and body mass index (BMI). On the other hand, all patients with the POAF history at baseline were free from reoccurrence of AF at the long-term follow-up.

In another RCT by Lao and colleagues, the interaction among OSA, CPAP, and cardiovascular (CV) and cerebrovascular

(CeV) medications and the impact of medications on MACCEs as well as on survival in patients with comorbid OSA and CV/CeV were examined (NCT 00738179).[15] In this post hoc analysis of the SAVE trial, 131 patients were analyzed (63 in the CPAP arm vs. 68 in the no-CPAP arm), and 65% of the patients on CPAP had good adherence. During a median follow-up of 43.0 months, the independent factors for declining survival in patients with comorbid OSA and CV/CeV were angiotensin converting enzyme (ACE) inhibitors and nitrates. ACE inhibitors predicted increased death and secondary endpoints among patients allocated to CPAP but not in those with good CPAP compliance.[15]

Another RCT in adults with OSA and CVD was conducted by Zhao et al[16] (NCT 01261390). In all, 169 participants without severe sleepiness were randomized to CPAP or no-CPAP, addressing the impact of therapy on 24-hour systolic blood pressure (SBP) over 6-12 months. The 24-hour SBP was similar between the groups, whereas a significant effect was observed on the nighttime SBP (treatment effect −5.9 mm Hg [95% CI, −9.9 to −1.9]; *P* = .004).[16]

A recent post hoc analysis of the RICCADSA trial (NCT 2000519597)[17] study addressed the relationship between TNF-α polymorphism and TNF-α levels at 12 months among 239 CAD patients with OSA and showed that there was a significant change in circulating TNF-α levels from baseline across the genotypes from GA to GA and GA to AA, and that the relationship was more pronounced among the patients who were using the device for ≥4 hours per night. The patients carrying the TNF-α A allele responded less to CPAP therapy regarding the decline in circulating TNF-α levels despite good CPAP adherence. These findings may partly explain the cardiovascular heterogeneity in adults with OSA.

Continuous Positive Airway Pressure and Metabolic Outcomes

Dyslipidemia is a recognized risk issue for CAD. Obstructive sleep apnea and dyslipidemia are independently related to increased mortality, cardiovascular disease, and stroke. In another secondary investigation of the RICCADSA trial, Celik and colleagues included 196 patients with CAD and nonsleepy OSA (NCT 2000519597).[18] The participants were randomized to CPAP or no-CPAP, and they were all on lipid-lowering medication. CPAP did not have an additional lipid-lowering effect in the cohort.[18]

Similarly, Giampá et al[19] studied the impact of CPAP on metabolic syndrome in adults with OSA (NCT 02295202). They found that most patients using CPAP retained metabolic syndrome diagnosis after 6 months, although 18% of the patients allocated to CPAP were reversed compared to 4% in the group who were randomized to nasal dilator strips (placebo) (OR, 5.27; 95% CI, 1.27-35.86; *P* = .04).[19]

CONTINUOUS POSITIVE AIRWAY PRESSURE VS. BILEVEL POSITIVE AIRWAY PRESSURE TREATMENT IN OBESITY HYPOVENTILATION SYNDROME

Obesity, being an important risk factor in sleep-related disorders, also has an important role in PAP treatment choices. In a pilot RCT by Zheng et al[20] (ACTRN12605000096651) the effect of CPAP vs. bilevel PAP (BPAP) spontaneous mode on hypoventilation in adults with obesity and obstructive airway disease has been examined. Among 32 participants receiving treatment for 3 months, a greater improvement in $PaCO_2$ has been detected in the BPAP group compared to CPAP group (intergroup difference 9.4 mm Hg, 95% CI, 4.3-15 mm Hg). Patients in the BPAP group had greater changes in lung function and quality of life in comparison to patients who received CPAP.

Drug Therapy

To date, there is no effective pharmacological treatment for OSA. Recent advances regarding the pathophysiological features that lead to OSA point to the collapsibility of the upper airways, pharyngeal dilator muscle dysfunction, and ventilation instability. Specifically, sleep-related hypotonia of the pharyngeal muscles is thought to be due to impairment of noradrenergic activity in non-REM (NREM) sleep[21] and to muscarinic activity dysfunction in REM sleep.[22] Preliminary studies have shown a meaningful decrease in AHI using norepinephrine reuptake inhibitors (atomoxetine and reboxetine) in combination with antimuscarinics (oxybutynin or hyoscine butyl bromide).[23,24]

In a recent phase 2 RCT, Schweitzer et al[25] compared AD036 (fixed-dose combination of atomoxetine 80 mg and oxybutynin 5 mg), atomoxetine 80 mg alone, and placebo during 3 HSAT studies in OSA patients (NCT04445688). They found that AD036 significantly improved the OSA severity (AHI was reduced by 54% in median value) compared to the placebo. The time spent with SpO_2 < 90% as well as hypoxic burden was also significantly reduced in the AD036 group.

The efficacy of 4 mg reboxetine in addition to 5 mg oxybutynin (Reb-Oxy), another combination of antimuscarinic and noradrenergic drugs, was evaluated in adults with OSA by Perger et al[26] (NCT04449133). Reb-Oxy reduced AHI, hypoxic burden as well as oxygen desaturation index (ODI) compared with the values at baseline. Reboxetine–oxybutynin improved even muscle compensation and decreased the arousal threshold. Several surrogates of milder collapsibility were found to be related with greater responses to Reb-Oxy. The authors concluded that these findings confirm the idea that pharmacologic treatment for OSA may be most effective in adults with less severe pharyngeal compromise.[26]

In an RCT by Messineo et al[27], the effects of a histamin-3 -autoreceptor antagonist, betahistine (Beta), combined with an antimuscarinic, oxybutynin (Oxy), on OSA severity, OSA endotypes, and polysomnographic parameters were addressed. In a crossover, randomized, double-blind design, they included 13 adults with OSA who received the combination Beta-Oxy (96-5 mg) or placebo. Beta-oxybutynin increased the loop gain (respiratory control sensitivity) without any significant changes in OSA severity in terms of AHI, sleep efficiency, arousal index, or markers of hypoxemia.

In a recent RCT,[28] 68 adults with OSA who did not accept or tolerate PAP therapy allocated to placebo, sulthiame (STM) 200 mg or STM 400 mg for 4 weeks to explore safety and

tolerability of STM (registered at www.clinicaltrialsregister.eu). Sulthiame showed an acceptable safety profile, with significant improvement regarding OSA severity. More than 50% reduction in AHI was achieved in 40% of patients who were allocated 400 mg of STM, 25% of patients receiving 200 mg, and 5% of patients receiving placebo. Intermittent paresthesia was a commonly reported adverse event (79%, 67%, and 18% of participants receiving 400 mg STM, 200 mg STM, and placebo, respectively.

Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA), which is used as a glucose-lowering drug for patients with type 2 diabetes mellitus (T2DM) as well as for weight loss in obese patients. In a recent RCT, Jiang et al[29] addressed the impact and safety of liraglutide concerning OSA metrics, weight control, cardiac function, and glycolipid metabolism in adults with T2DM and severe OSA. In all, 90 participants with OSA who were on CPAP treatment were randomly allocated liraglutide or placebo for 3 months. BMI, AHI, and average systolic blood pressure decreased in the liraglutide group compared to baseline, whereas no significant changes were observed in the placebo group. Improvements in the OSA metrics were attributed to weight loss in the liraglutide group, reducing the upper airway adipose tissue compression or preventing the upper airway muscle collapse.

Persistent excessive daytime sleepiness (EDS) is reported by up to 41% of patients treated with PAP.[30] Solriamfetol is a dopamine and norepinephrine reuptake inhibitor that is used for the treatment of EDS in adults with OSA or narcolepsy. In previous studies, the TONES (Treatment of OSA and Narcolepsy Excessive Sleepiness) RCTs were conducted to address the efficacy and safety of solriamfetol for the treatment of impaired wakefulness in patients with narcolepsy type 1 or type 2 (TONES 2, NCT02348593),[31] OSA, and EDS (TONES 3, NCT02348606).[32] In a post hoc analysis of the TONES 2 and 3 studies, the researchers compared the impact of solriamfetol treatment on EDS in participants who had depression vs. no depression.[33] The occurrence of a depression history was 28.1% (in those with narcolepsy) and 23.5% (in those with OSA), respectively. The results suggested that solriamfetol was effective in treating EDS regardless of the occurrence of depression.

In other post hoc analyses, changes in weight were addressed at baseline and at end of study in participants with OSA or narcolepsy.[34] After up to 1 year of solriamfetol treatment, one-fourth of the participants achieved a weight loss of ≥5% relative to baseline, and there was a dose-response relationship (4.5% of participants receiving 75 mg achieved the targeted weight loss, and the corresponding values were 17.3% among the patients receiving 150 mg and 32.4% in the group receiving 300 mg solriamfetol).

Rosenberg et al[35] addressed the incidence and overall duration of common early-onset, treatment-emergent adverse events (TEAEs) weekly during solriamfetol treatment in the same cohort. They found that common early-onset TEAEs during week 1 were similar during the follow-up period, and they included headache, nausea, and decreased appetite (occurring from 2.5% to 8.5%).

Surgical Treatment of Obstructive Sleep Apnea

Postoperative hypoxemia commonly occurs after general anesthesia in obese individuals. Rosén et al[36] addressed whether early application of high-flow nasal oxygen (HFNO) would improve postoperative oxygenation compared with standard oxygen therapy following general anesthesia for laparoscopic bariatric surgery in obese adults. The results were neutral. Thus, HFNO treatment does not provide additional benefit compared to nasal oxygen in obese patients.

There are some challenges associated with the use of CPAP therapy in the postoperative period of untreated OSA patients. Sakaguchi et al[37] addressed whether the combination of high-flow nasal cannula and upper-body elevation would improve postoperative OSA management. High-flow nasal cannula was randomly applied with or without 30° head-of-bed elevation on the first and second postoperative nights to 23 patients with OSA. They concluded that the combination of high-flow nasal cannula and upper-body elevation was beneficial in reducing the AHI and nocturnal hypoxemia.

Uvulopalatopharyngoplasty (UPPP) has been one of the most common surgical treatment modalities for OSA. Tonsillectomy (TE) alone is a less extensive alternative. Sundman et al[38] investigated whether modified UPPP (mUPPP) is better than TE alone in treating adult patients with tonsillar hypertrophy and OSA. In all, 45 patients underwent mUPPP and 45 TE alone. After 6 months, the results did not differ significantly; mean AHI decreased by 43% in the mUPPP group and 56% in the TE group. Thus, mUPPP was not more effective than TE alone in patients with tonsillar hypertrophy and concomitant OSA (Table 1).[2-5,11,12,14-20,25-29,33-49]

Oral Appliance Therapy

In many past studies, oral appliances (OA) are effective, especially in mild to moderate OSA patients, and have better treatment adherence than PAP treatment. In recent years, importance has been given to the development of OA. Fransson and colleagues treated OSA patients with an OA aimed to determine the effect of sleeping positions.[39] In their study, 314 patients with OSA were included for addressing the effect of OA on positional OSA (POSA). The response to the treatment was defined as AHI below 10 and/or an at least 50% reduction in total AHI. The ratios were 56% for the non-POSA group and 69% for the POSA group, respectively (not significant).

Obstructive Sleep Apnea Management

Lajoie et al[40] (NCT03455920) investigated the noninferiority of diagnosis and management of uncomplicated sleep apnea by a clinical nurse in an RCT including 200 patients. The difference in mean change in ESS between groups 3 and 6 months were −0.71 and −0.21, respectively, indicating a noninferiority of the nurse-communicated management in 6 months. The noninferiority of the nurse-communicated management has also been reported in regard to Quebec Sleep Questionnaire results as well as PAP adherence. Thus, the assessment of uncomplicated OSA patients by a trained clinical nurse can be evaluated in sleep centers with busy schedules.

Along with increasing public awareness as well as technological developments, sleep health education and use of

Table 1. Clinical Trials in Sleep-Related Breathing Disorders Published Through January 2022 to August 2023

Authors	Year	Journal	Participants	Clinical Registration Number
Alvarenga et al[2]	2023	*Front Neurol.*	46	NCT01884454
Ertaş et al[3]	2022	*Int Urogynecol J*	60	NCT05250245
Tu et al[4]	2022	*J Clin Sleep Med.*	118	NCT01785303
Kalkhoff et al[5]	2022	*Am J Obstet Gynecol MFM.*	193	NCT02755831
Azarbarzin et al[11]	2022	*Am J Respir Crit Care Med*	226	NCT00519597
Eulenburg et al[12]	2023	*Ann Am Thorac Soc*	399	NCT00519597
Peker et al[14]	2022	*J Clin Med.*	147	NCT00519597
Lao et al[15]	2022	*BMC Pulm Med*	131	NCT00738179
Zhao et al[16]	2022	*J Clin Sleep Med*	169	NCT01261390
Celik et al[17]	2023	*J Clin Med.*	239	NCT00519597
Celik et al[18]	2022	*J Clin Med*	196	NCT00519597
Giampá et al[19]	2022	*Chest*	100	NCT02295202
Zheng et al[20]	2022	*J Clin Sleep Med*	32	ACTRN12605000096651
Schweitzer et al[25]	2023	*Sleep Breath.*	62	NCT04445688
Perger et al[26]	2022	*Chest*	16	NCT04449133
Messineo et al[27]	2022	*Nat Sci Sleep.*	13	ACTRN12621000158864
Hedner et al[28]	2022	*Am J Respir Crit Care Med.*	68	EU Clinical Trials Register 2017-004767-13
Jiang et al[29]	2022	*Sleep Breath.*	90	Shenzhen Yantian District 20180329
Krystal et al[33]	2022	*J Psychiatr Res*	710	NCT02348593, NCT02348606
Malhotra et al[34]	2022	*Sleep Med.*	1229	NCT02348632
Rosenberg et al[35]	2022	*J Clin Sleep Med*	710	NCT02348593, NCT02348606
Rosén et al[36]	2022	*Health Sci Rep.*	34	ISRCTN37375068
Sakaguchi et al[37]	2022	*Anesthesiology*	23	UMIN000037265
Sundman et al[38]	2022	*JAMA Otolaryngol Head Neck Surg.*	93	NCT02523248
Fransson et al[39]	2022	*Am J Orthod Dentofacial Orthop*	205	NCT02148510
Lajoie et al[40]	2022	*J Clin Sleep Med*	200	NCT03455920
Robbins et al[41]	2022	*BMJ Open*	1355	NCT04224285
Murphy et al[42]	2023	*Thorax*	82	NCT02342899, ISRCTN51420481
Horne et al[44]	2022	*J Clin Sleep Med*	100	missing
Boulos et al[45]	2022	*Stroke*	250	NCT02454023
Fridriksson et al[46]	2023	*Ann Am Thorac Soc.*	409	NCT03446560
Murase et al[47]	2022	*Chest*	168	UMIN000033607
Kazemeini et al[48]	2022	*Sleep Breath.*	10	NCT03716648
Wang et al[49]	2022	*Front Neurol.*	24	NCT03523013

sleep-related applications for smartphones remain important factors for investigators. In an open-label, randomized, parallel-group controlled trial by Robbins et al[41] (NCT04224285), the effect of a sleep health education combined with a personalized smartphone application on sleep, productivity, and health-care utilization has been examined among employees at a large health-care organization. An online Sleep Health and Wellness (SHAW) program was paired with a personalized sleep training program deployed via a smartphone application (Dayzz app). Having received 9 months of SHAW educational program and access to Dayzz app, the intervention group (n = 794) reported an increased sleep duration (in average, 21 minutes on work nights and 22 minutes on work-free nights) compared to the control group (n = 561) having received the intervention at month 10.

Telemonitoring

Home-based sleep studies are widely used in most sleep laboratories across the world for appropriate patient populations. Telemedicine facilitates the close follow-up of patients prescribed PAP therapies. These approaches also aim to prevent excessive health-care costs and work overload in sleep laboratories. Additionally, current guidelines have recommendations regarding the initiation of home NIV in subjects with clinically stable OHS in outpatient settings. Other investigators (NCT02342899)[42] have conducted a multicenter

open-labelled clinical trial to examine the cost-effectiveness of titration of 82 OHS patients in inpatient vs. outpatient settings in 3 months. Safety and efficacy analysis have demonstrated similar differences in inpatient and outpatient cases regarding $PaCO_2$ levels and equivalent per-patient costs (£2962 ± £580 vs. £3169 ± £525) with comparable clinical improvements, including health-related quality of life. The authors suggested that home NIV can be considered for managing stable OHS patients, depending on the preferences of the patient and the physician.

In-Person vs. Video Hookup Instructions: A Comparison of Home Sleep Apnea Testing Quality

Home sleep apnea tests (HSATs) (types 2-4 sleep studies) have been an alternative way of OSA,[43] in a possibly more comfortable, more accessible, and quicker manner compared to standard in-lab testing. Although there have been studies about improving different telemonitoring aspects of HSATs, there is yet not enough evidence to make the hookup procedure more telemedicine compatible. In a double-blind study by Horne et al,[44] 100 patients (of 127 screened patients) with supposed OSA were randomly assigned to receive either in-person or video hookup instructions for the Nox T3 device (Nox Medical, Reykjavik, Iceland) to compare the quality of the sleep study. The instructional video in the intervention arm explained the contents of the HSAT kit, attachment, and recording procedures using animations. The overall and sensor [any of the 4 sensors (pulse oximeter, nasal cannula, thorax, and abdomen respiratory inductance plethysmography belts)] signal quality of HSAT recordings were similar (on average of high quality for both groups, with over 90% of the recording durations being artifact-free (mean quality >90%) in the group randomized to in-person and video hookup instructions. The authors listed insecurity of the patients for the procedure by using video instructions, language barriers, and technological limitations (i.e., unavailable internet access) as possible barriers to be managed based on the reasons for refusal to participate in the study. In eligible patients, providing video recordings of hookup instructions for HSATs is a viable alternative to providing them in-person, allowing patients in remote and rural areas more effortless access to sleep studies and saving health-care personnel time.

SLEAP SMART (Sleep Apnea Screening Using Mobile Ambulatory Recorders after TIA/Stroke)

In an RCT by Boulos et al[45] (NCT02454023), 250 consecutively recruited patients with a history of stroke or TIA were randomized to ambulatory (performed in their hospital bed or at home) or in-laboratory sleep testing, and the rates of OSA diagnosis were 49% vs. 35% (P = .04), respectively. The functional outcomes, daytime sleepiness assessed at 6 months, were significantly improved in the prior arm compared to later in a cost-effective manner. Thus, screening for OSA with HSATs should be strongly considered to improve nonvascular outcomes for patients with stroke.

Effects of Early Intervention Telemedicine-Based Follow-Up in Sleep Apnea

Cloud-based telemonitoring of PAP therapy as a method of transmission of therapeutic data has been investigated lately for its effect on improving adherence rates. In a multicenter, randomized controlled superior trial by Fridriksson et al[46] (VGFOUREG663941) evaluated clinical utility and patient satisfaction of PAP follow-up with an early intervention telemedical protocol in 9 adults with OSA. Patients were allocated to either standard PAP follow-up or early intervention telemedical follow-up (with close telemonitorization regarding compliance, treatment efficiency, and mask leakage, and management of patients with related problems by teleconsultation or outpatient visit (if required) for the first month) for 3 months. Adherence to PAP treatment was higher in the intervention group, but the difference was comparatively small. The intervention group experienced less problematic mask leakage, but the proportion of switching mask types was still similar.

Multimodal Telemonitoring for Weight Reduction in Patients with Sleep Apnea

Murase et al[47] conducted a multicenter RCT including 168 obese (average BMI of 31.7 ± 4.9 kg/m^2) patients with OSA using CPAP (>1 month) (UMIN000033607). In the usual PAP telemonitorization group, PAP data was followed remotely, and monthly feedback calls were provided to increase PAP adherence. In the intervention group, on top of PAP telemonitoring, electronic scales, blood pressure monitors, and pedometers were implemented to transmit data from devices wirelessly for 6 months. Monthly feedback calls were provided by attending physicians to encourage patients to PAP adherence and body weight reduction. Multimodal telemonitoring was found to enhance weight loss more effectively compared to usual PAP telemonitoring, independent of the body weight at baseline.

Drug-Induced Sleep Endoscopy

The rapid developments in technological innovations have a great influence on the management of sleep disorders. The DISE has been an important topic for researchers and has been compared and combined with other modalities. In a pilot cross-over study by Kazemeini et al[48] (NCT03716648) compared the clinical effectiveness of subjective titration vs. objectively guided titration during polysomnography and drug-induced sleep endoscopy in mandibular advancement device (MAD) treatment for patients with OSA. In the study, which included 10 OSA patients and performed 3 different titration methods, targeted optimal protrusion and maximal comfortable protrusion were similar in both groups. Similar and nonsignificant differences have been reported in the reduction in AHI as well. Notwithstanding, a higher predictive accuracy has been observed (83.3% sensitivity and 100% specificity) in the DISE group.

The comparison of DISE-guided CPAP titration and conventional sleep center CPAP titration was also examined by Wang et al[49] in a randomized controlled crossover trial including 24 patients with moderate-to-severe OSA patients (NCT03523013). At the end of 2 months, the patients received both treatments. Similar outcomes regarding the upper limit of the pressure levels and equivalent residual AHI, as well as compliance, have been reported in both groups following 4 weeks of CPAP treatment. A significant association between epiglottis and tongue base collapse and 95% CPAP pressure has been reported. Multivariate regression analyses have

defined the epiglottis as an independent determining variable for 95% CPAP level. Although a high incidence rate of bradycardia (58%) was observed in the DISE group, all patients recovered following treatment. Thus, DISE-guided CPAP titration can be an option for uncomplicated OSA patients.

CONCLUSIONS

Important progress in the field of SRBD has occurred since January 2022. They cover important insights into the heterogeneity of cardiometabolic disorders among adults, OSA management, drug therapy for OSA, PAP therapy and cardiovascular outcomes, PAP in pregnancy, as well as the effects of surgical treatment and oral appliances. We also underline future directions in OSA management, telemonitoring, and DISE in the management of the SRBDs, especially OSA. We ascertain concurrently that more studies are needed in the fields of CSA, OHS, and ISRH.

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