Guidelines for the treatment of sleep disordered breathing in the elderly

A consensus by the International Geriatric Sleep Medicine Task Force

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Abstract

Background: Sleep Disordered Breathing (SDB) is a leading cause of morbidity world wide. Its prevalence increases with age. Due to the demographic changes in industrial societies, pulmonologists and sleep physicians are confronted with a rapidly growing number of elderly SDB patients. For many physicians it remains unclear how current guidelines for SDB management apply to elderly and frail elderly patients. The goal of this consensus statement is to provide guidance based on published evidence for SDB treatment in this specific patient group.

Methods: Clinicians and researchers with expertise in geriatric sleep medicine representing several countries were invited to participate in a task force. A literature search of Pubmed from the last twelve years as well as a systematic review of evidence of studies deemed relevant was performed.

Results: Recommendations for treatment management of elderly and frail elderly SDB patients based on published evidence were formulated via discussion and consensus.

Conclusions: In the last twelve years, there have been surprisingly few studies examining treatment of SDB in older adults and even fewer in frail older adults. Studies that have been conducted on the management of SDB in the older patient population were rarely stratified for age. Studies in SDB treatment which did include age stratification mainly focused on middle aged and younger patient groups. Based on the evidence that is available, this consensus statement highlights the treatment forms which can be recommended for elderly SDB patients and encourages treatment of SDB in this large patient group.

Key Words: Sleep Disordered Breathing, Apnea, Elderly, Old, Frail, Treatment, Management

Summarizing sentence: This article on the treatment of SDB in elderly patients gives an overview of the research done in the field and based on it clinical guidelines.

INTRODUCTION

The world today is facing an unprecedented aging of the population. According to the WHO, the number of people aged 65 years or older is projected to grow from an estimated 524 million in 2010 to nearly 1.5 billion in 2050, with most of the increase in developing countries (1).

The prevalence of sleep disordered breathing (SDB) in this age group, based on a definition of an apnea-hypopnea index (AHI; the number of apneas and hypopneas per hour of sleep of at least 10), is over 20% in various epidemiological studies (2,3,4). In frail elderly patients, prevalence rates reach as high as 60% (5). These data suggest that in the future, sleep medicine health professionals will be asked increasingly to evaluate the need to treat SDB in elderly patients over 65 years of age.

This aged patient group can differ from younger or middle aged patients with SDB in many ways. In fact, this large and growing population is a highly diverse group, as the aging process varies from one individual to another. Some individuals age very well without serious disease and function perfectly in daily life, i.e., they experience “successful aging” (6). Other older adults have many comorbidities, several handicaps and several serious diseases and consequently are frail. This phenomenon is named “pathological aging”. Yet other individuals are between the two categories representing the “usual aging” that may be associated with chronic but stable comorbidities but without significant dysfunction in daily life.

SDB, in older populations as in younger ones, is associated with serious outcomes including stroke (7,8,9), occult nocturnal hypertension (10), open angle glaucoma (11), falls with fractures (12), impaired quality of life (13), decreased pain tolerance (14), frailty (15) and

mortality (16,17,8,9). These potentially serious outcomes of SDB in elderly patients imply that treatment for SDB may be at least as necessary as in younger and middle aged SDB patients. Effective treatment of the disorder has been associated with major improvements in pain tolerance (14), in risk of falls (12), stroke (9) as well as diminished risk of cardiovascular morbidity and mortality (17). In view of these considerations it should not be surprising that untreated SDB in older adults is associated with significant medical costs (18). The potentially serious outcomes of SDB in elderly patients imply that treatment for SDB may be at least as necessary as in younger and middle aged SDB patients.

Despite the high prevalence of SDB in the older populations, the condition is frequently unrecognized and undiagnosed even in geriatric settings (18,19). Unfortunately, many older patients who do seek medical attention for SDB are dismissed as having no significant illness without formal assessment. At least three factors underlie the lack of recognition of SDB in older adults: 1. Clinical presentation of the disorder may often be atypical (5, 20, 21) and history taking and the interpretation of signs and symptoms related to SDB are extremely difficult (22). 2. Health professionals are not well prepared to screen and manage sleep problems especially in older adults. The disparity between a high prevalence of undiagnosed OSA (Obstructive Sleep Apnea) in the population and the low level of clinical recognition has been recognized in different patient groups (5; 20, 21). 3. Sleep laboratories are not easily accessible to many frail older adults living in nursing homes and long term care units. 4. We do not know in elderly, what is the limit between physiological and pathological in terms of number of sleep disordered breathing.

Regarding the latter issue, the low diagnostic rate of SDB in elderly might change with the changing diagnostic policies for SDB by healthcare insurances and providers. For example, in lieu of sleep laboratory based polysomnography (PSG), home sleep testing may now be covered in many countries. Regardless of which test is performed, older patients should be evaluated with a comprehensive geriatric assessment (23, 24). Nevertheless, treatment

outcomes regarding clinical symptoms, for example excessive daytime sleepiness, might be different in the different age groups as shown in the Stuart/Florida cohort of the Sleep in Primary Care Study (20).

Although in the past decades and more recently there have been several reviews and meta-analyses that have helped define therapeutic management for OSA, (25, 26, 27, 28, 29) the majority of these have focused on middle-aged populations. Given the uncertainty regarding effects of OSA treatment in elderly populations, we undertook a consensus process to analyze all treatment studies in older populations with SDB performed in the last twelve years. Our goal was to develop evidence-based practice recommendations. This paper is an outcome of that process.

METHODS

On invitation by the Geriatric Assembly of the German Sleep Society (DGSM) and individual members (N. Netzer, F.Almeida) of the Assembly Sleep and Respiratory Neurology of the American Thoracic Society (ATS), eleven experts in geriatric sleep medicine formed a panel representative of the diversity of opinions from the Americas and Europe and were members of the several societies involved in guidelines for sleep disordered breathing therapy, namely ATS and European Respiratory Society (ERS) as well as American Academy of Sleep Medicine (AASM), the Sleep Research Society (SRS) and the European Sleep Research Society (ESRS). In addition, the group aimed to cover different fields involved in the treatment of SDB, namely psychiatry, pulmonary, geriatric medicine, dentistry, neurology, behavioral science, and airway physiology.

The panel met for the first time in Berlin, Germany, December 2012 and thereafter on several other occasions at various sites in 2013-2015, and decided on the structure of a systematic review of publications covering therapy of SDB in older patients. After much discussion, there was consensus to define “older” as aged 65 years and over as this age is the most frequently

used cut-off for elderly in the scientific literature. Papers were only included in this review if the population studied included patients with a mean age of 65 or older, a majority of patients 65 years of age or older, or included older adults of 65 years and older in their sample and gave the results stratified by age (i.e., were results in the older adults the same or different than in the younger adults).

Pubmed/Medline publications from the last 12 years until May 31, 2015 were searched with keywords of “sleep disordered breathing”, “sleep apnea”,”OSA”, “OSAS”, OSAHS”, “central sleep apnea”, “therapy”, “aged”, “elderly. This resulted in a total of 1740 publications with abstracts in English language. A team of two panel members reviewed the literature to examine how many studies were primarily on older adults and fulfilled the above described inclusion criteria. In a second step, a team of two other panel members performed a second screening of the 1740 abstracts based on the sole criteria of whether the publication dealt with SDB therapy in the geriatric age group. This resulted in a total of 178 publications (all in English language) meeting criteria.

The 178 full papers were then distributed to five teams of two panel members each. The scoring teams were formed with the following subspecialties within the panel: Noninvasive ventilation therapy, dental and oral appliance therapy, cardiologic and surgical therapy, supplemental oxygen therapy and alternative treatment options including drugs.

Each paper was evaluated for whether it met the inclusion criteria and each was scored for the evidence level based on the GRADE working group into four evidence levels: “High”, “Moderate”, “Low” and “Very Low” (30) and parallel each paper was scored according to the evidence scoring of the Scottish Intercollegiate Guidelines Network grading (SIGN, see table 1) (31). SIGN was chosen parallel to GRADE to determine evidence levels of studies because it ranks original randomized controlled studies highest, before metanalyses, which seemed to be more appropriate for the development of principle of practice parameters than

the usual evidence grading, which ranks metaanalyses in the highest position, and because it gives in addition to GRADE (four levels) a higher differentiation of evidence of papers into eight levels (1++ - 4). In addition a Jadad score was assigned to each study to assess the level of possible bias of each study (see table 2) (32).
For the clinical recommendations or guidelines the GRADE ranking for “strong” or “weak” from the GRADE working group has been applied (30).

Each team created a table of publications that fulfilled the inclusion criteria and wrote the corresponding section for this publication. When there were insufficient numbers of publications meeting inclusion criteria, results from publications in younger adults were summarized, with the understanding that those results may or may not apply to the elderly and the frail elderly. Each team also provided recommendations for the principle of practice parameters within their subspecialty. The final recommendations of the expert consensus for each treatment are presented at the end of each chapter.

EVALUATION AND CLINICAL RECOMMENDATIONS

Positive Airway Pressure (PAP) and Servoventilation Treatment

It is well documented that OSA is well treated with PAP. There have been many studies on the effect of treating OSA on outcomes other than apnea-related symptoms, such as heart failure, hypertension, diabetes, etc.; however, few of these studies have been conducted on older adults or in frail elderly. Only 29 papers met the inclusion criteria and these 29 were reviewed, evaluated and are presented in Table 3. Two of these studies reviewed stratified the results by age and five papers represented different components of a single clinical trial.

The majority of the studies (n=21) evaluated populations with medical co-morbidities more prevalent in older adults (e.g. dementia, Parkinson’s disease, stroke, heart failure, COPD),

and the main outcomes were the effect of PAP treatment on either apnea or on some aspect of that co-morbidity.

As can be seen in Table 3, the evidence levels of these studies ranged from high of 1++ (one study) (33) to low of 2- . Only 13 were RTCs (Randomized Controled Trials), with the rest being observational in nature. The Jadad score for 20 publications were in the 0-3 range suggesting a higher risk of bias; eight were scored in the 4-5 range suggesting a lower risk and a higher quality study. Sample sizes ranged from a handful to over 4000.

Heart Failure or Cardiovascular Disease

Nine of the studies had a primary outcome of some form of heart disease, hypertension or renal disease measures (34-42). Results of these studies suggested that CPAP (Continuous Positive Airway Pressure) or ASV (Adaptive Servoventilation) treatment of the OSA and/or CSA (Central Sleep Apna) resulted in overall improvement in the primary outcome measures. These results were often compared to either no treatment groups or groups of non-compliant PAP patients. Most of these studies however were observational cohort studies with only three RCT (33, 34, 41). Preliminary results from a major RCT, the SERVE HF study, have been reported recently (43) that suggest that ASV specifically may have detrimental effects in chronic heart failure (CHF) patients with an ejection fraction of ≤45% across a broad age range who have predominantly central sleep apnea, so the value of this particular type of positive airway pressure delivery in some elderly patients with heart failure remains uncertain.

Overlap Syndrome

Although one might suspect that the overlap of OSA and COPD (Chronic Obstructive Pulmonary Disease) should be very common in the elderly OSA patient group, because COPD is very common in elderly patients, only one study was found which fulfilled the

inclusion criteria. But this high quality cohort study not only had a large elderly cohort in an overlap patient group, it was also stratified for age (43). The retrospective analysis of almost 800 sleep laboratory patients revealed that the prevalence for the overlap syndrome is significantly higher in elderly OSA patients compared to younger and middle aged patients and that auto CPAP and bilevel CPAP lead to a significant improvement of blood gases over a longer period of time in comparison to patients who were non compliant to CPAP or patients who had COPD alone.

Stroke

Three studies either included stroke patients as the full sample or had stroke as the primary outcome (45, 46, 47), and one study had mortality due to stroke as a secondary outcome (46). Two of the four studies were RCT with untreated participants as the control groups (45,46). For those studies with stroke or vascular events as the outcome, all showed fewer events in the PAP-treated group. The one study examining the effect of PAP on apnea–related symptoms in stroke patients found no improvement (47).

Dementia

Seven studies included patients with either Alzheimer's disease (AD) (48-53) or Parkinson's disease (PD) (53), and three of these examined the effect of PAP on cognition (48, 52, 53). The results suggested that PAP treatment in patients with AD or PD results in good adherence (see Adherence section below), reduced apnea-related symptoms (daytime sleepiness) and AHI , and led to deeper sleep (45-49,51). One study found that 3-weeks of PAP treatment resulted in some improvement in cognition, but a 3-week comparison to sham CPAP was underpowered (48). Two showed that long term use of PAP in AD patients resulted in slower cognitive deterioration (52,53).

Effect on Sleep Apnea

Nine studies either focused on the effect of PAP on OSA-related symptoms (daytime sleepiness, oxygenation) and AHI or included these outcomes as part of their studies (35,40,42,45,47,50,52,54,55). Of these nine, eight were RCT and one was a controlled open-study without randomization. Seven of the nine studies showed that PAP treatment of OSA resulted in improvement of breathing or of sleep architecture and daytime sleepiness (35,42,45,50,52,53,55). One study found that there were no significant improvements in any of the outcome measures including daytime sleepiness (47).

Adherence

Five studies focused on PAP adherence (52, 55, 56-58). An additional four studies reported adherence although it was not an outcome variable (42, 45, 47, 59). Of these nine studies, five were RCTs. Only three studies actually reported hours of PAP use (49, 55, 59), and this included one in patients with AD who wore the PAP for an average of 4.8 hours (49). These authors also found that more depressive symptoms were associated with worse adherence (49). In 6 papers, the authors all reported that adherence was high and was often associated with greater improvement in the outcome measures, but did not report actual hours of use. One study reported more modest usage (medians of 1 hr 52 mins to 2 hrs 22 mins) but did not correlate results with outcomes (55). One study reported that acceptance rates were lower in older patients than younger patients, but there was no difference in the number of hours used within compliers (56).

Mood

Five studies examined the effect of PAP treatment on mood or depression, all of which were RCTs (47, 49, 52, 55, 60), but two were from the same population of subjects (acute vs. long term use of PAP)(49,52). Both these studies showed improvement in mood with short- and long-term use. One study found no change in depression scores with PAP use (47), but another did (55).

Cognitive Function in elderly Patients without Dementia

The PREDICT multicenter study reported that a lower daytime sleepiness score and reduced risk factors for cardiovascular diseases in elderly CPAP users was acheived at the same cost as best supportive care; however neither CPAP nor best supportive care had an influence on mood and cognitive function (60). In contrast, the PROOF study found a significant improvement in cognitive function (assessed with different memory tests) after CPAP therapy in OSA patients with no AD or PD (59). The recent RCT from the Spanish Sleep Network noted evidence of improvement in neuropsychological functions on several different measures of cogntintion (55).

Quality of Life and Cost Effectiveness

Four studies had quality of life as one of main outcomes of PAP therapy in elderly patients (55, 58, 61, 62). One of the studies used the Sleep Apnea Quality of Life Index (SAQLI) and found a significantly better quality of life in the 21% who used CPAP (58). Another study reported substantial effect size differences in all quality of life measures over time in a CPAP group realtive to controls (55). One study was gender oriented and concentrated on sexual function and male health in older men with OSA (62). The authors found a better subjective male health quality in the CPAP users versus a control group without CPAP, and this result was independent of testosterone levels.

Summary

In summary, studies of PAP treatment of SDB in the elderly primarily showed improvement in variables of SDB (e.g., AHI, daytime sleepiness) as well as consequences of SDB including comorbidites and psychosocial factors. While studies of frail elderly (i.e., those with AD or PD) were well-controlled, the majority came from the same laboratory and the AD studies were primarily from the same cohort; therefore replications are needed. In addition, many of the studies were small sample sizes and did not have high evidence levels. Larger, randomized, controlled studies are still needed in older adults and the frail elderly.

Recommendations on the expert consensus level:

1. PAP should be used routinely for the treatment of SDB in older persons and in frail elderly, particularly those with stroke but without major heart failure with an ejection fraction ≤45%. GRADE: Strong
2. While additional randomized controlled trials are needed in patients with AD and PD as well as other frail elderly, these patients do tolerate PAP and treatment should be considered. GRADE: Strong
3. PAP leads to a significant improvement of oxygenation in patients with SDB and COPD (Overlap Syndrome) and should be routinely used in these patients. More studies are needed if additional oxygen further improves results. GRADE Weak
4. Due to the results of the large RCT “SERVE HF” and the following recommendations of all major pulmonary and sleep societies to abstain from servoventilation treatment in patients with heart failure (NYHA 2-4) with an ejection fraction ≤45% no recommendation can be given regarding PAP treatment for this patient group until further trials have shown that CPAP in comparison to servoventilation has no negative outcome on mortality.

Dental Treatment

Four articles met the inclusion criteria and were reviewed and evaluated. All four had an evidence level of 2- and are presented in Table 4. Only one of these articles had oral appliance treatment as its topic and this study also stratified results of a larger cohort for age. Three articles assessed denture wearing at night and all three had an elderly patient group and did not stratify by age.

Oral Appliance Treatment

Currently, the primary treatment for OSA is PAP, however, some patients are unable to tolerate and comply with PAP on a long-term basis. Oral appliances are now widely used for the treatment of snoring and mild-to-moderate OSA as primary therapy and for severe OSA as an alternative for patients who are unwilling or unable to tolerate PAP (63).

Oral appliances can be divided into two major types: 1) those that reposition the mandible forward, the mandibular advancement splints (MAS) or mandibular advancement device (MAD), and 2) those that hold the tongue forward, the tongue retaining devices (TRD) (64). In a recent review, a randomized control trial comparing MAS to PAP treatment confirmed that PAP is superior in reducing the AHI (65). Despite the greater efficacy of PAP in the reduction of apnea, both treatments equally improved quality of life, neuropsychological measurements, cardiovascular disease markers and mortality rate (66-68). This comparable effectiveness of PAP and MAS has been hypothesized to be related to a greater adherence to MAS when compared to CPAP.

Despite having currently more than eleven randomized control trials comparing MAS to CPAP, a vast literature on MAS efficacy, and many studies including patients older than 65 years in their sample, there is only one study to our knowledge which has evaluated this type of treatment separately for the elderly population. Marklund and collaborators described in a retrospective study the follow-up of 33 patients older than 65 years (mean age 68.5±1.7) with and without the use of a MAS (69). They found a statistically significant improvement in the AHI for the group using a MAS (AHI 22.3±16.7 at baseline and 10.4±12.9 with MAS).

While MAS shows an overall 50-60% chance of being able to reduce the AHI to normal levels(70), there are various studies attempting to identify predictors of success. While some studies found that an increase in age was negative predictor of MAS success (i.e. the older the patient the less likely to achieve treatment success), these studies have assessed mainly patients with an average age of 44 to 49 years of age (65, 71-75). One study, which included

about 5% of patients over the age of 65, did not find age as a predictor of treatment success in either men or woman (76). There is, therefore a lack of studies focusing on this population and further studies are required to assure the efficacy of MAS for the elderly population.

Another important point in the utilization of MAS is that there is a need of a minimum of 8 to 10 teeth per arch and good/constant dental hygiene and these characteristics are not always the case in the elder and/or frail population. In these cases, the oral appliance of choice is the TRD. This appliance can be used over dentures and/or reminiscent teeth. Still there is a need for manual coordination and likely the lack of tongue tremor to ascertain the proper insertion and retention of the TRD every night. One study comparing the TRD to MAS found similar efficacy but a higher adherence rate to MAS over TRD on dentate (non-denture user) (77). Previous studies also found similar TRD efficacy. Interestingly these studies mostly assessed dentate individuals younger than 65 years of age (78-82). The literature on TRD is limited and none of the studies assessed this type of treatment for the elderly or edentulous population.

Denture Wearing at Night

The incidence of edentulism (loss of teeth or no teeth) has dropped over the past decades, with a 10% decline in every decade. Despite this decline, it has been estimated that 24% of individuals aged 55 to 65 years will need 1 or 2 dentures in 2020, while 28% of adults between 65 and 75 and and 41.5% older than 75 years will need denture services in 2020 in the United States (83). Tsuda and collaborators, using the Berlin questionnaire, found that 42% of patients from an edentulous clinic showed a high probability of having OSA (84). Case reports also suggest edentualism as an OSA risk factor (85).

Dentists generally recommend the removal of dentures during sleep since constant wear is believed, though with small long-term scientific evidence, to increase denture irritation, stomatitis and bone resorption. Bucca and collaborators therefore assessed the impact of

wearing dentures during sleep on 2 consecutive nights in 48 patients (86). They found that 48% of patients had OSA while wearing their dentures during sleep and this incidence rose to 71% if the individuals removed their denture to sleep. Similarly, Arisaka and collaborators found that wearing dentures during sleep improved the apneas and hypopneas in 70% of individuals but interestingly, 14% showed a significant increase in the AHI while wearing dentures (87). This controversial aspect was confirmed by Almeida and coworkers who conducted a randomized trial and found an aggravation of OSA while wearing dentures (88). This worsening of OSA was predominantly related to individuals with mild OSA sleeping in the supine position (88).

Summary

In summary, larger randomized controlled trials are needed to better understand the role of dentures in the worsening or improvement of OSA. It is important to assess these individuals' characteristics while wearing and not wearing their dentures during polysomnography. Simple measures, such as sleeping with dentures, may play an important role in improving OSA and decreasing the requirement of treatment for this population.

Recommendations on the expert consensus level:

1. A clear recommendation for MAS, MAD or TRD as first line treatment in mild to moderate SDB can not be given at this point in time as only one study stratified the particiants by age. Further prospective clinical trials with higher evidence levels are needed in the elderly with SDB.
2. In case of CPAP failure, MAS, MAD or TRD treatment is recommended in elderly SDB patients as second line treatment after full assessment of a dental status. GRADE: Weak
3. A recommendation towards full/partial denture wear at night or non full/partial denture wear at night in elderly and frail elderly with SDB cannot be given at this point

of time as the results of the few clinical trials are too controversial to reach a conclusion.

Cardiac Resynchronization, Atrial Overpacing, Surgical Treatment, Upper Airway Stimulation, and Weight loss

Twelve papers for this treatment chapter met inclusion criteria, were reviewed and evaluated and are listed in Table 5. Two of these twelve studies (one pacemaker and one bariatric surgery) were stratified for age. The evidence level ranged from 1+ to 2- with six publications about pacemaker therapy having an evidence level of 1+ (see Table 5).

Heart Pacemakers – Cardiac Resynchronisation Therapy (CRT)

Pacemakers are very common in the elderly. Approximately 130,000 US citizens 65 years and older receive a pacemaker every year. According to a publication by the Grenoble work group, the prevalence for sleep apnea confirmed by PSG in pacemaker wearers was 59%, of which 21% had severe sleep apnea defined by an AHI > 40 (89, 90). According to several studies with sufficient evidence levels of 2 or more, CRT with the pacemaker per se reduces apneic events by increasing the cardiac output, reducing atrial afterload and therefore periodic breathing. According to a controlled open-study with 15 patients, mean age 67 years, CRT reduced apneic events and also reduced the increased pulmonary artery pressure (91). Three trials showed that CRT improves all types of apneic events significantly. In all these trials, CRT was also compared to atrial overpacing in a cross-over fashion (92-94).

Atrial Overpacing (AOP)

The physiologic concept behind putting the pacemaker on a higher frequency (overpacing) than with CRT is that the total stroke volume over time increases further and therefore the atrial afterload is even lower, leading to a further decrease in apneas. A recent randomized cross-over trial showed in 28 patients with a mean age of 77,9 years that an overpacing of 20

beats per minute (bpm) over the sensored mean heart rate resulted in a significant reduction of central events (95) (see Table 5). The only age stratified study which compared CRT and AOP in 15 subjects, mean age 74, found that AOP resulted in a higher reduction of all apnea events, but not hypopneas, compared to lower fixed heart rate, mean AI 18 with AOP vs 24 with fixed lower rate coming from a mean baseline of 35. The age stratification showed a stronger effect at lower ages (94).

Only two trials claimed that CRT and AOP reduced both central and obstructive events with slight favor towards AOP (92, 94). But several studies with sufficient evidence level had contrary results (93, 96, 97). All the studies had a small number of total subjects and often less than 10 patients aged over 65. The only study with a larger number of patients and patients all over 65 years suggested a positive effect of AOP on central, but not obstructive events (95).

Two studies investigated specifically obstructive events and OSAS. Both, with less than 20 patients, found that AOP had no effect on obstructive events (98, 99). Because of the high prevalence of pacemaker implementation in the higher age group, there are a higher number of publications meeting basic criteria and higher evidence levels in comparison to the overall role this form of treatment plays among SDB treatment. This has to be taken into account when interpreting the following recommendations on the expert consensus level.

Surgical ENT (Ear Nose Throat) Procedures/Upper Airway Stimulation

Within the 1740 publications screened, there were no articles meeting the inclusion criteria. This might be related to avoidance of elderly patients who might have a higher peri- and post operational risk as well as to a more sophisticated selection process in order to achieve higher success rates and better long term results of surgical treatment for OSA and heavy snoring. A good example for this is the actual hypoglossal nerve stimulation (HNS) study of the STAR Trial (Stimulation Treatment for Apnea Reduction), where selection criteria for

younger, non-obese OSA patients without concentric collapse in the velopharynx have been set at the highest level to avoid failure of the trial as has happened in other HNS trials (100). Less than a handful of patients in the STAR trial were over 65 years old.

Surgical Treatment for Weight Loss

One publication met the inclusion criteria of age stratification. This study looked retrospectively into a group of 5290 severely obese subjects with OSA, all of whom received surgery with a gastric banding for weight loss. The authors claimed that in the 216 geriatric patients (184 females) aged older than 65 years of the 5290 patients total, the operation was successful in all, bringing the AHI at a level below 10 (101). The retrospective analysis has a lower evidence level and the results should be replicated in prospective trials before a statement can be made regarding gastric banding surgery in geriatric patients with SDB. Two publications just missed the inclusion criteria but dealt specifically with an older patient group (>60 years) and had a higher evidence level (102, 103). In both publications the effects of weight loss after laparoscopic Roux-en-Y gastric bypass (LRYGB) was evaluated in the older patient group, all of whom had been severely obese before surgery. A total of 300 patients had a reduction of their sleep apnea and AHI and further comorbidities related to their severe obesity without major peri-operation complications. LRYGB has opened the possibility of bariatric surgery for older severely obese persons, for whom more invasive bariatric surgery has been too high of a risk before. LRYGB might become a major supportive treatment for all comorbidities of obesity including SDB in the near future.

Dietetic Weight Loss Treatment

None of the screened publications on dietetic weight loss therapy for SDB treatment met inclusion criteria. Therefore no statement can be made.

Recommendations on the expert consensus level:

1. In patients with heart failure, atrial fibrillation and central apneas there is evidence that pacemaker implement can alleviate central apneas and periodic breathing respectively. In such patients pacemaker implement can be recommended on an expert consensus level. GRADE:Strong
2. The evidence level is too low to give a recommendation in regard of favoring the type of pacemaker modus. Larger randomized controlled cross over trials are needed here in the future to make a statement.
3. No surgical ENT procedure can be recommended at this time as therapy for geriatric and frail geriatric patients with OSA, as there is no evidence of success in the elderly patient groups. Larger trials in the future should include age stratification. GRADE:Weak
4. Due to new noninvasive surgical methods with laparoscopic Roux-en-Y gastric bypass (LRYGB), for which several-year outcome data show some evidence of clinical success in older patients, this form of bariatric surgery can be considered as supportive treatment in multimorbid (not only sleep apnea) severely obese patients (BMI> 40) in the intermediate elderly age group between 60 and 70yrs. with SDB. PAP and other treatments should be adapted to the post OP status. GRADE:Weak

Positional Treatment and Drug Therapy

Two papers on positional treatment and seven on drug treatment met inclusion criteria, were reviewed and and evaluated. They are presented in Table 6. The evidence levels ranged from 1+ to 3 with two RTC drug trials reaching 1+. One of the drug studies was designed as a negative study and was age stratified.

Positional Therapy

The severity of sleep-related breathing disorders may vary considerably from night-to-night, depending on body position (104,105), although some data have suggested night-to-night variability in elderly persons occurs independently from position (106). In particular, the

supine body position is associated with a two-fold or more increase in the number of respiratory events in those patients with position-dependent sleep apnea. Positional therapy includes a wide range of methods aimed at preventing the patient from sleeping in the supine position, including pillows, vests, tennis-balls, positional alarms, and more. Case reports have documented the potential utility for positional therapy (104).

Positional therapy has been included in the recent clinical guideline for the treatment of obstructive sleep apnea by the Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine (107). The guideline identified positional therapy as an effective secondary therapy or a supplement to primary therapies for patients with OSA that have a low AHI in the non-supine position. Nevertheless, two recent reviews of positional therapies highlighted the fact that long-term compliance for positional therapy remains an issue (108) and that more high-quality research is needed to evaluate the effectiveness of this therapy (109)

One study described one night use of a specifically designed pillow to avoid the supine position in 22 patients, 9 of whom were older than 65 years (110). This study compared nocturnal respiratory parameters between a baseline night and a night with the supine-avoiding pillow in patients with mild to severe obstructive sleep apnea. In the paper the individual subject's data are given in a table which allowed us to identify the 9 patients that were between 67 and 73 years old. In these older patients the respiratory disturbance index decreased from an average of 20 (SD=9) to 7 (SD=4) and minimum SaO2 during the night rose from 85 (SD=7) to 89 (SD=4).

Another study that did not meet the inclusion criteria, but did evaluate the use of a vest for one night in 12 patients between 37 and 76 years of age with in-patients with positional obstructive sleep apnea (111). Although the authors did not stratify by age, they did report that the eldest patient did not improve with this treatment.

In contrast two recently published studies showed a significant effect for positional therapy with the new sleep position trainer in subjects of all ages. They included several patients > 65 yrs of age, but the average age was around 50 years and therefore did not meet inclusion criteria.There was no stratification for age (112,113).

Drug Therapy

There has been no drug therapy recommended for the treatment of SDB. For the treatment of central sleep apnea, evidence-based, recent guidelines found limited supporting evidence for acetazolamide and theophyilline after optimization of standard medical therapy and if positive airway pressure therapy is not tolerated (114). In addition, the guideline stated that zolpidem and triazolam may be considered for the treatment of primary central apnea only if the patient does not have underlying risk factors for respiratory depression.

For the treatment of OSA, the 2006 practice parameters for medical treatment of OSA evaluated but did not recommend selective serotonin uptake inhibitors (SSRIs), protriptyline, aminophylline, theophylline, or estrogen therapy based on the lack of sufficient treatment efficacy for OSA (115). While short-acting nasal decongestants were not recommended, the guidelines concluded that topical nasal corticosteroids may be a useful adjunct to primary therapies in OSA patients with concurrent rhinitis. In addition, modafinil was recommended for the treatment of residual excessive daytime sleepiness in patients with sleepiness despite effective PAP treatment and without other identifiable causes for the sleepiness. These recommendations concur with the most recent, 2009 Clinical Guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults (107).

In 2013, a Cochrane systematic review and meta-analysis on drug therapy for obstructive sleep apnea evaluated randomized, placebo controlled trials involving adult patients with

OSA (116). The review included data of 30 trials evaluating 25 different drugs but noted that most of the studies were small with methodological limitations and that the overall quality of the available evidence was low. The review also concluded that there is currently insufficient evidence to recommend any systematic pharmacological treatment for OSA. Nevertheless, donezepil was identified as the most promising proposition at present and the authors suggested topical fluticasone in patients with co-existing rhinitis, as well as paroxetine, physostigmine, acetazolamide and eszopiclone as possible fields of future research. These studies however were not in elderly.

Concerning the treatment of CSA in the elderly, we located one double-blind, randomized, cross-over trial that evaluated the use of acetazolamide in patients with systolic heart failure and Cheyne-Stokes breathing with an AHI above 15 (117). A total of 12 patients with a mean age of 66 years were treated for 6 nights with placebo or with 3.5 to 4 mg/kg acetazolamide and 30 mg potassium chloride, with the later given to compensate for acetazolamide-induced urinary potassium loss. Compared to the placebo condition, acetazolamide was associated with a mild to moderate reduction of the AHI, the central apnea index (CAI), and an increase in baseline oxygen and minimum saturation during REM and NREM sleep. Polysomnographic sleep parameters did not differ between acetazolamide and placebo.

A further study evaluated the treatment of anemia in patients with congestive heart failure and anemia (118). In this open label study, 38 patients with a mean age of 76 years and hemoglobin levels below 12 g/dL were treated for 3 months with erythropoietin and intravenous iron up to a target level of 13 g/dL. The presence of sleep apnea was not an inclusion criteria, but 37 of 38 patients had an AHI greater 10 during nocturnal polygraphy with most of the apneas and hypopneas being central. Treatment of anemia was associated with a mild to moderate reduction of sleep-related breathing observed both for central and obstructive apneas. In addition, a reduction of Cheyne-Stokes breathing and an increase in

minimal oxygen saturation during sleep was noted. Furthermore, daytime sleepiness improved after 3 months.

For the treatment of OSA in elderly subjects, we located one double-blind, randomized, placebo-controlled trial that targeted OSA (119). In this trial, 23 patients (68-86 years) with mild to moderate Alzheimer´s disease and AHI > 5 were randomized to receive 3 months of 5 mg donezepil or placebo. Compared to placebo, donezepil treatment improved the overall AHI and minimum oxygen saturation. In addition, REM sleep increased and the arousal index decreased. Finally, cognitive function assessed with the ADAS (Alzheimer Disease Assessment Measures)-cog (cognition) score was improved in the donezepil treated group compared to the placebo group.

A further double-blind, placebo-controlled, randomized trial (120) investigated whether the addition of ramelteon, a melatonin receptor agonist, improved sleep in elderly patients with sleep apnea and insomnia symptoms. Twenty-three patients (mean ages 74 and 70 years) received a standard 45 minute counselling session on sleep apnea and started APAP (Auto Positive Airway Pressure) treatment before being randomized to receive 8 mg of ramelteon (n = 8) or matching placebo (n = 15) for 4 weeks. Sleep onset latency during polysomnography was reduced in patients taking ramelteon while neither sleep efficiency, AHI, subjective sleep latency, nor sleep efficiency differed between groups subsequent to treatment. Also self-rated sleep quality, quality of life and daytime sleepiness was the same for patients treated with ramelteon vs. those treated with placebo. In addition, compliance with APAP treatment did not differ between groups and overall APAP adherence defined as ≥ 4 h of use for ≥ 4 nights per week was 47%.

Another drug that has been evaluated for the treatment in OSA is mirtazapine which had shown some effect on sleep-related breathing in randomized trials of adult patients (121). In a subsequent open label case series evaluating 15 mg mirtazapine at bedtime for 16 to 52 days in elderly patients with sleep apnea and refusal of CPAP reported mixed effects on

breathing parameters (122). While mirtazapine improved sleep-related breathing to some extend in half of the patients, it also worsened sleep-related breathing in the other half of the patients, despite improving sleep in all patients.

Based on the observation of a single case with moderate OSA and suspected ACE (Angiotesin Converting Enzyme) inhibitor induced cough with significant improvement of OSA after the ACE inhibitor was withdrawn and diuretics were introduced, a prospective case series included 9 patients with suspected OSA and on ACE inhibitor treatment, in whom ACE inhibitors were withdrawn and diuretics were introduced (hydrochlorothiazide at 25 mg/d combined with spironolactone at 25 mg/d) (123). The paper included data on a subgroup of 5 patients with cough that had an average age of 65.4 years and was therefore included in the present review. In these patients, AHI decreased in all and exhaled nitric oxide, a marker of airway inflammation, decreased in parallel after discontinuation of ACE inhibitors.

A recent crossover study in patients with COPD and overlap syndrome found no negative effects on nightly respiration in regards to AHI and Sa02 for the use of the orexin receptor antagonist and sleep drug survorexant. This study was age stratified using a different dosage, 30mg, for a patient group over 65years of age (124).

Other case reports have suggested value of topiramate, aripiprazole, and selenium (125-127) in the treatment of sleep apnea.

Summary

In summary, large controlled studies on drug therapy of sleep-related breathing disorders in the elderly are still lacking. Two drugs that have received support from the results of smaller randomised trials are donezepil for the treatment of OSA and acetazolamide for the treatment of CSA. Both drugs have been shown to be effective in the treatment of sleep-related breathing disorders in an elderly population with mild (acetazolamide) or moderate

(donezepil) effects. In addition, there is some indication that improvement of co-morbid conditions in elderly patients with sleep-related breathing disorders may show some benefit also for breathing disorders during sleep as observed for correcting anemia in patients with CHF and anemia in an open label trial.

Recommendations on the expert consensus level

1. Due to insufficient data, positional treatment cannot be recommended as treatment for OSA in the elderly. GRADE: Strong
2. More research is needed on the long-term effectiveness of drug therapy for the treatment of sleep-related breathing disorders in the elderly. At this point in time, no recommendation for drug therapy to treat SDB in the elderly can be given.
3. Acetazolamide might alleviate Cheynes Stokes breathing in elderly patients with heart failure but further randomized controlled studies would be needed and side effects in long term treatment investigated to make recommendations.
4. Drugs used to treat dementia, such as donezipil, melatoninergic drugs such as ramelton and agomelatine, and mirtazepin, erythropoietin, ace inhibitors and others can help to alleviate clinical symptoms of comorbidities coming with SDB but can currently not be recommended for the treatment of SDB in the elderly. GRADE:Weak
5. Clinicians should be aware that several drugs may aggrevate sleep apnea. GRADE: Strong

Supplemental Oxygen

Only two papers (one observational study and one case report, evidence level 3) were identified which fit the selection criteria and addressed the effects of oxygen treatment on functional outcomes in older or frail people with SDB. They are presented in Table 6. None of the studies was age-stratified.

Intermittent nocturnal hypoxemia (INH) is a frequent consequence of both central and obstructive sleep apnea. INH is associated with cognitive (128-131) and functional (132) impairments. A large epidemiological study showed that INH rather than the number of apnoeic events per se doubled the risk of dementia in previously non-demented older community dwelling persons over a follow up period of four years (133). In a study of geriatric patients admitted for rehabilitation, INH was associated with functional impairment in a dose response relationship. However, as polysomnography was not performed, apnea frequency and sleep fragmentation could not be ruled out as additional factors (134). Nocturnal hypoxemia increases sympathetic activity and may contribute to cardiovascular complications of SDB such as hypertension and arrhythmias (135). Oxygen supplementation might therefore be effective in improving symptoms and complications of sleep apnoea, even if it does not directly address the airway obstruction. At least one case report suggests benefit of nocturnal O2 administration (136).

One observational study included 200 consecutive geriatric in-patients with severe SDB defined as an ODI (oxygen desaturation index) > 30 events per hour. Each subject was first offered PAP therapy, and then offered nocturnal oxygen therapy at a rate of 3 L/min via nasal tubes as a second choice if they refused PAP. The mean age was 81±7 years. Twenty-two patients (11%) accepted PAP, 42 (21%) accepted oxygen supplementation, and 136 (68%) refused either treatment. Baseline functional status (Barthel index) was 48, 39, and 42 for PAP accepters, oxygen accepters and treatment refusers, and improved by 7, 22, and 24 points respectively by discharge. There was no difference in the level of improvement between oxygen and PAP, and regression analysis showed that oxygen supplementation was independently associated with functional improvement (137).

The information retrieved from this systematic review alone is clearly insufficient to inform guidelines on oxygen treatment in for OSA in the older or frail person. We have therefore

also adduced evidence from studies in younger populations and evidence form trials which reported the effect of oxygen on OSA itself, rather than from wider functional outcomes.

A recent meta-analysis of oxygen supplementation in younger and middle aged subjects with obstructive sleep apnea identified 14 randomized controlled trials including a total number of 359 patients (138). The sample size of the individual studies included was small, ranging from n=8 to n=63, and dose and duration of oxygen supplementation varied between studies making comparisons difficult. Only 10 studies reported the effect of oxygen treatment on the extent and severity of OSA itself, while five also reported functional outcomes (e.g., daytime sleepiness, depression). Oxygen supplementation significantly improved nocturnal oxygen saturation, and led to a small but overall non-significant reduction in apnea frequency. However, oxygen supplementation also increased the duration of apneas in 3/5 observational studies and in a larger comparison between oxygen versus CPAP with blood pressure (BP) as outcome CPAP had a clear advantage in decreasing BP over oxygen alone (139).

Functional outcomes were reported in five studies. Of these, one showed an improvement of depressive symptoms and sleepiness with oxygen therapy (140), one a reduction in cardiovascular events (141), and two reductions in daytime somnolence (142,143). The largest study, however, showed no improvement of daytime somnolence with oxygen, but significant improvement with PAP (139).

The increase of apnea duration, even in the absence of hypoxia, can lead to metabolic acidosis, and an increase in sympathetic activation (144), which could at least theoretically increase cardiovascular complications. This has not been observed in the meta-analysis or in the two studies in this systematic review, but could be a potential risk. This should be addressed formally in future studies of the effect of oxygen supplementation in OSA in older adults.

Summary

In conclusion, oxygen supplementation in subjects with sleep apnea and intolerance of PAP treatment seems rational, since oxygen supplementation corrects hypoxemia as well as PAP and has a minor, but non-significant beneficial effect on apnea frequency. Taking into account the high number of older subjects affected with sleep disordered breathing (4) and the high rate of intolerance of PAP treatment (145), randomized controlled trials in community dwelling and nursing home older people are warranted. Such trials should assess the effectiveness of oxygen supplementation in older people with sleep apnea and refusal of PAP treatment. They should also include determination of potential metabolic consequences such as acidosis, and functional outcomes such as the ability to perform activity of daily living, cognitive status, quality of life, the frequency of nursing home placement, and mortality. Only then the importance of oxygen therapy can be assessed unambiguously. Currently, this therapy should be considered as experimental.

Recommendations on the expert consensus level:

1. Oxygen treatment should not be used routinely for the treatment of obstructive sleep apnea in older persons. GRADE: strong
2. In older, frail or demented patients who refuse PAP, oxygen treatment may be considered, but blood gases should be checked to exclude metabolic acidosis. GRADE: weak
3. Randomized controlled trials of oxygen treatment in this patient group with functional outcome measures are needed to inform treatment guidelines.

DISCUSSION

To our knowledge, this is the first systematic review of original studies addressing the treatment of sleep disordered breathing in the elderly. It is also the first publication of an expert consensus on SDB treatment in older or frail patients.

Over the time frame of almost twelve years there were surprisingly few studies examining treatment of SDB in older adults and even fewer in frail older adults despite the large geriatric population and the high prevalence for SDB in this group. Studies of the management of OSA in the older patient population are rarely stratified for age. Studies which did include age stratification in SDB treatment mainly focused on the middle aged and younger patient groups. Had more studies in larger cohorts with a number of older patients included age stratification, a more advanced meta-analysis of data in the elderly would have been possible.Therefore one recommendation of the panel is to retrospectively age stratify SDB treatment trials and publish this sub data set, as in the Swedish oral appliance data set (69). In addition, new studies should also include age stratification in their analyses. Beyond stratification per se, formal analyses should examine to what extend age may be an effect modifier of treatment benefit.

It is unclear why there are so few publications on the treatment of SDB in the geriatric population and why there are few larger randomized controlled trials, although there are a large number of epidemiological studies of prevalence of SDB in the elderly. Reasons could include a higher refusal rate for PAP treatment by older persons, perhaps also influenced by views of their younger relatives. However, if an old person does accept PAP, compliance is good. This low rate would result in a lower number of treated older adutls to be included in studies. Staff in regular sleep laboratories do not specialize in geriatric patients and therefore may not be able to cope with the extended nursing needs of the elderly, and especially frail elderly (4,19). Home testing of geriatric patients might make these studies more feasible.

There are still few studies on frail elderly although they have most certain an even higher prevalence of SDB and might benefit from treatment. Reasons for this have been pinpointed above. More randomized controlled trials in geriatric patients with dementia are needed to determine if PAP in patients with dementia, improves cognitive function as in in middle aged or non-frail older patient populations.

However, in addition to the still limited number of publications to date, it is obvious that the topic

of geriatric sleep medicine is gaining more and more attention. The number of publications concerning elderly SDB patients just in the last year has expanded substantially compared to the years before. This also includes publications about therapy of SDB in frail elderly as presented here. Further recent epidemiologic publications with several hundred elderly subjects combined contain mainly data about the link between SDB in the elderly and a rapid cognitive decline (146-148). One very recent publication-encompassing a registry of of more than 25,000 OSA patients in Denmark followed up over more than ten years presents age stratified data comparing the survival rate of PAP users to OSA patients who were for various reasons not treated with PAP (149). The protective effect of PAP appeared particularly strong in older men >60yrs of age. Elderly women may not derive comparable benefit from PAP treatment relative to men. The reasons for this gender difference are not clear yet.

A limitation of this expert consensus panel is that clinical recommendations are based on a low number of trials with high evidence levels. Also, as with all expert panels, personal bias cannot be excluded. Experts from outside the Americas and Europe were not part of the panel. Therefore the recommendations included here had to reach 100% agreement among the expert panel. This is the reason that recommendations for the treatment of SDB in geriatric patients at the moment do not differ much from principle of practice parameters for the treatment of SDB in all age groups (150).

In summary, the individual recommendations are listed within each section, but the common theme is that more randomized controlled studies are needed in geriatric and frail elderly patients with SDB as comparable in other fields of general internal medicine (151).

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