Clinical Aspects in Sleep Disorders and Apnea

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Contents

Abstract

Sleep disorders are frequently reported complaints. Insomnia and hypersomnolence are symptoms often reported by patients and study participants. Sleep disorders with clinical consequences are not as common as complaints and symptoms might suggest. Sleep medicine is a new discipline which has developed its own curricula and physician specialization. Sleep medicine has developed a classification of sleep disorders with a manual with definitions and severity criteria. This classification will become part of the ICD-11 currently developed. The classification defines insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and other sleep disorders.

Diagnostic procedures include validated questionnaires; daytime testing of alertness and sleepiness; home recording of sleep-wake behavior, activity, and physiological signals; and finally a sleep laboratory investigation, cardiorespiratory polysomnography, with all signals recorded which change during normal and pathological sleep. Quantitative assessment of sleep, sleep stages, arousals from sleep, and vegetative functions during sleep is

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well-established, and normative values including age as modifier are well described.

Sleep disorders are recognized as risk factors for many other medical and mental disorders. Sleep disorders impair performance and may be perceived as early aging. Untreated sleep disorders cause costs at all levels of health care and need to be recognized and treated as appropriate.

Sleep disorders are a target to clinical pharmacology by being recognized and potentially excluded in any pharmacological trial. And sleep disorders are subject to drug discovery and development.

Purpose and Rationale

Sleep disorders have a high prevalence in the population. Prevalence is reported to be between 10% and 30% in the general population (Ohayon 2011). According to a health survey by the Robert-Koch Institute in 1998, about 14% of the German male population and 27% of the German female population complain about frequent or moderate insomnia (suffering from not sleeping) (Penzel et al. 2005). The survey did not check for sleep disorders according to medical definitions nor did the survey use validated and approved. Only three questions could be related to sleep disorders. These were "complaints about insomnia," "need too much sleep," and "being tired." Questions were rather unspecific. This had been recognized by many sleep researchers, and they initiated their own large sample surveys on sleep disorders (Ohayon and Zulley 2001). Assessment was performed on sleep dissatisfaction and sleep duration and more specific complaints on sleep problems. These extensive computer-driven interviews had a mean duration of 48 min per person. Definitely this is unpractical for general health surveys. A follow-up health survey by the Robert-Koch Institute between 2008 and 2011 contained much more specific questions compared to the first one in 1998 (Schlack et al. 2013). Some new questions were derived from the Pittsburgh Sleep Quality Index (Buysse et al. 1989), a well-validated questionnaire used in sleep medicine. The survey assessed the same complaints as previously and in addition more specific questions on sleep duration, problems in initiating and maintaining sleep, frequency of these complaints, perceived quality of sleep, and use of sleeping medication, all during the past 4 weeks. Based on the answers, the authors were able to estimate a prevalence of 5.7% for insomnia in Germany. This survey yielded the most recent and reliable prevalence data for Germany.

However in the German health insurance system, sleep disorders play a very small role. Whereas depression, the third most common diagnosis, is responsible for 5.6% of all days on sickness leave, sleep disorders are only listed for 0.26% of days for sickness leave (DAK report 2017). Still days for sickness leave doubled over the last decade. This reflects very well an important fact. Sleep disorders remain not to be a reason for consulting a physician in the first line. Sleep disorders remain not to be a reason for requesting for sick leave. Many patients do not report sleep complaints in the first line but often as a secondary symptom. Still sleep complaints, being difficulties in initiating and maintaining sleep or in suffering from non-refreshing sleep, are very common. Therefore it is important to investigate sleep complains and sleep problems in detail.

The first assessment is, both in patients and in presumably healthy subjects, whether they suffer from sleep problems as secondary problems or from a genuine sleep disorder. The field of sleep medicine has developed over the last three decades and has defined its own classification of sleep disorders since 1979. The latest version of the classification is called the International Classification of Sleep Disorders (ICSD-3) version 3 (AASM 2014). These are listed in the following Table 1.

One major change from the second edition of ICSD to this third edition is that the many different insomnia subtypes as carefully differentiated in the second edition had now been pooled together to only three definitions. They are now called a disorder. Specifically these are chronic insomnia disorders, short-term insomnia, and other insomnia. A chronic insomnia disorder requires a duration of symptoms for at least

Table 1 Categories of the International Classification of Sleep Disorders (AASM 2014) together with their subgroups and number of disorder definitions

Group	Subgroups	Number of definitions
Insomnia	Isolated symptoms and normal variants	5
Sleep-related breathing disorders	Obstructive sleep apnea disorders Central sleep apnea syndromes Sleep-related hypoventilation disorders Sleep-related hypoxemia disorder Isolated symptoms and normal variants	19
Central disorders of hypersomnolence	Isolated symptoms and normal variants	9
Circadian rhythm sleep-wake disorder	–	7
Parasomnias	NREM-related parasomnias REM-related parasomnias Other parasomnias Isolated symptoms and normal variants	15
Sleep-related movement disorders	Isolated symptoms and normal variants	13
Other sleep disorder	–	1
Appendix A: Sleep-related medical and neurological disorders	–	6

3 months. Previously there was a distinction between primary and secondary insomnias. Secondary insomnias were related to a primary psychiatric, medical, or substance abuse disorder. Moreover, the primary insomnias were distinguished in several more subtypes. However it turned out that symptoms and consequences do not allow to distinguish all these subtypes clearly and consistently. The differentiation was difficult, if not impossible to achieve. As a consequence they were pooled together as evidence suggests that untreated insomnia may result in adverse comorbid conditions. Another major change is that many other secondary sleep disorders were taken out of the classification. Only a few very prominent secondary sleep disorders remained in Appendix A as sleep-related medical and neurological disorders. Another change was that all different environmental-induced sleep problems were now forced to be diagnosed as either a full-blown disorder of the other definitions including all defined criteria or the problems remain as "other sleep disorder." With this, the third edition became more focused and much more condense with clear definitions and severity criteria. A list of all diagnoses defined is presented in Table 2.

With this table it becomes clear that the codes being used comes from different sections from ICD 10. Most codes came from G47 and F51 sections. Some other diagnoses were distributed across several other chapters. The new classification, as presented in the ICSD third edition (AASM 2014) is now well based on pathophysiology and is now mature enough to be stable. Finally it will be incorporated in the new ICD 11, which is currently developed, as a chapter of its own, entitled "Sleep-Wake Disorders." The proposal for the new chapter for ICD 11 follows the structure as described in Table 2 and in the ICSD third edition.

Sleep-Related Breathing Disorders

The group of disorders which attracts most attention from the health-care system is sleep-related breathing disorders. Within all types of sleep-related breathing disorders, obstructive sleep apnea

Table 2 List of all sleep disorders as they are defined and specified with their ICD 10 code. Diagnoses names and codes were taken from AASM coding manual 2014

Group of sleep disorder	Diagnosis	ICD 10 code
Insomnia	Chronic insomnia disorder	F51.01
	Short-term insomnia disorder	F51.02
	Other insomnia disorder	F51.09
	Excessive time in bed	–
	Short sleeper	–
Sleep-related breathing disorders	Obstructive sleep apnea, adult	G47.33
	Obstructive sleep apnea, pediatric	G47.33
	Central sleep apnea with Cheyne-stokes breathing	R06.3
	Central sleep apnea due to a medical disorder without Cheyne-stokes breathing	G47.37
	Central sleep apnea due to high-altitude periodic breathing	G47.32
	Central sleep apnea due to a medication or substance	G47.39
	Primary central sleep apnea	G47.31
	Primary central sleep apnea of infancy	P28.3
	Primary central sleep apnea of prematurity	P28.4
	Treatment-emergent central sleep apnea	G47.39
	Obesity hypoventilation syndrome	E66.2
	Congenital central alveolar hypoventilation syndrome	G47.35
	Late-onset central hypoventilation with hypothalamic dysfunction	G47.36
	Idiopathic central alveolar hypoventilation	G47.34
	Sleep-related hypoventilation due to a medication or substance	G47.36
	Sleep-related hypoventilation due to a medical disorder	G47.36
	Sleep-related hypoxemia	G47.36
	Snoring	R06.83
	Catathrenia	–
Central disorders of hypersomnolence	Narcolepsy type 1	G47.411
	Narcolepsy type 2	G47.419
	Idiopathic hypersomnia	G47.11
	Kleine-Levin syndrome	G47.13
	Hypersomnia due to a medical disorder	G47.14
	Hypersomnia due to a medication or substance	F11 – F19
	Hypersomnia associated with a psychiatric disorder	F51.13
	Insufficient sleep syndrome	F51.12
	Long sleeper	–
Circadian rhythm sleep-wake disorder	Delayed sleep-wake phase disorder	G47.21
	Advanced sleep-wake phase disorder	G47.22
	Irregular sleep-wake rhythm disorder	G47.23
	Non-24-hour sleep-wake rhythm disorder	G47.24
	Shift work disorder	G47.26
	Jet lag disorder	G47.25
	Circadian sleep-wake disorder not otherwise specified	G47.20

(*continued*)

Table 2 (continued)

Group of sleep disorder	Diagnosis	ICD 10 code
Parasomnias	Disorders of arousal from NREM sleep	–
	Confusional arousals	G47.51
	Sleepwalking	F51.3
	Sleep terrors	F51.4
	Sleep-related eating disorder	G47.59
	REM sleep behavior disorder	G47.52
	Recurrent isolated sleep paralysis	G47.53
	Nightmare disorder	F51.5
	Exploding head syndrome	G47.59
	Sleep-related hallucinations	H53.16
	Sleep enuresis	N39.44
	Parasomnia due to a medical disorder	G47.54
	Parasomnia due to a medication or substance	F11 – F19
	Parasomnia unspecified	G47.50
	Sleep talking	–
Sleep-related movement disorders	Restless legs syndrome	G25.81
	Periodic limb movement disorder	G47.61
	Sleep-related leg cramps	G47.62
	Sleep-related bruxism	G47.63
	Sleep-related rhythmic movement disorder	G47.69
	Benign sleep myoclonus at sleep onset	G47.69
	Propriospinal myoclonus at sleep onset	G47.69
	Sleep-related movement disorder due to a medical disorder	G47.69
	Sleep-related movement disorder due to a medication or substance	F11 – F19
	Sleep-related movement disorder unspecified	G47.69
	Excessive fragmentary myoclonus	–
	Hypnagogic foot tremor and alternating leg muscle activation	–
	Sleep starts (hypnic jerks)	–
Other sleep disorders		G47.8
Appendix A: Sleep-related medical and neurological disorders	Fatal familial insomnia	–
	Sleep-related epilepsy	–
	Sleep-related headaches	–
	Sleep-related laryngospasm	–
	Sleep-related gastroesophageal reflux	–
	Sleep-related myocardial ischemia	–

disorders present the highest prevalence and are responsible for the highest direct costs in health-care systems worldwide, related to sleep disorders. Sleep apnea is a disorder with respiratory cessations during sleep. An apnea is counted if the duration is longer than 10 s. Most apnea events last for 30–50 s, but they may last more than a minute. In parallel with the respiratory cessation, oxygen saturation decreases due to no breathing. Apnea events end with a central nervous activation with parallel increase in sympathetic tone resulting in increased heart rate and increased blood pressure during this so-called arousal. Apnea events are called obstructive if they are caused by a collapse of the upper

airways when sleeping. Partial obstruction will result in hypopnea events with similar effects as apnea events. Therefore both types of events are counted together and are related to total sleep time; the apnea-hypopnea index (AHI) is the measure for severity. Central apnea events are characterized by a cessation of airflow, but the upper airways remain open. These are observed usually in patients with cardiac problems (i.e., heart failure). Some apnea events may have both an obstructive component with an obstruction of the upper airways and a component with now respiratory efforts, similar to a central apnea. These events are called mixed apnea events. These apnea events are observed in patients who start a sleep apnea therapy, and then this picture is called treatment-emergent apnea – as listed in the above list of diagnoses. While a few apnea events are observed in anybody during sleep, if the number of these events exceeds 5 events/hour of sleep (AHI $>$ 5 events/hour), this is diagnosed as mild sleep apnea. If the number of apneas exceeds 15 events/hour, this is moderate sleep apnea, and if more than 30 events/hour of sleep are found, this is severe sleep apnea.

In early epidemiological studies, the prevalence of obstructive sleep apnea (OSA) was estimated to be 4% in men and 2% in women (Young et al. 1993). Many large epidemiological studies including the investigation of sleep apnea were carried out since. Studies were performed in several countries worldwide. Over time these studies reported an increasing prevalence (Peppard et al. 2013). Peppard et al. reported obstructive sleep apnea (AHI $>$ 15 events/hour) in 10–17% of men depending on age and 3–9% in women depending on age. More recent studies have reported even higher prevalence. A population-based cohort study in Lausanne (HypnoLaus) reported moderate to severe sleep apnea (AHI $>$15 events/hour) in 49% of men and 23% of women in consecutive participants aged 40–85 years (Heinzer et al. 2015). With this high prevalence, a discussion on the definitions of sleep apnea and on the medical relevance of sleep apnea has been inaugurated.

Because apnea events occur during sleep, affected patients are not aware of this. Patients do not report apneas themselves. A bedpartner may have observed apnea events during sleep or the patient turning blue due to low oxygen when breathing ceases. Most patients with sleep apnea snore as a sign of higher upper airway collapsibility. During an apnea event, when airflow ceases, there is no snoring. Therefore snoring is usually intermittent. Apnea events are terminated by arousals. Arousals are most often visible in the sleep EEG as an increase in EEG frequency and as a shift toward higher sleep stages (Bonnet et al. 2007). Arousals with their central nervous activation open the upper airways to regain breathing and the activation interrupts sleep continuity (Eckert et al. 2014). Therefore patients are not able to reach deep sleep (sleep stage N3) if severely affected. In addition, light sleep (sleep stages N1 and N2) and REM sleep are interrupted by many arousals causing fragmented sleep. As a consequence of fragmented sleep patients experience and report unrefreshing sleep and are often sleepy during daytime (Eckert et al. 2014). Sleep apnea accompanied by excessive daytime sleepiness had been called obstructive sleep apnea syndrome (OSAS) in the past. Today, we know that excessive daytime sleepiness is a typical but not always reported consequence of sleep apnea and sleep physicians avoid the term ‘syndrome’. The numerous hypoxia events and reoxygenation after each apnea during sleep cause a stress to the endothelial system (Lavie 2003). The increase in sympathetic tone with each arousal causes vasoconstriction with increases in heart rate and blood pressure. These periodic changes result in additional stress to the vascular system during sleep. With these rapid and frequent changes, the normal regulation of sleep and sleep recreation becomes severely impaired. The normal lowering of heart rate and blood pressure and the lowering of vascular load cannot take place. The normal hormone secretion pattern during sleep is impaired. As a consequence these changes in physiology impose a risk factor for cardiovascular disorders such as hypertension, cardiac arrhythmias, myocardial infarction, and stroke (Shahar et al. 2001). The association with hypertension is most obvious and had been reported early (Young et al. 1997). Sleep apnea is also a risk factor for diabetes and

metabolic disorders (Resnick 2003). Patients experience this as early aging and lower performance.

Treatment of Sleep-Related Breathing Disorders

The therapy of choice for obstructive sleep apnea is nasal CPAP (continuous positive air pressure) (Mayer et al. 2017). The therapeutic mechanism is mechanical. It is a pneumatic stenting of the upper airways (Sullivan et al. 1981). This treatment is very effective if the nasal mask is tolerated by the patient (Sanders et al. 2008). The upper airways are opened during sleep by a continuous flow of room air resulting in a positive pressure of 4–15 cm H_2O in average. The exact pressure needed in a particular patient is titrated in the sleep laboratory. The pressure needed is more or less constant for a particular patient. The pressure needed varies by 1–3 cm H_2O depending on sleep stage and body position. Usually higher pressure are needed during REM sleep and sleeping supine. Since couple of years, machines are available which perform a continuous assessment of the upper airway obstruction by a high-frequency oscillation method. High frequency means 20 Hz and the superimposed oscillation is generated by a loudspeaker creating air vibrations on top of the supplied air pressure. Sensing reflecting oscillations allow to determine the collapse of the upper airways. Then pressure is increased automatically until the airways open. These machines determine automatically the required air pressure and are called APAP machines, automatic titrating CPAP (Morgenthaler et al. 2008). For patients who cannot tolerate to exhale against an increased pressure, another group of machines was developed, which lower the air pressure as soon as the patient wants to expire. This lowering of pressure can be set by the sleep physician, and it is usually 4–8 cm H_2O lower than the inspiratory pressure. These machines are called BPAP or (Bilevel PAP). The time for inspiration and expiration may be set to limit if needed. All these machines do not present a classical ventilation therapy because there is just a nasal mask, there is no volume control, and airflow is continuous. However the distinction between more sophisticated modes, like a time-controlled BPAP and conventional ventilation, becomes more fuzzy. Due to the high number of patients with obstructive sleep apnea and with prescribed CPAP or APAP devices, this is an economically very important market with all consequences for health-care and health insurance systems.

Sleep apnea therapy with all kind of ventilator devices require using the device each night and wearing a mask during each night. Some patients cannot tolerate the nasal mask. Then therapy adherence declines and as a consequence treatment efficiency declines as well. Patients are seeking for alternative treatments. Several alternative therapies for sleep apnea were developed. The most common and popular alternative therapy is the use of mandibular advancement devices (MAD). The oral devices produce a protrusion of the lower jaw by an average of 8 mm up to 15 mm. The devices can be used only if teeth are healthy and stable. The protrusion has to be titrated to reach maximum effectiveness in terms of apnea reduction snoring reduction and while avoiding pain and discomfort during the night and next day. The devices open the upper airways somewhat more. Accordingly they may turn apnea events into hypopnea events and definitely reduce snoring. Depending on the severity of upper airway collapse, this treatment may reduce the number of apnea and hypopnea events to zero. Most often a number of events stay. On average in large patient groups of any sleep apnea severity, a reduction of AHI by 50% is reported. In selected patient groups, results may be better. Today MAD is recommended if the CPAP mask is not tolerated or if the upper airway collapse is not very severe. The upper airway collapse that is not very severe is observed best by checking the effective CPAP pressure during CPAP titration trials. If the effective CPAP pressure is low, say 6 cm H_2O, then there is a high chance of having a very effective MAD treatment.

Procedures

Diagnostic procedures in sleep medicine start first with an assessment of complaints and symptoms regarding sleep behavior and sleep habits. Then follows an assessment of complaints and symptoms. In order to standardize this assessment, a large number of well-established and validated questionnaires are in use. The questionnaires are then followed by clinical investigations to assess clinical features associated with the sleep disorder. A recording of a few characteristic physiological signals at home follow to assess respiration and oxygen saturation during sleep. The last and final procedure in the diagnosis of sleep disorders and sleep-disordered breathing in particular is polysomnography (PSG) in a sleep laboratory or sleep center. This requires trained personnel for the recording and for the interpretation of the recorded data. A sleep center is able to diagnose all disorders as specified above.

Questionnaires

A much used questionnaire covering many aspects with a focus on insomnia problems is the Pittsburgh Sleep Quality Index (PSQI) mentioned earlier already (Buysse et al. 1989). Another general and frequently used questionnaire is the Epworth sleepiness scale (ESS) (Johns 1991). This questionnaire consists of eight questions describing situations where one might fall asleep. The situations become increasingly severe and unwanted. Each question is answered with a likelihood of the situation ranging from zero to three. The maximum score is 24 then. Today a threshold of 11 is regarded as being sleepy more than normal. This questionnaire is used much in patients with central disorders of hypersomnolence and in patients with sleep-related breathing disorders. In patients with sleep-related breathing disorders, the ESS is recognized as not being sensitive and not being predictive for the diagnosis of sleep apnea. This is mainly due to the fact that sleepiness is not always a sign of sleep-related breathing disorders and that patients with sleep-related breathing disorders are not necessarily sleepy (Qaseem et al. 2014). However the association between sleep-related breathing disorders and sleepiness is so intuitive that the application of the ESS in these patients remains to be very popular.

If a patient complains about problems initiating and maintaining sleep, the Insomnia Severity Index (ISI) is used (Morin et al. 2011). This short questionnaire is now used in many pharmacological studies to assess the severity and interventional improvement of insomnia. In clinical sleep centers, this index is used to document insomnia and its severity. Sleep centers use the ISI often in combination with Beck Depression Inventory (BDI) in order to distinguish between depression and depression-induced insomnia and insomnia as the primary complaint.

For the assessment of a periodic leg movement syndrome (PLMS) and restless legs (RLS) as part of the sleep-related movement disorders, a specific questionnaire has been developed. This RLS-DI questionnaire is used in many studies and in clinical assessment of PLMS and RLS. This is a very useful and well-validated tool (Walters et al. 2003).

Sleep-related breathing disorders have a high prevalence as previously stated (Peppard et al. 2013). There is a body of evidence that sleep-related breathing disorders have cardiovascular consequences (Shahar et al. 2001; Marin et al. 2005). Therefore there is a clinical need to identify sleep apnea and treat patients if they suffer from moderate and severe sleep apnea (Mayer et al. 2017). Furthermore, evidence showed that surgical interventions of many kinds applied to patients with sleep-related breathing disorders result in much higher postsurgical complication rates. Therefore anesthesia guidelines recommend to assess sleep-related breathing disorders prior to elective surgical interventions. In pharmacological trials, there may be need to exclude sleep-related breathing disorders on a fast and reliable basis. This assessment should be simple and should have a high sensitivity with adequate specificity. Exactly for this purpose, several questionnaires were developed and tested. A systematic review and meta-analysis of questionnaires had been performed and sensitivity and specificity had been listed (Abrishami et al. 2010). A more

recent meta-analysis has resulted in a clinical guideline and can be used to review the range of studies using questionnaires and other methods as well (Qaseem et al. 2014). A questionnaire for screening for sleep apnea by anesthesiologists prior to surgical interventions had been presented and validated. This is the STOP-BANG questionnaire (Chung et al. 2008). Each letter stands for a question or finding. The STOP-BANG questionnaire asks for snoring (S), tiredness (T), observed and reported apnea events (O), being treated for high blood pressure (P), BMI higher than 35 kg/m^2 (B), age higher than 50 years (A), neck circumference higher than 40 cm (N), and male gender (G). Each positive answer adds a point. The risk for sleep apnea is increased if the score is 3 and higher (Ong et al. 2010). Sensitivity and specificity are given in Table 3. This questionnaire is regarded as having high sensitivity and specificity compared to other questionnaires. Another questionnaire developed for family physicians is the Berlin questionnaire (Netzer et al. 1999). This questionnaire was developed as a tool for general physicians to assess the risk for sleep apnea (compare Table 3). A very recent development is the NoSAS score which claims to be better than the STOP-BANG and the Berlin questionnaire (Marti-Soler et al. 2016). This questionnaire does not simply use yes/no questions but carefully assigns points to the same items used by the other questionnaires. Other research groups have developed clinical scores which combine clinical findings often seen in sleep apnea and a few questions to one apnea score (Flemons et al. 1994). In principle these scores are similar to the STOP-BANG questionnaire.

The questionnaires described above were selected because they have a worldwide distribution and validated translation into many languages. Of course there are more, sometimes regionally popular, questionnaires. In order to become considerably better than questionnaires, which means to achieve a higher specificity, a recording of physiological signals over the night is required. This is done with medical devices allowing long-term recording, often denoted as 'sleep lab' meaning 'polysomnography'. A simplified family of devices is denoted as polygraphy or home sleep apnea testing (HSAT). Practically, this method is now very much used in clinical practice to diagnose sleep apnea and to initiate treatment because it does not require a hospital or supervised bed. This method is described with more detail below.

Polysomnography

The reference method for the diagnosis of sleep-related breathing disorders is cardiorespiratory polysomnography. This method includes a quantitative assessment of sleep, respiration, vegetative functions, movements, and behavior. All physiological functions involved in sleep and in sleep disorders are quantitatively assessed. The method and its assessment are well described in the standardized manual of the AASM (Berry et al. 2016). The signals which track a physiological function for the duration of a night are listed in Table 4. Sensor methods were evaluated over the past and are now found to be reliable and satisfactory for good results. Electrode types, sensor types, and number of signals are well standardized, and polysomnographic equipment is available from several companies worldwide. Polysomnography is used both for research and clinical purposes. The biggest differences between systems are found in the flexibility of hardware and the accompanying software for the management of additional sensors and signals. This distinguishes systems which can be used for clinical purpose only and systems which can be used for research as well. Good software provides a good automatic analysis of signals which is used for a pre-evaluation in clinical work and which provides tools for quantitatively assessing signals for research purposes.

The sleep recording needs to be evaluated visually according to the rules specified in the AASM manual (Berry et al. 2016). The recorded signals are displayed in 30 s epochs and then evaluated or scored (Fig. 1). The sleep EEG with EOG and EMG is used to score sleep stages in categories wake (W) with alpha waves in the EEG; high muscle tone; light sleep (N1), which is transitional sleep with less than 50% of alpha waves lower

Table 3 Questionnaires for sleep-related breathing disorders. The values are given as percentages and stem from two studies (Silva et al. 2011 und Pereira et al. 2013). The "clinical score" is composed of snoring, age, blood pressure, and male gender (Flemons et al. 1994)

	AHI > = 5			AHI > = 15			AHI > = 30		
	Sensitivity	Specificity	Positive predictive value	Sensitivity	Specificity	Positive predictive value	Sensitivity	Specificity	Positive predictive value
ESS >10				39.0	71.4	64.8	46.1	70.4	68.7
Berlin questionnaire	86	25	91.7	91	28	73.4	89	18	45.9
STOP-BANG	90	42	93.7	93	28	73.9	96	21	48.6
NoSAS				79	69	47			
Clinical score	33	83	95.0	35	78	77.5	36	72	50.0
Home sleep testing	87	67	96.2	77	95	97.1	50	93	84.8

Table 4 Functions and associated signals assessed during polysomnography

Function	Signal	Sensor
Sleep	Electroencephalogram EEG	Electrophysiological electrode: 3–6 standardized positions
	Electrooculogram EOG	Electrophysiological electrode: Left and right eyes
	Electromyogram mental EMG	Electrophysiological electrode: 2 leads
Respiration	Airflow	Temperature-sensing sensors at the nose and mouth Pressure sensing (nasal prongs) Pneumotachograph with full face mask
	Respiratory effort	Inductive plethysmography with two belts Esophageal pressure
	Oxygen SaO_2 or pO_2	Pulse oximetry sensor Transcutaneous O_2
	Carbon dioxide CO_2% or pCO_2	End-tidal CO_2 from expired air with ultrared absorption sensor Transcutaneous CO_2
	Snoring	Microphone: Supraglottis or room
	Respiratory movement (indirect)	Radar/microwave technology Matt in the bed or mattress sensors ECG-derived respiration
Cardiac	Electrocardiogram	Electrophysiological electrode: 1 lead
Movement	Electromyogram of legs and arms	Electrophysiological electrode
	Body	Actigraphy or simple movement sensor
Behavior	Video	Room camera
	Voice	Room microphone
	Body position	3-D acceleration sensor
Additional options	Body core temperature	Rectal or ear probe, thermo-pill
	Gastric pH	Antimony sensor probe
	Electrodermal activity	Resistance probe, no standard
	Blood pressure	Finger photoplethysmography, pulse transit time as surrogate
	Pulse wave	Optical pulse plethysmography/pulse oximetry sensor, no standard sensors

muscle tone and rolling eye movements; light sleep with specific EEG patterns such as sleep spindles and K-complexes (N2); and slow-wave sleep or deep sleep with more than 20% of time per epoch with delta waves of a frequency between 0.5 Hz and 2 Hz and an amplitude of at least 75 microvolt (N3). The rapid-eye-movement sleep or REM-sleep is denoted as R and is characterized by mixed EEG waves, low muscle tone, and rapid eye movement. This sleep stage is associated with frequent reports of dreaming. The AASM manual sets rules how to score short awakenings, termed as arousals from sleep. These arousals are scored based on EEG activations and reflect cortical activation only (Bonnet et al. 2007). The AASM manual also sets rules how to classify obstructive and central apnea events, obstructive and central hypopnea events, and hypoventilation. The manual sets rules for scoring movement events to classify leg movements and periodic leg movements. A separate chapter defines all the parameters which are needed for a polysomnography report. These are specified below.

Cardiorespiratory polysomnography is attended by trained sleep nurses who can attach or readjust sensors when contact problems occur during the night. Sleep nurses attend all night in a sleep center to be available for patient calls as well. Even if simpler methods like questionnaires or home sleep apnea testing are used today, as soon as sleep-disordered breathing may be more complex or as soon as comorbidities are present in a particular patient, a polysomnography is

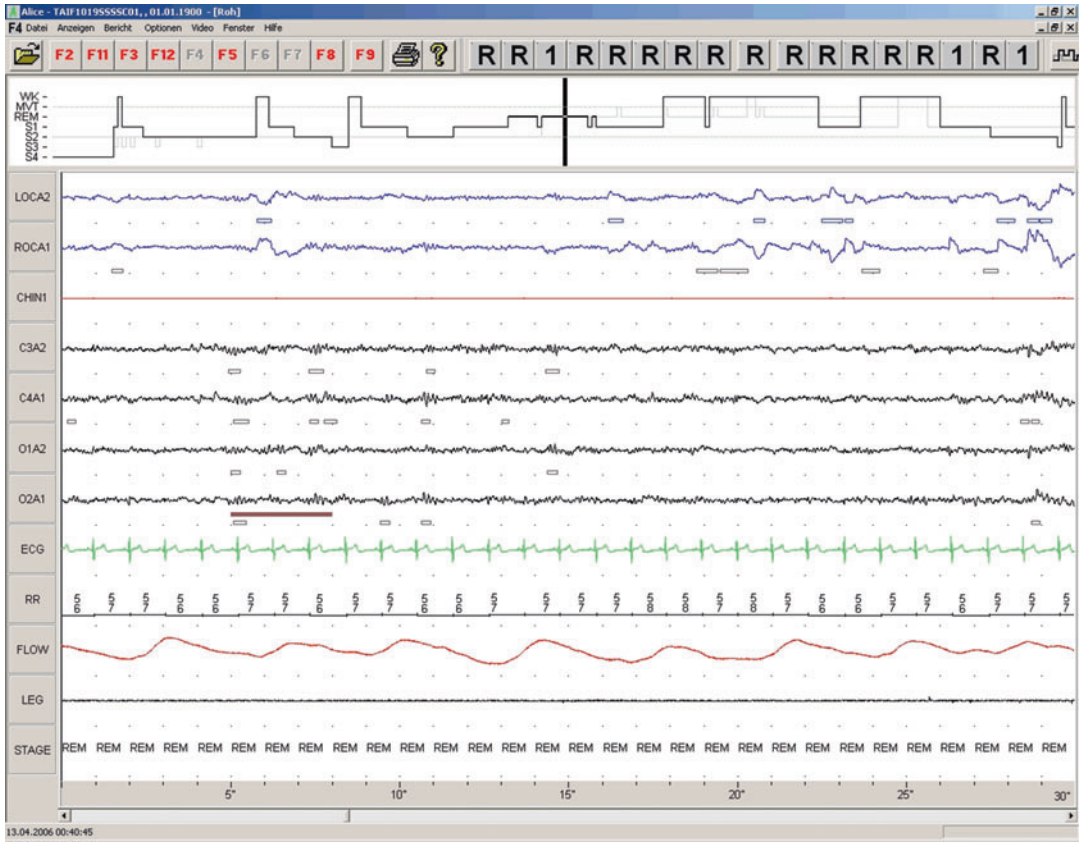

Fig. 1 Example of polysomnography with a 30 s epoch of REM sleep. Rapid eye movements can be observed in the EOG tracings (LOCA2 and ROCA1). A low muscle tone is visible (CHIN1). The EEG shows in four leads (C3A2, C4A1, O1A2, O2A1) mixed frequency low amplitude activity which is characteristic for REM sleep

required for a full assessment of the disorder (Qaseem et al. 2014; Mayer et al. 2017).

Home Sleep Apnea Testing – Polygraphy

In order to reduce costs and expand the capacities for the diagnosis of sleep-disordered breathing, many portable monitoring devices for sleep apnea were developed over the last two decades. A systematic review and meta-analysis for these devices had been compiled (El Shayeb et al. 2014). A review combined with a clinical guideline has been released for the management of sleep-disordered breathing as well (Qaseem et al. 2014). The portable devices have achieved high sensitivity and specificity up to an extent that they are used for out-of-center diagnosis of sleep-related breathing disorders in the majority of patients under certain conditions (Collop et al. 2011). There is an ambition to diagnose or at least recognize sleep apnea even simpler than that. Short tests during daytime or questionnaires are desirable. A number of tests had been developed and questionnaires as well. The questionnaires had been described above. The guideline by the American college of physicians (ACP) evaluated the modalities for the diagnosis of sleep apnea and concluded with recommendations in how far portable monitoring can be used and in how far questionnaires, described above, can be used for sleep-related breathing disorders (Qaseem et al. 2014): “The ACP recommends a sleep study for patients with unexplained daytime sleepiness. The ACP recommends

polysomnography for diagnostic testing in patients suspected of obstructive sleep apnea. ACP recommends portable sleep monitors in patients without serious comorbidities as an alternative to polysomnography where polysomnography is not available for diagnostic testing." A more recent position statement of the American Academy of Sleep Medicine states that home sleep apnea testing (HSAT) has to be prescribed by a physician, based on medical history and face-to-face examination (Rosen et al. 2017). The raw data of HSAT must be reviewed by certified sleep physician. An automatic analysis of raw data is not sufficient. A HSAT is not recommended to screen asymptomatic populations. HSAT systems are used worldwide. In some regions of the world, mainly in Europe, the are called Polygraph (PG), a term derived from 'polysomnography' but without the 'somno' component because polygraphy does not record sleep with EEG, EOG, and EMG.

To characterize and classify systems for the home sleep apnea testing, four levels had been introduced first (Flemons et al. 2003). When a cardiorespiratory polysomnography, as defined above, is meant, then this is called a level 1 diagnosis, which is the highest level with highest quality and with most effort made. Due to the requirement of attending personnel, this is performed in a sleep lab setting usually. If the same system is used at home or under experimental conditions outside a sleep lab, without attending personnel, then this is called a level 2 sleep assessment. A level 3 recording device describes a system which can record respiration (respiratory flow, respiratory movement, oxygen saturation), heart rate, and body position with usually 4–6 channels (Flemons et al. 2003). These systems were developed to record sleep apnea at home or elsewhere outside a sleep center. These are called HSAT or PG today. Simpler systems, such as an actigraphy, an oximetry with heart rate, and a respiratory flow recording, are called level 4 systems. They record typically 1–3 channels only. Developments during the last 10 years with sophisticated signal analysis from few signals allow to detect sleep apnea from few signals. Therefore another classification system had been introduced, the SCOPER system, which is based on assessment of functions instead of simply counting signals (Collop et al. 2011). The SCOPER system checks the validated assessment of sleep (S), cardiovascular functions (C), oxygen saturation (O), body position (P), respiratory effort (E), and respiratory flow (R). In order to see whether a specific system fulfills the criteria, validation studies are examined. With this it might be possible that a sophisticated analysis of pulse wave recording may reveal sleep stages in terms of wake, non-REM, REM sleep, heart rate, and respiratory effort to detect apnea events, all with one signal. Therefore this new SCOPER system is more appropriate to evaluate and assess usefulness of modern systems to diagnose sleep-related breathing disorders. A class of systems which did profit much from this new SCOPER classification where those making use of arterial peripheral tone based on finger pulse wave recordings (Yalamanchali et al. 2013). These systems use the finger pulse wave with a sophisticated analysis based on pulse amplitude changes and pulse-to-pulse interval changes over time instead of directly recording airflow or respiratory movement. The Watch-PAT system derives respiration, apnea events, both obstructive and central, and estimates non-REM and REM sleep from the pulse timing behavior. HSAT systems are those who fulfill the requirements to record sleep-related breathing disorders with sufficient sensitivity and specificity. Using the conditions described above, HSAT systems now become the diagnostic tool of first choice to diagnose sleep apnea unless comorbidities that are present in sleep apnea need to be excluded (Rosen et al. 2017).

Evaluation (Parameters and Statistical Evaluation)

The AASM manual explains how to evaluate sleep stages and all-related events. Beside this the manual specifies and defines parameters summarizing the evaluation and which should be included in a polysomnography report (Berry et al. 2016). The parameters and quantitative descriptions derived from polysomnography

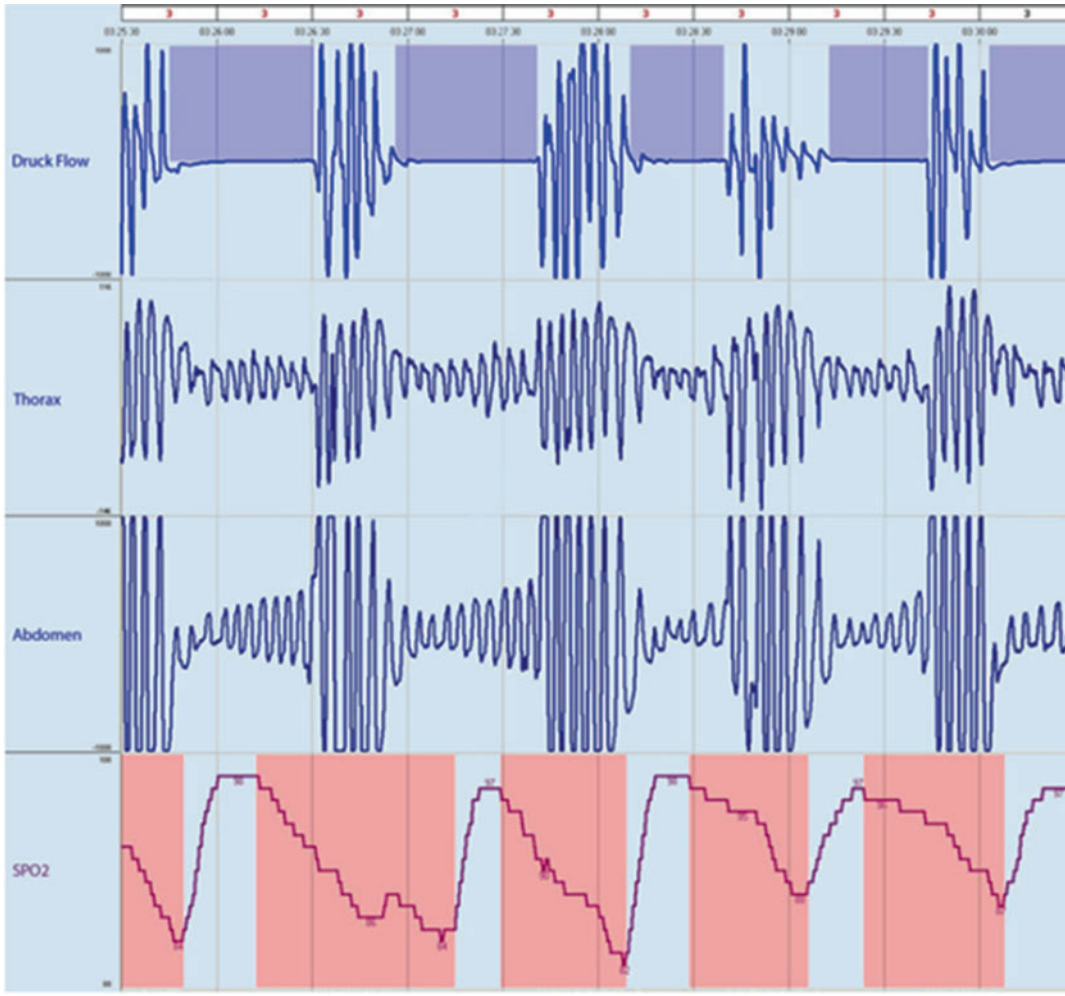

Fig. 2 A 5 min window with five obstructive apnea events is shown. The tracings from top to bottom present nasal pressure, thoracic movements, abdominal movements, oxygen saturation

relate to the following groups: global sleep metric, sleep stages, respiration, cardiovascular assessment, movement assessment, and further observations. Global sleep metrics are total recording time (TRT), the time between lights out and lights on, total sleep time (TST), and percent sleep efficiency, which is the ratio between TRT and TST. The sleep stages are specified by minutes in each sleep stage and percent related to TST, together with sleep latency, stage R latency, and wake after sleep onset. The arousals are quantified by total number and number related to TST, called as arousal index (ArI). Cardiac events are mainly noted as yes or no, and heart rate is given by highest, lowest, and mean values. Limb movements are given as total number and as an index related to TST, both with and without arousal. The respiratory parameters are a long list. This starts with number of apnea events, obstructive, central, mixed, hypopnea events, obstructive, and central and a sum of all events. An important step in the evaluation is to distinguish the type of respiratory events. Obstructive apnea events are those where a cessation of airflow is detected, but respiratory effort continues as recognized by movements in thoracic and abdominal belt measurements (Fig. 2). Central apnea events are those where a cessation of airflow is detected and no respiratory

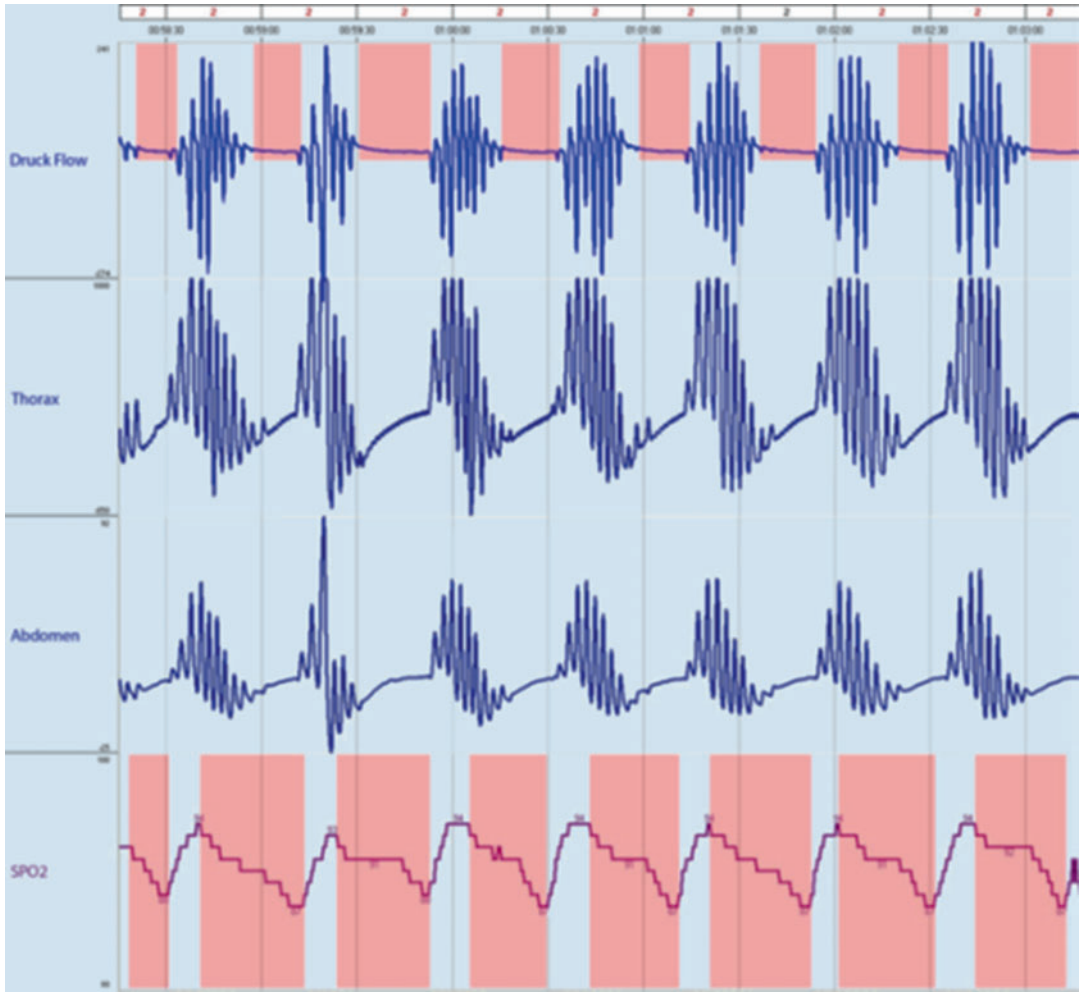

Fig. 3 A 5 min window with central apnea events forming a Cheyne-Stokes breathing pattern is shown. The tracings from top to bottom present nasal pressure, thoracic movements, abdominal movements, oxygen saturation

effort is found as recognized by movements in thoracic and abdominal belt measurement (Fig. 3). However both types of events are accompanied by drops in oxygen saturation (SpO_2). Usually obstructive apnea events are longer (30 to 60 seconds) compared to central apnea events (20 to 40 seconds). Correspondingly the drop in oxygen saturation, the desaturation is somewhat less in central apnea events. If the respiratory flow in cases of central sleep apnea forms a spindle like crescendo decrescendo pattern with a cycle lenght of 40 seconds or more, then this is called Cheyne-Stokes breathing (Fig. 3). This is typically found in patients with heart failure. The apnea-hypopnea index (AHI) is the sum of all events per TST. For the other event types, equivalent indices are calculated. As such there is an apnea index (AI) for obstructive, mixed, and central apneas. Then respiratory effort-related events and oxygen desaturation events are counted. The occurrence of hypoventilation, Cheyne-Stokes breathing, periodic breathing, and snoring is noted. Possibly additional oxygen saturation statistics can be presented.

The complete list of parameters with definitions is specified in the AASM manual for scoring of sleep and associated events (Berry et al. 2016).

Critical Assessment of the Sleep Recording

In the beginning of sleep research and sleep medicine polysomnography was the investigational tool for sleep centers. As sleep research moved into clinical sleep medicine, practical and economic aspects became more and more important. Today sleep apnea is mainly diagnosed using home sleep apnea testing (HSAT) as explained in more detail above. The role of polysomnography in the diagnosis of sleep apnea is decreasing (Mayer et al. 2017). This process is continuing and not finished (Hirshkowitz 2016). With technological developments, home sleep apnea testing becomes more sophisticated and as a consequence more sensitive and specific. This process does not only apply to sleep-related breathing disorders but also to other groups of sleep disorders. With new smartphone applications, it is possible to track sleep. However most smartphone applications were developed intuitively according to the thought: activity correlates to wake and no activity correlates to sleep. The lowest activity might correlate to very deep sleep. This does really reflect our knowledge about slow-wave sleep and REM sleep. Few smartphone apps had been validated. However this technological field is improving quickly. New apps make use of additional sensors like camera, noise, and external bed matts, and external pulse wave sensors. And new apps are validated against polysomnography. These new apps cross the line between simple gadgets for wellness and lifestyle to medical useful devices. It is possible that new apps are able to track sleep and wake and sleep problems over prolonged periods of time with adequate accuracy. However a good validation against polysomnography and considering the specific group of subjects being investigated is always needed. With these recent developments, the role of polysomnography in future may no longer be clinical routine recordings. But polysomnography may become a validation tool and a research tool again (Hirshkowitz 2016).

An important discussion is currently ongoing about the role of the AHI as a severity parameter for sleep apnea (Penzel et al. 2015). In view of the high prevalence as reported by some epidemiological studies (Heinzer et al. 2015) and in view of not showing any positive effect on cardiovascular mortality when treating patients with CPAP just according to their high AHI (McEvoy et al. 2016), there is some concerns that the AHI may not be the optimal parameter to express the severity of the disease. While this had been assumed for long and while it is clear that the pathophysiology is linked to the collapsibility of the upper airways (Eckert et al. 2014), the AHI was regarded as a simple and reliable surrogate for the severity of the disease. Previous studies did show that survival over 12 years is associated with the AHI and that an effective lowering of AHI by CPAP did result in much lower mortality and morbidity (Marin et al. 2005). Only with the recent studies, this parameter is challenged. Therefore a discussion is in place that previous studies did show such impressive beneficial results, because studies were performed on clinical populations seeking help in a hospital setting. And as soon as subjects without symptoms and without complaints are investigated and if they are treated according to AHI only, then these positive effects may disappear. There are thoughts that the AHI may be an indicator for an increased cardiovascular risk and that the elevated AHI must be seen together with the complete clinical picture with other symptoms and findings together. In order to clarify these different mechanisms, the model currently under development is that there are different phenotypes with obstructive sleep apnea (Penzel et al. 2015). Some subjects may develop sleep apnea as part of normal aging of the upper airways. Other subjects develop obstructive sleep apnea as an accompanying factor with obesity. Another group develops obstructive sleep apnea due to morphological retrognathia. Another group may suffer from a narrow upper airway or a more collapsible upper airway with excessive soft tissue. There may be also a group with neural deficits in respiratory regulation during sleep. A hypersensitivity to CO_2 may cause a hyperventilation and then an apnea as a compensation to hyperventilation. This compensation would be physiologic because during sleep, the respiratory system tolerates higher CO_2 levels. These concepts may form a

number of different phenotypes, which, until now, are not well defined and characterized.

Alternative Treatments for Sleep Apnea

The first-line treatment for obstructive sleep apnea is CPAP. CPAP with mechanical splinting of the upper airways has a very high effectiveness, if patient compliance with therapy is good. Since many patients cannot tolerate the nasal mask, the second choice for treatment is an individually fitted mandibular advancement device. Oral appliances or mandibular advancement devices are very popular and much better accepted by a majority of patients because they are more comfortable than a nasal mask. However this treatment is less effective (Schwartz et al. 2017). On average the AHI is lowered by 50%. Since the mandibular advancement device causes a protrusion of the lower jaw, a widening of the upper airway space is achieved. This widening is partial and may be enough to overcome the upper airway collapse. However it may be not enough in some subjects, and then apnea events are converted into hypopnea events. Hypopnea events might be converted into snoring. A conversion was not achieved because the widening by oral appliances was by far not enough. Accordingly there is a high variability across patient groups. Unfortunately the selection criteria for finding those patients who benefit most are not clear before treatment initiation. Some patients cannot tolerate an oral appliance in their mouth over the night. Other patients may not wear such a device due to their tooth conditions. If this therapy of second choice cannot be applied, then other alternatives need to be investigated.

Shortly after sleep apnea was discovered and about at the same time as CPAP was invented, a concept to open the upper airway by electrical stimulation of the corresponding nerve was patented. A nervus hypoglossus stimulating device was developed and first tested in models and soon thereafter applied to humans with obstructive sleep apnea (Schwartz et al. 2001). This pivotal trial in eight subjects proved the success of the concept. A few technological problems were detected when these eight subjects continued to use the nervus hypoglossus stimulation over an extended period of time. The principle was a sensing of inspiratory effort and a stimulation of the hypoglossus nerve during inspiration on one side only. The stimulation causes a protrusion of the tongue, and with this protrusion, the upper airways are widened and tissue becomes stiffer during the stimulation phase. A remote control and a timer in the stimulating device took care that the stimulation period was synchronized with the sleep period. It became clear that the positioning of the stimulating electrodes, the cuff around the nerve, had to be placed carefully on the right position in order to achieve maximum effects. The pivotal trial did show that widening by stimulation could lower AHI by 50% in average. Only a couple of years later, the idea was picked up again, and three competing companies brought devices into clinical practice to be evaluated in large trials in order to achieve FDA approval. Two companies did achieve FDA approval in the meantime. The large studies did fulfill safety, security, and efficiency expectations. If patients were carefully selected according to weight (BMI < 35 kg/m^2) and according to a reactive and oval-shaped upper airway, then the effectiveness of the stimulation treatment to lower AHI was somewhat higher than 50% (Strollo et al. 2014). The device is expensive compared to CPAP, and the procedure is invasive compared to CPAP. The titration is similar to CPAP, because during the titration night, the optimal electrodes for stimulation must be identified and the optimal current for stimulation must be set in order to achieve maximal widening and no arousal.

Patients with central apnea and Cheyne-Stokes respiration under conditions of heart failure may be treated for their heart failure first. If patients treated for heart failure according to guidelines and if Cheyne-Stokes respiration persists, then a trial of CPAP or other ventilation may be initiated if the LVEF is not below 45%. A new approach in these patients with central sleep apnea is to test pharyngeal nerve stimulation. However studies with this treatment are very small and long-term studies are missing. This phrenic nerve

stimulation therapy for Cheyne-Stokes respiration is seeking FDA approval now.

A considerable number of studies with various kinds of surgical interventions were performed in the past. Maxillofacial surgery was able to widen the upper airways effectively. If patients were carefully selected, then this procedure was highly effective. However only few patients do fulfill the restrictive selection criteria for this intense surgical procedure. Other ENT-related surgical procedures had the upper airways as a target. The therapeutic principle was always to remove obstacles in the upper airways to allow breathing during sleep. A much used method was the uvulopalatopharyngoplasty (UPPP) and also adenotonsillectomy. These surgical procedures, and their variants, had only partial success. The AHI was lowered by 30–50% depending on the study. In these cases only mechanical obstacles can be removed. The neural and functional components of upper airway collapse are impossible to be treated surgical. And unfortunately, a prediction on who might benefit more and who benefits less from surgical procedures could not be established despite many efforts.

Positional therapy is useful when sleep apnea has a major positional component. It is estimated that about 10% of patients with obstructive sleep apnea have a largely position dependent sleep apnea with more events or with a higher collapsibility when sleeping supine. These patients may benefit from positional trainers such as pillow vest or electronic devices which train the sleeping subject to avoid the supine position.

There are only few pharmacological therapy approaches in place. A good overview is provided by Gautier et al. (2017). Antihypertensive drugs may have some beneficial effects on sleep apnea. A few experimental trials could show only very small effects. Sleep apnea is associated with inflammatory processes and may potentially lead to atherosclerosis following hypoxia stress (Lavie 2003). Anti-inflammatory drug treatment has not been evaluated for effects on sleep apnea. Acetazolamide has been investigated in patients with sleep apnea both at normal and high altitude. A recent meta-analysis has investigated the effect of acetazolamide on sleep apnea in high altitude and found that acetazolamide does reduce apnea in terms of AHI but is more beneficial in healthy subjects than in subjects with sleep apnea (Liu et al. 2017). Anti-oxidative drugs may have a beneficial effect because they follow the same concept to prevent inflammatory consequences of the repeated intermittent hypoxia. Several studies are conducted now to systematically evaluate effects of several drugs. Another approach for drug applications is to influence local receptors of the upper airways (Wirth et al. 2013). However human trials have not been presented.

In summary pharmacological treatment will have a good chance as another alternative therapy. Especially in view of the change in concept for sleep apnea, there may be phenotypes where sleep apnea is not so severe but still annoying. If sleep apnea is reduced then potentially the corresponding increase in cardiovascular risk is reduced as well. Therefore we can expect beneficial effects of pharmacological treatment, if proven to be successful.

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