Sleep Medicine

A Comprehensive Guide for Transitioning Pediatric to Adult Care

Amir Sharafkhaneh
David Gozal
Editors

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Foreword

I am very pleased to write a foreword for this new publication on the need for seamless transitions from pediatric sleep medicine to adult sleep medicine especially as I think that the area has been neglected when compared to other aspects of sleep medicine.

When many experts are asked "why do we sleep" a common introduction to their answer is that we still don't know why. My own response is that we do indeed know why, and the role of sleep in the fetus and growing infant and child gives us the most robust and tangible high-level understanding of why. My response to the expert's "don't know" answer is to ask the corollary question, "why do we wake up?" My answer to the original question is that "we sleep so that we can wake up!"

The centrality of the brain in sleep was captured in a quote from the leading sleep researcher, Allan Hobson [1]: "Sleep is of the brain, by the brain and for the brain," a quote borrowed from the famous Gettysburg Address by President Lincoln. I would add that sleep's role is not limited to the brain but rather it is fundamental to the development and ongoing maintenance and entire functioning of complex organisms evident at the cellular and molecular levels.

For me, the most compelling evidence about the why of sleep is its role during development. The high proportion of the 24 h spent in sleep with high levels of REM in infants and children [2] underpins the biological work needed for growth, with REM-like phenomena occurring earlier in the fetus. To illustrate with one example, the growing brain of the fetus drives breathing, sucking, and swallowing in a primitive REM state. That these vital functions are driven by the fetal brain is clear evidence of the vital role of neural activity driving development. The simplicity of this example provides a starting point in understanding sleep. Breathing is not required for gas exchange in the uterus, so why is it occurring? If prevented, the diaphragm muscles don't develop properly, and the requisite need for a brainstem breathing rhythm does not occur at birth. This singular example is robust evidence that clearly shows the reason for such basic fetal "sleep" activity and strongly supports the notion that "sleep is of the brain, by the brain, for the brain," and I would add "and for everything else!" There can be little doubt that similar processes are occurring across all domains during the development of such complex biological systems. At the other end of the age spectrum, when maintenance and repair dominate the role of sleep, the now well-described process of brain washing—driven by sleep—provides yet another robust example of the many roles of sleep in biology.

Many examples are now being revealed at the cellular and molecular levels in the complex interaction of sleep and circadian clocks. Synaptic growth and mitochondrial repair stand out as examples. The question of "why" should be replaced with the many how's that are yet to be discovered.

Given the high level of importance of sleep in development, I wonder why pediatric sleep medicine, as a relatively new specialty, is so neglected? Perhaps this thought reflects my own local experience; however the relative numbers of dedicated pediatric sleep laboratories internationally compared to adult facilities seem to support this impression.

While my first glimpse of sleep apnea was reading the report in *Science* from Guilleminault et al. [3] "Insomnia with sleep apnea," my career in sleep and breathing began exploring potential causes of unexpected death in sleeping infants. Prolonged apnea in sleep with upper airway obstruction was a major focus of these unexpected deaths. Remarkably, sleep apnea was essentially unknown in the clinical world. In the modern connected digital world, we can find all research publications at "light speed" using search engines like Google Scholar. However, at that time, the few scattered early reports on sleep apnea were buried within specialist publications and journals that could take months or even years to arrive in the library. So it was that our small research group did not become aware of adult sleep apnea until the arrival in our university library of the proceedings in 1975 of the famous Rimini meeting held earlier in 1972 by Lugaresi [4]. This led to our first all-night recording of a patient with obstructive sleep apnea and COPD with acute on chronic respiratory failure in November 1975. This first study set in train for me a lifetime of research into sleep and breathing and the development of the first comprehensive in-hospital sleep laboratory for adults at the Royal Prince Alfred Hospital, and the beginning of clinical sleep medicine in Sydney.

However, as most of those in the clinical sleep field know, it took a great deal of effort and negotiation to set up a clinical sleep laboratory within the hospital setting. In his historical account of the beginning of sleep medicine in the US, Bill Dement [5] described the first attempt at setting up a service in Palo Alto with an advertising campaign in 1972/73 in the Bay Area of San Francisco offering help for individuals with sleepiness. He was expecting to find patients with Narcolepsy, but the service failed because of just a few patients. The clinical service only started again when measures of breathing were included in sleep studies introduced by his recruit, Christian Guilleminault, which led to the early period of the discovery of numerous patients with sleep apnea.

Administrators, including clinical leaders, considered our work as "merely" research, and strongly resisted the development of clinical sleep facilities, with other priority areas taking available resources. The introduction of nasal CPAP in 1981, a nonsurgical therapy, provided us with a powerful argument as the sleep facility was both a diagnostic and therapeutic service which was required to establish patients on CPAP. The fact that we could rescue patients with sleep apnea induced life-threatening cardiac and respiratory failure with the application of CPAP helped me convince the hospital managers to open a sleep laboratory as part

of our in-patient respiratory service. The expanding recognition of the extent of adult sleep apnea coupled with the dramatic improvement in these patients using CPAP was a key part of the expansion of sleep laboratories internationally and was a major stimulus for the growth of sleep medicine as a specialty. While all this work was in adult sleep, I continued to work to develop services for children, which led to the first pediatric sleep laboratories at Sydney's two major children's hospitals in 1990.

Whereas adult sleep medicine went through a period of exponential growth because of the prevalence of sleep apnea, and a practical, immediately accessible, method of treatment, this has not occurred in pediatric sleep medicine. Yet sleep apnea in pediatrics has a very long history in the clinic in the form of upper airway obstruction with lymphoid tissue. The early literature had very clear descriptions of sleep apnea even though the modern terminology was not yet used. The report by Menashe et al. [6] is one example of early clear descriptions of upper airway obstruction, both awake and markedly worsened in sleep, with dramatic clinical improvements after surgical removal of the obstruction. This problem was widely known clinically, as reported in the late 1800s (e.g., Hill [7]) and many other clinical reports. There can be little doubt that parents and observant clinicians would have seen the struggle to breathe with the obstructed upper airway and would have witnessed the worsening in sleep in such children (as reported so clearly by Menashe). There is no doubt that it was common clinical knowledge that surgical removal of adenoids and tonsils relieved the child of the obstructed breathing. Perhaps this common clinical knowledge of childhood upper airway obstruction and its therapy is part of the reason that pediatric sleep medicine has not developed to the extent that it deserves. Because adenotonsillectomy has such a dramatic effect in many of these children, the need for a sleep study in such children (and a fully equipped sleep laboratory) has never been regarded as essential. However, the sleep study—and a sleep laboratory—has been, and remains, a key element in expanding our knowledge of sleep in children. Moreover, I would argue that the critical role of sleep in development demands that we strive to expand and improve sleep services for infants and children, services that are not simply adaptations of adult sleep laboratories.

Over the last decades, it has become apparent that diseases such as sleep apnea that begin in childhood may last a lifetime and that care needs to be transitioned with optimal expertise across the age boundaries commonly applied in clinical practice. This book does just that and builds upon previous similar experience with other chronic disorders of childhood by providing examples and opportunities to get it done well.

I congratulate the editors of the publication of this new monograph on the lifespan elements of sleep dynamics, and particularly on the challenges posed by the transition of pediatric sleep disorders into adult age. There is no doubt that expanding our dialogue across the various age-based artificial partitions of the various specialties should help in driving the growth in sleep medicine, and most importantly promote optimal outcomes for our patients.

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A Brief History of Sleep Medicine in Children and Adults

1

Amir Sharafkhaneh, Max Hirshkowitz, and David Gozal

1.1 Introduction

Sleep and dreaming puzzle the human mind as far back as we know, and discussions about sleep and dreams are found going back to ancient cultures and in every archeological scripture. The real understanding about sleep and wakefulness however grew as soon as better tools became available to study the central nervous system, including recordings of electrical activity using EEG and neuroimaging including functional MRI (fMRI). Further studies into physiology and biology of the nervous system using various animal models allowed better understanding of how various states of wakefulness and sleep occur. Combining the findings of almost the last two centuries with clinical observations of astute practitioners enabled us to better understand a long list of sleep disorders and formulate disease-specific criteria for diagnosis and management of such conditions. Therapies aimed at either palliation of symptoms or seeking curative approaches stemmed from the increased recognition of sleep-related ailments. Along the scientific and clinical advancements, various associations with focus on sleep sciences and sleep disorders began to form and along came scientifically and clinically oriented international, national, regional, and local conferences and meetings. With increasing demand for sleep services,

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sleep centers and sleep medicine training programs exponentially expanded in capacity all over the world. Additionally, with recognition of the potentially adverse effects of sleep disorders and sleep deprivation on safety, various regulations were developed to provide safer environment and operation. As would be expected, legal cases have been brought to courts to further investigate effects of sleep deprivation on professional performance and as part of the determinants leading to accidents or disasters. Although different aspects of sleep science and medicine started at different points in time, in their emerging beginnings that all have grown in parallel. This chapter is a brief review of the history of sleep medicine. There are several detailed reviews written by authors who have firsthand knowledge of the field. We refer the readers to these in depth [1–4].

1.2 Sleep Medicine in Ancient Cultures

Sleep and dreaming are topics that have been discussed frequently in various cultures going back several millennia. There is no doubt that humans are fascinated with sleep in general and more particularly with dreams. In the context of the lack of understanding of brain function by previous civilizations, it is a fascinating opportunity to witness a process in which we and almost any other living organism enter a coma-like state that may resemble death and return from this adventure refreshed while unavoidably repeating it daily. Not surprisingly then that the topic of sleep has been discussed to various degrees in ancient cultures. The current available literature points to discussions in Indian, Egyptian, Greek and Romans, Chinese, and other ancient cultures. Many of these ancient cultures viewed sleep and death similarly, sleep as temporary death, and the other as a permanent event.

Literature discovered from ancient Egypt elaborates on health and disease with some focus on sleep. In particular, dreams and their interpretation were given major importance. For example, then and now, in the Middle East and North Africa, dream of death of an individual is interpreted as the life of that person being prolonged. The story of the dream of pharaoh interpreted by Joseph is a typical example of how ancient Egyptians took their dreams seriously. Egyptian physicians used poppy seed, alcohol, and nightshade (scopolamine) in addition of purging and enemas for treatment of insomnia [4, 5].

Chinese ancient culture and to some degree the current traditional Chinese medicine believe in two forces of positive (yang) and negative (yin) that in balance create health or disease. Chinese believed in the humoral system that regulated various bodily functions including sleep. They used different methods including acupuncture, massage, breathing exercises, and various herbal medicines (ephedra and ginseng) to treat ailments including insomnia [5].

Indus Valley civilization goes back for thousands of years. The traditional Indian medicine is called Ayurveda. According to Ayurveda principles, three basic types of energy exist in each individual. These include Vata (the energy of movement), Pitta (energy of digestion/metabolism), and Kapha (energy of lubrication and structure). Accordingly, hypersomnia is considered to be the disturbance of Kapha and

insomnia is due to the disturbance in Vata. Sleep was divided into being physiologic or pathological (due to a disease). Proper sleep also was linked to happiness, strength, knowledge, and even longevity [6].

Greeks both through their literature and through their scientific dialogues are among the earlier civilizations that discussed and documented sleep-related topics in their writings. Alcmaeon (about 500 BC) proposed that sleep is produced by withdrawal of blood from the body surface to larger central vessels. Hippocrates and later Aristotle discussed sleep in more depth in their writings. Among medications, narcotics from opium poppy were used to induce sleep-like states [5].

In contrast to other cultures, physicians from Rome theorized that sleep is caused by partial or complete splitting of atoms. Interestingly, neural theory of sleep as loss of central control of peripheral muscles also was discussed in ancient writings from Rome [4].

1.3 Sleep in the Scriptures

Jewish, Christian, and Islamic scriptures all have repeatedly discussed sleep and in particular dreams. Sleep is seen as an essential physiologic function given by the Creator. The scriptures consider sleep similar to death except that sleep is temporary, while death is final loss of consciousness. In the scriptures, the value of good sleep, especially the one that is at night, is mentioned and recommended, with 8 h sleep per day being advocated as desirable [7]. Scriptures view the dreams as a method of prophecy. The most famous of them are the dreams of Joseph, the son of Jacob. In the scriptures, various dreams experienced by Joseph while he was with his father and subsequently Joseph's role as a trusted interpreter of the dreams of the pharaoh are emphasized and attest to the unique importance of the underworld activated by sleep to control the events and future reality of wakefulness. The dreams may have been considered as a method of communication and of conveying commands by the Creator. An example in the Bible is the dream of Joseph to take Mary as his wife. As a matter of fact, interpretation of the dreams is considered a very important and a scary task that can only be assumed by a few selected ones who possess singular clairvoyance. Many elements of sleep hygiene, restorative effects of sleep, circadian rhythms of sleep, and discussions about treatment of insomnia and excessive daytime sleepiness are discussed in the religious texts including the Bible, Talmud, and Quran [4, 5, 8, 9] and the related texts of these holy books as drafted by religious scholars. In general, scriptures consider sleep an essential function and dreams were a way of the Creator commanding and prophesizing. Interpretation of scriptures affected the communities of the followers. Further, the interpretations of the scriptures are influenced by the cultures and the advancement of sleep science. Interestingly, the religious establishment significantly influenced practice of medicine in the earlier part of the Middle Ages (AD 476 to AD 1453). Establishment of medical schools during the latter part of the Middle Ages allowed for a transition to more observation-based medical diagnosis and treatment rather than mysticism for all ailments including sleep disorders [4].

1.4 Scientific History of Sleep Medicine

Theories about sleep and dreaming were and remain abundant and have originated from philosophers, clinicians, and scientists. Many of these theories were generated by observations of individuals during sleep. The theories includes the vascular theories related to increased (congestion) or decreased blood (anemia) supply to the brain, the neural theories (reduced neural activities), chemical theories (accumulation of substances or neurotoxins), and behavioral theories [4, 10]. Interestingly, most of these theories either in their entirety or partially have been refuted by the recent advances of the last 80 years. However, it was not until scientific tools to study the nervous system became available that our understanding of sleep became better defined.

The electroencephalogram (EEG) was developed as a noninvasive tool to study the brain during sleep and answer the fundamental question of whether the brain in sleep is active or inactive. To this end, Nathaniel Kleitman stated that "It is perhaps not sleep that needs to be explained, but wakefulness" [11]. This tool gradually moved from the research laboratory to clinical practice and tremendously helped to diagnose and treat many sleep disorders. Understanding of sleep would not have been possible until the discovery that neurons are connected through synapses and knowing that the cells communicate with each other through electrical signals and neurotransmitters. Luigi Galvani (eighteenth century) elucidated the electrical activity of nervous system, Richard Caton (1875) discovered the electrical activity of the brain, and Hans Berger (1929) recorded the electrical activity of the brain (electroencephalogram) during wake and sleep [5, 10]. He identified alpha rhythm (also was called Berger's wave) in addition to recognizing that when a person fell asleep, the alpha rhythm disappeared.

Subsequently, studies in early decades of the twentieth century by groups from Harvard University and the University of Chicago showed that in fact sleep has its own characteristic electrical activities [12]. The discoveries showed different stages of sleep including calm wakefulness with dominance of alpha, periods of synchronized slow activities, and periods of sleep with increased activity.

The next important stage in understanding sleep physiology comes with the ability to study eye movements using electro-oculogram which helped scientists to discover rapid eye movements (REMs) and associate these movements with dreaming. Indeed, when patients were awakened during REM sleep periods, they could describe vivid dreams while they were not able to do so when they would be aroused from a quiet sleep. Additionally, the increases in heart rate and breathing rate that were seen during the rapid eye movements contrasted with the slowing of respiration and cardiac frequency during non-REM sleep [13, 14]. The next important piece of information about sleep came after studying subjects' sleep in the entirety of the night and discovering the alternating pattern of non-REM and REM sleep [15]. Subsequently, REM sleep muscle atonia was discovered, and consequently REM sleep was defined as sleep with rapid eye movements, dreams, and active brain EEG similar to wakefulness but in the presence of diffuse muscle atonia [10].

After defining the various stages of sleep, further studies investigated the neurophysiological mechanisms involved in transitioning from one state to another. Discovering the link between hypothalamic pathology and hypersomnia and the link between lesions of preoptic area and anterior hypothalamic region to insomnia were major breakthroughs in connecting the anatomy to sleep-related symptoms [16]. Further studies in the early 1900s showed that stimulation of central thalamus results in sleep [5]. One of the earlier discoveries on this topic was understanding that reticular activating system may be feeding the cortex and thus maintaining wakefulness [17]. Later, Michel Jouvet in Lyon, France, demonstrated that stimulation of the caudal mesencephalic region and pontine tegmentum leads to a REM-like state and coined the term "sommeil paradoxal" (paradoxical sleep) to REM sleep [18]. The discovery of two peptides (1998) in the hypothalamic area, by two independent groups, with effects on wakefulness and appetite (and hence named hypocretin/orexin) significantly increased our understanding of neurophysiological mechanisms of sleep, REM sleep, and narcolepsy [3].

Another aspect of sleep science focuses on circadian rhythms that exist in all living beings. The anterior hypothalamus was identified as the main region governing the biological clock by Curt Richter (1965) and more specifically the suprachiasmatic nucleus [19]. Further studies in the 1960s and 1970s clarified the circadian variations in endocrine function and thermoregulation and ultimately extended the concept of circadian rhythms to all cells denoting the presence of a major central clock and a myriad of peripheral clocks regulated by the central one [5]. As recently as 2017, the fundamental discoveries of molecular mechanisms controlling the circadian rhythm led to the attribution of the Nobel Prize in Physiology or Medicine to Jeffrey C. Hall, Michael Rosbash, and Michael W. Young.

1.5 History of Polysomnography in Sleep Medicine

Polysomnography, i.e., the objective scientific method used for studying sleep, developed in the second quarter of the twentieth century. The polysomnogram, born out of electroencephalography, originated in psychophysiology, matured with clinical science, and ultimately became employed by sleep medicine. Owing its roots to electroencephalography and other electrophysiological recording techniques, polysomnography rapidly evolved from its role for scientific inquiry to clinical applications [20]. A major issue with EEG at the beginning was the inability to record for long periods of time. Gibbs and Garceau were able to construct a one-channel EEG machine by adapting the Weston Union Morse Code ink-writing undulator, while Albert Grass who was working on earthquake seismographs created a three-channel EEG machine. After 1938, EEG rapidly gained popularity as both a research and a clinical tool. Polygraphic recording devices (e.g., the Grass Model 1) became then commercially available [20].

As use of polysomnography became widespread, the lack of standardization in scoring became apparent. In a very interesting study, Monroe compared 28 raters from 14 sleep centers who scored the same 398 min of a sleep study. The study

showed that the interrater reliability was low and recommended standardization of sleep stages [21]. In 1967, a committee of experts, led by Allan Rechtschaffen and Anthony Kales, took on the task of developing standard rules for scoring sleep stages. The result of this work was published as "A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects" and is known of R&K scoring rules [22]. In 1971, "A Manual for Standardized Techniques and Criteria for Scoring of States of Sleep and Wakefulness in Newborn infants" was published [23]. The R&K guidelines were developed for normal sleep and had major limitations when used in clinical settings. Thus, the American Academy of Sleep Medicine developed an improved and expanded scoring manual named "AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications" in 2007. Subsequently, the board of Directors of the AASM mandated that the scoring manual be updated regularly and be published online. The Version 2.0 is the first scoring manual transitioned to a true digital format [24]. The latest update to the scoring manual, Version 2.6, was published in 2020. The AASM updated the visual scoring of sleep in infants 0–2 months of age in 2016 [25]. Additionally, international groups formed to develop standards for recording and scoring clinical polysomnographic information. Notable among these groups is the team that published an atlas for cyclic alternating pattern scoring and the World Association of Sleep Medicine (WASM) in collaboration with the International Restless Legs Syndrome Study Group (IRLSSG) who updated the guidelines for periodic leg movement assessment (which ultimately was adopted virtually unchanged by the AASM) [26, 27].

Another major advancement in the field of sleep disorders was the creation of a system for sleep disorder classification that could be used for clinical diagnosis and coding of all known sleep disorders. This task was commissioned by the Association of Sleep Disorders Centers (ASDC) and the first publication appeared in the SLEEP journal in 1979 [28]. Subsequently, the International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD) was developed [3]. Since then, the American Academy of Sleep Medicine updated the manual under ICSD-2 in 2005 and later ICSD-3 in 2014 [29].

The emergence of sleep apnea as a highly prevalent disorder was the engine driving the huge expansion of the use of clinical PSG. Currently, 80–90% of all clinical PSGs conducted attempt to rule in or rule out sleep-disordered breathing. For 40 years, attended polysomnography dominated as the preferred technique for evaluating sleep apnea and/or titrating positive airway pressure therapy. The widespread recognition of sleep apnea as a significant medical condition affecting nearly one billion people around the world was paired with a PSG's billable CPT code and produced a meteoric rise in sleep medicine. However, economics drove the market toward finding a less expensive alternative; thus, the cardiopulmonary recording arise, also known as home-sleep testing (HST) or out-of-center sleep testing (OCST). HST involves making overnight recordings of airflow, respiratory effort, oxyhemoglobin saturation level, heart rate, and sometimes snoring sounds and EEG. Its only validated use is to verify the presence of sleep apnea [30]. Other HST devices use non-flow-based evaluation of respiration and cardiac functions during

sleep, and with current microelectronics and sophisticated digital processing analytics, this field is developing extremely rapidly and creating many different instruments enabling diagnostic approaches for sleep apnea and other sleep disorders.

1.6 History of Sleep Medicine as a Medical Field

The field of sleep medicine grew out of the advancement in understanding of sleep, development of reliable tools, and recognition of various sleep disorders by patients and clinicians. Research in the field of sleep medicine continues increasingly and thus expands the clinical field of sleep. Out of this growth is better understanding of physiology of sleep and improved classification of the sleep disorders to better diagnose and manage these ailments and discovery of novel molecular targets for developing therapeutic agents. Of course, the field of sleep medicine would not have grown as much if it was not for the societies related to sleep, various related scientific meetings, establishment of various sleep clinics, and sleep medicine training programs.

The progress of a medical field depends not only on how science moves forward on the field but also on how the related experts and scientists organize and form scientific and professional societies. The first professional society related to sleep and their related meeting in the USA, with international representation of sleep scientists, was the Association for the Psychophysiological Study of Sleep (APSS) organized by Dr. Dement in 1961. This initial organization also created a yearly meeting to present scientific data. The meeting proceedings were originally published in the *Psychophysiology* (the journal for the Society for Psychophysiological Research) which showed the image of a polysomnographic tracing on its cover. For the first time in 1971, the APSS meeting went outside the USA to Bruges in Belgium and published a meeting book titled *The Sleeping Brain*. Along with the growth of APSS, the European Sleep Research Society (ESRS) was formed in 1972 with the leadership of Dr. Koella [31]. As APSS and clinical sleep services grew, the Association of Sleep Disorder Centers (ASDC) with initially only five member centers started to function in early 1976 with Dr. Dement as its president and Dr. Weitzman as vice president [3]. Out of ASDC came development of a specialty board exam for sleep medicine. Along the APSS and ASDC, the Japanese Sleep Society was formed and later led to the Asian Sleep Society. Additional outcome of APSS, ASDC, and ESRS was the journal *SLEEP* with its first issue in 1977. The ESRS later in 1992 developed its own publication named *Journal of Sleep Research*. As field of sleep grew, other major sleep-related societies including the Australian Sleep Association (1988) and the Chinese Sleep Research Society (1994) were formed. In the meanwhile, in the USA, the Association of Polysomnographic Technologists (APT) was formed in 1978, and a board of polysomnographic technologist registry (BRPT) administered its first examination in 1979. These groups ultimately formed a confederation in 1986 called the Association of Professional Sleep Societies (reusing the initials APSS), and ASDC was renamed the American Sleep Disorders Association (ASDA) the following year (eventually becoming the American Academy of Sleep Medicine [AASM] in 1999) [20].

The World Federation of Sleep Research Societies (WFSRS) was formed in 1987 to facilitate international collaboration among professional sleep societies. WFSRS ceased to exist after it merged with the World Association of Sleep Medicine (WASM) to form the World Sleep Society (WSS). While WFSRS focused on sleep research, clinical researchers and practitioners felt the need to create an international society to exchange sleep medicine information. Consequently, WASM was founded in June 2003 with the main mission to advance sleep health worldwide by promoting sleep medicine education, research, and patient care with more focus on the areas of the world where sleep medicine is less developed [32]. *Sleep Medicine* is the official journal of WASM. In 2011, WASM and WFSRS started discussing and developing a path to create a unified organization to cover sleep internationally. Out of this effort came the World Sleep Society (WSS) in 2016. The WSS has a similar mission to WASM. With formation of WSS, WASM ceased to exist on 31 December 2017. With the expansion of sleep, currently WSS has more than 40 associate society members from all over the world [33]. Additional societies have emerged along with their journals. For instance, the Society of Behavioral Sleep Medicine has emerged as a very promising organization and venue aiming to implement psychology- and psychiatry-related methods to sleep disorders and improve the understanding of sleep regulation and interactions with personality, physiology, mood, and emotions. Similarly, the National Sleep Foundation was founded in 1990 with the specific mission of unraveling activities that link sleep and health through theory, research, and practice. NSF's mission is to improve health and well-being through sleep education and advocacy. As the global voice of sleep health, NSF has assembled experts in sleep to develop and publish evidence-based consensus guidelines and recommendations in crucial areas such as sleep duration, sleep quality, sleep satisfaction, and drowsy driving, among others. NSF is known internationally for its annual Sleep Awareness Week® and Drowsy Driving Prevention Week® advocacy campaigns. NSF conducts research programs including the annual Sleep in America® poll and quarterly Sleep Health Index® which are designed to explore sleep health topics of interest and report on the status of sleep health in large and small population groups. In 2015, NSF launched its journal *Sleep Health* to provide a multidisciplinary peer-reviewed platform for sleep's role in population health. NSF's journal and public health textbook *Foundations of Sleep Health* complement its work translating rigorous science and scholarship into practical guidance so anyone and everyone can be their Best Slept Self® [34].

The first clinic for sleep disorders was established by the late Dr. Dement as Stanford University Narcolepsy Clinic, later morphing into a comprehensive Sleep Disorders Clinic [2]. As clinical PSG gained ground, sleep disorder centers began to open. Some notable early programs included the ones in Baptist Memorial (Memphis), Baylor College of Medicine (Houston), Western Psychiatric (Pittsburgh), Presbyterian (Oklahoma City), Ohio State (Columbus), Montefiore (New York), Henry Ford (Detroit), Mount Sinai (Miami), Stanford University (Palo Alto, CA), University of California (Irvine, CA), and Holy Cross (Mission Hills). This core group collaborated on a variety of projects and their leaders were instrumental in

developing PSG applications for sleep medicine [20]. These sleep disorder centers created a nucleus from which the Association of Sleep Disorders Centers (ASDC) grew. The main focus of these sleep centers was to conduct clinical PSG procedures. AASM accredited for the first time a sleep center in 1977. As of 2022, there are 2582 AASM-accredited sleep disorder centers (personal communication with AASM).

1.7 Education and Training History of Sleep Medicine

As the field of sleep medicine grew and needs for sleep clinical services became apparent, so came the need to provide training and certification in the field of sleep medicine. ASDC formed an education committee in charge of developing a curriculum for sleep medicine. As training programs started, a plan for certification for the purpose of competency was envisioned. Dr. Helmut Schmidt led the ASDC subcommittee in charge of certification. Many of the materials came from the recordings performed at Stanford and Cincinnati. The first exam was administered by Thomas Roth, Helmut Schmidt, and Christian Guilleminault at Stanford and later was moved to Columbus Ohio. ASDC administered the sleep medicine competency evaluation from 1978 to 1990. Subsequently, the American Board of Sleep Medicine as an independent certification body administered the exam from 1991 to 2006 and issued the certificate abbreviated as Diplomat-ABSM to 3445 diplomats [35]. Initially, the candidates responded to written true-false questions and oral questions. However, starting in 1980, the exam was taken in a two-part format administered on separate days. Sleep medicine was recognized as an independent subspecialty by the Accreditation Council for Graduate Medical Education (ACGME) in 2003 which paved the way for developing a subspecialty exam by the American Board of Medical Specialties (ABMS). Since 2007, ABMS has been administering the certification examination in sleep medicine. Initially, the exam was administered biannually, but currently, the applicants can take the certification exam annually [36]. Since 2011, the only pathway for ABMS Sleep Medicine certification is through Accreditation Council for Graduate Medical Education (ACGME)-accredited 1-year sleep medicine fellowship training [35].

Another milestone in the field of sleep medicine was the publication of *Principles and Practice of Sleep Medicine* by Kryger, Roth, and Dement in 1989 with 739 pages. The latest (7th) edition of this book was published as a two-volume set in 2021 with 213 chapters in 2240 pages. The *Principles and Practice of Pediatric Sleep Medicine* came out in 2001 and with the second edition in 2012 expanded the field. A third edition of this book is expected soon.

In summary, sleep and dreams have perplexed human beings since the dawn of humanity. However, it is really the major advances that occurred during last 100 years or so that have immensely increased our knowledge and understanding of sleep and sleep disorders and their treatment. History of sleep is clearly in the making, and we are all part of it.

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Neurological Aspects of Sleep Medicine, How Sleep Evolves, and Regulation of Function

2

Lourdes M. DelRosso, Raffaele Ferri, and Oliviero Bruni

2.1 Introduction

The brain undergoes dynamic structural and functional changes across the life span. Some of these changes are more evident in the transition from adolescence to adulthood. The various structures, regions, and neural networks undergo maturation and development of their distinct trajectories and connections. In the past century, the discoveries and advances in diagnostic technology methods have contributed to our understanding of the neural networks involved in sleep; in particular, electroencephalography (EEG) and magnetic resonance imaging (MRI) have shed light on the identification of specific brain areas/structures involved in the physiology of sleep and wakefulness. These and other techniques have allowed the identification of sleep stages and the changes of sleep stages and EEG activity across the life span. For instance, markers of sleep such as K-complexes, sleep spindles, and slow wave activity (SWA) have been studied in relation to changes across various age groups [1, 2].

Healthy sleep is necessary for normal growth, development, cognition, and overall good physical health [3]. For instance, the finding that short sleep duration in the first 3 years of life is associated with hyperactivity/impulsivity and lower cognitive performance on neurodevelopmental tests at 6 years of age is very important and is

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consistent with previous evidence for short-term effects of sleep loss. Furthermore, it has been reported that specific cognitive deficits and high hyperactivity scores at 6 years of age are most strongly associated with a pattern of short sleep duration at 2.5 years of age suggesting that insufficient sleep during the first few years of life may have long-standing consequences [4].

The Millennium Cohort Study on 11,000 children showed that nonregular bedtime at the age of 3 years is independently associated, in girls and boys, with lower reading, math, and spatial scores. Girls who never had regular bedtimes at the ages of 3, 5, and 7 years had significantly lower reading, math, and spatial scores, while for boys this was the case for those having nonregular bedtimes at any two ages (3, 5, or 7 years) [5].

However, sleep is not a static but rather is a dynamic state, involving variations in cerebral blood flow, neurotransmitters, immune response, and metabolic changes [6]. The understanding of the changes across the life span can help the sleep physician understand processes that occur in sleep and wakefulness while helping adolescents in their transition into adulthood.

In this chapter, we will further explore the neurological aspects that can influence sleep and wakefulness in the adolescent patient during transitioning into adulthood. We hope that this understanding will add to our set of tools to evaluate and treat patients with sleep disorders.

2.2 Brain Changes Across the Life Span

Recent advances in neuroimaging techniques have demonstrated important changes in brain structure, function, and metabolism across the life span. In 1990, Van Der Knaap et al. [7] demonstrated changes in the brain metabolism of children aged 3–16 years, using magnetic resonance spectroscopy. The transition from childhood to adulthood has also been shown to be accompanied by increased levels of γ-aminobutyric acid (GABA) in the frontal cortex, while, in the subcortical region, the levels of glutamate were found to be decreased. Glutamine increases during the first years of childhood and then decreases from childhood to adulthood and continues decreasing until elderly. This glutamate reduction was postulated to represent a maturational change in the function or the density of glial cells [8].

Structural Brain Changes

Brain volume peaks at the age of 10.5 years in females and 14.5 years in males, following a decline (inverse U-shaped trajectory) with aging (Box 2.1) [9]. The cerebellum follows a similar inverse U shape, with a peak volume a little bit later at 11.3 years in girls and 15.6 years in boys, but the cerebellar vermis does not show changes across the life span [10]. The gray matter also shows an inverted U-shaped trajectory, and the white matter volume increases through adolescence, probably secondary to the increase in myelin [9]. These trajectories, shape, and changes in volume

may help to clarify functional phenotypes and changes in sleep disorders. An example is seen in the changes in periodic leg movements across the life span described by Ferri et al. [11] who found peculiar changes only in the periodic leg movements mirroring changes in dopaminergic networks, not shared by the other leg movement indices. These changes also include maturation and changes in brain connectivity networks. Synaptic density, for example, is low at birth, increases significantly over the first years of life to a maximum during mid-childhood, and then declines across adolescence, so that synaptic density at 10 years is approximately the double of that found at the age of 20 years [12]. The maximum synapse density varies in a way that is specific to each brain region and reaches a maximum at different ages, for example, the highest synapse density for the auditory cortex occurs at 3 months of age. Tests of brain glucose utilization have been used as markers of nerve cell functional activity. Regional cerebral blood flow increases during infancy until school age and then decreases to adult levels at around the age of 16–18 years [13].

Box 2.1 Summary of Brain Changes from Adolescence to Adulthood

1. Brain volume peaks at the age of 10.5 years in females and 14.5 years in males.
2. White matter increases through adolescence.
3. Synaptic density is maximum during childhood and decreases in adolescence.
4. Regional brain flow increases during childhood but decreases to adult levels at age 16–18.

Functional Changes in Neurotransmitters

The maturation and development of the human brain also involves the maturation and development of the neurotransmitter systems. Unfortunately, research on the difference between the individual changes in neurotransmitters remains sparse. A deeper understanding of these changes is of utmost importance, particularly in the area of psychopharmacology and treatment of sleep disorders with medications approved and studied in adults but with unknown effects in adolescents.

Studies have shown a U-shaped progression of norepinephrine levels (Box 2.2) in plasma with an initial sharp drop starting at 5 years and reaching the lowest levels at the onset of puberty, after which they tend to increase until the age of 40–60 years [14]. Adrenergic receptors in the brain of animal models have shown an increase in the first years of life, followed by a plateau and subsequent decline during the young adult years [15]. There are also important functional differences in the upregulation of noradrenergic receptors. While in adults higher norepinephrine levels in the brain cause downregulation of receptors, in the developing brain, higher norepinephrine levels cause upregulation of alpha-2 receptors. One must think of the psychopharmacological applicability of this finding, in particular using medications that are

proven to be effective in adults and extrapolating their use in adolescents. An example is the use of tricyclic antidepressants which may not be effective in children (or adolescents) but are effective in adult depression [16].

Dopamine is essential for movement, arousal, and reward, among other important functions. Dysfunction in dopaminergic networks has been implicated in restless legs syndrome and periodic leg movement disorder, among other sleep disorders. Dopamine levels peak in various brain regions during adolescence. Animal models have also shown a prepubertal peak in D1 and D2 receptors in the brain, with a subsequent plateau and decline during adulthood [17].

Serotonin is also involved in sleep and arousal, among other functions. Positron emission tomography studies have demonstrated that serotonin synthesis capacity increases in the first years of life, decreasing to adult levels by the age 14 [18]. Brain area-specific and receptor-specific changes are seen in childhood and adolescence but with an overall peak in serotonergic activity in the child brain [15]. The clinical implication of these findings is related to side effects of selective serotonin reuptake inhibitors.

Box 2.2 Trough and Peak Levels of Neurotransmitters in Childhood and Adulthood

Neurotransmitter	Age at trough level	Age at peak level
Norepinephrine	Adolescence	Adulthood
Dopamine	Older adult	Adolescence
Serotonin	Adolescence	Childhood

2.3 EEG and Sleep Changes

It has been shown that distinct patterns of EEG activity become associated with different behavioral states when the cortex becomes able to generate its own oscillatory rhythms, independent of sensory stimulation. One could speculate that the goal of neural activity during the development is to refine cortical circuits, by pruning and synaptic potentiation, and this process seems to occur at all times, during wakefulness or sleep [19]. In normal healthy infants, sleep cycles typically last a mean of 50–60 min (range: 30–70 min). Wakefulness represents only 8–10% of a 24-h day in infants up to 8 weeks post-term. Until approximately 44 weeks of conceptional age, sleep cycles repeat in a polyphasic pattern across the 24 h, interrupted approximately every 3–4 h by an awakening for care and feeding. Within a given sleep cycle, REM sleep lasts 10–45 (mean 25) min, NREM near to 20 min, and transitional sleep about 10 min. NREM and REM sleep are typically evenly distributed during the night.

The most conspicuous changes in sleep architecture during infancy and early childhood are (1) decrease in total sleep time, (2) gradual consolidation of periods

of sleep at night or wakefulness during the day, (3) decrease in the intensity of (EEG power) of NREM sleep stage 3 slow-wave activity (SWA), and (4) a steady decline in the percentage of sleep time spent in REM sleep [20]. We will proceed to discuss these changes in more detail.

Scholle et al. [21] published normative values for one-night PSG in children aged 1–18 years using the American Academy of Sleep Medicine (AASM) sleep scoring to standard criteria [22]. They found that sleep architecture showed significant changes with increasing age. REM latency, awakening index, sleep efficiency, mean sleep cycle duration, and number of sleep stage shifts increased with age. Total sleep time, wakefulness after sleep onset, movement time, number of sleep cycles, NREM sleep stage 3, and REM sleep decreased. Sleep parameters which showed a dependency on Tanner staging, as well as corresponding age, were total sleep time, awakening index, REM latency, NREM sleep stages 2 and 3, number of sleep cycles, and mean sleep cycle duration. No gender dependencies were found. The delta power of NREM sleep stage 3 EEG activity decreases by more than 60% between the ages of 10 and 20 years. SWA also declines across recurring periods of NREM sleep within a night. Longitudinal studies have shown that the delta power of the sleep EEG begins to decrease at around 11.5 years and is reduced by 60% at 16 years. The fall in delta power begins earlier in girls than in boys (consistent with age-related changes in gray matter volume) but with time the overall rate decline becomes similar between girls and boys at 16 years of age (Box 2.3).

The main characteristics of the normal adolescent EEG are indistinguishable from the adult EEG. In fact, the AASM allows to score sleep recordings of patients aged 13 years and older based on adult criteria. During wakefulness, the EEG is characterized by beta waves and gamma waves with low voltage (5–10 μV) and high frequency (30–120 Hz) [23]. During relaxed wakefulness, alpha rhythm appears in the EEG with a frequency of 8–13 Hz. During sleep, REM, NREM, and its sub-stages (N1, N2, and N3) can be identified by their unique EEG, electrooculography (EOG), and electromyography (EMG) findings.

Sleep stage N1 is characterized by low-amplitude, mixed frequency activity (4–7 Hz) for more than 50% of an epoch. Vertex sharp waves can be observed in sleep stages N1 and N2 with a maximum duration of 0.5 s. The EOG can show slow eye movements (SEM) during N1. Stage N2 is characterized by the K-complexes and sleep spindles. K-complexes have a negative followed by positive deflection and last at least 0.5 s. K-complexes decrease with age both in frequency and amplitude [24]. This change is thought to be secondary to age-related changes of the thalamocortical regulatory mechanisms. Sleep spindles have a frequency of 11–16 Hz and last at least 0.5 s. Two types of sleep spindles have been reported in the literature: slow (11–12 Hz), which is found over the frontal regions, and fast (14 Hz), which is found over the central and parietal regions. Each type of spindle shows a different maturation course. Centroparietal spindles appear to gradually increase with age, while frontal spindles decrease from early childhood to adolescence and become stable at 13 years of age [25]. Stage N3 slow waves have a frequency of 0.5–2 Hz with a minimal amplitude of 75 μV. One of the most dramatic changes in sleep architecture during adolescence is the significant decline in slow wave sleep (60%

between 11 and 16 years) [26]. Delta power begins to decline at 11 years and shows a steep decline until about the age of 17 years during which this decline begins to slow down. It has been suggested that this decline in slow wave sleep is associated with maturation of networks in the frontal cortex.

Synaptic pruning during adolescence is accompanied by a reorganization of neuronal connections, whereby mistargeted axons and unused synapses are eliminated and connectivity becomes more specific. The decrease of synaptic density during adolescence, which is reflected by changes in gray matter, proceeds asynchronously in different brain areas, in line with the maturation of specific cognitive functions. Changes in synaptic density are paralleled by changes in slow-wave amplitude [12, 26] and brain metabolism, presumably due to the increased energy requirements associated with increased synaptic activity [27].

During development, none of the classical frequency bands change as dramatically as the slow wave activity (SWA) band. The change of the amplitude of slow waves parallels the number of synapses, that is, reduced synaptic density following pruning is reflected by a decline in amplitude, and the location over which maximal SWA can be measured undergoes a shift from the posterior to the anterior regions of the scalp across childhood and adolescence, matching the time course of cortical maturation, as tracked by MRI and behavioral studies [28], most likely reflecting cortical plasticity during development. SWA is highest over the posterior regions during early childhood and then shifts over the central derivations to the frontal cortex in late adolescence. This trajectory of SWA topography matches the course of the cortical gray matter maturation. Interestingly, synaptic density and slow-wave amplitude are highest shortly before puberty and decline thereafter during adolescence, reaching overall stable levels during adulthood. SWA is not merely reflecting cortical changes but plays an active role in brain maturation [29]. Thus, sleep SWA might be considered as a reliable indicator of net changes in average synaptic density/strength, both in the course of the night (sleep homeostasis) and in the course of development. Investigation of sleep SWA topography during childhood and adolescence confirmed this assumption by showing that the location on the scalp exhibiting maximal SWA changed during development, shifting from the posterior to the anterior scalp regions with time [28]. The changes in SWA topography probably reflect synaptic changes accompanying the pruning process during cortical maturation. Another link between cortical maturation and slow waves arises from a study that compared the SWA decrease during adolescence with alterations in gray matter volume [2, 30].

A study recently highlighted the connection between sleep restriction and neural growth in school-age children revealing a local sleep homeostatic response following acute sleep restriction, as indicated by the increase in SWA, over the parieto-occipital areas and the negative relationship between the homeostatic SWA increase in adjacent, parieto-temporal areas and local myelin content in the optic radiation. These data suggest high plasticity in the parietal-occipital areas in children, which is consistent with anatomical, neuroimaging, and behavioral data. The SWA rebound after sleep restriction in children is strongest at the beginning of the night and levels off with time in about 60 min, which is consistent with existing knowledge of the

homeostatic time course of sleep regulation. The parieto-occipital region is implicated in processing visual signals (occipital lobe) and sensory information (parietal lobe), thus affecting planned movements, spatial reasoning, and attention; based on the study, these regions may be more vulnerable to a lack of sleep [2].

The main characteristics of REM sleep are the rapid eye movements seen in the EOG with an initial deflection lasting less than 0.5 s and the simultaneous loss of muscle tone characterized by the absent chin tone on EMG. The loss of muscle tone is called REM sleep atonia. Quantitative EMG analysis has demonstrated that adolescence is the stage with the most evident REM sleep atonia which decreases during adulthood [31].

Box 2.3 Summary of EEG Changes During Sleep from Childhood into Adulthood

NREM	REM
Slow wave sleep decreases during adolescence	Latency increases with age
K-complexes decrease with age both in frequency and amplitude	Amount decreases with age
Centroparietal spindles gradually increase with age, while frontal spindles decrease from early childhood to adolescence and become stable at 13 years of age	Atonia peaks during adolescence and then decreases with aging

2.4 Circadian and Homeostatic Changes

Process C (circadian regulation) and process S (homeostatic regulation) are part of the two-process model of sleep regulation proposed in 1982 by Alexander Borbely; these biological processes regulate the timing and length of sleep [32]. Process C represents the 24-hour sleep-wake cycle regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus and has the core body temperature and melatonin levels as the main markers [33, 34]. Process S, or the homeostatic process, refers to the propensity to fall asleep, based on the previous amount of wakefulness [35] and has as main markers NREM sleep and slow wave activity [36]. Sleep occurs when process S approaches the upper threshold of process C, and wakefulness occurs when process S approaches the lower threshold of process C [32].

Circadian Changes from Adolescence to Adulthood

Growing evidence supports that endogenous circadian period is altered during puberty and explains the development of delayed sleep phase in adolescents. Pediatric sleep doctors commonly see and evaluate teenagers who are often thought to have insomnia due to the inability to fall asleep earlier than 11 pm or midnight, yet, when allowed to go to sleep at these times, sleep latency is brief and sleep is continuous until spontaneous awakening 9 h later. This is the hallmark of a delayed

circadian cycle. The disorder ensues when school demands a wakeup time at 6 or 7 am allowing only for 6 or 7 h of sleep. The adolescent then presents with symptoms of daytime sleepiness, fatigue, and poor school performance. There is consensus that sleep requirements are about 9 h of sleep at night for adolescents and do not change significantly across puberty. Delayed bedtime and early school wakeup time contribute to sleep insufficiency during school days and are the causes of catching up sleep in the morning during weekends and of common complaints of excessive daytime sleepiness in adolescents.

Research has shown a significant association between this circadian delay in adolescents and puberty. Females start showing a delay in sleep time approximately 1 year earlier than males, paralleling the onset of puberty. The maximum delay in sleep time also occurs earlier in females than in males (19.5 vs. 20.9 years). Global research has also demonstrated that this delay in sleep onset occurs in adolescents irrespective of cultural or geographical differences. This delay in sleep correlates with the pubertal development of secondary sexual characteristics and persists for weeks after sleep schedule is adjusted [37] (Box 2.4).

Few mechanisms have been postulated to explain the association between circadian delay and puberty. The first and more obvious, due to the relationship with puberty, involves the potential role of gonadal hormones in the regulation of the circadian rhythm. Gonadectomy and/or administration of estrogen, testosterone, or progesterone in rodents has shown an immediate effect on the circadian cycle [38]. The effect of gonadal hormones on circadian rhythms can be attributed to their modulation of the suprachiasmatic nucleus either by producing anatomical changes, entrainment, or rhythm generation [39]. Another mechanism proposed for changes in circadian rhythm during adolescence and early adulthood suggests that age-related sleep changes are associated with intrinsic changes in the circadian process, such as age-related variation in the patterns of clock gene expression [40] or changes in neuronal synchronization at the level of the suprachiasmatic nucleus. This may be particularly applicable to changes seen in circadian rhythms of the core body temperature and melatonin production in the elderly [41].

Homeostatic Changes from Adolescence to Adulthood

The decline in N3 during adolescence parallels a decline in homeostatic sleep pressure. Jenni et al. [42] demonstrated that older mature adolescents (tanner 5) exhibited slower buildup of homeostatic sleep pressure when compared to prepubertal or early pubertal children; EEG after sleep deprivation, however, showed similar changes in adolescents and adults [42]. These findings have important implications as adolescents are often seen in sleep clinics for concerns of delayed sleep onset. Typical recommendations to increase sleep pressure by prescription of sleep deprivation may not work due to their reduced homeostatic drive (Box 2.4).

In conclusion, changes in both circadian and homeostatic processes are responsible for the sleep-onset delay seen during adolescence. Since both processes change simultaneously [43], the delay during this age period is quite

evident. After adolescence, the return to earlier sleep time is not completely understood but may continue to be associated with a balance between process C and process S.

Box 2.4 Summary of Circadian and Homeostatic Changes

Circadian delay occurs during adolescence.
Decrease in homeostatic pressure accompanies the decline in slow-wave sleep.

2.5 Clinical Implications

In order to provide effective clinical sleep recommendations to our patients, we need to have a better understanding of the physiological and structural neurological changes that occur across the life span and, for this particular textbook, the changes that occur during the transition from adolescence into adulthood which can translate into changes in sleep time and duration.

Changes in brain maturation and growth have shown increased peaks of activity or concentration of various neurotransmitters involved in sleep and wakefulness. The peak in activity may be associated with significant side effects to medications commonly used to treat sleep disorders in adults or children (i.e., dopaminergics), and caution must be established when using these treatments off label with particular attention to activating side effects, or exacerbation of symptoms.

Circadian and homeostatic control of sleep simultaneously change during adolescence explaining the delay in sleep onset that occurs in this age group. The understanding of this physiological change will help sleep physicians with strategies to improve sleep and daytime functioning in their patients. Such strategies include policy changing advocating for late school times, counseling to families about sleep requirements, and choosing activities that start at times that match the natural brain sleep schedule.

2.6 Summary

Changes in sleep time and duration occur during childhood and adolescence and may or may not persist into adulthood. The changes during adolescence have been studied in relation to the two-process model of sleep regulation and in terms of the contribution of hormonal changes and social demands during this period. Although changes in brain development, neuronal connectivity, and neurotransmitter modulation are known during this period, their contribution to sleep and sleep disorders still need to be elucidated. Importantly, the understanding of sleep neuropharmacology requires a complete understanding of these changes during adolescence and early adulthood.

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3 Cardiorespiratory Changes as They Relate to Sleep in Transition from Pediatric to Adulthood

Giora Pillar

Abbreviation

CPAP	Continuous positive airway pressure
ED	Endothelial dysfunction
OSA	Obstructive sleep apnea
SDB	Sleep-disordered breathing
UAW	Upper airway

3.1 Introduction

The cardiorespiratory system plays a major role in sleep, with a bidirectional relationships. It both affects sleep and is affected by sleep. Sleep deprivation or reduced sleep quality or sleep-disordered breathing (SDB) is associated with a wide range of diseases and adverse health outcomes, both physical and mental, and specifically in children may also affect maturation (physical, mental, emotional). Some specific factors may result in individuals vulnerability to SDB. The interrelationship between the cardiorespiratory system and sleep may be affected by age and may change during development. They are influenced by a variety of complex internal and external factors. The current chapter describes various anatomical and physiological changes in cardiovascular characteristics and their effects on sleep, during the transition from childhood into adulthood. It focuses on characteristics that are likely to affect or be affected by sleep such as upper airway (UAW) anatomy/physiology, cortical/autonomic arousal thresholds, and vascular endothelial function.

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3.2 UAW Anatomy

Anatomical abnormalities in the upper airway (UAW) play a major role in the pathophysiology of obstructive sleep apnea (OSA) in all ages. In children, it is very common to find hypertrophy of adenoids and/or tonsils, while in adults, anatomical abnormalities may consist of fat deposits within the UAW making them narrow, crowded posterior pharyngeal space (with or without enlarged tonsils), long UAW, or change in the antero-posterior to lateral dimensions of the UAW. In some specific pediatric syndromes, airway anatomy can be compromised. These include children with Apert, Crouzon, or Pfeiffer syndrome, who develop obstructive sleep apnea (OSA) mainly due to midface hypoplasia. Midface advancement is often the treatment of choice, which results in moderate success [1]. It has recently been shown that in children with craniosynostosis syndromes the cross-sectional retropalatal area is predictive of OSA [2]. Children with Pierre Robin (PR) sequence [3] or Treacher Collins syndrome [4] commonly suffer from OSA due to retromicrognathia or mandibular hypoplasia [5]. There are several common imaging techniques utilized to demonstrate these, such as CT, MRI, or video nasopharyngoscopy (VNP) [6]. Mandibular distraction with mandible advancement which increases the airway lumen is an effective treatment in such children [7]. Several such children who suffered from severe OSA who required tracheostomy were completely cured following this procedure [8]. Additional disorders which may be associated with inadequate airway anatomy include cleft lip and palate [9], Chiari malformation [10], Schwartz-Jampel syndrome [11], and achondroplasia [12, 13]. Down syndrome is an additional well-established disorder associated with high prevalence of OSA. It affects both the anatomy and the physiology of the UAW, making them vulnerable for collapse. Children with Down syndrome commonly have lymphoid hyperplasia, macroglossia, and narrow nasopharynx [14–16], along with hypotony of the upper airway dilatory muscles. Additional anatomical features of Down syndrome include pharyngeal and maxillary hypoplasia and sometimes constricted maxillary arch with nasal obstruction. Maxillary expansion has been suggested to relieve airway obstruction in these children [17]. In adults, the most recognized anatomical risk factor for OSA is obesity, especially the male-type obesity which can be observed by increased neck circumference. Retrognathia, a small, crowded posterior pharyngeal space (with or without enlarged tonsils), and/or nasal obstruction can also result in susceptibility for airway obstruction. The current chapter focuses on two major anatomical changes which occur in the transition from childhood to adulthood: changes in tonsillar and adenoidal sizes and changes in upper airway length.

3.3 Tonsils and Adenoids

Adenotonsillar hypertrophy is the most common cause of OSAS in children, but not in adults. Understanding the natural history of adenoids and tonsils and the factors responsible for their growth and regression during development is of great importance especially for planning the treatment of OSA. While in children both adenoids

and tonsils generally have a major effect on the UAW, obesity when present may have a major effect as well [18]. The impact of adenotonsillar size on childhood OSA may be altered by both age and obesity [19, 20]. Tagaya et al. [19] emphasized that the correlation between adenoid size and OSA is more prominent in preschool children than in school-aged children. In quite many other studies, the correlation between adenotonsillar size and severity of OSA was relatively small. Although generally in most children with OSA the majority of the studies indicate that there is increased tonsillar and adenoidal size [19, 21–25], it cannot well predict the severity of the OSA. However, adenotonsillectomy has been shown as the most effective treatment for children with OSA [26–31]. Since adenoid and tonsil hypertrophy is similar between genders, it may explain the similar prevalence of OSA in prepubertal boys and girls (as opposed to the well-established substantial male predominance in adults with OSA). The adenoids are midline structures of lymphoepithelial tissue located in the superior aspect and the roof of the nasopharynx. They are part of the Waldeyer ring, whose components include the adenoids, the palatine tonsils, and the lingual tonsils. They are composed of lymphoid tissues which are considered (along with other lymphatic tissue in the nasopharynx) as the first line of defense against ingested or inhaled pathogens. They are part of the lymphoid system and are involved in the development of both B and T cells. Within the adenoidal tissues, the immune system battles against infections. Activation of B cells within the adenoids leads to their proliferation and hypertrophy. Recent studies have provided some evidence that adenoids produce T lymphocytes as well [32–34]. They can be identified in utero (usually as early as the seventh month of gestation) and typically grow until ages 4–7 when they reach their peak size. Commonly, their hypertrophy is in parallel to upper respiratory tract infections, but their hypertrophy can also be seen without chronic infections. They then tend to diminish in size until they are almost unseen at puberty and adolescence in most individuals [32, 33, 35]. Early studies reported that in general adenoids and tonsils reach approximately 200% growth by late childhood and then involute during adulthood [36]. Other studies also showed that adenoids decrease in size with age, typically atrophying completely by the teenage years [37]. In a recent Japanese study, it was reported that adenoidal and tonsillar size gradually decreased when compared between lower primary school stage (ages 3–6) and young adult stage (ages 18–20 years). However, they showed that sometimes adenoids, and even more often tonsils, do not completely vanish and in some individuals they may persist into adulthood [38]. Chuang et al. [39] on the other hand reported that increased neck circumference and tonsillar hypertrophy were the most influential factors for younger children, whereas adenoidal hypertrophy became more important at an older age [39]. It should be highlighted that even when the lymphoid tissues of the adenoids and/or tonsils do not decrease with age, their impact on the upper airway diminishes since the upper airway grows substantially and thus the ratio of lymphoid size within the lumen tend to decrease even then [38]. Persistence of adenoid tissue into adulthood is an uncommon clinical finding and when seen should raise suspicion of immunocompromised patients, in whom this finding may be caused by regressed adenoid tissue reproliferating in response to infections [19, 32–35].

Similarly to adenoids, tonsils tend to grow during childhood, reach the maximal relative size around age 5.1–8 years [40], and then regress. In some adults, tonsils may remain enlarged into adulthood. There are several methods for assessing tonsillar size such as by subjective score during physical examination, imaging techniques such as MRI or transcervical ultrasonography, endoscopy, digital morphometrics based on a laser ruler, and more. This chapter does not focus on the way of assessing tonsillar size but rather on their change from childhood to adulthood and on their impact in terms of sleep-disordered breathing. In children without sleep-disordered breathing, using MRI, Arens et al. [41] reported that soft tissues, including tonsils and adenoid, grow proportionally to the skeletal structures during the development from age 1 to 11 years [41]. Cohen et al. [40] on the other hand reported that the bony nasopharynx and the pharyngeal tonsil tissue both grow during childhood. Different growth rates result in the narrowest airway in the age group of 5.1–8 years [40]. While the transition from childhood to adulthood is associated with reduced tonsillar size, it is usually also associated with increased weight, which questions the relative contribution of each to OSA. In a study by Dayyat et al. [20], 412 children with OSA, with or without obesity, were assessed for tonsils and adenoid sizes and Mallampati class scores. They reported that the magnitude of adenotonsillar hypertrophy required for any given magnitude of obstructive apnea-hypopnea index (AHI) is more likely to be smaller in obese children compared to nonobese children. Increased Mallampati scores in obese children suggested that soft-tissue changes and potentially fat deposition in the upper airway may play a significant role in the global differences in tonsillar and adenoidal size among obese and nonobese children with OSA [20]. Interestingly, in obese adolescents aged 12–16 years, Schwab et al. [42] found that increased size of the pharyngeal lymphoid tissue, rather than enlargement of the upper airway soft tissue structures, is the primary anatomic risk factor for OSA. Thus, they suggested that adenotonsillectomy (and not only weight reduction) should be considered as the initial treatment for OSA in obese adolescents [42].

When tonsils remain enlarged into adulthood, they definitely have an effect and may contribute to OSA. Tonsillectomy in adults with OSA and tonsillar hypertrophy revealed positive therapeutic results in many studies [43–45]. Furthermore, tonsillar hypertrophy may have an effect on other therapies. Tschopp has recently shown that tonsil grade and volume both showed a significant correlation with preoperative AHI [43]. They have performed uvulopalatopharyngoplasty (UPPP) to their patients and found that the AHI reduction after surgery increased significantly with larger volume and higher tonsil grade [43]. They concluded that large tonsils are responsible for higher preoperative AHI values, and their removal leads to greater reduction of initial AHI. Interestingly, in contrast to previous studies, Jara and Weaver reported that subjective tonsillar grade was more strongly associated with AHI than objectively measured tonsillar volume [46]. They therefore concluded that the space that the tonsils occupy within the oropharyngeal airway, rather than their actual measured volume, is more predictive of OSA severity [46].

To summarize this part, pharyngeal lymphoid tissues (tonsils and adenoids) tend to grow during childhood initially more than the upper airway, resulting in a peak

relative size during early childhood. These tissues tend to shrink during adolescence into adulthood, but not in all. When these tissues remain enlarged in adults, they do play a role in the pathophysiology of OSA and their removal results in alleviation of sleep-disordered breathing.

3.4 UAW Length

The length of the pharyngeal airway (from the hard palate to the epiglottis) is also of great importance while dealing with UAW anatomical changes from childhood to adulthood. It is a physical characteristic of a collapsible tube to increase collapsibility as the tube is longer. In adults, it was previously reported that UAW length was higher in normal males compared to females, even after correction for body height [47]. It was therefore concluded that UAW length may play a role in the male predisposition to pharyngeal collapse [47]. Furthermore, a major impact of UAW length on pharyngeal mechanics and collapsibility have been demonstrated utilizing computational modeling [47]. In adolescents, however, it has been found that the UAW length in pre-pubertal children is equal between genders, while following puberty, males were found to have longer upper airways than females (corrected for height). This study of 69 healthy adolescents who had undergone CT scans of the neck may therefore partially potentially explain the relatively strong male predominance in adults but not in children with OSA [48]. The transition from childhood to adolescence was not associated with general lengthening of the corrected UAW length (UAW length divided by height) but rather with gender effects [48], i.e., the ratio of UAW length to body height becomes higher in males vs females. Thus, gender-related differences in upper airway length may explain to some extent the male predisposition to airway collapse that occurs in post-pubertals and adults. Moreover, data show that UAW length is greater in patients with OSA than in controls, with a positive significant correlation between the UAW length and the severity of OSA [49]. This was the case in both adults [49] and children [50]. Fifty children aged 10.3 ± 0.6 years with syndromic craniosynostoses (50% boys, 48% with OSA) underwent both UAW imaging and sleep studies. Those with OSA had significantly higher UAW length ($P = 0.016$) [50]. Interestingly, weight gain and obesity may play a role in this regard as well. It was recently reported that weight gain leads to significant fat infiltration in the tongue, causing the hyoid to move downward and lengthen the airway in patients with OSA [51]. The apnea-hypopnea index (AHI) strongly correlated to airway length and tongue size [51]. Furthermore, 24 weeks of weight reduction program in patients with OSA resulted in UAW length shortening, although the exact mechanisms remained unclear [52]. Thus, UAW length is an important anatomical feature of the airway which should be taken into consideration when assessing tendency to collapse and potential explanation of OSA in both children and adults. It seems that the most relevant change that occurs from childhood to adulthood is the greater corrected UAW length in males vs females. The higher UAW length seen in OSA vs non-OSA patients seems similar in children and adults.

3.5 UAW Physiology

Susceptible predisposed UAW anatomy requires increased neuromuscular activity during wakefulness regardless of age. This is a compensatory mechanism to maintain UAW patency in patients with OSA in all ages (neuromuscular protection). Although the anatomical component is different in children as discussed above, the upper airway dilator muscle role seems quite similar to adults. Children have generally smaller UAW than adults but, nevertheless, snore less and have less apnea. This may reflect more solid neuromuscular protecting responses. Children's upper airway is more stable than that of adults and is considered less collapsible during sleep. This probably results from substantial neuromotor activation which are only slightly diminished from wake to sleep. Marcus et al. have assessed the neuromuscular responses of the UAW muscles to increasing CO_2 and to negative pressure, in children with or without OSA. They demonstrated that healthy children had a significantly higher UAW muscle response to both hypercapnia and negative pressure during sleep, compared to children with OSA who had no response at all [53]. Isono et al. have studied the collapsibility of the passive pharynx in children, in setting with no upper airway muscle activities. They investigated both the site of UAW collapse and the pressure required for collapse. They reported that in children with SDB, the common sites of collapse were the levels of adenoids and/or tonsils, and the closing pressure were positive, while in normal children the sites of collapse were the soft palate edges or the tongue bases, and the closing pressures were negative (subatmospheric). Collapsibility of the retropalatal and retroglossal segments were significantly higher in children with SDB compared with healthy children [24]. Testing the UAW collapsibility before and after applying topical anesthesia in the airway revealed similar results. Gozal et al. demonstrated increased UAW collapsibility during wakefulness in children with OSA [54]. By assessing UAW cross-sectional area utilizing acoustic pharyngometry measurements in response to topical anesthesia, they showed significantly greater reduction in children with OSA compared to others. They suggested that UAW dynamic testing during wakefulness in response to a topical airway anesthetic may provide a useful clinical adjunct to the evaluation of snoring children, with more accurate identification of those children with SDB [54]. The major stimulus which drives children's UAW dilator muscles' responses (predominantly the genioglossus) is negative (collapsing) pressure (similar between children and adults). The negative pressure during inhalation while awake leads to activation of dilator muscles, which results in opening of the airway. This is their physiological way to maintain upper airway patency during wakefulness despite tendency to collapse due to anatomical predisposition (narrow airway). Genioglossus activity is significantly higher during wakefulness in children with OSA compared with control subjects, indicating the need to protect narrow airway from collapsing during wakefulness [55]. However, in the wake-sleep transition, children with OSA demonstrate a greater decline in genioglossus activity, resulting in sleep-disordered breathing [56]. In contrast to adults, in some children genioglossus activity returns to normal during sleep, suggesting that some chemical or mechanical compensatory mechanisms remain active during stable non-REM sleep

in children [56, 57]. This may explain the relatively milder sleep-disordered breathing severity in children compared to adults.

In adults similar mechanisms exist. Patients with OSA are characterized by anatomically small airway (see above) and therefore vulnerability to collapse. This UAW tendency to collapse activates a similar negative pressure reflex mechanism during wakefulness, resulting in increased dilator UAW protective muscle stimulation. This neuromuscular compensatory mechanism protects the UAW from collapsing during wakefulness. The genioglossus muscle in apnea patients functions at nearly 40% of its max capacity during wakefulness, while in control subjects the muscle functions at only about 12% of maximum [58]. This dilator muscle activation during wakefulness is driven by negative pressure as evident by the observation that continuous positive airway pressure (CPAP) can reduce the level of activity in the genioglossus muscle of patients with OSA to near normal levels [58]. Thus, were it not for this increased activity of the pharyngeal dilator muscles, the airway of the apnea patient would substantially narrow or collapse even during wakefulness. Thus, the individual's propensity for UAW collapse during sleep depends on two variables: (a) the predisposing anatomy and (b) the level of pharyngeal dilator muscle activity. Similarly in children, this reflex-driven augmentation of dilator muscle activity compensates for deficient anatomy in patients with OSA during wakefulness. During sleep, there is a marked attenuation or loss of this reflex mechanism even in normal subjects. A tight relationship between pharyngeal negative pressures and genioglossal muscle activation during wakefulness has been shown in both controls and patients with OSA, utilizing a model of passive negative pressure ventilation [59]. Using the same model, it has been found that the constant relationship between negative epiglottic pressure and genioglossal EMG was markedly reduced during sleep while applying inspiratory resistive loading [60] or while ventilated with negative pressure [61]. Therefore, during sleep there is a markedly elevated pharyngeal airflow resistance compared to wakefulness. At the transition from wakefulness to sleep, there is a reduction in genioglossal EMG paralleling increased resistance. Thus, while the negative pressure reflex is able to maintain genioglossal EMG during wakefulness, this reflex fails to do so during sleep. Furthermore, not only response to negative pressure is reduced during sleep but also the muscle response to increasing CO_2. The tight association between dilator muscle activation and increasing CO_2 during wakefulness is substantially diminished during either stage 2 or slow wave sleep [62]. To summarize this part, a similar neuromuscular mechanism may play a role in both children and adults, although the potency of it may be higher in children. There is a reflex negative pressure and/or CO_2-dependent protecting mechanism which is diminished during sleep, leading to falling dilator muscle activity and airway collapse [63–67]. The finding that the protective genioglossal activation is almost completely lost during REM sleep may help to understanding why AHI increases during REM in most adults [68]. Thus, both children and adults do have a similar neuromuscular compensatory mechanism to activate dilator muscles of the UAW, although it appears that the UAW is more stable in children, who are less likely to collapse than adults. One of the best ways to show this is by assessing their critical pressure to collapse.

3.6 Critical Pressure for UAW Collapse (Pcrit)

The critical pressure required to close the UAW of humans is termed Pcrit [69–73]. The measurement of an UAW Pcrit during sleep is a useful measure of an individual's propensity or vulnerability to pharyngeal collapse [69–73]. Table 3.1 presents UAW Pcrit values in normal and patients with OSA. One good way of separating anatomical tendency to collapse from physiological neuroprotective muscle activation is by studying passive airway. Such a study by Isono et al. found that children with SDB had positive closing pressure Pclose (above atmospheric pressure), while healthy control children had negative Pcrit (subatmospheric). Collapsibility of the retropalatal and retroglossal segments was significantly higher in children with SDB compared with healthy children [24].

Similar findings were reported in adults. Adult patients with OSA often require positive pressure to maintain airway patency during sleep (i.e., positive Pcrit, need for continuous positive airway pressure therapy during sleep). Patients with mild disease or simple snoring tend to have a slightly negative Pcrit, whereas normal controls have a substantially negative Pcrit (−10 to −15 cmH_2O) [62, 73, 74]. The UAW collapsing mechanism in children is like adults [24, 57], although their closing pressure is generally lower (more negative, indicating stable airway). These Pcrit measurements, which reflect both anatomy and neuromuscular activity, also support an UAW anatomic abnormality among patients with OSA [62, 71, 73–75]. The change in pressure-volume slope (assessment of Pcrit) with maturation appears to represent a loss of neuromuscular reflex control of the UAW muscles during sleep. The rightward shift in this relationship in children can be best attributed to increased anatomic loads. Interestingly, a simple wakefulness test has been recently proposed as a surrogate of Pcrit, the upper airway collapsibility index measured in response to negative pressure pulses delivered in early inspiration during wakefulness [76].

The transition from childhood to adulthood passes through adolescence, in whom upper airway reflexes during sleep to activate UAW dilator muscles in response to negative pressure stimuli and hypercapnia are generally lower than in children, but higher than adults. It has been shown that these reflexes decline during adolescence, albeit with much individual variability [77]. Obesity obviously also plays a role in increasing the Pcrit (more collapsible). Huang et al. [78] had studied lean and obese adolescents without OSA and compared them to obese adolescents with OSA. In the hypotonic state, the lean controls had a flatter slope of the

Table 3.1 Upper airway Pcrit values

	Critical pressure for UAW collapse (Pcrit)
Healthy children	Less than −30 cmH_2O
Healthy adults	Less than −10 cmH_2O
Patients with snoring	−10 to −5 cmH_2O
Patients with OSA predominantly hypopnea	−5 to 0 cmH_2O
Patients with complete apneas	Positive (above atmospheric pressure)

pressure-flow relationship than the OSA and obese control adolescents. In the activated state, however, the slope of EMG of the genioglossus versus nasal pressure was greater in the obese control group than in the OSA or lean control groups, indicating they have a better compensatory neuromuscular sensitivity which protects them from OSA despite their obesity. Thus, it seems that age plays a role in affecting the Pcrit such that it is generally more negative in children and then increases with age (i.e., airway becomes more collapsible) when it is higher in adults than in adolescents.

3.7 Duration of Apnea and Arousal Threshold (Cortical, Autonomic)

The termination of any sleep-disordered breathing event occurs due to arousal, which can be complete (cortical) or subcortical (autonomic). The stimulus which causes the arousal varies and can be hypoxemia, hypercapnia, or intrathoracic pressure swings (negative pressure due to inspiratory effort). The sensitivity of the arousal system and the pace these stimuli arise during the course of the SDB event determine the duration of the event. All of these factors change with age from childhood to adulthood.

The duration of each SDB event is a characteristic which may be inherited [79]. It is largely determined by the arousal sensitivity, or arousal threshold, with longer events reflecting lower arousability (or higher arousal threshold). Thus, in those with longer SDB events, it can be estimated that their sensitivity of the respiratory chemical control system is lower [80]. This characteristic may be genetically determined [81]. Recently, it has been shown that short respiratory event duration (i.e., lower arousal threshold) predicts mortality [82]. Individuals with shorter respiratory events may be predisposed to increased ventilatory instability and/or have augmented autonomic nervous system responses that increase the likelihood of cardiovascular consequences of OSA [82]. Thus, the arousal threshold of any individual may be of great importance for both affecting the severity of the OSA, the oxygen desaturation, the hypercapnia, and the phenotype (i.e., those with lower arousal threshold may present, in addition to OSA, with symptoms of insomnia). Even if this characteristic is being genetically determined [79, 81], it seems that age plays a role as well, with children having higher arousal threshold which gradually decreases with age.

In small infants and preterms, arousal threshold is generally low, which actually may protect them from sudden infant death syndrome (SIDS). It has been reported that a history of prematurity with neonatal apnea has a persisting effect on decreasing arousability from sleep and these infants may be at increased risk for SIDS [83]. However, starting from age 4–6 months when deep sleep develops and delta slow wave EEG waves appear, the arousal threshold becomes substantially high [84]. The highest delta power is usually seen in children aged 2–5 years and then starts to gradually diminish over the years [84]. It has been shown that delta power density declined by 25% between ages 12 and 14 years [85]. A decline of 29% was

similarly reported between ages 9 and 13 years [86]. This decline was seen similarly in both boys and girls, although the magnitudes were lower in girls, suggesting that their delta power density decline started earlier [85]. Mixed effect analyses demonstrated that delta power density was strongly related to age. Arousal threshold shows age dependency as well. In children with OSA compared to controls, it has been shown that they have slightly blunted arousal responses to hypercapnia, when arousal was determined by EEG (i.e., cortical arousal) [87]. However, they do show intact autonomic arousability, and their sleep disordered breathing events may be terminated by autonomic rather than cortical arousals [88–91]. Sometimes, subtle EEG changes assessed by fast Fourier transform (FFT) analyses of the EEG (spectral analyses) show some degree of cortical involvement, although many times in children it is more autonomic arousals than cortical ones which are seen at the termination of SDB events [92]. Sometimes in children due to this high arousal threshold, sleep-disordered breathing event may be manifested as prolonged periods of partial upper airway obstruction without evidence of cortical arousal [93]. This is usually not the case with adults. In adults, almost all SDB events are associated with both cortical and autonomic arousals [94–97]. In fact, changes in EEG are required in order to score an arousal at the termination of hypopneas. Thus, age-related changes in arousal threshold do play a role in determining the duration of SDB events, albeit there is a substantial personal variability in this regard. Generally, the relatively high arousal threshold seen in children may drive relatively long hypoventilation events which may be seen almost solely by monitoring CO_2. In shorter events commonly only autonomic arousals are noted at the termination of the events, whereas in adults both autonomic and cortical (EEG change) are generally seen at the termination of SDB events. Since arousals are probably the most important mechanisms by which SDB events are terminated, the arousal threshold becomes a very important factor in individuals' OSA severity. Arousals may increase the severity of the sleep-disordered breathing by promoting greater ventilatory instability [98], or loop gain. This ventilatory instability may also be affected by age.

3.8 Ventilatory Control Instability (Loop Gain) and Arousal Effects

Instability in ventilatory control mechanisms may also affect SDB, since desynchrony between the diaphragm and the dilator muscle activity may result in airway collapse [99, 100]. If the diaphragm is activated prior to the activation of the upper airway dilators, then negative pressure develops in the UAW when the airway walls are relaxed, which may lead to their collapse. Younes et al. reported that the chemical control system is less stable in patients with severe OSA, which may worsen their OSA [101]. The stability of the negative feedback chemoreflex control system may be quantified by the loop gain. It reflects the ratio of the ventilatory response to chemical stimuli (loop gain = ventilatory response/ventilatory

disturbance) [102]. Thus, lower loop gain (closer to 1) reflects more stable ventilatory chemoreflex control. The overall loop gain is composed of two parts: the controller which senses the stimulus and the plant component which responds to decrease the stimulus. There might be various delays between the two parts. Chemoreceptor sensitivity to blood gases reflects controller gain, and the effectiveness of the lungs to alter blood gases reflects the plant gain. The product of controller and plant gain provides the overall loop gain of the system (loop gain = controller gain × plant gain) [102]. Since arousal response in children is relatively blunted [87, 103], it may reflect lower loop gain (closer to 1) and more stable ventilatory control. This may contribute to the stability of respiration in children, with generally lower sleep-disordered breathing indices observed in their studies. It may also explain the commonly seen hypoventilation and increased CO_2 levels in children with OSA [104–107]. On the other hand, a study of 134 children (77 with and 57 without OSA) recently reported that plant gain was higher in children with OSA than in those without OSA [108]. Plant gain correlated positively with severity of OSA. Children with more severe OSA and abnormal lung function had higher plant gain and a lower controller gain compared to the rest of the population [108].

In adults, loop gain was found to be higher in OSA versus controls, which remained high following CPAP treatment, suggesting an inherent elevated loop gain in these patients [109]. However, others reported similar loop gain magnitudes between patients with OSA and controls, although the patients had faster responses and more oscillatory dynamics, suggesting unstable upper airway mechanics and an underdamped chemoreflex control system [110]. This may be another important factor that contributes to OSA [100, 102, 111]. However, loop gain is not necessarily a cause of OSA, as it actually may be affected by OSA. For instance, in a study of 30 patients with OSA, high loop gain was reduced by surgical treatment, suggesting that elevated loop gain may result from OSA [112]. In vulnerable patients with collapsible airway (Pcrit near atmospheric pressure), loop gain may have a substantial impact on apnea severity [113]. Once hypoxemia and/or hypercapnia develop during a SDB event, a transient arousal from sleep is required to terminate the event. This results in activating the upper airway muscles and reestablishing airway patency. Without such an arousal, profound hypoxemia and hypercapnia would likely ensue. The possible mechanisms leading to arousal include direct stimulation of peripheral and central chemoreceptors by rising $PaCO_2$ and falling PaO_2, afferent CNS input from the lung, chest wall, or upper airway receptors resulting from the increasing ventilatory effort that develops over the course of an apnea, or direct stimulation of the reticular activating system by respiratory neurons activated by the apnea process [114, 115]. Regardless of the cause, arousal is more likely to occur in adults than in children, which may lead to the generally higher SDB indices seen in their sleep studies. Thus, it seems that respiratory control does play a role in UAW and OSA, in addition to the anatomical and upper airway features described above, although the exact role of loop gain is still not fully understood, in both adults and children.

3.9 Endothelial Function

One more potential cardiorespiratory age-dependent phenomenon which may relate to sleep apnea is endothelial function or dysfunction. Endothelial function represents the local control of the arterial endothelial cells to release vasoactive substances which may vasodilate (by releasing nitric oxide) or vasoconstrict (by releasing endothelin) the artery in response to various factors. Endothelial dysfunction (ED) represents the inability of the endothelium to correctly respond to local ischemia and failure to vasodilate the artery when appropriate. It is considered a very powerful early marker of cardiovascular disease. Since ischemic heart disease is by far more common in adults than in children, it was much more studied in adults than in children. However, some studies, both in adults and in children, showed it may result from OSA [116–120]. Indeed, work from Gozal's laboratory showed that endothelial dysfunction is more likely to be present among non-obese 6–9-year-olds with OSA compared to controls [120]. Furthermore, obesity and OSA additively contributed to the magnitude of endothelial dysfunction, supporting the concept that both conditions are associated with a risk for cardiovascular complications [121–123]. In addition, some of the variance in endothelial function has been ascribed to circulating endothelial progenitor cells [124]. Similarly, it has been shown that 3–11-year-olds with OSA were at increased risk for ED compared with habitually snoring children [125]. These authors also showed that ED was affected by age, BMI, and intermittent hypoxia and sleep fragmentation during sleep [125]. This observation strengthens the causal relationship between OSA and ED. The causality association between OSA and endothelial dysfunction can be further demonstrated by the finding that ED improved and sometimes completely reversed following adequate and effective treatment of the underlying OSA [120, 126]. We have shown that children with OSA had a severity-dependent deterioration of their endothelial function between the evening and the following morning, suggesting again the causal relationship between OSA and ED [127]. Moreover, it was found that exosomal miRNA-360 may have a role in mediating the ED found in children with OSA and/or obesity [128]. Lipoprotein-associated phospholipase A2, which is an independent risk factor for cardiovascular disease, was also found to be increased in children with OSA and/or obesity [129].

In adults and elderly, many factors were reported to be associated with ED in patients with OSA. These include male gender, BMI, waist circumference, hip-to-waist ratio, neck circumference, blood pressure, cholesterol levels, plasminogen activator inhibitor-1, calcium channel blocker use, and β-blocker use [130]. Unlike the findings in children, in whom treatment of OSA was associated with normalization of endothelial function, in adults there were conflicting reports in this regard, which may reflect irreversible damage to the endothelial layer in adults but not in children. Yamamoto et al. reported that neither CPAP nor mandibular advancement device had improved the ED following 8 weeks of treatment [131]. Similar findings were reported by Bakker et al. [132]. Others, on the other hand, found a significant improvement of endothelial function with effective treatment of OSA [126, 133]. Thus, it appears that age plays a role in the ED seen in patients with OSA

predominantly by the duration of the disease, since initially (in children or in adults with relatively short duration of OSA, before cardiovascular disease is present) ED may be reversible with treatment, but after cardiovascular complications are already present, treatment of OSA is less likely to improve endothelial function.

3.10 Summary

In summary, cardiorespiratory changes occur with age and affect the different phenotypes of OSA from childhood to adulthood. While in children the most common anatomical risk factors are tonsils or adenoids, in adults it is obesity. Airway length, which is generally shorter in children and is similar between genders, becomes longer especially in male adolescents and adults. UAW dilator muscles respond to negative pressure during wakefulness similarly in children and adults, although it appears that the UAW is more stable in children, who are less likely to collapse than adults, as can be evident by more negative collapsing pressure Pcrit. Transient arousals from sleep which reestablish the airway patency and ventilation after SDB events are more likely to occur in adults than in children, in whom frequently there is only autonomic response without a cortical arousal. This may lead to long duration of hypoventilation with hypercapnia seen in children but not in adults. Both children and adults tend to develop ED as a complication of OSA, but in children it is more likely to be reversible with treatment, perhaps due to the shorter duration of disease prior to treatment. Recognizing these age-related changes, especially for clinicians who treat adolescents and young adults, is of considerable importance.

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Sleep Assessment

4

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4.1 Introduction

Sleep assessment is a key component for health appraisals [1]. Accurate sleep assessment improves our awareness of individuals' health. Though often overlooked, sleep continuity, quantity, quality, and satisfaction closely mirror and influence mental and physical health. Proper sleep assessment, however, requires specific age-appropriate tools and standardized metrics. Generally speaking, sleep assessment tools include both laboratory and nonlaboratory techniques.

Laboratory assessment requires up-to-date medical equipment, properly trained (and possibly clinically certified) technical staff, and experienced professionals trained in sleep medicine. Consequently, laboratory sleep assessment entails considerable expense. To direct and optimize laboratory utilization, proper screening and preassessment are required. Many questionnaires have been developed and

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validated to facilitate such assessments with varying degrees of accuracy. Sometimes called "pencil-and-paper" assessments, self-reporting questionnaires obviate the need for electronic equipment, a specialized testing facility, and highly trained technologists and, therefore, prevent major costs. In the following chapter, we will first introduce a variety of reliable and validated sleep questionnaires often used by clinicians and researchers before describing *polysomnography*, the gold standard laboratory sleep assessment tool.

4.2 Adult Questionnaires

Sleep Quality

Sleep quality is an important concept. However, sleep clinicians and researchers do not completely agree upon what constitutes sleep quality. From a self-reported standpoint, subjective sleep quality entails an individual's satisfaction with their own sleep. In contrast, an expert panel after reviewing the literature identified several laboratory-based quantitative sleep quality parameters [2]. One approach to assessing sleep quality focuses on various sleep problems and disturbances, that is, identification of elements that constitute negative contributions to sleep quality. An alternative strategy involves examining positive aspects contributing to the presence of satisfying, restorative sleep. When taken together, the combination of positive and negative factors essentially provides a marker for *sleep health*.

Another crucial issue with respect to sleep quality involves the possible mismatch between indexed sleep quality and self-reported sleep satisfaction. Some individuals with apparently normal sleep continuity, duration, and in the absence of any apparent sleep disorders may be dissatisfied with their sleep. Conversely, other people with clearly disrupted sleep and with obvious markers indicative of the presence of specific sleep disorders will rate their sleep as being of high quality and satisfying. This incongruence between sleep quality and sleep satisfaction highlights several important elements: (a) our current lack of a thorough understanding of sleep in all of its dimensionalities, (b) the strong influence that abnormal sleep imposes on self-awareness, (c) the overriding effect of personality type (i.e., augmenters vs. minimizers) on self-report, and (d) the fact that the combination of these and other factors affects sleep perception and estimation.

In the following section, we describe two validated, well-established, and widely used tools for assessing sleep quality.

Pittsburgh Sleep Quality Index (PSQI) [3]

The PSQI is the most common sleep quality assessment tool. It has been adapted and translated into many languages and consistently yielded high validity and usability; consequently, it is used all around the globe. This self-rated questionnaire assesses sleep quality and sleep disturbances over a 1-month time interval [3]. It consists of 19 individual items, creating seven sub-scores: subjective

sleep quality, sleep latency (i.e., how long it takes to fall sleep), sleep duration, habitual sleep efficiency (i.e., the percentage of time in bed that one is asleep), sleep disturbances, use of sleep medication, and daytime dysfunction [3]. The global PSQI score is then calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality [4]. It is worth mentioning that this questionnaire can be used to subjectively assess an adult population's sleep pattern, thereby making it applicable to both individuals in a clinical setting and also in epidemiological studies [1].

In evaluating and normalizing PSQI questionnaire, studies in various countries demonstrate the instrument's reliability and validity of its psychometric properties [5–10]. In a meta-analysis of studies in which psychometric indicators of this questionnaire have been tested, the results supported good reliability and good validity [11].

Sleep Health Index [12]

The National Sleep Foundation created and validated a brief questionnaire that aimed to assess general sleep health [12]. This 12-item questionnaire indexes the three factors deemed essential to sleep health: (a) sleep duration, (b) sleep quality, and (c) sleep disorders. The instrument went through extensive development, refinement, and validation. This included cognitive testing, pretesting, and regression analysis. It has been subsequently used as a population survey instrument.

Sleep-EVAL

This approach is not as readily available and consists of a sophisticated software that enables epidemiological studies to be conducted on a variety of sleep-related issues. Developed by M. Ohayon at Stanford, it has provided extensive opportunities to evaluate a large array of sleep issues including sleep satisfaction. It consists of a telephone interview in which the questions are directed by the Sleep-EVAL expert system software which was designed specifically to conduct epidemiological studies on sleep habits and disorders in the general population [13–15]. It is a nonmonotonic, level 2 expert system. The causal reasoning mode implemented in the software allows the system to formulate diagnostic hypotheses and then validate them through further queries and deductions. Topics covered during a typical interview cover sociodemographic information, sleep/wake schedules, sleeping habits, medical and psychiatric treatments, and sleep disorders according to DSM and ICSD classifications. Studies performed in the general population and in clinical settings have shown that Sleep-EVAL is a valid instrument in the assessment of sleep disorders. In the general population, a kappa of 0.85 was obtained in the recognition of any sleep problem when diagnoses obtained by two lay interviewers using the interview-based software were compared against those obtained by two clinical psychologists. In clinical settings, concordances >0.70 to >0.90 were obtained on insomnia and obstructive sleep apnea syndrome diagnoses [16, 17].

Sleepiness

Sleepiness plays a significant role in an individual's performance, personal feelings, and social relations. Questionnaires provide a useful and practical assessment method. Such instruments are commonly used clinically and scientifically for evaluating perceived sleepiness [18]. In this section, we describe the several widely used, validated, and well-known questionnaires used to evaluate the presence of daytime somnolence.

Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a simple self-administrated questionnaire routinely used by clinicians to assess daytime sleepiness [19]. This questionnaire was developed in 1991 based on data gathered from a random sample of healthy people and patients with sleep disorders. The aim was to measure the general level of daytime sleepiness [20]. Respondents are asked to rate their usual chances of dozing off or falling asleep during the day in various less-active situations [21]. There is a claim that the ESS scores and patients' dissatisfaction of their sleepiness are correlated [21]. It is also claimed that ESS scores can accurately describe the person's average sleep propensity [22]. The ESS score (the sum of 8 item scores, 0–3) can range from 0 to 24. It is within normal to score 2–10 [22]. The psychometric indices of ESS have been verified by researchers [23, 24], making it a suitable tool for evaluating sleepiness. A meta-analysis result confirmed that Cronbach's alpha of ESS can range from 0/70 to 0/90 (based on various studies) [20]. However, the ESS has not fared as favorably when matched against more objective tools of sleepiness [25–27].

Other less frequently used questionnaires include the Stanford Sleepiness Questionnaire, which was developed by Dr. W. Dement and has undergone psychometric validation, and a Daytime Fatigue Scale that aims to differentiate somnolence from fatigue [28, 29]. Their relatively restricted use has progressively led to their not being frequently utilized in common clinical settings.

Insomnia

Insomnia is a common sleep disorder. It includes difficulty falling asleep, difficulty remaining asleep and/or awakening too early, and not being able to get back to sleep [30]. Insomnia is associated with other diseases, for example, diabetes [31] and heart disease [32]. Additionally, the results of a meta-analysis reported a correlation between insomnia and several psychiatric disorders such as depression, anxiety, and alcohol or other addictions [33]. Some surveys have estimated the prevalence of insomnia among Western European countries at between 20 and 40% [34]. A review of 50 epidemiological studies reported that the prevalence of insomnia in the general population was 9–25% [35]. Overall, it is estimated that 30% of people worldwide have experienced insomnia to some extent during their lifetime [36]. Insomnia tends to be a complex, multifactorial disorder. Therefore, researchers in this area

have focused much attention toward creating proper tools. In the following paragraphs, we introduce suitable, well-recognized insomnia assessment tools.

The Insomnia Severity Index (ISI)

The Insomnia Severity Index (ISI) is a short self-evaluated questionnaire designed to help clinicians make therapeutic decisions concerning patients suffering from insomnia. This tool evaluates subjective symptoms and the consequences of insomnia (i.e., level of worry or distress) [37, 38]. It is worth mentioning that ISI's content corresponds, to some extent, to diagnostic criteria for insomnia disorder [38]. The ISI is composed of seven items assessing sleep onset, sleep maintenance, early morning awakenings, interference with daily functioning, perceived prominence of impairment attributed to the sleep problem, concerns about sleep problems, and satisfaction with sleep patterns. The regular period of recall is within the most recent month [39]. The perceived severity of each item is rated on a 0–4 scale. The total ISI score is calculated by summing the scores from the seven items and ranges from a minimum of 0 to a maximum of 28, with higher scores reflecting more severe sleep problems. In clinical assessments, the ISI total summary score falls into one of four ISI categories: with scores 0–7, 8–14, 15–21, and 22–28 indicating no clinically significant insomnia, sub-threshold insomnia, moderate insomnia, and clinically severe insomnia, respectively [39]. Research findings confirm the ISI as a reliable and valid tool to identify people who suffer from insomnia, and the tool is also sensitive to treatment-related changes [39]. This questionnaire is also suitable for use with older adults and can clarify insomnia symptoms [40]. The ISI has clinical research and primary care services applications [41]. Finally, the ISI is commonly used to assess ethnically and culturally diverse populations and has been translated and validated extensively in many common languages around the world [42–45].

Athens Insomnia Scale (AIS)

Athens Insomnia Scale is a self-rated instrument for assessing insomnia symptoms in patients with sleep disorders. The assessment is based on ICD-10 code sets. It measures eight factors among which the first five factors (sleep induction, awakening during the night, final awakening, total sleep duration, and sleep quality) are related to nocturnal sleep and the last three factors (well-being during the day, sleepiness during the day, and functioning capacity during the day) are related to daytime dysfunction [1]. It is obvious that the AIS can be utilized in both clinical and research areas [46]. Furthermore, this questionnaire emerges as a suitable tool for screening insomnia disorder [47]. The result of one study verified that this questionnaire has acceptable psychometric indicators and is an appropriate tool for insomnia screening [48]. It is widely used in countries with diverse cultures and languages. The instrument validity and reliability have also been confirmed [49–53].

Bergen Insomnia Scale (BIS)

The Bergen Insomnia Scale is a questionnaire constructed following current formal and clinical diagnostic criteria for insomnia. There are six items, of which the first three pertain to sleep onset, maintenance, and early morning wakening insomnia,

respectively. The final three items refer to not feeling adequately rested, experiencing daytime impairment, and being dissatisfied with current sleep [54]. Answers are ranked from 0 to 7, according to how many nights per week the respondent has suffered from each symptom based on their experiences in the past month. This scale is a quickly completable self-report tool. Research studies support its validity and reliability. Polysomnographic testing further attests to the instrument's accuracy and reliability [54].

Sleep Apnea

Recognition that sleep apnea represents a serious, potentially life-threatening illness increased the need for a quick screening approach in primary care services. Clinicians developed questionnaires to determine and evaluate sleep apnea symptoms. However, the signs and symptoms of sleep apnea can vary widely; thus questionnaire development has emerged as a not so simple process. The current questionnaires provide useful information about the signs, symptoms (and their severity), comorbid conditions, and possible adverse effects on the patient social and personal behaviors. In the following section, several widely used instruments are described.

Berlin Questionnaire (BQ)

The Berlin Questionnaire is a self-report questionnaire exploring factors related to the risk of having sleep apnea. The questionnaire focuses on snoring behaviors, wake-time sleepiness or fatigue, the presence of hypertension, and body mass index (BMI). Questions are organized into three categories, namely, snoring behaviors (five items), wake-time sleepiness (three items), and obesity and hypertension (two items). Overall, the questionnaire has ten questions. Patients can be classified into high risk or low risk based on their responses to the individual items and their overall scores [55]. The Berlin Questionnaire is useful as a clinical screening test and epidemiological tool. One meta-analysis result showed the BQ as suitably sensitive to sleep apnea disorder in sleep clinics [56] and in various clinical centers [57]. However, caution is suggested when applying BQ because results from several studies indicate poorly reliability in patients who suffer from hypertension. Additionally, some researchers have discouraged using this questionnaire as a screening method to identify patients in polysomnography tests [58].

STOP (SQ) and STOP-BANG (SBQ) Questionnaires

The STOP questionnaire is a concise and easy-to-use screening tool for sleep apnea. It was initially developed and validated in surgical patients at preoperative clinics [59]. This questionnaire has four items related to snoring, tiredness, stopping breathing during sleep, and hypertension [59]. The developers of STOP Questionnaire designed another assessment tool named STOP-BANG Questionnaire (SBQ). This novel questionnaire includes the four questions used in the STOP questionnaire and

four additional demographic queries, for a total of eight dichotomous (yes/no) questions related to the clinical features of sleep apnea (*s*noring, *t*iredness, *o*bserved apnea, high blood *p*ressure, *B*MI, *a*ge, *n*eck circumference and male *g*ender) [59]. A meta-analysis supported the validity and reliability of both SQ and SBQ for identifying sleep apnea [60]. Consequently, SBQ is considered a valid and useful sleep apnea screening test [61, 62]. Although the items age and BMI reduce SBQ accuracy [63], another study verified significant superiority of SBQ compared with SQ and BQ [64].

Sleep Apnea Clinical Score (SACS)

The Sleep Apnea Clinical Score (SACS) was developed to assess patients seen for emergency medical treatment. In attempts to shorten the waiting period and the cost of the diagnosis, this questionnaire had some potential advantages over polysomnography. In this questionnaire, clinical features useful to improve diagnostic accuracy of sleep apnea were evaluated. To create this questionnaire, the data obtained from previous standardized tools and the data related to polysomnography tests were used [65]. The SACS is based on habitual snoring, neck circumference, hypertension, and bed partner reports of nocturnal gasping/chocking respirations [65]. The total score ranges from 0 to 110, values below 5 indicating a low likelihood of sleep apnea, whereas values greater than or equal to 15 indicate a high likelihood [66]. Divergent validity for identifying sleep apnea was established by comparison to insomnia and sleepiness questionnaires (BIS and ESS, respectively) [67]. Another study confirmed SACS value for identifying sleep apnea. The test also helps to prioritize patients in oversubscribed clinical centers [68]. The original version of SACS was produced by a team of experts from Canada. Soon after, it was translated into several languages and adapted to different cultural settings [66].

Four-Variable Screening Tool (4VSC)

The Four-variable screening tool [69] is a score-based instrument consisting of four variables: gender, blood pressure levels, BMI, and self-reported snoring. These four parameters are categorized as follows: (1) sex, 1 point for males; (2) BMI (<21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, ≥30) which is assigned a value between 1 and 6; (3) blood pressure (systolic blood pressure [SBP] <140 mmHg or diastolic blood pressure [DBP] <90 mmHg, SBP 140–159 or DBP 90–99, SBP 160–179, or DBP 100–109, SBP ≥180 or DBP ≥110 mmHg) which is assigned a value between 1 and 4; and (4) snoring which is assigned 1 for a response of snoring almost every day or often and 0 for snoring sometimes, almost never, or unknown. The overall risk for each participant is calculated by adding the component scores for each variable, ranging from 2 to 18 points, and when using a cutoff value of 11 points, this screening tool exhibited an AUC of 0.90. In a study aiming to compare across instruments, namely, 4VSC, SQ, SBQ, and ESS, their ability to identify moderate to severe OSA assigned the highest sensitivity (87.0%) to SBQ, while the 4VS tool had the highest specificity (93.2%) and accuracy (79.4%) [70].

NoSAS Score

The recently developed NoSAS score allocates 4 points for having a NC >40 cm, 3 points for having a BMI of 25 kg/m^2 to less than 30 kg/m^2 or 5 points for having a BMI ≥30 kg/m^2, 2 points for snoring, 4 points for age >55 years, and 2 points for being male [71]. A score ≥8 points identifies subjects at risk of clinically significant OSA. The NoSAS score performed well when applied to the general population in a cohort from Switzerland (included in the HypnoLaus study) exhibiting an AUC of 0.74. In another general population cohort from Brazil, the EPISONO study, the NoSAS score showed an AUC of 0.81; of note, the NoSAS score indicated significantly better performance than the SBQ and then the BQ. However, in a study aiming to validate the NoSAS score in a multiethnic Asian cohort and compare its performance with the SBQ and BQ questionnaires, all three approaches performed similarly [72]. In another study, in which 2208 participants were recruited from clinical settings, the NoSAS score identified individuals at risk of clinically significant SDB (defined as an AHI threshold ≥20 events/h), with an AUC of 0.707, and was superior to SBQ or BQ [73].

No-Apnea Instrument

A simplified approach was recently developed for screening OSA among a high-risk population of patients referred for PSG evaluation [74]. This tool, termed No-Apnea, consists of two objective items, namely, NC and age. This model with a total score of 0–9 points used a cut-point ≥3 to classify patients at high risk of having any OSA (OSA ≥ 5), moderate/severe OSA (OSA ≥ 15), and severe OSA (OSA ≥ 30) and exhibited 78.1%, 68.8%, and 54.4% accuracies of correctly identifying OSA ≥ 5, OSA ≥ 15, and OSA ≥ 30, respectively. The potential value of this instrument in the general population or in elected cohorts remains to be evaluated, although it has performed comparably to other tools in women, obese, and insomniac patients [75–77].

GOAL Questionnaire

A four-item model, designated as the GOAL (gender, obesity, age, and loud snoring) questionnaire, was developed and subsequently validated, with item scoring of 0–4 points (≥2 points indicating high risk for OSA) [75]. This instrument has also demonstrated strong validity and reliability [78–80].

Other Aspects of Sleep

Sleep Duration and Timing

Adequate sleep duration is essential for good sleep health. To maintain general health, mood stability, and quality of life, most adults require 7–9 h of sleep nightly (however, some individuals are natural short or long sleepers). Nonetheless, chronic sleep deprivation not only may lead to dangerous sleepiness levels but is also associated with both physical and mental disorders [81–84]. Therefore, no sleep assessment is complete without evaluating some measure

of sleep duration. Knowing the extent of variation in sleep duration is also crucial because a chaotic sleep pattern can be a cause, effect, or both with respect to serious illnesses.

The Munich Chronotype Questionnaire (MCTQ) is a self-report questionnaire assessing individual sleep timing. It consists of five simple questions. The first question asks about the time of going to bed, the second about awakening and getting up, and the third about tendency to change sleep schedule. The final two questions concern day-sleeping and night-working. Sleep duration is then calculated based on questions 1 and 2. Based on the International Classification of Sleep Disorders (ICSD-2) criteria, a clinician can screen for possible circadian rhythm sleep disorders. Individuals going to bed earlier than 9:00 pm and awakening earlier than 5:00 am (who are not doing so because of a job or other external requirement) may have advanced sleep phase disorder (ASPD). We often refer to such individuals as "morning-types." Contrastingly, individuals going to bed later than 2:00 am (and have difficulty falling asleep if retiring earlier) and awaken later than 11:00 am may have delayed sleep phase disorder (DSPD) [85]. Persons exhibiting DSPD are known as "evening-types" and they usually go to sleep 3–6 h later than the rest of the society. The total sleep-time duration associated with these two disorders is often insufficient leading to waking-hour sleepiness or fatigue [85]. Psychometric evaluation of MCTQ shows good validity and considerable concordance with actigraphy [86, 87].

Sleep Hygiene

Sleep hygiene is a set of behavioral and environmental practices developed as an instructional aid to help people achieve regular and comfortable sleep. These practices, while easy to understand are, for some individuals, very difficult to follow. The reason is that some of the practices require lifestyle changes. Poor sleep hygiene often accompanies sleep disorders, especially insomnia. Sleep hygiene also plays an important role in public health [88].

The Sleep Hygiene Index (SHI) is a 13-item self-report instrument designed to assess the practice of sleep hygiene-related behaviors [89]. Each item is rated on a 5-point scale as follows: never (0), rarely (1), sometimes (2), frequently (3), and always (4). Total SHI scores range from 0 to 52, with a higher score representing poorer sleep hygiene [90]. High SHI scores are correlated with poor sleep quality and with the Insomnia Severity Index [91]. This questionnaire is widely used, has been translated into different languages, and applied to various cultures [91–94]. Studies have verified that SHI is a suitable tool not only for adults but also for adolescents [95]. Additionally, some clinicians rely on this questionnaire to screen and assess for poor sleep quality [94].

Psychological Factors of Sleep

One conceptualization about sleep problems, particularly insomnia, posits that there are three potential contributing components: physiological components, cognitive components, and behavioral components. Although all the three components undoubtedly have important roles in onset and persistence of sleep

problems, in recent years, psychological and cognitive factors have gained considerably more emphasis than before. Many studies concerning the role of cognitive factors in sleep problems (especially insomnia) emphasize the role of pre-sleep cognitions and nocturnal sleep-related cognitions. Recent studies in this area support the important role of psychological factors in sleep difficulties [37, 96–98]. Therefore, to understand sleep problems better, identify and treat patients suffering from such problems, and conduct research in these areas, we need proper metrics. Some available questionnaires are described in the following paragraphs.

Dysfunctional Beliefs and Attitudes About Sleep (DBAS)

Dysfunctional Beliefs and Attitudes about Sleep, as its name indicates, is a scale assessing beliefs, attitudes, expectations, and attributions about sleep and insomnia. It was developed by Morin in 1993. This scale is a self-rated inventory consisting of 16 items with 10 Likert-type scales, ranging from 0 (strongly disagree) to 10 (strongly agree). The total score is calculated from the average score of all the items on the scale and can range from 0 to 10, with higher scores indicating greater levels of dysfunctional beliefs about sleep [99]. In a research study, by using Cronbach's alpha test, the internal consistency of clinical population and the general population were reported as 0.77 and 0.79, respectively [99].

Sleep Problem Acceptance Questionnaire (SPAQ)

Sleep Problem Acceptance Questionnaire (SPAQ) was developed by Bothelius and colleagues in 2015 for measuring and quantifying the level of acceptance for the problems caused by insomnia. They evaluated the validity and reliability of the questionnaire in a cross-sectional study using exploratory and confirmatory factor analysis. Three samples were selected: a sample of 372 people (participants applying to two Internet-based CBT-I programs), a sample of 215 people (participants in two non-medication randomized trials for insomnia), and a sample of 233 people (enrolled after primary component analysis was done on sample A). Ultimately, a questionnaire with eight questions was retained; the questions are divided into "active engagement" and "willingness" factors. The results obtained by the developers of the questionnaire showed that accepting sleep difficulties has a significant correlation with variables of intensity of insomnia, experiential avoidance, sleep latency, time of waking up after sleep, dysfunctional beliefs and attitudes about sleep, and sleep-related behaviors [100].

Self-Efficacy for Sleep Scale (SE-S)

The Self-Efficacy for Sleep Scale consists of nine items with 5 Likert-scale type questions, ranging from 1 to 5. It measures the participant's sleep self-efficacy by asking them how confident they feel about accomplishing self-related behaviors. A score of 1 means "lack of confidence" and the score 5 means "complete confidence." Reliability was evaluated by using Cronbach's alpha test; Cronbach's alpha related to self-efficacy of sleep was 0.85 [101].

Metacognitive Processes of Sleep Scale (MPSS)

This questionnaire is theoretically based on the two-level model of cognitive arousal presented by Ong, Ulmer, and Manber in 2012, that is, primary arousal and secondary arousal [102]. The questionnaire has 23 questions. Factor analysis extracted four factors: balanced appraisals (with six items), cognitive flexibility (with six items), equanimity (with four items), and commitment to values (with seven items). MPSS validity was tested using Cronbach's alpha test. Results for total and first, second, third, and fourth factors were 0.84, 0.72, 0.75, 0.70, and 0.71, respectively. The questionnaire is scored based on a 4-point Likert scale: the score 1 means "disagree," the score 2 means "a little agree," the score 3 means "agree," and the score 4 means "completely agree." The total scores range from 23 to 92, with the higher score representing more positive metacognitive process [103]. MPSS significantly correlates with the Insomnia Severity Index (ISI) and the Pittsburgh Sleep Quality Index (PSQI) [103].

Pre-Sleep Arousal Scale (PSAS)

The Pre-Sleep Arousal Scale (PSAS) is the most well-known technique for evaluating pre-sleep arousal [104]. This questionnaire contains 16 self-report items [105], each rated on a 5-point scale that describes symptoms of arousal at bedtime. A patient rating of 1 stands for "not at all" while a rating of 5 stands for "extremely." This questionnaire has two subscales: cognitive arousal and somatic arousal. Eight items evaluate the former and eight evaluate the latter. Higher scores indicate higher pre-sleep arousal [106]. A study has confirmed that for both factors, there are significant differences between healthy people and patients suffering from insomnia [104]. Some researchers have reported cutoff scales less than 14 and less than 20 for subscales somatic arousal and cognitive arousal, respectively [107]. The Pre-Sleep Arousal Scale (PSAS) has been studied, and its psychometric indicators have been found as reliable and applicable in the context of various cultures [104, 105, 107, 108].

4.3 Assessment of Children's Sleep

Even though sleep problems are pervasive in a child's life, they are often ignored or minimized, or simply there is total unawareness by their caretakers of such issues. This may in part be due to the fact that the signs and symptoms of sleep problems in children differ from those of adults. The common sleep problems among children can be related to neglect, hyperactivity, mood swings, and learning difficulties [109]. Age-based differences in presentation have complicated the assessment of sleep problems among children. Questionnaires could help experts and researchers acquire beneficial information in the areas of psychology and behavioral psychology [110], but children may lack of sufficient knowledge and communication skills to provide useful feedback. Nonetheless, there are several questionnaires suitable for identifying children's sleep problems. Such instruments are also useful for

clinical research and sleep studies [111]. In this section, we have introduced several practical questionnaires. For an extensive review of such tools, the reader is referred to two comprehensive reviews [111–113].

Sleep Disturbance Scale for Children (SDSC)

The Sleep Disturbance Scale for Children (SDSC) was created to assess six categories of prevalent sleep disorders among children [114]. This questionnaire contains 26 Likert-type questions, investigating sleep states in children during the previous 6 months. Sleep disturbance is diagnosed based on the questionnaire's total score, with higher scores indicating more symptoms of disturbances [114]. Notwithstanding the total score, we can calculate the six separate scores for six separate factors in the questionnaire. Higher scores reflect greater risk of sleep disorders. Meanwhile, it is possible to calculate a T-score for each child, with T-scores over 70 echoing the existence of symptoms for sleep disorders [115]. The six types of sleep problems in children aged 6–15 years assessed include (1) initiating and maintaining sleep (DIMS), (2) sleep-disordered breathing (SBD), (3) disorder of arousal (DA), (4) sleep-wake transition disorder (SWTD), (5) disorders of excessive somnolence (DOES), and (6) sleep hyperhidrosis (SHY) [116]. This questionnaire has been translated into several languages, and its validity and reliability have been confirmed [115–117]. The instrument can be used both with healthy children and those with developmental difficulties such as Down syndrome [118].

Pediatric Sleep Questionnaire (PSQ)

The Pediatric Sleep Questionnaire (PSQ) was developed and validated as a research tool to evaluate and identify children at risk for sleep-related disorders [119]. It includes 22 items examining snoring and breathing problems, daytime sleepiness, observed apneas, inattention, and hyperactivity [120]. Answer choices for questions include "yes," "no," or "don't know." The "yes" answer choices are scored as one point, the "no" answer choices are scored as zero point, and the "don't know" are excluded from questionnaire scoring [120]. The questionnaire's total score tells us whether the child is healthy or not [121]. PSQ is a specified test for children in the 2–18-year-old age range and is completed by parents [111].

The PSQ questionnaire has been translated to several languages and its psychometric indicators have been verified in various countries [121–123]. In one study in the area of pediatric sleep problems, the result supported the suitability of PSQ as a screening method to identify patients who need medical tests urgently. It is also valid and reliable in epidemiological studies [123].

Children's Sleep Habit Questionnaire (CSHQ)

Children's Sleep Habit Questionnaire (CSHQ) is a parent-report sleep screening tool designed for school-aged children [124]. CSHQ offers information in the area of the

sleep complaints among young children and could be used as a tool to detect sleep behavioral disorders. Questions are categorized into seven subscales: (1) bedtime behavior and sleep onset, (2) sleep duration, (3) anxiety around sleep, (4) behavior occurring during sleep and nighttime awakening, (5) sleep-disordered breathing, (6) parasomnias, and (7) morning waking/daytime sleepiness [124]. This questionnaire has 45 questions, among which 33 are numerically scored and the other 7 ones are itemized for sharing or giving other information related to sleep behaviors. The answers are scored on a 3-point scale: "usually" for a sleep behavior occurring five to seven times a week, "sometimes" for two to four times a week, and "rarely" for a sleep behavior which happens from zero to once a week [125]. Finally, all ratings are summed to create the total score and it could range from 33 to 99, for which a score over 41 indicates experienced sleep disorders, i.e., the considered total cutoff point for this questionnaire is 41 [125]. This questionnaire has adequate psychometric properties and could be used as a tool with various applications in clinical research and other areas of the sleep study [126]. One study approved that this questionnaire, in addition to normal children, applies for children who suffer from difficulties such as autism spectrum disorder and it also has a high validity among this society [127].

Sleepiness

Cleveland Adolescent Sleepiness Questionnaire (CASQ) [128]

The CASQ was developed as a measure of daytime sleepiness for use with 11–17-year-olds. The CASQ's internal consistency was good, and preliminary psychometric evidence indicated that the CASQ has acceptable construct validity, with greater CASQ scores reflecting increased daytime sleepiness that were significantly associated with decreased sleep duration in both control participants and those with sleep-disordered breathing. However, the study did not utilize an objective measure of excessive daytime sleepiness such as the MSLT.

Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD)

The ESS-CHAD was developed as an extension of the version for adults and was found to be a reliable and internally valid measure of daytime sleepiness in 12–18-year-olds [129]. Further studies are needed to validate the ESS-CHAD among younger children and to establish accurate and reliable cutoff points for use in clinical or epidemiologic settings.

Other scales such as the Pediatric Daytime Sleepiness Scale (PDSS) have also undergone initial validation [130]. Additionally, a pictorial scale that accurately portrays cartoon-like figures suggestive of awake or sleepy faces has shown promise [131], and extensive use by one of the authors (DG) suggests its applicability and reliability in clinical settings, albeit without formal psychometric validation. Unfortunately, we're unaware of any comparative studies among these various scales and their validation against more objective measures of daytime sleepiness in children such as the MSLT.

OSA Screening Questionnaires

As in adults, the prevalence of snoring in children is elevated, and among those habitually snoring children, a proportion will ultimately suffer from OSA. In light

of the multiple adverse consequences associated with pediatric OSA [132], there is a need for early diagnosis and timely treatment. To this effect, there is a multitude of screening instruments that have been developed over the years. Rather than enumerate all of these, we have opted to present the one developed by one of the authors which has undergone extensive validation and has been translated and successfully adapted to multiple languages, cultural settings, and clinical or research purposes.

Indeed, Spruyt and Gozal [133] proposed a set of six hierarchically arranged questions derived from unbiased scrutiny of a large cohort of children. A specific cutoff score provided significant construct validity and acceptable sensitivity and specificity for the detection of high risk for OSA in children. Subsequent expansion of its use to clinical settings and to different languages has continued to demonstrate its robustness and overall accuracy properties [134–136]. *An example of this questionnaire is provided for the convenience of the reader.*

4.4 Polysomnography

Polysomnography (PSG) is the most common test performed at sleep disorder centers. It is an objective test used to identify specific pathophysiology. Polysomnography offers a way to describe human sleep physiologically and is now used as a clinical method to diagnose sleep disorders. It objectively provides valuable information about the total sleep duration, sleep structure, sleep-related breathing, sleep-related movement, and sleep quality [137].

Polysomnography in Adults

For adults, PSG is considered the gold standard for diagnosing several sleep disorders. PSG has an essential role in diagnosing, determining severity, and differentiating several sleep disorders [138]. Polysomnography is the most accurate method of measuring sleep and can identify a person's night sleep patterns [139]. This entails polygraphically recording electroencephalography (EEG), electrooculography (EOG), and submental electromyography (EMG). It allows differentiation of REM sleep and NREM sleep (stages N1, N2, N3) [139]. A standard PSG usually has 4 neurophysiological channels, but a clinical PSG often involves 8–16 channel recordings. Clinical PSGs include cardiopulmonary and leg movement recording [140].

Clinical indications for conducting PSG include suspicion of sleep-disordered breathing, narcolepsy, periodic leg movement disorders, REM-behavior disorder, parasomnias, and sleep-related epilepsy. However, current standards of practice do not recommend PSG for restless leg syndrome, circadian rhythm sleep disorders, and insomnia [141]. PSG for treatment-resistant insomnia can sometimes be useful, especially if sleep-disordered breathing is suspected. PSG interpretation requires training, time, and practice. Proper interpretation must take into account the patient's signs, symptoms, medical history, family history, and medications [142].

Polysomnography in Infants and Children

Sleep problems are highly prevalent throughout childhood. They occur in 25–50% of preschool children and up to 40% of adolescents [143]. Overall, obstructive sleep apnea (OSA) is not only common in children but can have significant risks and long-term complications. It can adversely affect cognitive, behavioral, cardiovascular, and metabolic functions. It can also impair the intellectual and emotional development of children [144]. These issues indicate the need to pay attention to sleep disorders in children.

PSG is the gold standard measurement tool for diagnosing sleep-disordered breathing in children. It can diagnose and differentiate central, obstructive, and mixed apnea [145]. The results of a review study showed that PSG in children can also be helpful for identifying sleep disorders other than sleep apnea. The results indicate utility for pathophysiology associated with excessive somnolence, parasomnias, sleep-related movement disorders, and restless leg syndrome in children [146]. The results of another study showed that PSG is a valuable tool for measuring and evaluating a range of sleep disorders in children [147].

It is recommended that all children have a clinical reassessment several months after tonsillectomy to determine if the snoring and OSA symptoms have resolved. This follow-up is especially important for children with obesity. In addition, postoperative PSG should be considered even in the absence of snoring or other symptoms to determine if additional treatment is still needed for the remaining obstructive sleep apnea [148].

In infants, similar to older children, PSG can detect obstructive, central, and mixed apnea. Therefore, PSG should be routinely applied to determine severity of respiratory disorders in infants at risk [149].

For children, PSG can be performed in two methods, the first being in a sleep laboratory and the second being a portable PSG performed at home. There are some doubts about the accuracy of the second option. Some studies have addressed this issue, and the results indicate that portable PSG can be useful in diagnosing sleep problems in children [150–152] even if they carry a much higher technical failure rate. It is worth noting that to be maximally useful, recordings should assess more than 6 h of sleep and have all channels (EEG, thoraco-abdominal bands, calculated airflow, and pulse oximetry) functioning for at least 90% of the total sleep time [152].

Performing PSG test for children and infants may have certain complexities and require special accommodations, including the presence of caretakers with the child. Staff who perform PSG test for children should have specialized training for both technical and social skills needed for working with infants and children. Infant and child PSG studies usually require different sensor devices (e.g., end-tidal or transcutaneous carbon dioxide monitors) and different monitoring techniques than adults. Nonetheless, using PSG to assess the sleep-in children and infants is rapidly increasing [153].

Appendix

Subject ID:					
Age		Date of Birth			
Sex	Male	Race & Ethnicity	White	N	
	Female		African American	Hispanic	
Weight	Lbs Kg		Asian		
Height	Ft Inch		Alaska Native / American Indian		
	Cm		More than one race		

Please answer to the following questions considering your child's sleep during past 6 months

	Never	Rarely (once per week)	Occasionally (twice per week)	Frequently (3-4 times per week)	Almost Always (more than 4 times per week)
Does your child stop breathing during sleep?					
Does your child struggle to breathe while sleep?					
Do you ever shake your child to make him/her breathe again when sleep?					
How often does your child snore?					
Do you have any concerns about your child's breathing while asleep?					
How loud does your child snore?	Mildly Quiet	Medium Loud	Loud	Very Loud	Extremely Loud

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Sleep-Disordered Breathing: Diagnosis

5

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5.1 Diagnostic Procedures

History and Physical Examination

The diagnosis of OSA starts with a sleep history, which commonly gathers data from three complementary approaches: (1) evaluation of OSA-related symptoms, (2) sleep habit evaluation, and (3) comprehensive evaluation of high-risk patients due to potential negative consequences. OSA is a complex disease and thus patients can manifest a large spectrum of different symptoms. Commonly, adult patients with OSA report loud snoring, witnessed apneas, awakenings with choking sensation, and excessive daytime sleepiness, the latter usually assessed by the Epworth Sleepiness Scale (ESS) [1]. Other common symptoms are nonrefreshing sleep, tiredness, morning headaches, and neurobehavioral problems [2]. On the other hand, a less common phenotype includes insomnia and fatigue as predominant

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symptoms, which is more particularly encountered in women. It is important to highlight that, due to subjectivity, there is a great variability among patients concerning the prevalence of symptoms, particularly sleepiness [3]. In children, the emergence of symptoms is much more subtle, even if younger patients are more susceptible to develop morbid consequences. As such, snoring may be the only symptom that parents may report, or snoring may be apparent along with snorting or gasping episodes, restless sleep, bedtime wetting, frequent nightmares or night terrors, bruxism, morning headaches, grumpy awakenings, tiredness, falling asleep in school or in the car, and problematic progression in academic performance at school. A particular feature of children who are at risk for sleep-disordered breathing is the presence of inattention with or without hyperactivity, the latter being much more frequent among non-obese children. As such, the concept of different phenotypes based on clinical presentation has been proposed to include type I (non-obese, hyperactive) and type II (obesity and excessive daytime sleepiness with inattention). Furthermore, social withdrawal and aggressive or oppositional defiant behaviors are also common.

Besides symptoms, major indicators of OSA include hereditary factors (family history of the disease) and known anthropometric factors linked with increased risk for upper airway obstruction, such as oropharyngeal and nasal abnormalities, large neck circumference, increased body mass index (BMI), or additional markers of obesity [2, 4]. In addition, cardiorespiratory, cerebrovascular, and metabolic comorbidities potentially linked with OSA should be investigated [5]. Table 5.1 summarizes sleep assessment procedure, whereas Table 5.2 shows criteria for OSA diagnosis according to the American Academy of Sleep Medicine (AASM) [6].

Table 5.1 Sleep evaluation in the diagnosis of OSA [4]

High-risk patients	– Obesity (BMI >35) – Congestive heart failure – Atrial fibrillation – Treatment refractory hypertension – Type 2 diabetes – Stroke – Nocturnal dysrhythmias – Pulmonary hypertension – High-risk driving populations – Preoperative for bariatric surgery
Symptoms of OSA	– Snoring – Witnessed apneas – Gasping/choking episodes at night – Excessive sleepiness not explained by other factors – Nonrefreshing sleep – Nocturia – Morning headaches – Sleep fragmentation/sleep maintenance insomnia – Decreased concentration and memory – Decreased libido – Irritability

Table 5.1 (continued)

Suggested features of OSA	– Increased neck circumference (>17 inches in men, >16 inches in women) – BMI ≥ 30 kg/m^2 – A modified Mallampati score of 3 or 4 – Retrognathia – Lateral peritonsillar narrowing – Macroglossia – Tonsillar hypertrophy – Elongated/enlarged uvula – High arched/narrow hard palate – Nasal abnormalities (polyps, deviation, valve abnormalities, turbinate hypertrophy) – Overjet – Musculoskeletal abnormalities

BMI body mass index, *OSA* obstructive sleep apnea

Table 5.2 Criteria for OSA diagnosis [6]

Diagnosis of OSA		Parameters			
A + B criteria	A	Presence of ≥1 symptoms or diseases			
		– Sleepiness – Nonrestorative sleep – Fatigue – Insomnia	– Breath holding – Gasping – Choking	– Snoring and/or – Breathing interruptions	– Hypertension – Mood disorder – Cognitive dysfunction – Coronary artery disease – Stroke – Congestive heart failure – Atrial fibrillation – Type 2 diabetes mellitus
	B	Polysomnography or home sleep apnea testing – ≥5 predominantly obstructive respiratory events per hour			
C criteria		Polysomnography or home sleep apnea testing – ≥15 predominantly obstructive respiratory events per hour			

OSA obstructive sleep apnea

For children, it is important to follow the guidelines as formulated by various professional societies [7–9]. More generally, adoption of the concept of habitual snoring (defined as snoring recognized by caretakers at least 3 nights per weak, particularly if loud) that also exhibits an additional problematic symptom is an excellent rule of the thumb to make the decision to evaluate further with some objective diagnostic testing.

OSA Screening Questionnaires

Major advantages of questionnaires are readiness and negligible cost. However, clinical questionnaires are not recommended as single tools for OSA diagnosis due to their limited accuracy. Nevertheless, despite their low specificity (large number of false-positive cases) [10, 11], standardized questionnaires show overall high sensitivity, and thus they can be useful for screening purposes. Accordingly, questionnaires can be easily performed in clinical practice to identify patients with higher risk for OSA both in primary care and in specialized care. Some authors suggest their usefulness in low-income countries where PSG is not available [12].

There are several standardized questionnaires aimed at assisting physicians in the detection of OSA. The Berlin questionnaire (BQ) [13], OSA50 [14], and STOP-BANG [15] are probably the most popular, while No-apnea, GOAL, NoSAS, and Obstructive Airway Adult Test (OAAT) [16] have been also widely assessed [17–26]. There are few studies comparing the diagnostic ability of these questionnaires with each other, and some inconsistencies have been reported [12, 27]. Table 5.3 shows the most widely used questionnaires.

Table 5.3 Main questionnaires used for identifying patients with a high pretest probability of OSA [10]

Questionnaire	Initially developed	Parameters	Level of OSA risk	Diagnostic accuracy (AHI > 15 events/h)
Berlin Questionnaire	Primary care	10 questions pertaining to the following 3 categories – Snoring – Daytime sleepiness – Hypertension	• *High:* ≥2 categories with positive score • *Low: 1 or no categories with positive score*	• *Sensitivity*: 0.77 (0.73–0.81) • *Specificity*: 0.44 (0.38–0.51) Assessed in [12]
STOP-BANG Questionnaire	Surgical patients at preoperative clinics	4 questions (yes/no) regarding the following signs/symptoms – Snoring – Tiredness – Observed apneas or choking – High blood pressure Plus 4 clinical attributes (yes/no) – Obesity (BMI >35 kg/m^2) – Age (>50 years) – Neck circumference (>40 cm) – Male gender	• *High: score of 5–8* • *Intermediate: score of 3–4* • *Low: score of 0–2*	• *Sensitivity*: 0.90 (0.86–0.93) • *Specificity*: 0.36 (0.29–0.44) Assessed in [12]

Table 5.3 (continued)

Questionnaire	Initially developed	Parameters	Level of OSA risk	Diagnostic accuracy (AHI > 15 events/h)
OSA50	Primary care	Four components (yes/no) – Age ≥ 50: yes 2 points – Snoring: yes 3 points – Witnessed apneas: yes 2 points – Waist circumference (>102 cm male; >88 cm female): yes 3 points	High risk ≥5 points	Sensitivity: 0.94 Specificity: 0.31 • Assessed in [14]

AHI apnea-hypopnea index, *BMI* body mass index, *OSA* obstructive sleep apnea

In children, a large number of questionnaires have also been developed over the years with overall remarkable similarity in their performance even if some are better than others. These questionnaires for the most part exhibit excellent sensitivity but relatively lower specificity, making them robust tools for screening purposes but not accurate enough to be used as an alternative to a diagnostic test [28–33].

More complex multivariate predictive models for OSA have been proposed, including a variety of additional symptoms (infections, high blood pressure, attention deficits) and measures (palatal height, maxillary, and mandibular intermolar distances). Despite these models demonstrated higher ability to discriminate OSA, particularly for higher diagnostic thresholds for the disease, they still show a great imbalance between sensitivity and specificity, leading to a marginal use in clinical practice [23].

Comprehensive Sleep Studies

History and questionnaires provide physicians with relevant information on the presence or absence of the disease. Nevertheless, definitive diagnosis of OSA must be confirmed using appropriate devices for comprehensive sleep testing [10]. Table 5.4 summarizes the four traditional categories of devices for sleep analysis according to the complexity (number of physiological signals involved) and the setting (supervised vs. unattended) [34]. These approaches are applicable to both adults and children with some caveats that will be addressed below.

Table 5.4 Main characteristics of equipment used in the different approaches for adult OSA diagnosis according to AASM [10, 34]

Category	Site	Channels	Advantage	Disadvantage	Recommendation
Type I or PSG	Attended, inside sleep laboratory	≥7 data (EEG, EOG, EMG, ECG and respiratory channels) (typically ≥16)	Sleep parameters	– High cost – Complex – Limited availability – Patient inconvenience – Disturb sleep quality – Intrusive – Time-consuming	– Moderate-to-high probability of OSA without comorbidity (strong) – Low-to-moderate probability of OSA – Patients with significant diseases, suspected CSA, or hypoventilation (strong) – Suspected other sleep disorders than OSA – Nondiagnostic HSAT and suspected OSA (strong) – Initial PSG negative and suspected OSA (weak)
Type II or Home PSG	Unattended, outside sleep laboratory	≥7 data (EEG, EOG, EMG, ECG, and respiratory channels) (typically ≥ 16)	– Sleep parameters – Lower cost than Type I – Improved sleep quality – Preferred by the patient	– Intrusive – Time-consuming – Relative lack of portable devices	– Predominantly for research purposes – Further studies are needed
Type III or RP	Unattended, outside sleep laboratory	3 ≤ channels < 7 (airflow, snoring, respiratory excursion, body position, heart rate, oxygen saturation)	– More accessibility – Lower cost and workload than types I and II – More comfortable and convenient for patients	– Not sleep parameters – Relative lack of portable devices	– Moderate-to-high probability of OSA without comorbidity (strong) – Unable to perform PSG because of immobility or infirmity – Confirm treatment efficacy

(continued)

Table 5.4 (continued)

Category	Site	Channels	Advantage	Disadvantage	Recommendation
Type IV	Unattended, outside sleep laboratory	<3 (oxygen saturation and heart rate, or just air flow)	– Easy interpretation – More accessibility than type III – Lower cost than type III	Lack of information about many sleep and respiratory parameters	Screening OSA in moderate-to-high probability

ECG electrocardiogram, *EEG* electroencephalogram, *EMG* electromyogram, *EOG* electrooculogram, *HSAT* home sleep apnea testing, *OSA* obstructive sleep apnea, *PSG* polysomnography, *RP* respiratory polygraphy

Polysomnography

In-laboratory polysomnography (PSG) is the gold standard method for OSA diagnosis. PSG provides essential information on the duration and quality of sleep, sleep stages, and transient events (electroencephalographic, muscular, cardiac, and respiratory events) during sleep. Current AASM guidelines [35] delineate scoring and interpretation rules as well as technical aspects concerning PSG performance and analysis based on cumulative published evidence.

Electroencephalographic channels and associated recordings (electrooculogram and electromyogram) are an essential part of a PSG. EEG, EOG, and EMG signals are used to analyze the macro- (sleep stages) and micro- (electroencephalographic events) structure of sleep. Table 5.5 summarizes the main characteristics of sleep stages and common electroencephalographic events [35].

Cardiorespiratory recordings involving airflow, respiratory movements, electrocardiogram, pulse oximetry, and body position compose the second main part of a PSG, aimed at characterizing and quantifying respiratory events. Monitoring snoring and hypoventilation are optional in adults but is required in children, particularly assessment of alveolar hypoventilation since many children may manifest sleep-disordered breathing almost exclusively by developing extended periods of elevated carbon dioxide levels during sleep. Table 5.6 shows the types and definition of polysomnographic respiratory events involved in the diagnosis of sleep-disordered breathing in adults [35]. Additional physiological recordings have been proposed to be included in the PSG, such as the divided nasal cannula [36]. However, no improvement was found in terms of the accuracy of AHI.

In order to obtain reliable and confident diagnosis, the AASM recommends a minimum of 4 h of total sleep time (6 h for children) for high-risk patients undergoing PSG, while this limit increases to 6 h (and >16% of total sleep time REM sleep in children) in clinical trials in order to account for a potentially broader spectrum of OSA severity [3].

OSA severity is categorized according to the AHI, which accounts for the combined number of apneas and hypopneas per hour of sleep. Although the most appropriate diagnostic threshold for positive OSA has been under great discussion for

Table 5.5 Main characteristics of states and electroencephalographic events during sleep [35]

Scoring	Definitions
W	1. Alpha rhythm (posterior dominant rhythm); occipital region with eye closure, attenuating with eye opening 2. Eye blinks: vertical eye movements at 0.5–2 Hz 3. Reading eye movements: slow phase followed by rapid phase 4. REM: irregular; lasting <500 ms 5. SEM: more regular; lasting >500 ms
N1	1. SEM: more regular; lasting >500 ms 2. LAMF: 4–7 Hz (theta) 3. V waves: 0.5 s in Central region 4. Sleep onset: first epoch of any stage other than W, usual N1
N2	1. K complex: well-delineated, negative sharp wave immediately followed by a positive component standing out from the background EEG; duration >0.5 s; maximal in the frontal region 2. Sleep spindle: train of distinct sinusoidal waves 11–16 Hz and duration >0.5 s; maximal in the central region
N3	1. Slow wave activity (0.5–2 Hz) and >75 uV; frontal region
REM	1. REM: irregular; lasting <500 ms 2. Low chin EMG tone: baseline no higher than any other sleep stage and usually lowest level of the entire recording 3. Saw-tooth waves: trains of sharply contoured or triangular, often serrated, 2–6 Hz waves; maximal over central region; may precede a burst of REM 4. Transient muscle activity: short, irregular burst of EMG <0.25 s; superimposed on low EMG chin or leg tone
Major body movements	1. Movement or muscle artifact obscuring the EEG for more than half an epoch to the extent that the sleep stage cannot be determined 2. If alpha rhythm is present, even <15 s, score Wake 3. If no alpha rhythm is discernable, but the epochs before or after is scored as W with major body movements, score as stage W 4. Otherwise, score the epoch as the same stage as the epoch that follows it
Arousal	1. Abrupt shift of EEG frequency including alpha, theta and/or frequencies above 16 Hz 2. At least 3 s long 3. Must have 10 s of stable sleep preceding the change 4. During REM requires a concurrent increase in submental EMG for at least 1 s

EEG electroencephalogram, *EMG* electromyogram, *LAMF* low-amplitude mixed frequency, *REM* rapid eye movements, *SEM* slow eye movement, *V waves* vertex sharp waves

years, currently, the following severity degrees are widely accepted in adults [10]: mild OSA, $5 \leq$ AHI < 15 events/h; moderate OSA, $15 \leq$ AHI < 30 events/h; and severe OSA AHI ≥ 30 events/h. Because the collapsibility of the upper airway is lower in children than in adults, the number of respiratory events in healthy children is <0.5 events/h of sleep. Accordingly, the criteria for OSA severity have traditionally been adopted as follows: >1–5 events/h corresponds to mild OSA; >5 to 10 events/h represent moderate OSA and >10 events/h is viewed as severe OSA in the pediatric age. However, for children older than 14 years of age, application of adult or pediatric OSA severity criteria is at the discretion of the physician.

Table 5.6 Scoring criteria for respiratory events in adults [35]

Event		Definitions
Apnea		>90% drop from baseline; for at least 10 s
	Obstructive	Continued or increased inspiratory effort throughout event
	Central	Absent inspiratory effort throughout event
	Mixed	Absent of inspiratory effort for first part of event followed by resumption of inspiratory effort in the second portion of event
Hypopnea		All criteria are needed – >30% drop from baseline; for at least 10 s – >3% desaturation from pre-event baseline or arousal; >4% desaturation from pre-event baseline
	Obstructive (optional)	All criteria are needed: snoring, increased inspiratory flattening, paradox appears
	Central (optional)	None of the criteria appears: snoring, increased inspiratory flattening, paradox appears
RERA (optional)		Sequence of breath lasting at least 10 s lead an arousal that shows – Increased respiratory effort – Flattening of the inspiratory portion of signal Must not qualify for apnea of hypopnea
Hypoventilation (optional)		Either of the next occur – Increase in arterial PCO_2 to a value >55 mmHg for >10 min – >10 mmHg increase in arterial PCO_2 during sleep and exceeds 50 mmHg for >10 min
Cheyne-Stokes		Both of the next criteria occur – Episodes of >3 consecutive central apnea or central hypopnea separated by a crescendo and decrescendo change in breathing amplitude within a cycle of >40 s – Episodes of >5 central apnea or central hypopnea per hour of sleep associated with crescendo/decrescendo breathing pattern recorded for over 2 h of monitoring
AHI		Number of apneas and hypopneas per hour of total sleep time
RDI		AHI with the addition of RERAs per hour of sleep during polysomnography
REI		Number of apneas and hypopneas per hour of total recording time on home monitoring devices for sleep apnea

AHI apnea-hypopnea index, *RDI* respiratory disturbance index, *REI* respiratory event index, *RERA* respiratory effort-related arousal

Despite been the standard index to diagnose OSA, the AHI does not completely reflect the complex heterogeneity of the disease. Its main drawback is related to its inability to differentiate among the clinical phenotypes of OSA [3] or predict all negative consequences of the disease [2]. Similarly, it has been found that different measures of hypoxia are better predictors of outcomes and adverse events than the AHI [37]. However, notwithstanding the limitations of AHI regarding more precise patient phenotyping, severity-dependent associations between AHI and some of the common morbid consequences of OSA have been detected despite the marked heterogeneity of morbid phenotype [38], whereby other morbidities do not exhibit significant associations with AHI [39].

In the same regard, PSG has widely known limitations. It is complex, time-consuming, and intrusive for patients. In addition, regarding equipment and

specialized staff, PSG is costly leading to limited accessibility and availability. Therefore, due to the high prevalence of the disease worldwide, it is not a cost-effective approach to evaluate all patients suspected of suffering from the disease. Accordingly, simplified alternatives are being sought, particularly to conduct portable sleep studies at home and under the lead assumption that such transition to home will not curtail the accuracy and reliability of the alternative tests.

Home Sleep Apnea Testing

In recent years, abbreviated and portable at-home sleep apnea testing (HSAT) has emerged as an alternative or complementary diagnostic tool for OSA. There is a great number of commercial devices currently available. In 2007, the AASM established the characteristics and minimum requirements of HSAT devices [40]. Their use as an alternative to standard PSG was subsequently accepted only in uncomplicated patients showing high pretest probability for the disease [18, 40].

Concerning the physiological signals recorded by abbreviated HSAT devices, three signals are considered relevant and widely recommended: blood oxygen saturation from oximetry, respiration from nasal pressure or alternatively respiratory bands, and heart rate from ECG or from the pulse oximetry signal.

The implementation of HSAT procedures differs among countries. In Europe, simplified portable monitoring has been widely accepted, firstly supervised in the hospital setting and then unattended at home [41]. Similarly, up to 40% of total patients are referred to HSAT in Canada [42]. In contrast, routine HSAT use in the patient's home in the USA has been slower to be adopted due to some regional limitations related to reimbursement and personnel structure. As no EEG is recorded, abbreviated HSAT devices do not provide information about sleep, nor do these recordings provide sleep time or arousals, which limits their ability for ruling out the disease [10]. Therefore, the numerator of events does not include arousals and the denominator is larger since it denotes total recording time (TRT), while PSG actually includes total sleep time (TST; obviously TRT > TST), such that unless the disease is more severe, there can be clear underestimations or mis-estimations in any given patient. Indeed, a remarkable overall underestimation (high false-negative rate) has been consistently reported [43–45]. Accordingly, in-lab PSG or further follow-up should be considered when HSAT results are negative. Therefore, the cost associated with repeated test due to false-negative results (17%) [40] and technical failures (18%) [46] must be taken into account [47]. The main limitations of HSAT are summarized in Tables 5.7 and 5.8. These limitations of HSAT are further magnified in pediatric settings, because the severity criteria are much more stringent and the numerator to calculate the AHI is much smaller [50].

Conversely, the main advantages include less cost and less intrusiveness for patients. Particularly, higher cost-effectiveness ratio of HSAT compared to in-lab PSG has been reported in appropriately selected patients [51–55]. In regard to patient's comfort, contradictory data have been recently reported [56, 57]. "Real-world" studies are needed to prospectively assess preferences and satisfaction of patients with HSAT. Additionally, reduced workload in sleep laboratories and reduced waiting times for diagnosis and treatment are commonly reported benefits for both specialists and patients. Finally, HSAT enables multiple-night assessment

Table 5.7 Limitations of HSAT leading to OSA underestimation [48]

Limitations of HSAT
RDI is calculated using TRT instead of TST: TRT is higher than TST, leading to underestimation
No measure of REM sleep: OSA underestimation in patients with REM-predominant OSA
No measure EEG arousals: OSA underestimation if hypopneas associated only with arousal
Less supine time sleep at home compared with sleep lab setting: OSA underestimation in patients with supine-predominant OSA
Self-placement of sensors can be cumbersome and confusing, leading to poor-quality recordings
The home environment may be less conducive to sleep than the sleep lab if there are environmental disturbances to sleep

EEG electroencephalogram, *OSA* obstructive sleep apnea, *RDI* respiratory disturbance index, *REM* rapid eye movement, *TRT* total recording time, *TST* total sleep time

Table 5.8 Factors affecting suitability of HSAT [49]

Patient-related factors	1. Neuropsychological 2. Severe physical disability with inadequate care attendance 3. Unsuitable home environment 4. Discretionary
Sleep disorder-related factors	1. Consideration of other sleep disorders: central sleep apnea, hypoventilation, heart failure, neurological disorders, sleep-related movement disorder, parasomnia or seizure disorder, unexplained hypersomnolence 2. Video confirmation of body positional, rotational aspects or other associated movements

at a reasonable cost, minimizing the confounding effect of the widely known night-to-night variability of OSA [3].

Concerning the different types of HSAT approaches (Table 5.4), comparable clinical (BMI, ESS, blood pressure) and treatment (CPAP adherence) outcomes have been reported in OSA patients diagnosed using ambulatory PSG (type II) compared to in-hospital standard diagnosis [58]. Despite more limited cardiopulmonary data, respiratory polygraphy (RP) (type III) is able to expedite diagnosis [53]. Similarly, it has been found useful to increase availability of both diagnosis and treatment resources in patients with mobility issues and major illness [10]. A major meta-analysis on the effectiveness of type III monitors reported good diagnostic performance (AUC ranging from 0.85 to 0.99) for the common OSA severity cut-offs and no significant differences in clinical management parameters between patients diagnosed using either PSG or type III monitoring [53]. In the context of children, the jury is still out and the consensus at this stage pending additional large-scale studies is still in favor of minimizing the use of HSAT and preferably conducting PSG unless the regional circumstances and resources lead to substantial delays in diagnosis [59–61].

Accurateness and reliability of more simplified devices (type IV) are still under debate, particularly single-channel blood oxygen saturation (SpO_2) from oximetry. Respiratory disturbance index (RDI) from RP and oxygen desaturation index (ODI) from oximetry have been found to provide similar predictions of actual AHI, showing small differences compared to the known night-to-night variability [62].

Nevertheless, the AASM demands further evidence on the efficiency of unattended oximetry and similar single-channel approaches as reliable tools for OSA diagnosis (currently recommended only for screening purposes), particularly in mild or asymptomatic patients and in the presence of other sleep disorders (central sleep apnea) or significant concomitant diseases [10]. Concerning cardiorespiratory comorbidities, several studies have assessed the usefulness of simplified screening tests for OSA in patients with hypertension [63], heart failure [64], and stroke [65]; in the presence of COPD [66, 67] or morbid obesity [68]; in patients remitted for surgery [69]; and in hospitalized elders [70].

The interest on oximetry recently increased due to its ability to characterize intermittent hypoxia. Several studies reported that hypoxia level correlates with mortality, cardiovascular outcomes, and cancer incidence better than the standard AHI [3, 71–73]. In this regard, novel oximetric indices have been proposed to parameterize intermittent hypoxia linked with OSA, such as the hypoxic burden [73], the hypoxia load [71], or the desaturation severity parameter [74].

A similar evolutionary trend has occurred in the context of pediatric settings. The Oxygen Desaturation (≥3%) Index (ODI3) and McGill Oximetry Score (MOS) are widely used as predictors of moderate-to-severe OSA (apnea-hypopnea index-AHI >5 episodes/h), an indication for adenotonsillectomy [75, 76]. In a recent study, we have shown that the optimal cutoff values for the ODI3 and MOS were ≥4.3 episodes/h and ≥2, respectively. Nevertheless, the ODI3 emerged as the better performing index for detecting moderate-to-severe OSA in habitually snoring children when PSG is not available [77].

Blood Biomarkers

Sleep apnea is known to trigger mechanisms leading to metabolic and endocrine dysfunctions, such as inflammation, hypoxemia, and oxidative stress, which can be readily detected by blood tests. Accordingly, blood biomarkers have been proposed to enhance the diagnosis of OSA [10, 78]. Common biomarkers are glycated hemoglobin (HbA1c), C-reactive protein (CRP), erythropoietin (EPO), interleukin-6 (IL-6), and uric acid [78]. Similar efforts in children have yielded remarkable accuracy under specific circumstances in the detection of disease, in the identification of residual OSA after treatment, or in the evaluation of comorbidities associated with OSA [79–85].

Some biomarker combinations have been found to correlate with sleep apnea severity, emerging as potential user-friendly and low-cost tools for OSA screening in high-probability patients [86–90]. Nevertheless, further research is encouraged in this topic to obtain successful diagnosis and treatment strategies, mainly by means of big data and machine learning techniques [3, 91].

5.2 Diagnostic Strategy

As mentioned above, attended in-lab overnight PSG is the gold standard tool for OSA diagnosis. Nevertheless, due to the widely known drawbacks of PSG and the increased frequency of visits linked with suspected sleep apnea, the aforementioned

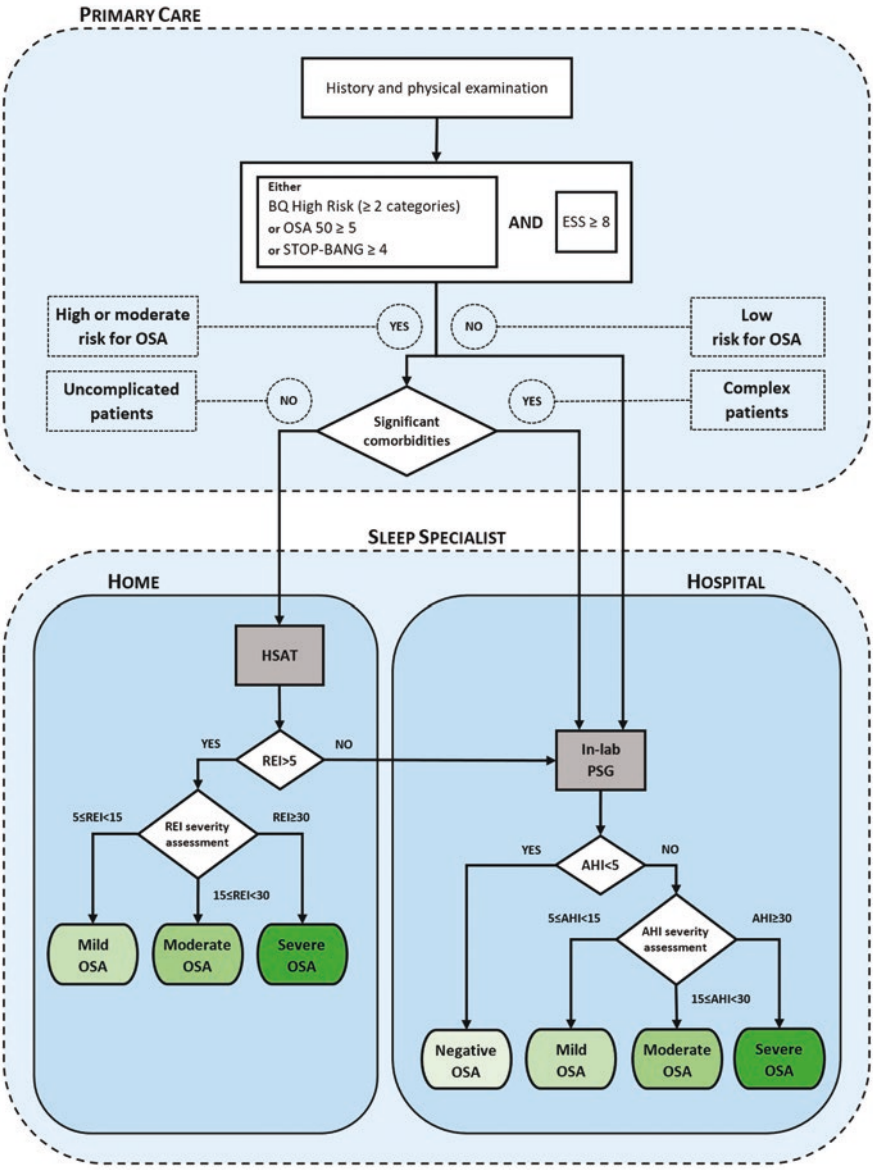

Fig. 5.1 Flowchart summarizing the diagnostic strategy for OSA detection involving primary care, HSAT and in-laboratory PSG

simplified methods have been implemented within the diagnostic protocols in order to conduct sleep studies at home, reduce costs and waiting lists, and expedite both diagnosis and treatment. Figure 5.1 shows a flowchart with the diagnostic strategy for OSA detection according to the current evidence and recommendations.

The main recommendations to conduct standard PSG in a sleep laboratory are:

- Patients with significant comorbidities (such as severe pulmonary disease, congestive heart failure, or neuromuscular weakness)
- Patients with risk of central or mixed sleep apnea or other sleep disorders
- Patients with low probability of OSA
- Pediatric patients except for resource-constrained settings

Currently, according to the AASM, HSAT is a suitable alternative to in-lab PSG for the diagnosis of OSA in patients showing moderate-to-high pretest probability without certain comorbidities [10]. Positive OSA is diagnosed in patients showing symptoms and AHI/RDI/REI ≥5 events/h from PSG or HSAT or, alternatively, AHI/RDI/REI ≥15 events/h regardless of symptoms (Table 5.2).

The scarcity of sleep specialists and sleep units forces primary care to increase its role in the detection of OSA [92]. In this framework, general practitioners have two possible pathways to manage patients in order to speed up diagnosis and treatment. Patients scoring positive using a validated screening questionnaire (either BQ positive, OSA50 ≥5, or a STOP-BANG cutoff of ≥4) and showing ESS ≥8 are assigned moderate-to-high risk for OSA and referred directly for in-lab PSG (complex patients) or HSAT (uncomplicated patients) [93]. It is important to point out that patients with negative scores in the proposed questionnaires should not be definitively excluded for OSA [93]. In this situation referring patients to a sleep unit will be required.

Alternatively, other authors proposed a two-step screening strategy involving questionnaires and simplified HSAT in primary care. In a first stage, a battery of sleep questionnaires is applied. Then, abbreviated HSAT approaches can be used in the second stage, e.g., single-channel nasal airflow or pulse oximetry. This two-step approach seems to increase specificity becoming very useful to rule out OSA in primary care while not overstretching sleep units [94, 95].

Application of similar strategies with specific caveats that are exclusively applicable to children are being developed and will hopefully become incorporated into consensus guidelines in the few years to come.

Impact of COVID-19 Pandemic on Diagnostic Strategy for OSA

The coronavirus disease 2019 (COVID-19) significantly affected healthcare systems worldwide [96, 97]. Social distancing, confinement of population, and additional countermeasures aimed at minimizing virus spread have changed protocols of all medicine disciplines, including sleep laboratories. Particularly, face-to-face in-hospital visits for PSG involved an increased risk for both patients and sleep-related professionals. Moreover, domiciliary approaches also carry infection risk.

Accordingly, during a pandemic, sleep experts strongly recommended to stop performing all kinds of sleep studies, except to hospitalized patients showing high risk of sleep apnea that could worsen their health status [98]. Table 5.9 summarizes

Table 5.9 Recommendations for in-laboratory sleep assessment during a pandemic

Recommendations
To check body temperature
To ask about novo respiratory symptoms or in contact with a case
To use personal protective equipment (facial mask and gloves)
To use full personal protective equipment when dealing with confirmed cases of infection (protective gown, gloves, facial mask, goggles, and cover boots)
Hand hygiene on arrival and departure and whenever needed

main recommendations when conducting sleep studies in an epidemic context. After the study, the equipment must be disinfected or undergo quarantine if used by infected patients [98]. The epidemic also affects treatment management due to the risk of viral shedding via mask leakage in CPAP devices [99].

Predicting how this epidemic will finally influence protocols and strategies for management of the disease is difficult. Nevertheless, e-health and HSAT approaches will probably arise as suitable tools to minimize face-to-face diagnosis and follow-up visits [100].

5.3 Decision Support Systems in OSA Diagnosis

Physicians must deal with several data sources to reach a definitive diagnosis of OSA, including symptoms, anthropometric and clinical variables, and data from biomedical recordings. In this regard, PSG is the main source of information, as it allows physicians to score major electrophysiological and cardiorespiratory events in order to quantify the AHI. Nevertheless, many long-term recordings compose each PSG and many and complex rules must be taken into account to score each type of event. In this context, computer-aided diagnosis systems have been developed as valuable tools that are able to assist physicians in the laborious diagnosis of the disease. Particularly, artificial intelligence has been found to expedite interpretation of physiological signals by decreasing heterogeneity and subjectivity in the PSG scoring task, as well as decreasing the high workload for sleep experts. In fact, the AASM Foundation identified artificial intelligence as a strategic area in which research focused on according to its 2020 Strategic Research Award program.

Figure 5.2 shows how artificial intelligence algorithms are usually used to assist in OSA diagnosis. Regarding conventional machine learning methods, artificial neural networks and support vector machines have been predominantly used due to its nonlinear architecture and generalization ability, able to model real-world complex data with fast and effective processing [101]. In the last several years, ensemble learning techniques, based on the combination of multiple classifiers in order to increase prediction ability, outperformed previous approaches in this context [102].

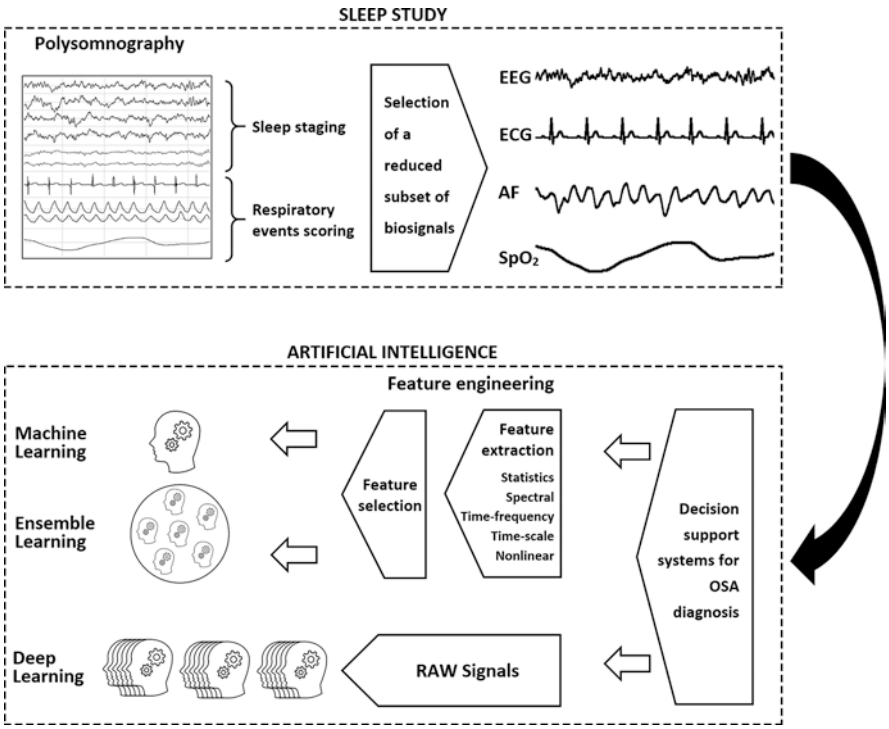

Fig. 5.2 Artificial intelligence-based approaches to formulate decision support systems for OSA diagnosis

Deep learning is currently replacing conventional machine learning approaches in several fields of industry and medicine, including sleep research. Deep learning minimizes major shortcomings of classical pattern-recognition algorithms based on feature engineering, which could potentially remove relevant information when composing the initial feature space of input variables [103]. Deep learning models use all the data contained in the signal and compose their own internal features, thus maximizing the diagnostic ability of the signal. Deep neural networks, particularly convolutional neural networks (CNNs), are the most widely used deep learning approach. Similarly, auto-encoders, deep generative models, and recurrent neural networks are also deep learning methods able to characterize biomedical signals [104].

The two main tasks focus the efforts of researchers and developers in the context of decision support systems for OSA management, namely, the development of automated algorithms for sleep staging, aimed at analyzing the macro- and micro-structure of sleep, and automated analysis of cardiorespiratory recordings, in order to obtain simplified and reliable diagnostic tests for OSA. Table 5.10 shows the main tasks involving artificial intelligence in the context of OSA diagnosis.

Table 5.10 Tasks commonly addressed by means of machine learning and pattern-recognition techniques

Physiological domain	Classification approach	Task
Sleep	Stage-based	Binary: wake vs. sleep
		Multi-class: wake vs. N1 to N3 vs. REM
	Event-based	Arousals, k complexes, spindles
Respiration	Subject-based	Binary: non-OSA vs. OSA
		Multi-class: non-OSA vs. mild OSA vs. moderate OSA vs. severe OSA
		Regression: AHI/RDI/ODI estimation
	Event-based	Apneic vs. normal breathing
		Apnea vs. hypopnea events
		Obstructive vs. central nature

Automated Sleep Staging from Polysomnography

The interpretation of a PSG is a cumbersome and time-consuming task even for trained experts. Artificial intelligence provides reliable and accurate algorithms to analyze both the macro-structure (sleep/wake time, sleep stages) and the micro-structure (transient events, such as arousals and spindles) of sleep. Particularly, spectral analysis, nonlinear methods, and patter recognition techniques have been found to provide essential information on electroencephalographic dynamics during sleep and sleep-related breathing disorders [102, 105]. Commercial software by major medical companies in the framework of PSG analysis already implements automated tools for sleep staging. Nevertheless, scoring neuromuscular signals is really challenging for automated algorithms, and accuracy greatly depends on the number of categories (sleep stages) involved in the classification task. Furthermore, performance is also influenced by the type and number of biomedical recordings used (EEG channels and EOG/EMG).

Concerning pattern recognition, according to exhaustive comparisons, a combination of complementary signal-processing approaches including wavelet analysis together with random forest, which is a kind of ensemble learning classifier, is able to reach high efficiency in sleep-staging tasks [106–108]. Recently, a number of studies applied deep learning techniques to accomplish sleep-staging both in healthy subjects and patients with suspected sleep disorders, reporting accuracies ranging from 67.4% to 92.2% [109–117].

Automated Diagnosis of Sleep Apnea

Decision support systems in the context of OSA diagnosis focus on two main goals: (1) providing a reliable and accurate diagnosis using the least amount of signals, promoting the use of simplified portable monitors able to increase availability and accessibility to sleep-related diagnostic resources, and (2) providing physicians

with automated tools able to decrease the high workload linked with scoring respiratory events.

Regarding abbreviated tests for OSA, the scientific community has focused on the analysis of a reduced subset of cardiorespiratory signals, mainly heart rate variability (HRV) from electrocardiogram (ECG), SpO_2 from oximetry, and airflow (AF). Two approaches are commonly used to characterize changes in these biomedical recordings: time-domain and frequency-domain analyses [118, 119]. In addition, as biological systems have major nonlinear interactions, nonlinear analysis has demonstrated to provide additional and complementary information to conventional linear and frequency-domain methods [120–124]. Similarly, wavelet transform (time-scale analysis) and bispectrum (high-order spectra) have been proposed as reliable alternatives to conventional Fourier analysis in the context of OSA [118, 119, 121].

In order to implement computer-aided diagnosis systems for OSA, binary and multiclass classifiers as well as regression models have been developed (Table 5.10). Classical statistical methods, such as linear (LDA) and quadratic (QDA) discriminant analysis and logistic regression (LR), reached remarkable diagnostic performance in binary classification tasks, whereas more complex machine learning methods including decision trees, neural networks, and support vector machines have demonstrated its usefulness in multiclass and regression problems [101, 118, 119, 125–128]. Recently, ensemble learning and deep learning techniques have been found to outperform conventional machine learning techniques in the framework of OSA diagnosis [104, 129–131].

Digital Health Technologies in the Management of Sleep Apnea

In the last years, e-Health systems and mobile (m)-health applications through smartphones raised as reliable tools for unattended portable testing and therapy monitoring in the context of OSA management [132, 133]. The increasing recognition of good sleep quality as synonym of health and the need of periodic follow-up in chronic sleep-disordered breathing foster the usefulness of telemedicine in this framework. In this regard, the AASM points out the usefulness of telemedicine for improving accessibility to and availability of sleep experts and sleep-related healthcare resources [134].

Regarding high-quality medical applications for clinical practice, e-health/m--health tools mainly focus on long-term therapy tele-monitoring, while remote PSG or alternative simplified sleep studies at home are less frequent [135–137]. On the other hand, the vast majority of smartphone-based applications focus on wellness and lifestyle monitoring for nonspecialized general use, mainly for sleep tracking and sleep quality assessment with a lack of appropriate scientific validation [138–140]. Concerning suitable assessment, the FDA recommends validation against PSG since it is currently the gold standard method for OSA diagnosis. In this regard,

overall, sleep-related parameters provided by mobile Apps correlate poorly with PSG and further improvement is needed [141].

While recent advances focus on simplifying devices to increase portability, accessibility, and comfort, experts point out the lack of direct measures of brain activity, the need for estimating total amount of sleep, and measuring the duration of respiratory events to obtain a reliable and accurate diagnosis of OSA [3].

Advantages and Limitations of Artificial Intelligence in the Management of OSA

Sleep medicine, particularly for sleep-related breathing disorders, can significantly benefit from artificial intelligence and big data techniques due to the huge volume of data involved in the process of diagnosis, including not only PSG but also data from clinical history, anthropometric variables, biomarkers, or genetics, among others. In the last decade, conventional machine learning techniques demonstrated their usefulness in addressing problems related to automated classification of sleep stages, respiratory events, and, overall, sleep apnea severity [142]. In addition, current increased computational capabilities have led novel deep learning algorithms to outperform stablished limits, reaching correlations above 0.95 in the estimation of the AHI [143] and multi-class kappa above 0.80 in sleep staging [113, 144].

Beyond particular sleep staging and respiratory event scoring tools, artificial intelligence is expected to enhance therapy management and patient outcomes in order to reach the so-called personalized medicine in the context of sleep apnea [142, 145]. In this regard, machine learning has been recently proposed to identify the most appropriate diagnostic pathway for OSA patients. In the work by Stretch et al. [146], a predictive model is trained to decide which patients are referred directly to in-hospital PSG and which ones are more likely to benefit from abbreviated sleep testing at home. Nevertheless, as pointed out in a recent report by the AASM, artificial intelligence is not going to replace sleep experts but to augment efficiency and accurateness of sleep laboratories [147].

On the other hand, common drawbacks of machine learning and artificial intelligence are limited generalizability; output variables and performance metrics difficult to interpret, potentially leading to loss of relevant information; lack of transparency of proprietary algorithms, leading to the so-called black boxes; and subjectivity of standard rules used to label training samples, as automated learning mostly relies on supervised training.

In addition, some major challenges must be still overcome in order to generalize the use of expert systems in clinical practice, such as regulatory laws concerning software certification and logistics linked with computer support, as well as ethical and legal issues [148]. Regarding ethics, it is important to highlight that the clinician is solely responsible for the decisions related to patient diagnosis and treatment.

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Transitional Care of Sleep-Disordered Breathing: Management

6

Thomas J. Dye and Narong Simakajornboon

6.1 Introduction

Sleep-disordered breathing (SDB) consists of a wide range of conditions including obstructive sleep apnea (OSA), central sleep apnea, and sleep-related alveolar hypoventilation. In this chapter, we will focus on OSA which is characterized by complete or partial upper airway obstruction during sleep resulting in intermittent hypoxemia and sleep fragmentation [1]. If left untreated, it can lead to cardiovascular, metabolic, and neurocognitive complications. The prevalence of OSA has been estimated to be 1–4% in older children [2–4]. Several factors play a role in pathophysiology of OSA in children including adenotonsillar hypertrophy, craniofacial abnormality, and obesity. Although adenotonsillar hypertrophy is the most common cause of OSA in children, obesity is increasingly recognized as the major contributing factor for OSA in children and adolescents. Epidemic of obesity around the world leads to increased prevalence of OSA in children and adolescents which will persist into adulthood [5]. In addition, the advances in medical technology result in

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survival of children with craniofacial syndrome, neurological disorders, and genetic disorders such as Down syndrome. This population is at greater risk for OSA and requires long-term management of OSA into adulthood.

Management of OSA involves surgical and nonsurgical interventions. Although adenotonsillectomy is the first line of treatment in children, the use of noninvasive positive pressure ventilation is the mainstay for management of OSA in adolescents and young adults. Other treatment options include medications, supplemental oxygen, oral appliances, positional therapy, upper airway surgeries, and hypoglossal nerve stimulator. Medications such as nasal steroid or leukotriene antagonists have been studied in children; the data in adolescents and young adults are limited [6–10]. Supplemental oxygen has been used mainly in infants [11], but adult data suggest the benefit in those with high loop gain. Both oral appliances and positional therapy have been used for management of OSA in adults, but there is limited data in children and young adults. Although there is limited evidence on upper airway surgeries in the management of OSA in pediatric population, certain population such as craniofacial syndrome and genetic disorders such as Trisomy 21 are more likely to benefit from surgical intervention.

The overall remission rate of OSA based on polysomnography in children and adolescents was 30% based on a recent longitudinal study, and 22% of adolescents and young adults continued to have significant OSA at follow-up [5]. Therefore, a significant proportion of children and adolescents with OSA continue to have persistent OSA into adulthood. Without a well-organized transition care program, young adults with OSA may not receive adequate treatment which can lead to long-term consequences. In addition, the economic burden of untreated OSA is quite significant [12, 13]. Therefore, it is important to develop a transition care program in children and adolescents with OSA. In this chapter, we will provide an overview of the management of OSA and discuss issues related to transition of care from childhood through adolescence to adulthood.

6.2 Overview of Management of OSA in Children and Adolescents

Adenotonsillectomy

Adenotonsillar hypertrophy is the most common etiology of OSA in children; therefore, adenotonsillectomy is the first line of treatment. There are several studies evaluating the effectiveness of adenotonsillectomy on OSA with various methodologies, but only one randomized controlled study [14]. Adenotonsillectomy has been shown to improve or normalize respiratory parameters in 60–70% of children [15–17]. In addition, several studies have shown that adenotonsillectomy improved cardiovascular parameters and may have a significant effect in reversing the cardiovascular and neurocognitive consequences of OSA [18, 19]. Several factors can influence adenotonsillectomy outcomes including age, race, severity of OSA, obesity, and coexisting medical conditions such as asthma and allergic rhinitis [17].

Medications

Several studies have shown the role of upper airway inflammation in the pathogenesis of OSA. In addition, glucocorticoid receptors were expressed in adenotonsillar tissue in children and were more abundant in OSA patients [20]. A randomized double-blinded crossover study demonstrated a reduction in AHI and adenoid size after 6 weeks of intranasal steroid in children [8]. Leukotriene antagonists such as montelukast is another medication used for mild OSA. Several studies have shown the effectiveness of montelukast in reducing OSA severity and the size of adenoid [6, 9]. In addition, additional studies have demonstrated that a combination of montelukast and nasal steroid led to a reduction in AHI and other respiratory parameters [7, 10]. Studies on other medications such as nasal decongestant has yielded conflicting results but overall is not effective in the management of OSA. Nasal steroid, montelukast, and a combination are often used in children with mild OSA. The duration of treatment ranges for 6 weeks to 3 months. There is a lack of data on the long-term effect of medical therapy such as nasal steroid and leukotriene antagonists.

PAP (Positive Airway Pressure) Therapy

PAP consists of various devices including CPAP (continuous positive airway pressure), BPAP (bilevel positive airway pressure), ASV (adaptive servo ventilation), and AVAPS (average volume-assured pressure support). CPAP, the most common form of PAP therapy for OSA, is increasingly used in pediatric population. The mechanism of CPAP involves stenting or stabilizing effect of upper airway and normalization of genioglossus activity resulting in improvement in both respiratory events and sleep architecture. CPAP is indicated in children and adolescents who are poor surgical candidates, those who fail to respond to adenotonsillectomy, and those with underlying neuromuscular disorder, craniofacial abnormalities, genetic syndrome, and chronic lung disease. Increased incidence of obesity in children and adolescents leads to increased pediatric population who are on CPAP and are likely to require CPAP in the long term.

Successful initiation and continuation of CPAP in children are challenging and require unique approach to patients and family [21]. In fact, half of children who are started on CPAP will not cooperate at initiation. Therefore, CPAP treatment in children requires strategies to maximize initial and ongoing adherence. Most pediatric sleep programs have a specialized program to initiate and follow children and adolescents with OSA treated with CPAP. The need for a specialized multidisciplinary program for CPAP therapy play a role in the challenge in transitioning children and adolescents with OSA to an adult program.

Dental Appliance

Rapid maxillary expansion (RME) has been shown to be effective in young children with OSA especially those children who have maxillary transverse deficiency (cross

bite) or upper jaw constriction without comorbidity [22, 23]. A meta-analysis showed that improvement was higher in those with previous adenotonsillectomy or small tonsil (73–95%) than those with tonsillar hypertrophy (61%) [23]. There are limited data on long-term outcome. In general, it should be considered in children with maxillary transverse efficiency and persistent OSA after adenotonsillectomy. There is limited evidence of oral appliance in children and adolescents. It can be considered in adolescents with mature dental development.

High-Flow Nasal Cannula and Supplemental Oxygen

High-flow nasal cannula has been examined in one case series and two prospective studies [24–26]. It has been shown to be effective with significant reduction in respiratory events and improvement of oxygenation in CPAP-intolerant children with OSA or as an alternative to CPAP. These studies were conducted in a small number of subjects with wide age ranges from infants to adolescents.

Supplemental oxygen has been studied in infants and young children with OSA. In infants, oxygen has been shown to reduce the frequency of obstructive respiratory events and improve overall oxygenation parameters without significant adverse effect on alveolar ventilation [11]. In children, oxygen also reduced frequency of respiratory events but may lead to potential adverse effect on alveolar ventilation [27, 28]. Supplemental oxygen is often used in infants and children with developmental disabilities such as Down syndrome who have problem tolerating CPAP [29].

Other Treatments

Positional therapy is one of the treatment options for OSA in adult. There are a few studies evaluating the effect of position on SDB in children. Pereira et al. found that respiratory disturbance index (RDI) was higher in supine position in children less than 3 years, except in infants between 8 and 12 months when there was no effect of position [30, 31]. Another study found that the apnea hypopnea index was similar in all positions, but the apnea index was higher in supine position [32]. Overall, there is inadequate evidence to recommend positional therapy in children and adolescents.

Weight loss is an important intervention as part of the management of OSA. Intensive weight loss program in residential facility has been shown to be effective with resolution of OSA in 71% of obese teenager with OSA [33, 34]. Bariatric surgery has been shown to be effective in reducing frequency of respiratory events in obese adolescents with OSA [35–37]. Both intensive weight loss program in residential facility and bariatric surgery are limited to only morbidly obese children and adolescents. In addition, weight loss alone may not be sufficient in eliminating OSA.

6.3 Overview of Transition of Care

Several studies have shown the importance of effective care transition from pediatric to adult care in children and adolescents with chronic diseases. A well-organized transitional care has been established in patients with chronic diseases such as hemophilia, diabetes, asthma, cerebral palsy, and congenital heart disease [38–42]. However, a national survey in the United States found that 83% of youths with special healthcare needs did not receive a proper transition preparation [43].

A recent longitudinal study with 10-year follow-up has shown that the overall remission rate of OSA based on polysomnography was 30% (obstructive AHI < 1 event/h). In the same study, the incidence of significant OSA (obstructive AHI > 5 events/h) in adolescents and young adults at follow-up was 22% [5]. Therefore, a significant proportion of OSA in childhood will persist into adulthood. Without a transitional care program, young adults with OSA may not receive adequate treatment. Untreated OSA can lead to cardiovascular, neurocognitive, and metabolic consequences. In addition, the economic impact of untreated OSA is quite significant [12, 13]. Therefore, it is important to develop a transitional care program in children and adolescents with OSA.

Although transition process has been described in children with various chronic conditions, a transitional care in the management of OSA is somewhat unique as it involves patients with heterogeneous conditions ranging from obese adolescents to patients with complex medical conditions such as neuromuscular disorders, genetic disorders, and craniofacial abnormalities. In both obese adolescents and those with complex medical conditions, there are several issues that need to be addressed during transition period besides OSA.

The goal of transitional care is to provide uninterrupted and coordinated care before, during and after transfer of care ultimately leading to better long-term functioning and outcomes [44, 45]. Late adolescence is a challenging phase as the youths face many life and social changes such as moving away from home, starting college, or new job which may complicate the process of transitional care [46]. In the United States, the age of care transfer usually starts between 18 and 21 years of age although it varies among institutions, but in the Asian countries the age at transition is likely to be older [46, 47]. The American Academy of Pediatrics, American Academy of Family Medicine, and American College of Physicians have issued a guideline with four recommended components of a transition plan: (1) assess for transition readiness, (2) plan a dynamic and longitudinal process for accomplishing realistic goals, (3) implement the plan through education of all involved parties and empowerment of the youth in areas of self-care, and (4) document progress to enable ongoing reassessment and movement of medical information to the receiving (adult care) provider [38].

Currently, there are no established guidelines on transitional care in patient with SDB especially OSA. We will outline a structured transitional care program in OSA and discuss issues related to specific treatment of OSA and issues related to specific

conditions with high prevalence of OSA including obese adolescents and adolescents with chromosomal and craniofacial abnormalities (using Down syndrome as a prototype).

6.4 Structured Transition Care Program in OSA

The medical management approach in children and adolescents is often family focused and parental-guided decision-making model of care, while that of adult medicine is patient focused and self-directed model of care [45]. This different approach in pediatric and adult care can lead to problems with transitional care. A structured transition program is very important to allow coordinated and collaborative process among patients, parents, and pediatric and adult clinicians. There is no standard guideline on how to transition patients with OSA. We are outlining the following aspects of transition process.

1. Timing of transition. It is important to start a transition process at an early age to allow adequate time for transition. In our center, we usually start discussing transition process when adolescents with OSA reach 18–20 years of age. This is corresponding to the age that adolescents and youths have major life events including graduating from high school, seeking employment, or going to college. The transition of care should be ideally done during a period of medical stability [48]. At the time of transfer, adolescents with OSA should be on stable CPAP regimen with good adherence or have completed multistep surgeries. The transition usually takes some time, and most patients would be successfully transferred to adult care by 20–25 years of age. Adolescents with developmental disabilities and complex medical conditions such as those with autism, Down syndrome, or cerebral palsy may take longer as these patients have other medical issues that would require transition to all related medical services. In addition, self-directed decision-making skill may take some time to develop in these patients.
2. Multidisciplinary team approach. As adolescents with OSA are often managed by a pediatric multidisciplinary team, it is important to involve the team in the transition process. Regular meetings should be set up between pediatric and adult providers to discuss specific issues related to the care. It is a good opportunity to educate adult providers of unique aspect in the care of adolescents and young adults [49].
3. Combined adult and pediatric transition clinics. In a program with a large number of pediatric patients with OSA, the combined clinics would allow better communication of all team members and facilitate transition of care. This is a setting to introduce adult physicians and their teams to the patients and family. Another option is to have alternating pediatric and adult clinics prior to an official transfer. This setting will encourage a transition to individual decision-making and autonomy while being in a familiar pediatric clinic setting. A written healthcare transition plan should be created and updated at each transition clinic.

4. Documentation and transition of medical records. As transitional care often involves moving from one to another institution, the availability of medical records including a transitional care plan from pediatric institution to adult providers is very important.

6.5 Issues Related to Specific Treatment of OSA

Positive Airway Pressure Therapy

The main management of OSA in adolescents and young adults is the use of noninvasive positive pressure ventilation with nasal CPAP or BPAP. In a large pediatric institution, long-term CPAP use is often managed in a multidisciplinary CPAP adherence program involving sleep physicians, psychologists, sleep technicians, nutritionists, and social workers. There are a few studies evaluating the effectiveness of interventions such as addition of dedicated respiratory therapists and intensive behavior intervention in a structured CPAP program [50–52]. This program is designed to be family focused and the decision is often guided by parents. This approach is suitable for children and early adolescents or even young adults with developmental disabilities. An adult CPAP program is structured to promote patient's autonomy and involves a smaller number of personnel. Because of different approaches in an adult program, some adolescents may decide to return to the pediatric sleep program due to inability to cope with this type of approach. In preparation for transition, it is important to prepare adolescents and young adults for patient's autonomous decision-making process. In addition, adolescents undergo major life changes that would make medical care a low priority. Consequently, adolescents and young adults may be lost to follow-up during a transition period and thus are at increased risk of poor CPAP adherence and inadequate treatment [46, 53]. Therefore, it is important to carefully plan a transition process with emphasis on collaboration between pediatric and adult clinicians. At the start of transition, it is important to prepare adolescents and their family to encourage gradual changes to self-management of CPAP [53]. It is important to educate patients about OSA, treatment options, and the importance of treatment adherence. At the same time, pediatric sleep providers should seek adult counterparts to get an input for designing a transition program. Most patients in the adult CPAP program are middle aged or elderly population. Adult sleep providers may not be familiar with problems related to adolescents and young adults. The common interventions to promote CPAP adherence in adolescents and young adults are similar to adults such as patient engagement and education. However, there are certain interventions that are unique to adolescents and young adults such as adjustment during colleges or encouraging caregiver support with CPAP therapy especially in those with developmental delay. If possible, a joint clinic between pediatric and adult providers would help in facilitating communication and improving continuity of care.

Medical Therapy

Although medical therapy has been shown to be effective in children, the evidence in adolescents and adults is limited. Those with allergy history are likely to benefit from this therapy. The issue with medical therapy is that there are limited data on long-term use. In addition, recurrence of OSA can occur after discontinuation of medical therapy. Adolescents and young adults with OSA being managed with medical therapy often transition to different therapy such as nasal CPAP or may be lost to follow-up.

Surgery

Surgical options are increasingly considered in adolescents and young adults with OSA especially those with craniofacial syndrome and genetic syndrome such as Down syndrome. The planning and implementation of surgery are often done in a multidisciplinary team including ENT, plastic surgery, radiology, pulmonary, and sleep medicine. At Cincinnati Children's Hospital Medical Center, surgery is planned by the Upper Airway Center or the Craniofacial team. Most adolescents and young adults with OSA have multilevel upper airway obstruction; therefore, these patients often require multiple stepwise surgeries. The morbidly obese adolescents may benefit from a bariatric surgery. A new treatment modality such as hypoglossal nerve stimulator has been studied in children and adolescents with Down syndrome and OSA [54, 55]. These patients undergoing upper airway surgery, hypoglossal nerve stimulator, or bariatric surgery would require long-term follow-up after surgical intervention. Therefore, a transition program is very important. As in CPAP adherence program, the program in adolescents is focused on both patient and family and is slowly changed to patient's focus in young adults. However, adolescents and young adults with craniofacial and genetic syndrome may have cognitive delay and parents often guide the decision. This type of approach can create problems during transition to adult programs with emphasis on autonomous decision-making process. From these reasons, young adults with OSA undergoing upper airway surgeries often follow up in pediatric centers. There is an urgent need to develop a well-structured transitional program in this area.

6.6 Issues Related to Specific Conditions with High Prevalence of OSA

Obesity

Weight management is an integral part in the management of obese children and adolescents with OSA. Both weight loss program and bariatric surgery have been shown to improve OSA. There are limited data on transitional care in this population despite the fact the transition from adolescents to young adult is considered a critical period for weight control [56]. One systematic review found only a few

clinical guidelines on this topic [57]. There is lack of a well-organized transitional care program in obese adolescents. Obesity by itself may not be perceived as a chronic disease. In fact, most of transitional care in obese adolescents is often related to morbidities associated with obesity such as hypertension or diabetes [58]. Obese youths are less likely to maintain health insurances or seek preventive care services [59, 60]. In addition, when they seek preventive cares, it is unlikely that they will receive effective weight management counseling [61]. The lack of transitional care would lead to inadequate or loss to follow-up of obese adolescents and young adults in a weight loss program.

Another treatment modality for obesity is bariatric surgery. It is the most effective treatment for severe obesity in adolescents and young adults. In addition to weight loss, bariatric surgery has been shown to improve or resolve OSA in children and adolescents [35–37, 62]. Bariatric surgery has been increasingly considered in adolescents without consistent recommendations for transition to adult providers [63]. Although it has been shown to be very effective in obese adolescents, there are limited data on potential long-term consequences of bariatric surgery such as nutritional deficiency and loss of bone mineral density in pediatric patients [63, 64]. In addition, weight loss alone may not be sufficient in eliminating OSA; therefore, a transitional program is needed to provide assessment and management of comorbidities including OSA and to monitor long-term complications of bariatric surgery. In our experience, some proportion of obese adolescents with OSA may be lost to follow-up in sleep apnea clinics after bariatric surgery. There is a need to develop a standardized program for making transition care for post-bariatric surgery. This program should integrate evaluation and management of OSA in the guideline.

Chromosomal Anomalies and Craniofacial Syndrome

In discussing transitional issues related to chromosomal anomalies and craniofacial syndrome, we will use Down syndrome as a prototype. Down syndrome is the most common cause of chromosomal abnormalities estimated to affect around 1 in 700 births. There are approximately 200,000–250,000 people with Down syndrome who live in the United States. Down syndrome represents a significant subset of children and adolescents with SDB who will eventually require transition to adult care [65–67]. When considering transitional care of SDB, special focus should be paid to those patients with Down syndrome. This population is of particular relevance to sleep medicine clinicians due to the fact that Down syndrome is a relatively common condition and is associated with high likelihood of developing OSA. Clinicians evaluating SDB should be familiar with the symptoms, polysomnographic features, and exam findings that are specific to patients with Down syndrome. There are also differences in management paradigms which are of particular importance during the time of transitional care.

Though OSA is not uncommon in the general pediatric population, it is much more common in children and adolescents with Down syndrome. The prevalence of

OSA in this population is estimated to be between 57 and 79%, a number which approaches 100% in groups referred to sleep medicine clinics [68–71]. In addition, OSA is often severe and is seen at a younger age in children with Down syndrome when compared to other children with OSA [29, 72]. Based on meta-analysis, more than one third of children and adolescents with Down syndrome and OSA are estimated to have an AHI of greater than 10/h [73]. The reason for an increased prevalence of OSA in Down syndrome is multifactorial including coexisting hypotonia, increased rates of obesity, and craniofacial abnormalities such as midface hypoplasia, macroglossia, and glossoptosis [74, 75].

It is recommended that all children with Down syndrome undergo polysomnography by age 4 [75]. This recommendation is due to the high prevalence of OSA and because the traditional means in office evaluation are not well suited for predicting the presence of OSA in children with Down syndrome. In young children with Down syndrome, multiple studies have shown that tonsillar size does not correlate well with polysomnography results. Likewise, obesity has proven to be an unreliable predictor of OSA [68, 71, 72, 76]. Beyond physical signs, several studies have demonstrated that parental reports of symptoms such as snoring, witnessed apneas, and gasp arousals are unable to reliably predict the presence and severity of OSA. A history of congenital cardiac abnormality also does not correlate with OSA [72, 76]. There are conflicting data with regard to age and OSA. Some studies have demonstrated that the obstructive index tends to increase with age [77, 78], while others have found the opposite to be true [71, 76]. Regardless, there is an increased tendency to have severe OSA persists into adulthood for those patients with Down syndrome [79]. While individual signs or symptoms cannot serve as reliable predictors of OSA in Down syndrome, predictive models using composite data are being developed and may prove to be useful tools in the future [80]. In the interim, however, diagnostic polysomnography will remain the standard of care for children and adolescents. This fact remains critically important during the transition from pediatric to adult care because despite these recommendations, polysomnography remains underutilized. In a large cohort of children and adolescents with Down syndrome, less than half had actually underwent polysomnography [81]. Therefore, it is important that during the transition to adult care, adolescents without traditional symptoms should be evaluated for SDB. Furthermore, given the high likelihood of residual OSA, postoperative polysomnography should be performed regardless of the severity of residual symptoms.

From the standpoint of polysomnography, consideration of polysomnographic data should be considered when adolescents with Down syndrome transition to adult care. While OSA is very common in this population, the makeup of the respiratory events may be different than what adult sleep technicians and physicians are accustomed. With regard to the types of obstructive events seen in children and adolescents with Down syndrome, obstructive hypopneas tend to occur more frequently than obstructive apneas [76]. The opposite is true for adults (without Down syndrome), though this is somewhat dependent on the definition of hypopnea that is

used [82, 83]. Central sleep apnea is also a relatively common finding, though this tends to decrease with age. The opposite is true for hypoventilation, as pCO_2 has been shown to trend upward with age [77].

Because the challenges facing those with Down syndrome are diverse, specialty clinics are recommended to ensure that all health screening measures and standard care recommendations are met [84]. Likewise, given the diverse pathology which contributes to SDB in Down syndrome, a multidisciplinary care model should be implemented to address sleep concerns and SDB. The team should include clinicians specializing in sleep medicine, otolaryngologists with expertise in sleep surgery, and psychologists to address barriers to adherence to PAP therapy and to assess behavioral issues. However, implementation of these teams can result in unconscious barriers to transition to adult care both from the clinician standpoint and the patient. Therefore, it is important to consider utilizing transitional care services. This can be as a standalone consultant or as an integrated member of the clinical team.

With regard to specific treatments, several options exist beyond the standard adenotonsillectomy. PAP therapy is used with many patients achieving a relatively high degree of adherence over time. Supplemental oxygen is frequently used in young children with Down syndrome and is the most common OSA treatment modality for infants with Down syndrome [29]. While hypoglossal nerve stimulator is more frequently used in adults, it has been also used in adolescents with Down syndrome [55]. Other surgical interventions include glossectomy, turbinate reduction, and lingual tonsillectomy. Regardless of the surgical intervention, residual SDB is highly likely and therefore postoperative polysomnography is also recommended [85, 86]. Drug-induced sleep endoscopy can also be considered following adenotonsillectomy to guide additional surgical interventions [87].

Because adolescents with Down syndrome have other medical morbidities, transition cares should involve all other services involved in the care. However, a recent study has identified patients with Down syndrome as an underserved subgroup of children with special healthcare needs as many of them experience disparities in access to transition care [88]. Due to developmental disabilities, adolescents with Down syndrome may be less likely to take responsibility of their care [88]. The American Academy of Pediatricians (AAP) recommends that clinicians should discuss issues related to transition into adulthood, including guardianship and long-term financial planning from early adolescences [89]. Interestingly, the AAP guideline recommends discussing symptoms related to OSA at every well-child visit from 5 to 13 years old; however, the same guideline does not mention OSA issues in health supervision of early adolescents or young adults (13–21 years or older). From the practical standpoint, it is somewhat difficult to make transition of SDB in early adolescents because this is a period when the patient may not be on stable management regimen of SDB. In our center, we normally consider initiating a transition at around 18 years or older when the patient is on stable CPAP/BiPAP or completes multistep surgeries to correct upper airway obstruction.

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7 Technology Approaches for Chronic Noninvasive Ventilatory Support in Chronic Respiratory Conditions

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Key Points

- The number of children on chronic noninvasive ventilatory support has increased exponentially over recent decades, and this has significant implications in planning transition to adult services.
- For transition, many of these patients have complex needs and require more individualized planning and collaborative care partnerships between pediatric and adult clinicians.
- New modes of ventilation aim to make ventilation more responsive, improving the delivery of ventilatory support and patient comfort, though further research is still needed to determine whether this translates into improved long-term clinical outcomes.
- Telemonitoring and modern apps have the potential to encourage and empower patients and improve clinical care by enabling problems to be identified at an early stage, though there are still legal and regulatory issues to be resolved.

7.1 Introduction

The number of children on chronic noninvasive ventilatory support (NIV) has increased exponentially over the past few decades. Studies have shown that its use in certain patient groups such as Duchenne's muscular dystrophy (DMD) can change the natural course of the disease, significantly increasing life expectancy.

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NIV can also alleviate symptoms of sleep-disordered breathing, reduce hospital admissions, and improve quality of life. This together with improvements in NIV technology and the successful establishment of care pathways and home NIV packages has resulted in a profound alteration in attitude toward its role in chronic respiratory conditions. Its acceptance as part of standard clinical care in the management of neuromuscular patients has resulted in its application in a wider range of conditions such as neurometabolic diseases and cerebral palsy. This increasing ubiquity means more healthcare professionals and families are aware of its potential. Certainly in this age of social media, a significant number of referrals for consideration of NIV have been at the request of families. The combination of increasing use of NIV and improved medical care, such as assisted airway clearance and optimizing nutrition, has led to improved survival. Taken in conjunction with the future impact of novel therapies such as nusinersen for SMA which are predicted to further extend life expectancy, an increasing number of young people on NIV will be transitioning to adult services. This has significant implications for the planning of adult transition services.

This chapter focuses on current and developing technology that is used in providing noninvasive ventilatory support to patients with chronic respiratory conditions and discusses the issues that may arise as care is transitioned from childhood to adulthood.

7.2 Bilevel Positive Pressure Ventilation

Bilevel positive pressure ventilation (BiPPV) can be broadly classified into volume targeted ventilation and pressure targeted ventilation. A hybrid form of the two volume-assured pressure support ventilation has recently been developed and will be discussed in the section on new ventilatory modes below. In pediatrics, home BiPPV is predominantly pressure targeted, whereby airflow is adjusted to generate a pre-set inspiratory positive airway pressure (IPAP). The positive pressure in expiration (EPAP) set aims to help splint the upper airway open through the expiratory part of the cycle, recruit alveoli, and thus increase functional residual capacity, thereby reducing work of breathing. The tidal volume delivered will therefore depend on the pressure support (IPAP-EPAP) delivered, the patient's respiratory effort and inspiratory time, and the mechanical properties of their lungs and chest wall. This contrasts with volume targeted ventilation which delivers a preset tidal volume, but the airway pressure generated by this volume is not predictable and leaks are not as well compensated for. The common modes of BiPPV include timed (T) mode, spontaneous (S) mode, and spontaneous/timed (ST) mode.

The main indication for long-term BiPPV is the treatment of chronic respiratory failure. In health, the central drive appropriately recruits the respiratory muscles to support the respiratory load. This equilibrium is disrupted if any of these three components are affected. BiPPV seeks to redress this equilibrium and is used in the following conditions: central alveolar hypoventilation conditions such as congenital central hypoventilation syndrome, rapid-onset obesity with hypothalamic

dysfunction, hypoventilation and autonomic dysregulation (ROHHAD), apnea of prematurity, neurometabolic syndromes, Arnold-Chiari malformation; conditions where there is a functional decrease in respiratory muscle capacity, e.g., neuromuscular disease, scoliosis, and chest wall deformity; and conditions resulting in an increase in respiratory load, e.g., interstitial lung disease, bronchiolitis obliterans, chronic lung disease of prematurity, and cystic fibrosis (CF). We will discuss an example from each of these three categories.

Central Alveolar Hypoventilation: Congenital Central Hypoventilation Syndrome

Congenital central hypoventilation syndrome (CCHS) is characterized by alveolar hypoventilation due to ventilatory insensitivity to hypercapnia and hypoxemia particularly during sleep and autonomic dysregulation [1]. Most patients therefore require ventilation just when they are asleep, although some of the more severe phenotypes may require it for periods when they are awake as well. Children with CCHS are typically ventilated via tracheostomy in the first few years of life to ensure optimal oxygenation and ventilation and thus neurocognitive outcome. When older, those who only require ventilation when asleep may then be changed over to noninvasive BiPPV. A few centers have opted to avoid tracheostomy and start noninvasive ventilation right from time of diagnosis and good outcomes have been reported [2]. The American Thoracic Society CCHS clinical policy statement recommends aiming for an $SpO_2 \geq 95\%$ and end-tidal carbon dioxide tension between 30 mmHg and 50 mmHg (ideally between 35 and 40 mmHg) [1]. Home oxygen saturation monitoring is necessary, and some centers also provide a home carbon dioxide monitor. It is important to remember that these children do not display the normal physiological responses to hypoxia and hypercapnia. Should they become unwell, objective measurements of SpO2 and CO2 are needed as they can have low oxygen saturations with minimal or no signs of respiratory distress and may need additional time on their ventilator.

Functional Decrease in Respiratory Muscle Capacity: Neuromuscular Diseases

Neuromuscular diseases are one of the most common medical conditions in which BiPPV is used. While previously it was started in patients when they developed daytime hypercapnia, there is now a more proactive interventional approach. Most clinicians start BiPPV once there is evidence of nocturnal hypoventilation. It is important to screen for nocturnal hypoventilation in high-risk patients, such as those who are non-ambulant and those with a vital capacity of <60% [3], because symptoms are often subtle and develop so gradually that patients do not realize, or attribute their increased tiredness to their neuromuscular condition. In addition to symptomatic improvement following treatment of nocturnal hypoventilation,

BiPPV can also help reduce respiratory exacerbations and improve survival [4]. Prior to elective surgery such as scoliosis surgery, it is often useful to familiarize patients to BiPPV so that it can be used in the perioperative period [5]. Recent guidelines on the respiratory care of SMA patients even recommend that in infants and non-sitters, BiPPV should be started in all patients with symptoms such as tachypnea and increased work of breathing, even before documented respiratory failure, to palliate dyspnea and prevent chest wall deformity [6].

Increased Respiratory Load: Cystic Fibrosis

The physiological rationale for the use of NIV in patients with severe CF lung disease is that it helps unload the respiratory muscles, reduce work of breathing, increase minute ventilation, and improve gas exchange [7]. It has been shown to stabilize patients who are in hypercapnic respiratory failure [8], and a recent trial of 29 adult CF patients randomized to either nocturnal NIV, plus oxygen if required, or just oxygen showed that nocturnal NIV increased event-free survival (defined as failure of therapy with $PaCO_2 > 60$ mmHg, or increase in $PaCO_2 > 10$ mmHg from baseline, lung transplantation or death) over a 12-month period [9]. Data from the UK CF registry suggests that NIV improves lung function (FEV_1), but this does not translate into improved survival, and research into explanations for this disconnect is needed [10]. Its use as a bridge to lung transplantation is widely accepted, but its current use has expanded beyond this scope, though validated criteria for starting chronic NIV are still lacking.

Monitoring

After initiation on BiPPV, and indeed CPAP, regular long-term monitoring and follow-up are crucial. Pressure requirements change with the growth and development of the child and also with changes in his/her clinical condition. The interface will need to be upsized. It is important to monitor for side effects such as skin erythema or breakdown leading to pressure sores over the nasal bridge and flattening of the midface. Adherence is the other crucial element to monitor and it is important to obtain objective adherence data from ventilatory downloads. This will be discussed in greater detail in the following section on CPAP.

7.3 Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) involves the delivery of a constant airway pressure throughout the respiratory cycle. Similar to the principle for EPAP, this maintains airway patency, improves functional residual capacity, and thus decreases work of breathing. The most common indication for home CPAP in children is obstructive sleep apnea, while some require it to treat airway malacia [11,

12]. For OSA, the American Academy of Pediatrics recommends CPAP if either adenotonsillectomy is not performed or if there is residual OSA postoperatively [13]. This is in line with ERS guidelines which also recommend CPAP as part of the stepwise approach to the treatment of OSA [14, 15]. Patients requiring CPAP therefore tend to be children who are at higher risk of having residual OSA post-adenotonsillectomy, for example, those who are obese or have other medical comorbidities with resultant structural obstruction or increase in upper airway collapsibility such as Down syndrome or craniofacial syndromes.

The AASM PAP Titration Task Force recommends that when initiating CPAP, all patients should receive adequate education, hands-on demonstration, careful mask fitting, and acclimatization. A titration PSG then needs to be performed to determine the peak end-expiratory pressure (PEEP) required. The study should start with a minimum PEEP of 4 cmH_2O and be increased until obstructive respiratory events (apneas, hypopneas, respiratory effort-related arousals, and snoring) are eliminated or the maximum recommended PEEP is reached [16]. This maximum PEEP is 15 cmH_2O in patients younger than 12 years old and 20 cmH_2O in patients older than 12 years old. If the patient does not tolerate the PEEP or if the maximum PEEP has been reached and obstructive events are still seen, BiPPV can be trialed.

CPAP is very effective at treating OSA when used correctly; however, adherence can be challenging across all age groups [17]. In children, qualitative research has highlighted the importance of health education and family involvement in developing strategies that facilitate CPAP use specific to individual families [18]. Caregiver-reported self-efficacy—the belief that they have the ability to successfully administer CPAP—has also been identified as an important predictor of short-term CPAP adherence [19]. This highlights the importance of patient and family education. Most units invest a lot of intensive resources when initiating CPAP, with a multidisciplinary team of experienced staff, often in an inpatient setting on a sleep and ventilation unit, with frequent initial follow-up after discharge home to troubleshoot and identify any problems at an early stage. The inpatient model is mainly in countries with strong national health services and has demonstrated good results in children [20] and adults with intellectual disability [21]. US medical insurance companies are unlikely to pay for such inpatient stays, but good adherence when CPAP is initiated in an ambulatory setting is definitely possible [22]. When a tertiary hospital in the USA restructured their CPAP program, hiring a dedicated behavioral psychologist/program director and respiratory therapist to provide more intensive input and comprehensive care, follow-up and attendance for CPAP titration rates significantly improved [23].

Attempts have also been made to improve comfort and therefore patient tolerability. Devices now have options such as ramp, where pressures start low when the CPAP is initially started at the beginning of the night and gradually increase to the target PEEP over a pre-set period of time, and expiratory relief, where the device lowers the pressure delivered slightly when the patient exhales so it is easier to breathe out. Humidification can be added to the circuit to reduce the drying effects on the nose and mouth. There are now also a range of different interfaces available commercially, from nasal masks, full face masks, total face masks, nasal pillows,

and hybrid versions, so finding one that fits the patient well and which they find comfortable is much easier compared to in the past.

Auto CPAP is a mode of CPAP where the device auto-adjusts the PEEP between the minimum and maximum set by the prescriber according to the analysis of the flow curve and airway resistance by the device software. It is designed to be more comfortable for the patient, because the PEEP delivered is adjusted to what the patient requires instead of being fixed the whole night. A meta-analysis showed that in adults, auto CPAP improved compliance by 11 min per night and reduced sleepiness as measured by the Epworth Sleepiness Scale by 0.5 points compared with standard fixed CPAP [24]. Whether this translates into clinical significance is uncertain. In children, it was previously not clear whether the device algorithms were sensitive enough to accurately detect obstructive events. Khaytin et al. performed a retrospective study of 44 children with OSA initiated on auto CPAP comparing auto CPAP pressures with that from their titration PSG [25]. While titration PSG pressure was 8[7–11] cmH_2O median [IQR], the mean auto CPAP-derived pressure was 6.2[5.6–7.6] cmH_2O, peak mean pressure 9.4[7.7–11.1] cmH_2O, and average device pressure ≤90% of the time 8.1[7.2–9.7] cmH_2O. Auto CPAP-derived pressures correlated with the titration PSG-derived pressures, leading the authors to conclude that auto CPAP determines pressures that are close to the titration pressures and thus can be used in the pediatric population. It must be noted however that these were older children with a median [IQR] age of 13.01[9.98–16.72] years and the manufacturers have a minimum weight recommendation of 30 kg for this mode, so results cannot be extrapolated to younger children.

Recent big data analysis of an adult CPAP telemonitoring database has also shown that patients who are nonadherent may benefit from switching over to BiPPV [26]. Device use increased by 0.9 h/day; residual AHI and unintentional mask leak also improved. After the switch, 56.8% of the 1496 patients achieved the US medicare definition of adherence, namely, use of CPAP for ≥4 h per night on at least 70% of nights during a consecutive 30-day period during the first 90 days of initial usage, compared with none prior to the switch.

Obesity Hypoventilation Syndrome

The number of children with obesity hypoventilation is still relatively small, though increasing with the current obesity epidemic we are seeing. ATS guidelines for adults with the condition were recently published in which three randomized controlled trials and an observational study comparing CPAP with BiPPV were identified [27–30]. No differences in mortality, cardiovascular events, and healthcare resource use between the two groups were identified. Both modalities were similarly effective in improving daytime sleepiness, sleep quality, quality of life, dyspnea, sleep-disordered breathing, gas exchange, and the need for supplemental oxygen [31]. There was also no significant difference in adherence. Considering CPAP is less complex and less expensive, the recommendation was therefore that CPAP rather than BiPPV be the initial treatment for stable patients with concurrent

severe OSA, which is the majority of OHS patients [32]. In patients who do not have concomitant severe OSA, BiPP may be of greater benefit, but more research is needed.

7.4 New Modes of Ventilation

Hybrid Modes

Volume assured pressure support (VAPS) modes use intelligent algorithms to adjust the pressure support delivered to ensure a stable respiratory target, thus combining the advantages of pressure targeted and volume targeted modes of ventilation. The two main versions available commercially for home NIV are average volume-assured pressure support (AVAPS) and intelligent volume assured pressure support (iVAPS). AVAPS adjusts the pressure support delivered by varying inspiratory positive airway pressure (IPAP) between the IPAP min and IPAP max to guarantee the tidal volume set by the prescriber. iVAPS similarly adjust pressure support delivered within the predetermined limits but target alveolar ventilation instead of tidal volume. In pediatrics, these hybrid modes have mainly been used in patients with neuromuscular disease and CCHS.

VAPS in Neuromuscular Disease

Neuromuscular disease is the most common condition in which VAPS is used in pediatrics. Its proponents highlight the increased safety of a guaranteed tidal volume. Furthermore, assuming the algorithms work as designed, as the patient's ventilatory requirements change with disease progression, the pressure support delivered should change accordingly. The literature supporting its use in children is still emerging and mainly extrapolated from adult studies. In pediatrics, a case report described the use of AVAPS in a 3-year-old girl with multiminicore myopathy [33]. She had significantly different ventilatory requirements during her different sleep stages. When ventilated on ST mode, despite high pressures of 20/6 cmH_2O with good synchronization, there were still significant desaturations and elevated CO_2 to a maximum of 92 mmHg. Changing to AVAPS allowed her to be on lower pressure settings for periods of the night, with higher pressures only when required, and resulted in improved oxygen saturation and CO_2 profiles.

In adults, Kelly et al. performed a randomized cross-over trial of iVAPS versus standard pressure support (PS) ventilation. Patients recruited were newly diagnosed with nocturnal hypoventilation and naïve to NIV. Seven neuromuscular disease, 8 obesity hypoventilation, 1 scoliosis and 2 COPD patients completed the protocol, giving a total of 18 patients. While there was no difference in the ventilatory outcome and sleep quality, iVAPS delivered a lower median pressure support compared with standard PS. Encouragingly, the mean nighttime use for iVAPS mode was also greater than for standard PS by over an hour. These findings suggest that using VAPS modes of ventilation may help reduce any deleterious effects of high pressure such as barotrauma, increased leak, and gastric distension. Furthermore, if VAPS

device algorithms can ventilate as effectively as the standard PS ventilation initiated by a skilled healthcare professional, home NIV could become more easily available as the clinical experience required for initiating home NIV could potentially be reduced.

VAPS in Congenital Central Hypoventilation Syndrome

In CCHS, alveolar hypoventilation is typically worse during NREM sleep compared with REM sleep; thus, the VAPS mode of ventilation where the pressures delivered vary over the night according to patient need may be advantageous. A retrospective chart review of eight CCHS pediatric patients who underwent two PSGs, one on standard ST mode and one on iVAPS mode, showed that iVAPS was associated with a reduction in the maximum $TcCO_2$ during NREM sleep (43.0 (40.0–46.0) mmHg vs. 46.5 (45.0–48.0) mmHg for ST mode, ($p < 0.05$)) [34]. A trend toward improvement of sleep efficiency in iVAPS mode was also reported. A case report describes a 10-month-old infant with CCHS who was changed from ST mode to VAPS mode which enabled better control of ventilation, with a more stable carbon dioxide profile [35]. We have similarly had experience of a few school-aged patients with CCHS who displayed less variability in their overnight CO2 and fewer arousals/awakenings when changed from ST mode to VAPS mode.

Adaptive Servo-Ventilation

Adaptive servo-ventilation (ASV) was designed for patients with central sleep apnea (CSA), complex sleep apnea, and periodic breathing. The ventilator constantly monitors the patient's breathing pattern and minute ventilation, adjusting the pressure support it delivers to break the cycle of hyperventilation and central apneas that occur. There was some initial interest in this novel mode of ventilation in pediatrics. However, very few pediatric patients have Cheyne-Stokes respiration, and the majority who need treatment are managed successfully on standard BiPPV or oxygen. Similarly, those with periodic breathing respond well to oxygen which appears to stabilize their breathing pattern. Furthermore, the minimum weight recommended by most manufacturers is 30 kg. Most pediatricians were therefore awaiting results from adult studies before considering incorporating ASV into clinical practice.

One such study which emerged was the SERVE-HF trial which investigated the effects of adding ASV to standard medical management on survival and cardiovascular outcomes in patients with heart failure with reduced ejection fraction and predominant CSA [36]. There was no difference between the ASV and control group in the primary endpoint—a composite of time to first event of death from any cause, life-saving cardiovascular intervention, or unplanned hospitalization for worsening heart failure—but an increased risk of all-cause and cardiovascular mortality in the ASV group emerged. It was unlikely that adverse remodeling or worsening of the heart failure was the reason for this increased mortality as there was no significant effect on cardiac structure and function, cardiac biomarkers, renal function, or

systemic inflammation [37]. ASV is therefore now contraindicated in patients with left ventricular ejection fraction of ≤45%.

To date, it is a mode of ventilation mainly reserved for adults. In a recent case report, it was used in an 11-year-old boy who had a diencephalon anaplastic ganglioglioma with right frontal metastasis, who had received treatment with neurosurgery, chemotherapy, and radiotherapy [38]. Posttreatment, the child was in remission but had developed epilepsy and hypopituitarism. He was referred because of snoring, apneas, excessive daytime sleepiness, and deterioration in school performance. Magnetic resonance imaging of his brain showed herniation of the cerebellar tonsils into the foramen magnum. He had severe mixed sleep apnea syndrome with both central and obstructive events (CAI 17/h, OAHI 92/h). Transcutaneous CO_2 monitoring revealed alveolar hypoventilation with a mean $PtcCO_2$ of 48 mmHg, a maximal $PtcCO_2$ of 53 mmHg with 21% of the recording time with a $PtcCO_2$ above 50 mmHg. He was started on BiPPV in ST mode but did not tolerate it. He had posterior fossa decompression, but unfortunately the repeat sleep study showed no improvement. A trial of ASV was successful and he has been stable on it for the past 4 years.

7.5 Telemonitoring

One of the most promising technological advances is that of telemonitoring. It is the digital/broadband/satellite/wireless or Bluetooth transmission of physiological and other noninvasive data. Telemonitoring could in theory play a useful role in the initiation, titration, and follow-up of NIV. Certainly, most modern ventilators are now enabled with built-in Wi-Fi connectivity and not only have the capability to transmit a plethora of ventilator data to the clinical team, but clinicians can also remotely adjust ventilatory settings. Adherence can be monitored, and instead of waiting until the next clinic visit for the ventilatory download data, any problems could be identified more quickly (Fig. 7.1). It potentially would reduce the burden of patients traveling to hospital for appointments, enable the delivery of more personalized medicine, and may be more cost-effective. However, there are significant issues that still need to be resolved, such as responsibilities and potential obligations of healthcare professionals, including during out-of-hours monitoring. If data showing a problem is transmitted over a weekend when it is not being monitored, whose responsibility is it should the patient come to harm? Data security and confidentiality also raise complex issues.

Telemonitoring can come in various forms and the following are two examples. Trucco et al. performed a 2-year multicenter telemonitoring trial of children and young people with NMD on NIV [39]. Weekly home overnight monitoring of oximetry and heart rate was transmitted in conjunction with weekly scheduled phone calls to the patients, who were asked set questions enquiring about symptoms such as cough, dyspnea, and temperature. The information was scored and a deviation of >3 from baseline was considered an exacerbation in which case the clinician would be alerted and the appropriate medical advice given. The telemonitored patients had

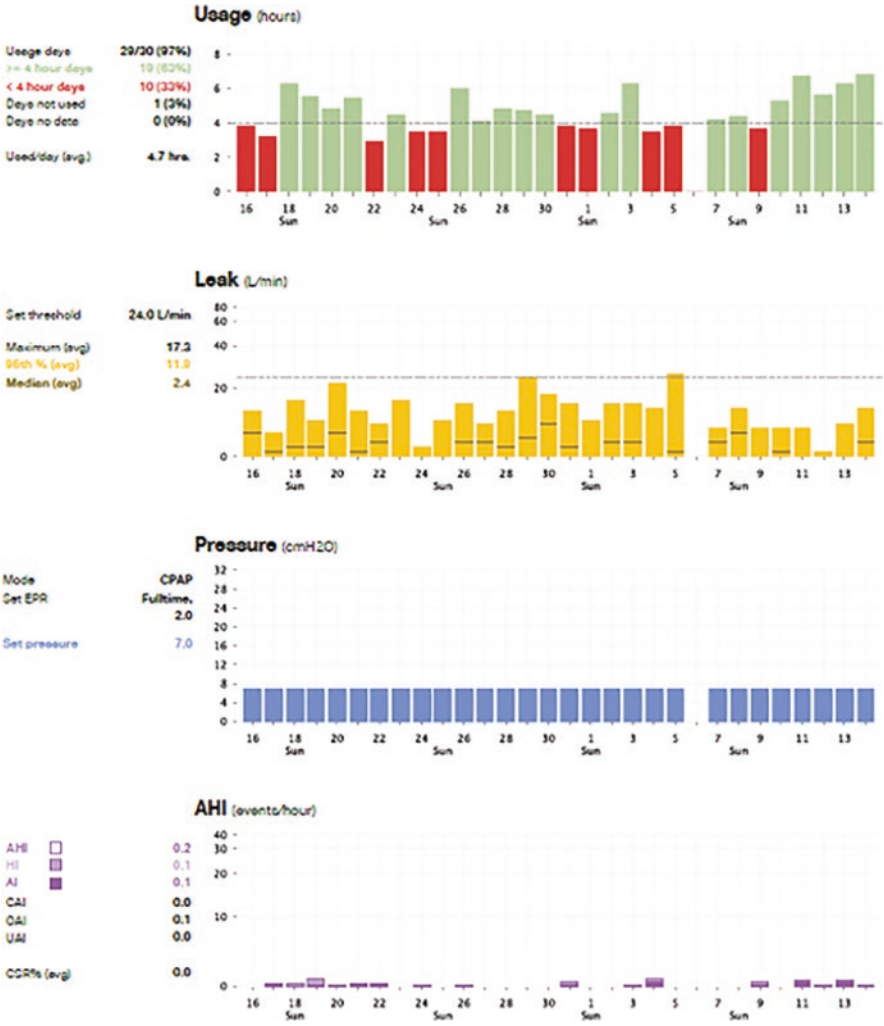

Fig. 7.1 Example of data that can be obtained remotely from CPAP device via telemonitoring: usage, leak, pressure delivered, and AHI. This was from a patient who was on CPAP 7 cm

fewer hospitalizations, and when they were admitted, their median length of hospitalization was also significantly shorter than control patients. Caregivers also reported they were very satisfied with the remote monitoring.

The Tele-OSA trial randomized adult patients into four arms: usual care alone, usual care plus telemedicine web-based education on OSA, usual care plus CPAP telemonitoring, or usual care plus both telemedicine-based education and telemonitoring [40]. Telemonitoring involved automatic processing and analysis of the device data by the cloud-based application which then provided automated feedback messaging to the patient, i.e., it did not require additional provider intervention. CPAP

telemonitoring, both alone and with telemedicine-based education, improved 90-day adherence, whereas just telemedicine-based education did not.

The European Respiratory Society published a statement on telemonitoring of ventilator-dependent patients in 2016 [41]. It highlights how telemonitoring is both a challenge and an opportunity and urges governments to develop guidelines and ethical, legal, regulatory, technical, and administrative standards. The economic advantages are yet to be proven, especially as it needs to be compared with standard home care, which in itself is very variable, not only among different countries but even within the same country. The taskforce concludes that "much more research is needed before considering tele-monitoring a real improvement in the management of these patients."

7.6 Active Patient Monitoring

Applications have also been developed to enable patients to monitor their own sleep, track progress, and stay motivated on CPAP. Malhotra et al. assessed the impact of a real-time feedback patient engagement tool on CPAP adherence compared with usual medical care [42]. Patients received a score each night calculated from four parameters: hours of CPAP use, mask seal (leak), obstructive events per hour, and mask on/off events. Educational messages with advice on how to make therapy more comfortable and to build confidence, congratulatory messages to reinforce positive behavior, and encouragement messages to help motivate patients were also sent via email or text message. A total of 42,679 patients in the active patient engagement (APE) group were 1:2 matched on propensity scores to 85,358 control patients. More patients in the APE group achieved the US Medicare definition of adherence (87.3% vs. 70.4%). Mean hours of CPAP use were also higher in the APE group than the control group (5.9 h vs. 4.9 h, $p < 0.0001$). This was not a randomized trial, and participants in the APE group had to actively choose to join the program or were encouraged to do so by their healthcare provider and so may have higher health-related motivation. Nevertheless, it shows that modern technology can be a useful adjunct to the usual clinical care.

7.7 Transition of Patients on Noninvasive Ventilatory Support

A significant number of these patients are now transitioning to adult services. In a retrospective cohort study of children on long-term NIV for chronic respiratory conditions, over an 18-year period, at a tertiary hospital in the UK, 40% of patients ($n = 181$) transitioned, 24% died, and 9% were able to discontinue ventilatory support [43]. These trends are worldwide, not just in developed countries. For example, Leske et al. recently reported their experience in Argentina – since commencement of their pediatric home ventilation program in 2007, 16.4% of patients have transitioned to adult services [44].

As has been discussed, the range of patients on noninvasive ventilatory support is extremely broad, which adds complexity to the planning of transition services. On one end of the spectrum, there are patients who have obstructive sleep apnea on nocturnal CPAP but are otherwise healthy. On the other end, there are patients with complex needs such as severe cerebral palsy, gross motor function classification system level 5, needing BiPPV for nocturnal hypoventilation, with severe neurocognitive impairment, seizures, kyphoscoliosis, are gastrostomy fed, and completely reliant on their parents for all cares. There are also patients with NMD whose disease progression is resulting in loss of independence, increasing reliance on NIV, and in whom new health problems may be emerging, making a smooth transition even more crucial for both their physical and psychological health.

A 2015 survey of pediatric pulmonary program directors in the USA regarding the transition process of their respiratory technology-dependent patients to adult pulmonary care highlighted a lack of standardized transition programs for these patients [45]. 78.1% did not use a standard protocol for transition, 41.4% had no process in place, and often, the pediatric providers were not satisfied with their current practices or the involvement of the adult team. Thus, what are some of the barriers and potential facilitators to transition, of these patients?

Barriers and Facilitators to Transition of Patients on Noninvasive Ventilatory Support

In some countries, one of the most significant barriers is the lack of adult services to which these patients can be transitioned to [46]. Sometimes, the adult equivalent of a pediatric physician with the skills to manage a particular patient group may simply not exist where the patient lives. Similar to how in the historical past cystic fibrosis was a disease managed mainly by pediatricians, as patients did not survive into adulthood, pediatricians sometimes continue to look after these patients well into adulthood because there is no one they can transition them to. An example in the UK is it can be very difficult in certain areas to find an adult physician who is happy to be the main physician looking after patients with severe cerebral palsy on NIV, who have multiple morbidities in other systems in addition to their respiratory ones.

There may also be loss of insurance coverage and cost of care barriers [47]. In the USA, for example, pediatric and their partnering adult hospitals sometimes do not participate in the same medical insurance plans. To receive care at the partnering adult hospital, patients would need to change insurance providers which then impacts on durable medical equipment, nursing, and pharmacy services which the patient has been reliant on over the years. The alternative would be to stay with the same insurance company but transition to another adult hospital participating in the same insurance plan, but which might not have the optimal pulmonary expertise.

Dale et al. recently reported the results of their qualitative research exploring the transition of patients who had gone through the home mechanical ventilation (HMV) transition program of a tertiary children's hospital with their partnering adult hospital [48]. Facilitators of transition which they identified included early

transition discussion, joint pediatric-adult HMV transition clinic visits, written information about adult services, and communication training for the adolescents to strengthen their ability to communicate their medical history and needs with the clinical team. Transition barriers identified included lack of referral to other medical specialists, developmental delay or disability of the patient, and limited information on adult community funding structures.

Examples of Good Practice

An audit conducted by a tertiary pediatric hospital in Canada found that only 38% of youth on CPAP for OSA attended their first adult sleep clinic at the partnering adult hospital [49]. Those who did attend still demonstrated clear gaps in knowledge, such as the reason for attending clinic, their OSA diagnosis, the importance of continuing CPAP use, and the need for follow-up. They therefore developed the Sleep Disorders Pediatric Transition program. At 10 years of age (or time of diagnosis for older patients), parents are given the "Ready, Set…Good 2 Go Timeline" and resource information booklet. At 10–13 years old, age-appropriate discussions on tests and treatment for OSA occur, strategies are employed to teach young adolescents how to assist with CPAP under parental supervision, and reviewing adolescents alone in clinic is discussed with parents. At 14–16 years old, independence strategies for medical therapies; tracking appointments and everyday life are discussed; education on health, development, and future independent living is provided; and a readiness checklist is completed by the adolescent. Six to nine months prior to the formal handover of care, referral is made to the adult sleep physician, and the patient is evaluated by the adolescent medicine team who will address any psychosocial concerns. Three months prior, standardized education on OSA and CPAP is provided, knowledge is assessed, and the patient's health passport and medical summary are completed. During the first adult sleep clinic which is also attended by the pediatric team, the clinical history and examination are documented and CPAP adherence is assessed. Several other transition programs we know of for patients on noninvasive ventilatory support are based around a similar theme.

When handing over to the adult team, it is obviously important to provide medical details such as ventilator settings, sleep study results, etc., but patients often appreciate it when the adult team are interested in getting to know them as a person as well. A page in our institution's transition paperwork "All about me" where the young person writes down the things which they feel are important the adult team should know about them has proved to be very helpful. One youth was an avid local football team supporter and it turned out that the adult physician was similarly so. A significant part of the first clinic appointment was spent discussing football, which helped break the ice and established a good rapport.

Where appropriate, there needs to be a clear plan for escalation of therapy should the patient become acutely unwell. Handover should also include any previous discussions around the patient's ceiling of care including the patients' wishes on whether they would consider tracheostomy ventilation in the future.

7.8 Conclusion

This chapter has discussed some of the technological advances that have accompanied and facilitated the increasing use of long-term noninvasive ventilatory support in chronic respiratory conditions. Newer modes of ventilation aim to make ventilation more responsive, improving the delivery of ventilatory support and patient comfort. While research is still needed to determine whether this translates into improved long-term clinical outcomes such as quality of life and morbidity, it highlights the progress being made in the strive for personalized medicine. Should it be confirmed that VAPS algorithms are as effective at achieving good ventilation as standard ventilation initiated by experienced healthcare professionals in controlling nocturnal hypoventilation, NIV could become more accessible as it may potentially reduce the clinical skill required for initiating chronic NIV. Telemonitoring and modern apps have the potential to encourage and empower patients and improve clinical care by enabling problems to be identified at an early stage, though there are still legal and regulatory issues to be resolved. However, with improving outcomes, new challenges arise to occupy clinicians. Thus, with the corresponding increase of NIV patients transitioning to adult care, it is important to remember that transition is a process, not a single event of transferring care. For it to be successful, common themes include information, communication, planning, and coordination. These are often patients with complex needs and they require more individualized planning and collaborative care partnerships between pediatric and adult clinicians.

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8 Chronic Noninvasive Ventilatory Support in Various Chronic Respiratory Conditions Including Protocols

Amee Revana, Shahram Moghtader, and Ritwick Agrawal

8.1 Introduction

Noninvasive ventilatory support is the primary modality for treating various chronic respiratory conditions associated with sleep disorders. The primary mechanism of noninvasive ventilation is by delivering ambient air at a higher pressure than the surrounding environmental pressure. Depending on the primary chronic respiratory condition, the elevated pressure helps in various aspects such as reducing the upper airway resistance by splinting open the collapsed airway, delivering adequate minute ventilation by assisting with additional breaths, and augmenting the tidal volume, which may be suboptimal for adequate ventilation. Since their first usage in the 1980s, the technology of delivering noninvasive positive pressure ventilation for sleep disorders has improved significantly. These span from a more compact design, newer modalities of delivering positive pressure breathing, and advancements in the collection of usage information from the device and remotely over a cloud server. This chapter will discuss various chronic noninvasive ventilatory modalities available across the life span from pediatric to adult populations with sleep disorders. We will also discuss the unique challenges patients and healthcare practitioners face when transitioning a pediatric patient on noninvasive ventilation to an adult provider.

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8.2 Noninvasive Ventilation Modes and Settings

Positive airway pressure ventilation can be further classified based on its impact on the various phases of the respiratory cycle. For example, in the case of obstructive sleep apnea, the primary goal is to improve upper airway resistance, while for chronic hypoventilation disorders, the common goal is to have adequate ventilation [1].

There are different modes of delivery of positive airway pressure therapy. Standard conventional modes of therapy are continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP). CPAP delivers a continuous amount of pressure during inspiration and expiration. With BPAP, there is a higher inspiratory positive airway pressure (IPAP) and lower expiratory positive airway pressure (EPAP). The difference between the IPAP and EPAP is referred to as the pressure differential [2].

There are several advanced modalities which utilize proprietary algorithms. These devices optimize minute ventilation with respiratory targets including expiratory tidal volume (Respironics, AVAPS [average VAPS]) or alveolar ventilation (ResMed, iVAPS [intelligent VAPS]) [3, 4]. Frequently, positive airway pressure may not be enough and may require supplemental oxygen in combination.

A detailed review of the various modes of ventilation is beyond the scope of this chapter. However, in general, one of the primary determinants of choosing the appropriate mode of ventilation is to determine if the minute ventilation is adequate in a spontaneously breathing patient (authors' proposed algorithm; Fig. 8.1). Most patients with sleep-related breathing disorder breathe spontaneously and can exhibit adequate alveolar ventilation. There is a small subset of patients who demonstrate inadequate ventilation, ultimately leading to hypercapnia. A typical example of spontaneously breathing patients is those who have obstructive sleep apnea. In this group of patients, the goal of noninvasive ventilation is to reduce upper airway resistance.

In most cases, the addition of positive airway pressure to a spontaneously breathing patient is adequate enough to alleviate upper airway collapse while sleeping. It is delivered by CPAP and its variations, such as automatic positive airway pressure therapy (APAP) and BPAP. The second subset of patients with sleep-disordered breathing are those who have reduced minute ventilation leading to chronic alveolar hypoventilation. These are related to etiologies such as obesity hypoventilation syndrome and other sleep-related hypoventilation syndromes, central sleep apnea, spinal cord injury, prior cerebrovascular accidents, encephalitis, and medications. In these cases, various advanced therapies are utilized in order to improve the minute ventilation [5].

The minute ventilation is a product of respiratory rate per minute and the tidal volume. In the case of reduced respiratory rate per minute, the ventilator delivers backup breaths, in addition to the spontaneous rate. This mode is often referred to as S-T mode. In this mode, the ventilator senses the patient-triggered breaths, and if there is a delay in triggering, it delivers a backup breath. Furthermore, in cases

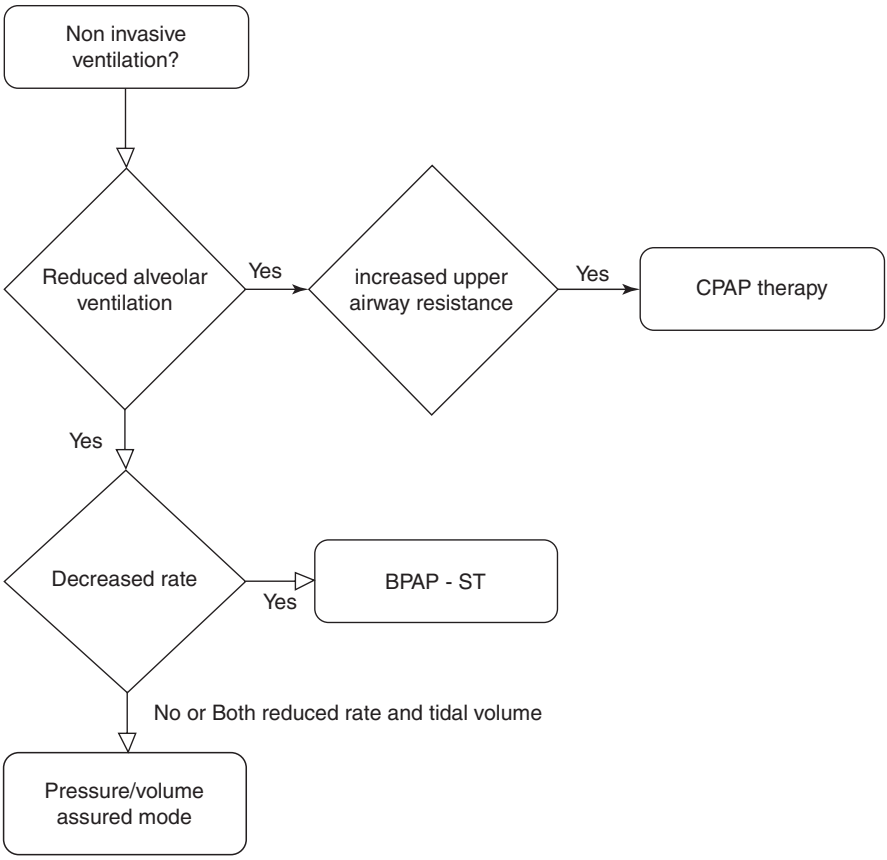

Fig. 8.1 Authors' suggested decision support algorithm for selection of noninvasive ventilation modality

where the tidal volume is not adequate, the ventilator assists in delivering optimal tidal volume based on the patient's requirement and ideal body weight.

There are two ways by which optimal tidal volume is delivered. The first mode is pressure-targeted ventilation. In this mode, constant analysis of flow rate and airway pressure is performed to ensure that the targeted pressure is achieved. In pressure-targeted ventilation, the volume delivered is not fixed and varies from breath to breath. The second mode of delivery is the volume-targeted ventilation that ensures there is a similar volume from breath to breath. In several cases, the advanced ventilators have algorithms that utilize a combination of pressure and volume-targeted modes to achieve an optimal tidal volume. Patients who have coexisting conditions may benefit from different targets of ventilator management. For example, in a patient with coexisting obstructive sleep apnea (OSA) and central sleep apnea (CSA), the goal of ventilator therapy is to reduce upper airway resistance and ensure that the minute ventilation is optimal [6].

8.3 Sleep-Related Hypoventilation and Central Sleep Apnea

Chronic ventilatory insufficiency or hypoventilation can lead to critical hypoxemia and bradycardia due to hypoventilation, which can result in acute, subacute, and chronic complications. Although in children, the most common cause of sleep-related hypoventilation is OSA, non-obstructive sleep-related hypoventilation should also be recognized and addressed. These conditions are generally genetic or neurologic and include congenital central hypoventilation syndrome (CCHS) and late-onset central hypoventilation syndrome (LO-CHS) or the newer recognized condition of rapid-onset obesity with hypothalamic dysfunction with hypoventilation and autonomic dysregulation (ROHHAD) syndrome.

Hypoventilation in adults conventionally is defined as an arterial blood gas PCO_2 as high as 50 mmHg and a serum bicarbonate level of more than 25 meq/L with or without associated hypoxemia. However, this is for patients during wakefulness. Per the American Academy of Sleep Medicine (AASM), sleep-related hypoventilation in children is defined as a $PaCO_2$, $PetCO_2$ (end-tidal), or $PtcCO_2$ (transcutaneous) of more than 50 mmHg for more than 25% of the total sleep time. The $PtcCO_2$ monitoring is the preferred monitoring method as it is noninvasive and more reliable than the $PetCO_2$. However, it is not always available. Central apneas are periods of lack of airflow in conjunction with no respiratory effort. In the pediatric population, central apneas are defined as lack of airflow with no respiratory effort for 20 s or two respiratory breaths in duration that are associated with an arousal or 3% oxygen desaturation. The central apneas can be as long as up to 20 s, which may not be abnormal, particularly in premature infants. In adults, central apneas are defined as lack of airflow with no respiratory effort for 10 s or more. The events may be associated with an arousal. CSA secondary to hypoventilation results from the lack of wakefulness stimulus to breathe in patients with poor neuromuscular ventilatory control.

Congenital central hypoventilation syndrome (CCHS) is a genetic disorder that was first described in newborn infants in 1970 due to a defect in the paired-like homeobox 2b (PHOX-2B) protein on chromosome 4p12 [7–9]. About 10% of the cases are severe enough to require mechanical ventilatory support during both wakefulness and sleep. This gene has an autosomal dominant pattern of inheritance in 92% of the cases.

The main feature of CCHS is abnormal ventilatory control associated with some abnormalities of the autonomic nervous system. Other clinical features of the children affected by CCHS are a variety of autonomic dysfunctions, ophthalmic abnormalities, cognitive dysfunction, neural crest-derived tumors, and Hirschsprung disease [9–13].

The typical presentation is a full-term infant with no apparent difficulties during labor and delivery; however, the infant becomes hypoxemic and hyperventilates during sleep with shallow breathing and a tidal volume at the level of dead space ventilation (~2 cc/kg of body weight). These infants are often diagnosed during the neonatal period, but some may be diagnosed later in life (see LO-CCH). Most neonates born with severe, classic CCHS require intubation and mechanical ventilatory support.

The diagnosis is made on clinical grounds of hypoventilation during mainly non-REM sleep associated with hypoxemia as well as an elevated PCO_2 to about 60 mmHg or more during sleep. The workup involves ruling out primary pulmonary and cardiac disorders, inborn errors of metabolism, and neuromuscular disorders using the appropriate evaluations, labs, and imaging studies. The polysomnogram typically shows an elevated $PtcCO_2$ or $PetCO_2$ of more than 50 mmHg for more than 25% of the total sleep time and hypoventilation with a tidal volume of no more than about 2 cc/kg. Additionally, the PHOX-2B mutation contains a sequence of 24 to 33 or more polyalanine repeats. The genotype relates to the need for continuous ventilatory dependence.

The management often requires intubation and mechanical ventilation in the early periods of the diagnosis. Often these babies would need a tracheostomy for a more secure mode of adequate ventilation primarily during sleep. In severe cases, some of these patients may require mechanical ventilation during sleep and diaphragmatic pacing during wakefulness to maintain adequate ventilation [14, 15]. In milder cases, after the initial passage of the infancy period, sedatives should be avoided, and general anesthesia should be administered with a great deal of caution with close monitoring during the recovery period.

The American Thoracic Society recommends the following surveillance measures for patients with CCHS: routine sleep studies; echocardiography; arterial, venous, or capillary blood gases; neuroimaging; Holter monitoring (looking for sinus pauses that may require a permanent pacemaker placement); and neurocognitive testing [13]. Most of these infants and children require lifelong medical and continuous nursing and home care support.

Late-onset central hypoventilation syndrome (LO-CHS) is also PHOX2B gene related, but the presentation starts later during childhood or early adulthood rather than in infancy [13, 16, 17]. These cases present with unexplained cor pulmonale, difficulty weaning off mechanical ventilation after anesthesia, the low normal cognitive status associated with hypoxia, apparent life-threatening events, and exposure to hypercarbia and hypoxia (such as underwater breath-holding) and unresolved central sleep apnea after treatment for OSA [18]. These patients should undergo pulmonary function testing and cardiac evaluation. The preferred mode of treatment is with noninvasive ventilation such as BPAP during sleep.

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysfunction (ROHHAD) syndrome is a diagnosis of exclusion (not related to the PHOX2B gene). The presentation is with rapid, severe weight gain during early childhood after a period of normalcy and not associated with an increase in height. These children also show signs of hypothalamic dysfunction with hyperphagia, various endocrinopathies, autonomic nervous dysfunction, and sleep-related hypoventilation. These patients are also at risk for neural crest tumors [19–23]. The diagnosis is made by ruling out other types of central hypoventilation syndromes; polysomnography; imaging of the brain, chest, and abdomen; and endocrinological evaluation. Like other forms of central hypoventilation syndromes, these children fail to respond to hypoxemia and hypercarbia during respiratory ailments and require regular follow-ups as the condition can be life-threatening. These patients may need noninvasive or sometimes invasive ventilatory support.

As mentioned previously, central sleep apnea is much less common than obstructive sleep apnea in children. In general, brief central apnea pauses shorter than 20 s that are not associated with arousals and desaturations are not considered clinically significant. In children, clinically significant central sleep apnea frequently occurs in premature babies or is associated with brainstem or central nervous system (CNS) disorders due to congenital, traumatic, genetic, or systemic issues as the control of the respiratory system is involved. Overall, apneas in premature infants can last up to the 44th week postmenstrual age. These babies are also at risk for apneas post-surgery under general anesthesia until the 60th week of postmenstrual age [24]. In young children, CSA is often due to neurologic disorders affecting the respiratory center, including brain tumors and brain lesions such as Chiari malformations, some craniosynostoses, and achondroplasia. Additionally, CNS-depressing medications, epilepsy, and infections should be on the differential for central apneas. Children with Prader-Willi syndrome and Down syndrome are also at risk for CSA [25–27].

In adults, the prevalence of CSA is greater in older individuals as compared to younger adults. Central sleep apnea can be primary (idiopathic) or secondary such as those seen in association with heart failure, stroke, a medication or substance, or high-altitude periodic breathing. In those with heart failure and stroke, Cheyne-Stokes breathing is often seen. Polysomnography reveals ≥5 central apneas and/or central hypopneas per hour of sleep, and the number of central apneas and/or central hypopneas is >50% of the total number of apneas and hypopnea [28]. The primary management of the CSA in adults is the treatment of the underlying condition such as CHF or removal of medications causing the CSA. Furthermore, advanced modalities of noninvasive ventilation such as BPAP, BPAP-ST, and others may be utilized to ensure adequate minute ventilation. As a word of caution, in patients with an ejection fraction ≤45% and who do not respond to CPAP, adaptive servo-ventilation is contraindicated due to worse outcomes [29].

Treatment of CSA in infants and children includes the reduction of sedative medications or surgical management of the nervous system lesions as deemed appropriate. In circumstances in which the etiology is unknown, noninvasive ventilation in the form of BPAP with a backup rate (ST mode) is recommended. Typically, the pressure differential during BPAP mode is 4 cm H_2O. There is limited data available in terms of identifying an adequate backup rate. Therefore, the PSG can best guide the optimal backup rate by resolution of central apneas or alveolar hypoventilation. In both children and adults, a backup rate set at 2 breaths below the patient's spontaneous rate during calm wakefulness breathing can be a starting point. Small increases of 2 breaths can be titrated upward [30].

The transition of children with central apnea into adulthood requires a concerted effort on the part of caregivers and the home care companies supplying these patients and their families with the needed equipment and supplies. Few studies have been performed that address some of the lifelong challenges that these patients and their caregivers endure [31–33]. Children are recommended to have serial polysomnograms in order to optimize pressure settings as they grow. Adults are recommended to have repeat polysomnograms as needed. In summary, these patients and their

caregivers have many ongoing medical and psychiatric complications as a direct result of their heavy reliance on technology to maintain their livelihood.

8.4 Noninvasive Ventilation in Conditions Involving Neuromuscular Weakness

Neuromuscular weakness secondary to various conditions such as congenital myopathies, Duchene muscular dystrophy, and amyotrophic lateral sclerosis (ALS) can lead to chronic respiratory failure. Respiratory compromise is the result of inspiratory and expiratory muscle weakness with relative sparing of the diaphragm. Patients with neuromuscular weakness often have impaired cough and inability to clear lower airway secretions and hypoventilation. Speech dysfunction, scoliosis, gastroesophageal reflux, and recurrent respiratory infections may further contribute to insufficient respiratory function. During sleep, respiratory insufficiency occurs secondary to decreased ventilatory drive and respiratory muscle inhibition.

Noninvasive ventilation in patients with neuromuscular weakness is indicated when spontaneous respiratory effort cannot achieve adequate alveolar ventilation. These include daytime hypercapnia, symptomatic nocturnal hypoventilation, asymptomatic nocturnal hypercapnia, and respiratory muscle weakness, as indicated on pulmonary function tests. Noninvasive ventilation is the standard practice for patients with respiratory insufficiency secondary to chronic neuromuscular weakness, in both children and adult patients. Supplemental oxygen without ventilator assistance may not provide sufficient support and may even blunt the respiratory drive [34]. There is variability in practice in terms of when to initiate noninvasive ventilation. However, consensus statements recommend the use of pulmonary function tests and polysomnogram to help standardize and highlight care for this patient population in both children and adults.

The use of noninvasive ventilation in patients with neuromuscular weakness has been shown to improve alveolar gas exchange, improve survival, reduce respiratory infections, and decrease hospitalizations as well as the length of hospitalization [35]. Typically, once evidence of nocturnal hypoventilation or daytime symptoms of respiratory insufficiency is identified, noninvasive ventilation is initiated via a nasal interface [36]. Patients with neuromuscular weakness may not demonstrate signs of respiratory insufficiencies, such as pulmonary retractions. Therefore, initiation of noninvasive ventilation in patients with neuromuscular weakness requires clinical monitoring via overnight polysomnography (PSG). Overnight PSG includes end-tidal CO_2 or transcutaneous CO_2 and overnight pulse oximetry, which indicates respiratory parameters.

Pulmonary function tests are often reviewed during each clinical visit. They serve as an objective value to indicate respiratory insufficiency, thus supporting the effort to initiate noninvasive ventilation. There is variable data in children that support the initiation of noninvasive ventilation when the vital capacity is 60% predicted [37–39]. They should be screened at every clinical visit and when they are able to perform the maneuver. Assessment for sleep-disordered breathing should be

performed when the vital capacity is less than 60% predicted or when the neuromuscular weakness has progressed to being confined in a wheelchair [37]. In adults, a vital capacity of less than 60% predicted is a good predictor of sleep-disordered breathing, whereas a vital capacity of less than 40% predicted is a good predictor of sleep-related hypoventilation [38, 40]. Therefore, consensus guidelines recommend initiating nocturnal noninvasive ventilation with a vital capacity of less than 60% predicted and/or at the onset of sleep-disordered breathing [37, 38].

In children, the first visit by a pulmonologist early in the course of the disease—no later than 4–6 years of age—is recommended (ATS consensus statement). Screening should at least be yearly, more frequent if the disease progression is uncertain or there is evidence of clinical deterioration [39].

In addition to history and clinical findings, yearly polysomnographic studies are recommended, as the patient or caregiver may not easily recognize symptoms of chronic respiratory failure. Children continue to grow, and thus their respiratory requirements change. Polysomnography is the gold standard in identifying sleep-disordered breathing and titrating noninvasive ventilation [41]. Screening for symptoms of chronic respiratory failure, including sleep-related hypoventilation and sleep-disordered breathing, is recommended every 6 months in adults, as the symptoms during sleep may be subtle. This includes screening for excessive daytime sleepiness, headaches, poor concentration, fragmented sleep, difficulty breathing, etc. [37, 38].

If access to polysomnography is limited or unavailable, then the use of nocturnal pulse oximetry may be helpful in both children and adults. However, if abnormal, they should undergo a more extensive diagnostic sleep assessment such as transcutaneous or end-tidal carbon dioxide monitoring. Transcutaneous carbon dioxide monitoring or end-tidal carbon dioxide monitoring can provide evidence of daytime and/or sleep-related hypoventilation. If this is not available, serum bicarbonate can help identify chronic respiratory dysfunction. In addition, trending the serum bicarbonate after initiating noninvasive ventilation can help identify optimal pressure settings and/or ventilatory support.

During the initiation of noninvasive ventilation, the pressure settings should start at lower settings and gradually increase to adequately treat the respiratory insufficiency. The AASM recommends a minimum IPAP-EPAP differential of 4 cmH_2O and the maximum differential of 10 cmH_2O [41]. For patients with neuromuscular weakness, a low EPAP (typically between 4 and 5 cmH_2O) is recommended, as this prevents rebreathing and is more tolerable [34, 39]. Higher EPAP values may be uncomfortable and more likely to contribute to poor adherence.

Due to the neuromuscular weakness, patients are at risk for aspiration of oral secretions during sleep. Therefore, a nasal interface is recommended upon the initiation of noninvasive ventilation. Few interfaces have been approved for children. However, many are used off-label. Full-face masks can be helpful in neuromuscular patients as they tend to have weakness of the masseter muscle and thus are prone to having air leak from the mouth [34]. Clinical correlation is strongly encouraged as the benefit of adequate adherence may outweigh the risks of using a full-face mask.

Success with noninvasive ventilation is multifactorial. This includes the identification of an optimal pressure setting and proper fitting interface. Mask fitting, as well as the need for a chin strap, can occur during the overnight PSG. In children, this should be reviewed at every clinic evaluation, as facial features tend to change as they transition into adulthood.

During the transition from pediatric care to adult care, repeat sleep studies to optimize pressure settings are recommended. However, there is limited data in regard to how often this should be done and at what age to continue as needed. Routine clinical follow-up helps with improving adherence as well as troubleshooting problems that may occur with the use of noninvasive ventilation. Skin breakdown can be recognized and sought by erythema at pressure points where the mask has direct contact to the skin. On rare occasions, the erythema can progress to forming blisters and eventually drainage. Skin breakdown can signal when a repeat mask fitting as facial structures can change from adolescence into adulthood. There is limited data that favor nasal interfaces over full-face interfaces. Nasal interfaces will reduce the risk of aspiration of oral secretions. However, air leak from the mouth can be problematic and contribute to fragmented sleep and insufficient support from the noninvasive ventilation. Full-face masks may be bulky in pediatric patients and typically conform to adult facial structures and thus contribute to air leak from multiple areas around the mask.

As a child continues to grow into adolescence and eventually into adulthood, open discussion across the multidisciplinary team regarding when to initiate noninvasive ventilation and promoting good adherence is strongly encouraged. This encourages transparency and shared decision-making through different milestones and allows the individual to develop their own decisions about their healthcare needs. Additionally, this helps individuals identify their needs to an adult provider as they transition from pediatric to adult care.

8.5 Noninvasive Ventilation and Transition of Care

Taking care of a child who requires noninvasive ventilation can be challenging for caregivers. It is even more of a challenge for an adolescent who is transitioning into an adult. Early on, caregivers are the leaders and decision-makers in their child's care. They ensure the responsibilities in the overall healthcare of the child. Over time, the physician and caregiver discuss long-term goals of the noninvasive ventilatory support and decide that it will be required long term as a part of the child's—soon to be young adult's—health plan.

As the child grows, the parent and healthcare provider need to shift the care responsibilities gradually to the child. Transferring the ownership of care should be structured and carefully managed to ensure that the transition period is easily adaptable and maintained as the child matures to become an independent young adult. The timeline is variable as it often depends on the developmental maturity and readiness of both the caregiver and the child.

Unfortunately, there are various barriers when transitioning pediatric sleep medicine patients to adult care. Children with complex medical histories are transitioned more due to advancements in medical technology. The use of noninvasive ventilation in acute and chronic conditions has improved prognoses, thus prompting more children to be transitioned into adult care [42].

There is no evidence-based literature to our knowledge that reviews barriers in transition in regard to patients with noninvasive ventilation. Therefore, the authors of this book chapter identified several barriers via an unofficial survey of pediatric and adult sleep providers. Some of the barriers that were identified include family resistance in leaving a pediatric provider, lack of coordinated care of noninvasive ventilation supplies, lack of adult interest and/or trained providers who are willing to take care of complex patients, access to care, insurance coverage issues, and having adequate records in regards to past test results. Out of these, lack of trained providers and willingness to take care of patients with complex medical histories was identified as the topmost reported barrier.

There are no evidence-based protocols that delineate how pediatric care of noninvasive ventilation should be managed during the state of transition. However, several readily available tools have been used by various subspecialties such as gastroenterology, rheumatology, and pulmonology. Some examples of resources include CF RISE (Cystic Fibrosis: Responsibility, Independence, Self-Care, and Education) and Gottransition.org. These available resources all have some commonality, and thus the authors of this chapter will outline these principles as the backbone to transitioning a patient from pediatric care to adult care in regard to the management of noninvasive ventilation.

Successful transfer of a young adult from pediatric care to adult care is multifactorial. It requires collaboration with the caregivers, healthcare providers, and supporting staff [43]. There are several tools available in aiding in the transition of care. The authors of this book chapter have summarized core elements from various sources to directly support providers who are transitioning patients who require chronic noninvasive ventilation. The transition involves the development of a transition policy, early referral, managing and educating the caregiver initially, and, then as the child grows older, assessing for readiness for both the caregiver and the child/young adult, bridging the care with an adult provider, handoff to adult care with the proper documentation and support, and acceptance of care from the caregiver, young adult, and adult provider (Fig. 8.2).

Fig. 8.2 Proposed transition of pediatric sleep care to adult sleep care involving patients requiring chronic noninvasive ventilation

Developing a transition policy is the initial step in the transition of care. This policy outlines the approach to transition, whom to transition, as well as when to transition. This step also involves the early stages of discussing the process of transition with families. Early referral is the next step in the transition. This process involves identifying an adult sleep medicine provider that is readily available in the location of the family. This includes identifying a practice that accepts the insurance carrier as well as identifying a durable medical supply company that is able to serve the patient at their home location. In addition, the provider will begin to put together documents that include the most recent history and physical; sleep study results; current settings as well as the type of device the patient is using, mask size, and type of mask the patient has used in the past as well as what the patient is using currently; adherence data and history of adherence; barriers to adherence; as well as the discussed plan as to when repeating a sleep study to reassess the severity of sleep-disordered breathing as well as re-titration study to optimize pressure settings.

At each follow-up clinic visit, the pediatric provider should assess the readiness for transition. This can initially start by asking the patient to summarize their overall status of care or ask why they require the noninvasive ventilation. The patient should be able to troubleshoot problems with their device as well as demonstrate proper mask placement. Assessments may take place during multiple visits and may vary based on the developmental maturity of the patient. This may also involve meeting the adult sleep provider with the pediatric sleep provider. This is also the time to encourage both the caregiver and patient to share fears and concerns about transitioning care. Once the caregiver and patient have accepted the decision to transition, the discussion should shift as to identifying a realistic timeline as to when the transition should occur. While this is being discussed, the pediatric provider should ensure that the family has enough supplies, such as an extra mask, filters, tubing, and contact numbers for the pediatric provider and the durable medical company if they run out of supplies.

After a timeline has been established, the next step of transition is the actual handoff from the pediatric provider to the adult sleep provider. Handoff is the time the provider exchanges and discusses the overall care plan, including when the noninvasive ventilation was initiated, barriers to good adherence, current settings, and an overall plan for the patient. This allows the adult provider to ask questions that may not be clear in the documentation. Following the handoff, there is acceptance of care by the adult sleep provider. The pediatric sleep provider should be available for questions and provide support in the availability of supplies for noninvasive ventilation until the adult sleep provider can meet the patient officially. Furthermore, the adult sleep practice will update the durable medical supply company with respect to the new provider. The last step will close the loop of communication and begin to reinforce the care that was provided by the pediatric sleep provider to ensure a safe and reliable transfer of care.

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Insomnia Across the Life Span

9

Mary Rose, Sara Nowakowski, and Lisa Medalie

Throughout our lives, our sleep, as with our waking experiences, shifts and changes dramatically, dependent upon our physiological, cognitive, psychological, and environmental influences. Though there is substantial change to our sleep across our life span and development, there is also sometimes dramatic change within individuals, depending upon environment, health, and stressors. The broadest and most common clinical complaint among adults is difficulty falling and staying asleep; for teens, it is delayed sleep and difficulty waking. The chief complaint for toddler and elementary school-aged children is sleep resistance. It is critical to define what is meant by insomnia when discussing sleep across the life span, as the complaint manifests so vastly different in its presentation at different ages that it is scarcely the same disorder. In this chapter, we will discuss common differential diagnosis and insomnia manifestation at different stages of life, provide a fictional example of insomnia through the life span, and move through the course of life of a fictional person, Carmen, to whom we have given a lifetime of insomnia. There is a greater risk for those who experience insomnia symptoms in childhood to continue experiencing insomnia into adulthood [1]. Thus, from a preventative perspective, understanding the natural history of insomnia across the life span is important not only for various developmental stages but how these changes may occur

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throughout one's own lifetime. Those with childhood-onset psychophysiological insomnia have moderately but significantly higher reports of nightmares. This group also reported having had longer sleep latencies, significantly more "fear of the dark," and more frequent nightmares during childhood than the adult-onset group [1].

Inadequate sleep opportunity is an additional cause of curtailed sleep, which, though not by definition insomnia, may lead to its presentation. In clarifying the nature of a patient's insomnia complaint, it is essential to determine whether adequate sleep opportunity exists. Adequate sleep opportunity is usually obvious when a patient describes lying awake in bed for hours unable to sleep; thus, there is not actual have difficulty sleeping, but simply not enough hours devoted to obtaining sleep. This can occur for various volitional reasons (e.g., choosing to engage in activities other than sleep) or due to factors outside the patient's control (e.g., caregiving, work). Differentiating insomnia from inadequate sleep opportunity is usually accomplished through a detailed examination of the patient's sleep schedule. Inquiring about the patient's perception of reasons for sleep difficulty will also be illuminating when attempting to differentiate inadequate sleep opportunity from insomnia.

When viewed as a complaint in lieu of a disease, the imposing cultural and environmental pressures impact what we perceive to be "normal" and "abnormal." In some cultures, elective restriction of sleep has become so prevalent that it is the "norm" though in no way "normal' from a biological and health perspective. Normative data are available to us of self-reported sleep times, and experimental data have provided us with what is "needed" for optimal health and performance [2]. Despite the widely held belief that TSTs have been changing over the past several decades with increases to our smart device use, and societal pressures, meta-analysis of studies from the past 50 years does not support this [3].

Psycho-physiologically, emotional, and cognitive arousal may have a myriad of triggers. We will discuss some of those, which are more common at various ages in this chapter. Though not the focus of this chapter, careful recognition of the impact of insomnia—differentiating between daytime sleepiness and fatigue—is essential to assessment, treatment, and management.

Another important consideration in insomnia assessment is discerning whether daytime impairments such as fatigue are due to insomnia or other causes. Fatigue and tiredness are common daytime sequelae of insomnia. However, their presence is not necessarily indicative of insomnia or another sleep problem. Patients may attribute their daytime functioning and energy level entirely to their sleep, discounting other possible sources of fatigue. It is incumbent on the clinician to consider whether non-sleep medical or psychological comorbidities may account for the patient's daytime symptoms of fatigue. In cases where insomnia is present but comorbidities also contribute to daytime impairments, treatment expectations will need to be adjusted accordingly; correcting the insomnia problem may not result in complete resolution of daytime fatigue. Additionally, pregnancy and conditions related to the female reproductive system, such as polycystic ovarian syndrome and premenstrual syndrome, may cause fatigue.

9.1 Infancy

In infancy, a major contributor to poor sleep is colic, as one of the most challenging of early pediatric disruptions to sleep, causing significant discomfort and pain, with often unidentified dietary causes at the root. Colic pain can be extremely disruptive to infants. Mothers with poorer sleep (lower self-reported sleep quality and a higher number of night waking resulting from infant awakenings) perceived their infants as having lower mood and as being more distressed and tearful [4]. Moreover, insufficient sleep and more time tending to the infant at night predicted poorer maternal-infant attachment [5]. Several studies have documented the relationship between sleep disturbance and subsequent reports of depressive symptoms at a later time among perinatal women later in pregnancy [6, 7] or in the early postpartum period [7–9]. Interventions to improve maternal sleep and fatigue are limited, perhaps because of the universal nature of the experience and the belief that disturbed sleep is an unavoidable part of motherhood. Behavioral interventions are the primary treatment options [10, 11]. In addition, several randomized controlled trials have evaluated interventions promoting infant sleep by providing education and training on infant sleep strategies to limit the development of unwanted sleep associations, increase the infant's ability to self soothe, and recommend environmental modifications to consolidate infant sleep at night. These trials demonstrated longer and more consolidated sleep periods compared with infants in control conditions [12–14].

Thus, the start of our insomnia patient's story begins when she was 2 months old.

Carmen developed colic. Her mother rocked her in the bathroom and massaged her stomach, but nothing seemed to alleviate her distress. Carmen's mother, overwhelmed with sleep deprivation and helplessness, found herself increasingly frustrated and guilt-ridden that she was failing as a mother and unable to bond with and help her child. These frustrations were perceived by the tiny Carmen and contributed further to her own distress and heightened discomfort. As this was her mother's first child, she knew very little about infant sleep patterns and tried to prevent Carmen from sleeping in the day, in hope that this would improve her night time sleep. This was an abysmal failure. Carmen's pediatrician explained that infants needed numerous sleep cycles throughout the day and night for several months. He referred her mother to a support group to help her through the colic period and gain support in how to manage the difficult wakes.

9.2 Early Childhood

A 2004 national survey revealed that 27% of children are sleeping less than the recommended amount for their age [15]. Behavioral insomnia, the most common sleep disorder, has a very high prevalence rate (20%–30%) [15, 16]. Insomnia of childhood involves bedtime resistance, difficulty falling asleep independently, and/or frequent night awakenings [17]. It is notable that in childhood, our understanding of insomnia is largely based upon the parents' experience of the child's behavior, while for older children, adolescents, and adults, psychophysiological insomnia as

the driver of the complaint is recognized. This likely stems from our tendency to be more focused on behavior, and management of behavior, rather than be insightful of the possible cognitive and emotional turmoil of the child.

Early childhood is marked by numerous developmental changes, which include changes to circadian rhythm, and total sleep needs. Additionally, greater exploration of independence, and a surge in self-assertion, often leads to increased bedtime resistance. Developmentally, children in the preschool years are experimenting with challenging limits and pushing boundaries of their independence. During this period of life, routine and limit-setting are essential to establishing expectations and healthy habits. However, it is likely that parents may underreport sleep problems, which seemed brief, resolved without major battle, or perceived to be developmentally within a normal range of difficulty. Obstructive sleep apnea (OSA) can masquerade as primary insomnia and is often underreported in pediatrics [18, 19], dismissed as a disorder of concern only for the obese and middle age. Cardiopulmonary implications of OSA in otherwise healthy children may be less serious than in older adults, but its possible impact on insomnia (associated with increased heart rate and adrenalin output) and daytime functioning warrants attention.

Insomnia (particularly nighttime awakenings) at a young age can be caused by environmental circumstances. Socioeconomically disadvantaged children, who are disproportionately of racial/ethnic minority background, have been documented as having shorter sleep duration, more frequent night-wakings, and diminished sleep, compared with higher-income peers [20, 21]. However, a relatively recent study drawing data from 30 randomly chosen child care center indicated that African American children napped while in daycare longer than age-matched white and "other" race peer, bringing their total sleep time in a 24 h period to an equivalent total [22]. The reason for this fragmentation is not entirely clear, though the higher rate of poverty in the African American population may be associated with living in less safe neighborhoods, which in turn would contribute to insomnia associated with fears of safety and possibly to environmental noise in crowded conditions.

At age 3, Carmen was developmentally on target with major milestones. She napped for about 2 h in the early afternoon, and her parents maintained a relatively consistent routine for her at bedtime. Following bath time and story, she would sleep in her own room in a toddler bed, often with her cat. Generally, she slept from 8 p.m. to 6 a.m. with very rare wakes. On rare occasion, she seemed restless and snored lightly.

By age 4, Carmen was enrolled in PreK. She continued to be developmentally on track, though she had some difficulty staying on target in the schoolroom, chatting with friends, and not following directions. Bedtime remained at 8 p.m., and her nocturnal routine continued. Carmen began to have some resistance to bedtime, however, often running and hiding after dinner as bedtime approached, and became increasingly likely to have tantrums as bedtime approached. Due to changes in their work schedule, her parents were having a difficult time maintaining her 8 p.m. bedtime, and due to her resistance, they would intermittently relent and allow her to stay up longer. Subsequently, tantrums became increasingly problematic.

9.3 School Age

Children who are more emotionally aroused may have greater fears of the dark and/or nighttime. Disorientation when they fall asleep in one room and an arousal in another may add to likelihood of a partial arousal and/or anxiety. Anxious children may have illusionary experiences with objects in their rooms, which provokes arousal (e.g., seeing a monster in the closet from a pile of clothes). Nightmares are most common in middle school-age children and can impact not only the child's sleep throughout the night but that of the parents who may be abruptly awoken by screaming. Imagery rehearsal training (IRT), a therapeutic technique used to rescript nightmares into more neutral or pleasant themes, has been found an effective treatment tool not only for adults [23, 24] but for children with nightmares [25, 26]. Behavioral modification has been used as an effective tool to help children establish/reestablish an adaptive association with the bed and bedroom to ensure a more consistent and healthy routine surrounding bedtime [27, 28]. Sleep resistance in school-aged children is a common complaint of parents but can usually be managed with implementation of a consistent pattern of continued progression toward the bedroom during wind down, building positive bedtime associations, and regular sleep schedule [28–31]. Recognizing and managing sources of anxiety is also likely to facilitate a faster sleep onset. Children are additionally responsive to a variety of relaxation techniques; guided imagery has been successfully used for children with chronic pain [32, 33] and meditation [34]. Early identification and management of insomnia at the school age is essential. A Norwegian study followed a community sample (n = 1037) biennially from 4 to 14 years of age between 2007 and 2017 using a semi-structured clinical interview of parents and children for insomnia. During the 10-year period examined, 18.7% had insomnia at least once. Insomnia was a relatively stable concern, with 22.9%–40.1% of the children retaining their diagnosis 2 years later [35].

By age 5, Carmen's mother noticed that her snoring was more regular. Her pediatrician recommended a sleep consult for Carmen. A polysomnographic (PSG) sleep study was ordered, which suggested obstructive sleep apnea (OSA), with an apnea hypopnea index of 6. Carmen was sent to an ear, nose, and throat (ENT) specialist, who performed a tonsillectomy and adenoidectomy. Carmen's sleep doctor also recommended stricter reinforcement of bedtime and avoidance of intermittent reward of the later bedtime when she had tantrum to avoid bedtime. Carmen was provided a more structured routine and storytelling each night. Carmen's sleep improved, and she was doing well in school and at home, though she was a somewhat anxious child, who had difficulty with adjusting to change. When she was 8, Carmen's family experienced a significant financial crisis when her parents' business declared bankruptcy. Carmen was forced to switch schools, and the family had to move from their home. At this time, Carmen started to wake screaming in the early hours of the morning. Her mother or father would come to her room and console her. In the morning, Carmen would talk about her frightening dreams. Soon after, the nightmares started, and Carmen began resisting bedtime again, protesting that she was scared of the dark. As her parents were now

working steadily to rebuild their business, they allowed Carmen to "run free" in the evenings, which resulted in her greater use of electronics and sugary foods. She often fell asleep on the couch in the family room with the TV on, and her father would carry her to her bedroom later. Often, because of her darkness fears, they would allow her to leave a light on in her bedroom at night. They visited a psychologist specializing in sleep. Carmen went through IRT, and the family learned better sleeping habits for Carmen to include falling asleep only in her bed and with a dim red bulb night-light to avoid interference of her melatonin production at night. When she was 10, the nightmares were still occasional, and she continued to occasionally fall asleep on the couch.

As Carmen approached middle school, her parents had greatly rebuilt their company. They moved to a wealthier section of town, and in middle school, Carmen was enrolled into a private school. Overall, her parents felt the family was doing well, and they enjoyed greater freedom with their time and resources. Academic and social pressure built up for Carmen, however, in her new school.

9.4 Adolescence

Adolescence is associated not only with emotional, cognitive, and physical mayhem, but with great changes to social pressures, schedules, and expectations by teens and parents. Likewise, sleep undergoes dramatic changes, particularly with regard to circadian rhythm. Cross culturally, findings have consistently shown that the timing of bedtime on school nights gets later across the middle school and high school years (roughly ages 11 through 17 years) [36–39]. This shift is particularly devastating to teen development, as it is in conflict with societal schedules and pressures. Circadian rhythm disorders phase syndrome is misinterpreted by parents and physicians as insomnia, though a natural circadian shift developmentally expected during adolescence, some adolescents also experience significant insomnia. In one study of four providences in China, sleep difficulties, including insomnia, were independently associated with suicide attempt [40]. Pre-sleep cognitive arousal has been shown to significantly impact sleep onset latency in adolescents [41]. Holstein examined data from eight comparable surveys among 11–15-year-olds in Denmark between 1991 and 2018, from the Danish arm of the international *Health Behaviour in School-aged Children* study. The authors found that there was a significant steady increase in insomnia complaint during adolescents from 7% to 13.4% [42]. Insomnia appears to shift disproportionately from male to female in early adolescence [35, 43] and remains higher in female adolescents compared with males [43]. Having insomnia at one time point is a considerable risk for subsequent insomnia, indicating that insomnia is persistent and warrants clinical attention [35].

Carmen had adjusted well to her new school but continued struggling with anxiety regarding expectations academically and socially. She took several sports and after-school activities and by the time she was 16 was often not getting home from practices and competitions until 9 p.m. She then still had 2 h of school work to complete. One summer, when she and her parents realized that she was not falling

asleep routinely at about 2 a.m. and not getting out of bed until noon, they again met with the sleep psychologist. Carmen's schedule was slowly shifted to an earlier rise time each week, coupled with sunlight or bright light exposure 30 min upon rising, until she was able to achieve the 7 a.m. wake time she would need when she restarted her junior year. She also went through CBT for her anxiety and made a more realistic plan for after school activities to achieve a better school-life balance.

9.5 Early Adulthood

Early adulthood is associated with dramatic changes in autonomy. Young adults gain enormous responsibilities with all of the liberties and burdens associated. New pressures are associated with moving out of the home, career choices, more significant intimate relationships, development of new peer groups, and a shift into the world of employment. Though these changes will occur at different years of life depending upon one's culture, socioeconomic status, and family dynamic, the decades of one's 20s and 30s is generally a time of early career development and decisions regarding family planning and work goal setting. During this time, sources of psychophysiological insomnia may be associated with any of these changes. The standard of care for insomnia is cognitive behavioral therapy for insomnia (CBT-I) [44, 45]. CBT-I has few if any side effects; its principals are translatable to other conditions, such as mood disorders, and it has been shown to have the greatest long-term benefit of any other treatment.

Pregnancy

Pregnancy brings about significant fluctuations in hormones that affect the sleep-wake cycle and cause physiologic changes that lead to sleep disturbance. These changes involve hormonal, anatomical, and physiologic shifts, which are essential to maintain the pregnancy. Common pregnancy symptoms, such as anxiety, urinary frequency, backache, fetal movement, general abdominal discomfort, breast tenderness, leg cramps, heartburn, and reflux, can cause sleep disturbance. Cross-sectional and longitudinal studies that use subjective (self-report) and objective (PSG) measures of sleep have consistently documented increased wakefulness after sleep onset and decreased sleep quality during the first trimester relative to pre-pregnancy [46, 47]. During the third trimester, there is an increase in sleep disruptions with typically 3 to 5 awakenings per night [48], and approximately 21% report disturbed sleep at levels consistent with a diagnosis of insomnia disorder [46, 49]. The prevalence of sleep disturbance among perinatal women is as high as 58% [50–52]. The presence of insomnia has a significant impact on quality of life and daytime functioning, and its management is imperative. Cognitive behavioral treatment for insomnia (CBT-I) is a promising intervention for insomnia during pregnancy. A recent study of 187 pregnant women recruited from a low-risk maternity clinic and trade show revealed that pregnant women preferred CBT-I over pharmacotherapy or

acupuncture for treatment of insomnia [53]. Preliminary evidence in an open-pilot trial of 13 pregnant women with insomnia revealed improvements in diary- and actigraphy-assessed sleep onset latency, sleep efficiency, and total sleep time [54]. In addition, symptoms of depression, pregnancy-specific anxiety, and fatigue also improved following treatment [54]. Another full-scale randomized clinical trial of CBT-I in 179 pregnant women revealed significant improvements in self-reported insomnia and depressive symptoms [55].

Postpartum

Sleep disturbance during the postpartum period and its effects on maternal role functioning and mother-infant interactions are not well understood. Both self-report and actigraphy studies have demonstrated that nearly 30% of mothers have disturbed sleep after the birth of their baby. The precipitous drop in hormone levels after the birth and unpredictable infant sleep patterns can affect a new mother's sleep. Longitudinal studies have documented that the first 6 months postpartum are associated with a significant increase in wakefulness after sleep onset and a decrease in sleep efficiency compared with the last trimester of pregnancy [56, 57]. Sleep begins to normalize around 3 to 6 months postpartum, when infants begin to establish their own circadian rhythm, distinguish between day and night, and sleep for longer periods of time during the night. Some women may also react to infant waking with catastrophic predictions about the consequences of these disruptions that, in turn, lead to hyperarousal and prolonged wakefulness even after the baby is content and asleep. Sleep disruptions that may have begun with pregnancy or postpartum-related stressors develop into an insomnia disorder, maintained by maladaptive compensatory behaviors [58] and conditioned hyperarousal.

In her 30s, Carmen married. It was an exciting time for her; though being prone to worry, she found herself often focused on fears about her pregnancy. Her anxious baseline made her vulnerable to bouts of insomnia due to worry and rumination. Often she was able to avoid her anxious thoughts through keeping busy and using distraction. It was not until nighttime when she was alone with her thoughts in the dark, and unable to distract, that her anxieties began to overwhelm her and keep her from sleep. It seemed as though all of the weight of the day had waiting for her to get into bed, and she found herself focused on fears about sleep itself, often long before she retired to bed. Carmen met with a psychologist again who worked with Carmen on CBT-I to better identify dysfunctional thoughts, particularly about sleep, and to modify her arousal and maladaptive associations between the bedroom and sleep. She also helped Carmen how to better differentiate fatigue and sleepiness cues and to put less pressure on herself to "perform" sleep. After about six sessions, Carmen had achieved substantial improvements to her sleep onset latency and the quality of her sleep, though she continued to need work on protecting time during daytime to evaluate factors likely to impede her sleep and how to better manage them.

9.6 Middle Age

Middle life comes with numerous changes. Both men and women have significant changes to hormones, which often negatively impact their sleep. Additionally, family dynamic is changing. We face mid-career changes and decisions, begin thinking about retirement, and often develop a greater number of medical issues and physical limitations. Despite this, we may also be more secure in our career goals and planning, more adept at handling change, and more resilient to the effects of physical challenges, including sleep loss [59, 60]. Psychosocial challenges associated with middle age may include dramatic changes to our family unit, with children exiting the home, and/or the opportunities for starting children dissipating.

Menopause

Menopause is a natural process defined as the cessation of menstruation because of degeneration of ovaries and follicles accompanied by changing ovarian hormone levels (estrogen and progesterone). The World Health Organization [61] characterizes menopause as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation. Menopause occurs between 50 and 52 years of age for Western women, but the range can vary based on race and ethnicity as well as lifestyle factors [62]. Many women go through the menopausal transition with few or no symptoms, whereas a small percentage of women suffer from symptoms severe enough to interfere with their ability to function effectively at home, work, or school. Common complaints include hot flashes, night sweats, insomnia, mood changes, fatigue, and excessive daytime sleepiness. In the 2005 NIH State-of-the-Science Conference panel report on menopause-related symptoms, sleep disturbance was identified as a core symptom of menopause [63]. The prevalence of insomnia is estimated at 38% to 60% in peri- and postmenopausal women [63–65]. The Wisconsin Sleep Cohort found that perimenopausal women and postmenopausal women were twice as likely to be dissatisfied with their sleep as premenopausal women [66]. The prevalence on nocturnal hot flashes/night sweats is generally believed to occur in 60% to 80% of women during the menopausal transition [67]. When hot flashes occur during the night, they frequently awaken women from sleep. Vasomotor symptoms, including nocturnal hot flashes and night sweats, may be a precipitating factor in the development of insomnia, but physiologic arousals, behavioral conditioning, and misguided coping attempts seem to prolong insomnia [68]. CBT-I has been shown to be efficacious for the treatment of chronic insomnia in midlife women [69–71].

The year that Carmen turned 50, her daughter moved out to college. Carmen had been experiencing greater moodiness, and bouts of insomnia began to creep into her sleep on a more regular basis. Her new puppies needed to go out frequently and often woke her during the night. When they came back in, all three would return to the bed. Carmen now found herself waking at about 3 a.m. on most nights, often from hot flashes. Often to return to sleep, she had to go to the guest room (dogs in

toe) as her husband's snoring would often keep her awake. Carmen was nearing retirement and worried about her daughter and what she would do when she retired. She met with her gynecologist who treated her hot flashes; she reduced the temp of her bedroom and went back to the tools she had learned in CBT to create a better plan for managing anxiety and her pending retirement. She also progressively retrained the puppies to go out later to avoid needing to get up for them.

9.7 Older Adults

Age is associated with numerous changes, which are likely to impair sleep. With regard to architecture, slow-wave sleep is reduced substantially in the elderly [72]. Changes to health, iatrogenic impact of medication, social changes such as losing a partner, caring for a spouse, and loneliness are all areas which should be considered in understanding development of insomnia. Lifestyle issues such as alcohol use (slowed metabolism), inactivity, and lack of daylight from being primarily inside may also contribute to difficulty with sleep onset, wakefulness after sleep onset (WASO), and early morning awakenings. CBT-I has been shown to be efficacious for the treatment of chronic insomnia in randomized trials of older adults [73]. It is critical that older adults receive comprehensive evaluations for factors which may be impacting their sleep such as dementia, medical and medication management issues, and anxiety.

When Carmen reached 80, she began to have increasing trouble with her memory and balance. She rarely went outside and had frequent anxiety, fragmented sleep, and nocturia. She began to feel increasingly more isolated and alone. She had stopped driving as she no longer felt safe doing so and relied upon her neighbors and an agency to help her with groceries. Her physician found that Carmen was taking the wrong dose of some of her medications, had been given a sedating sleep agent by someone not versed in geriatric medicine, had continued to drink a nightly martini, and had become very isolated from others. He changed her medications, treated a urinary tract infection, and added an antidepressant, which would help with her anxiety. A sleep study was performed, which suggested mild OSA for which Carmen was put on continuous positive airway pressure (CPAP), and her nocturia subsided. Behaviorally, he asked her to open window shades each day and schedule a weekly activity with a friend. After consulting her, her physician spoke with her daughter, who decided to take a position closer to Carmen, and gave instructions to more routinely see and check on her as well as to set up her weekly medications to avoid errors. Carmen's sleep improved, as did the overall quality of her life.

9.8 Conclusion and Future Directions

Carmen's story highlights the significant changes in sleep throughout the life span and varying needs from her healthcare team from one life stage to the next. Within the past two decades, understanding on the developmental shifts in sleep and how

insomnia manifests throughout the life span has been dramatic. As we age, we encounter physiological and psychosocial changes, which dramatically impact the quantity and quality of our sleep. Future research to develop insomnia interventions for specific age groups is warranted. Understanding how sleep changes throughout the life span is essential to a comprehensive approach of care. Thus, given the complexity of sleep throughout the life span, the field of sleep would benefit from more highly skilled providers trained in both pediatric and adult care.

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Parasomnias: Diagnosis and Management

10

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10.1 Introduction

Sleep is a dynamic physiologic process that involves various interactions with neurotransmitters in an effort to make transitions from wakefulness to non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Parasomnias are unwanted physical events or experiences that can occur while falling asleep, during sleep, or during an arousal from sleep. Therefore, it can occur during NREM sleep or REM sleep or during the transitions to and from different stages of sleep. The events can involve complex movements or behaviors. When self-injury or injury to others and/or adverse health effects from the sleep disruption occur, then the parasomnias are labeled as a clinical disorder. According to the International Classification of Sleep Disorders-3 (ICSD-3), parasomnias can be classified into one of three categories: NREM-related parasomnias, REM-related parasomnias, and other parasomnias [1]. NREM-related parasomnias, also known as disorders of arousal, include confusional arousals, night terrors, sleepwalking, and sleep-related eating disorder. They can be characterized as a spectrum of a state of disassociation during NREM sleep. REM-related parasomnias include REM sleep behavior disorder, recurrent isolated sleep paralysis, and nightmare disorder. Exploding head syndrome, sleep-related hallucinations, and sleep enuresis are in a separate category of other parasomnias. Abnormal sleep-related movements will not be discussed in this chapter as they entail more complex movements and behaviors than parasomnias. This chapter will briefly discuss various presentations, etiology, and treatment options of parasomnias with a focus on the unique challenges that patients and healthcare providers encounter during the transition of care from pediatric to adulthood.

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10.2 Epidemiology

Parasomnias are more commonly seen in children than in adults. More specifically, children tend to have more slow wave sleep or NREM stage N3 sleep, and thus NREM-related parasomnias are more common in children than REM-related parasomnias. Children with underlying neurologic and psychiatric issues like epilepsy, attention deficit hyperactive disorder (ADHD), or developmental issues tend to experience parasomnias in childhood versus those children without these disorders. Lifetime prevalence of parasomnias range from 4 to 67% in adults and children, respectively [2]. There is no gender preference in regards to NREM-related parasomnias in general. Sleepwalking and confusional arousals tend to be more common in children and adults with a prevalence of 17% and 20%, respectively [2].

10.3 Disorders of Arousals

The American Academy of Sleep Medicine (AASM) via the International Classifications of Sleep Disorders-3 (ICSD-3) defines the group of disorders of arousals with the following diagnostic criteria:

1. Recurrent episodes of incomplete awakening from sleep.
2. Inappropriate or absent responsiveness to efforts of others to intervene.
3. Limited or no associated cognition or dream imagery.
4. Partial or complete amnesia of the episode.
5. The disturbance is not better explained by another sleep disorder, medical or psychiatric disorder, medication, or substance.

Most of the episodes in this group present during the first half or first third of the night as most episodes originate from NREM sleep. Disorders of arousals include confusional arousals, night terrors, sleepwalking, and sleep-related eating disorder. Sleep deprivation, stress, and medications are common precipitating factors for disorders of arousals. The underlying etiology of developing a disorder of arousal is unknown. There may be a genetic component particularly in those who sleepwalk. Typically, disorders of arousals are considered to be part of normal growth and development. However, they become an actual disorder when there are clinical consequences and/or persist past childhood age.

10.4 Confusional Arousals

Confusional arousals, also known as Elpenor syndrome, belong in the group of disorders of arousals. Other names for confusional arousals include sleep drunkenness. They typically involve incomplete, recurrent episodes of nocturnal awakenings from sleep and are associated with a state of confusion or disorientation during

and/or following arousals in slow wave sleep (stage N3). These occur while in the bed. Ambulation out of the bed or autonomic features such as extreme terror, diaphoresis, or tachycardia are absent. Children and adults experience partial or complete amnesia of the episode. The duration of confusional arousals can range from a few seconds to a few minutes. The majority of these episodes occur during the first third to half of the night as this is typically the part of the night in which slow wave sleep is more dense. They can also occur during the transition from sleep to wakefulness, which is common if fragmented sleep is present.

Confusional arousals are very common in children with a prevalence of about 15–17% [3]. They typically present around 2 years of age and tend to self-resolve spontaneously around 5 years of age. The prevalence of confusional arousals in adults is about 3.6–4.8%. Lifetime prevalence has been reported to be about 18.5% [1]. In adults, confusional arousals often go unnoticed unless they contribute to disruption to bedpartner. They are often observed in patients with sleep and/or psychiatric disorders [3]. Precipitants to episodes include insufficient sleep, hypnotic agents, and psychiatric agents.

Clinical history of the episode during a sleep evaluation is enough to make the diagnosis of confusional arousals for both children and adults. Typically, the caregiver or bedpartner is able to provide details in regard to timing of the episode, frequency, and precipitating factors. The sleep evaluation should screen for other sleep disorders such as sleep-disordered breathing and any sleep disorders that may contribute to insufficient sleep. Medication history and family history may identify other precipitating factors as well. Polysomnogram (PSG) is not indicated to make the diagnosis unless the history is not clear or involves an atypical presentation of confusional arousals. Video recordings of the episode in the patient's home setting may be helpful.

Treatment includes avoiding precipitating factors such as insufficient sleep and ensuring safety of the patient. Confusional arousals often occur with other parasomnias such as somnambulism. Medication is not indicated frequently. At this time, there is limited data for medications that treat confusional arousals available. Maintaining adequate sleep hygiene and reassurance are typically reinforced when discussing treatment.

For most children, confusional arousals self-resolve and do not progress into adulthood. There is no association with psychiatric disorders in adulthood as a result of childhood confusional arousals [1]. However, if there is a psychiatric diagnosis present, then screening for sleep disorders that contribute to insufficient sleep or sleep deprivation may identify a source for the etiology of confusional arousals. During the transition of care to an adult provider, review of the past medical history including interventions that have been used in the past is recommended. Screening for other types of disorders of arousals is also recommended during the transition period. Re-emergence of confusional arousals should trigger an evaluation for other sleep disorders or causes of fragmented sleep. This could include stress, anxiety, inadequate sleep hygiene, or a combination of reasons.

10.5 Sleep Terrors

Sleep terrors, also known as night terrors, are characterized by episodes of sudden terror commonly initiating with a startling vocalization such as a distressed scream. Children can sit upright in their bed, scream and express intense fear, and periodically run wildly into walls and furniture trying to escape an unseen danger that can potentially lead to self-harm. During an episode, autonomic hyperactivity is manifested, and symptoms such as mydriasis, diaphoresis, tachypnea, tachycardia, flushed face, agitation, tremulousness, and increased muscle tone can occur. It is not uncommon for adults to get out of bed and run further, leading to violent behavior if someone tries to restrain the adult. The individual may appear to be awake during most, if not the entire episode with diminished cognitive response. Most sleep terrors occur during the first third part of the night and typically can range from more than a few minutes up to 30–40 minutes. Eyes frequently are open and sometimes appear "glassy" with a confused-like stare. Talking and shouting are often confusing and incomprehensible. Sometimes, both adults and children can experience inconsolability for an extended amount of time [1, 4].

It can be challenging to awaken someone from a sleep terror which may increase the state of panic, intensify the episode, and/or prolong it. If the child or adult is awakened abruptly, they are occasionally confused and usually experience amnesia of these episodes the following morning [1, 4]. These episodes can be troublesome for the family members as it may contribute to sleep disruption. Prolonged discussion of the episodes with the child experiencing sleep terrors can contribute to bedtime resistance with subsequent insomnia [2].

Sleep terrors are typically diagnosed based on a detailed sleep history that is reported by the individual and the bed partner or family member in addition to clinical findings. A video recording of the event taken by the family member can be helpful with diagnosis. Sleep diaries can help the provider understand whether sleep insufficiency is a contributor to triggering sleep terrors. Children with gastroesophageal reflux may experience abrupt arousal from sleep and pain, and thus it is important to differentiate this from sleep terrors [4]. Differentiating from true terrors or nocturnal panic attacks is important. Typically, the individual is experiencing these anxious symptoms or episodes during the daytime while awake [5]. Polysomnography should be considered if there are concerns of nocturnal seizures.

Reassurance and education should be provided given sleep terrors resolve typically by late adolescence. Ensuring safety of the individual is important so that they do not harm themselves during an episode such as falling out of the bed. Encouraging the family members not to disturb the individual during an episode will potentially help decrease the length of the episode and frequency of episodes [5, 6]. Precipitating factors such as insufficient sleep or poor sleep quality should be treated to help avoid increased frequency of sleep terrors. Practicing good sleep hygiene, implementing consistent routine, as well as avoiding caffeine can help ensure optimal quality and quantity of sleep [4]. Those sleeping in a different environment as well as situational stress or anxiousness can provoke a sleep terror. If episodes are

frequent and cause self-harm, medications should be considered in both adults and children such as benzodiazepines (diazepam and clonazepam) and tricyclic antidepressants (clomipramine, imipramine), which suppress NREM sleep and minimize episodes [4, 5]. Scheduled awakenings or awakening the child 30 min prior to the anticipated time of the sleep terror has some effectiveness but could result in sleep disruption, further leading to daytime sleepiness [4]. Hypnosis and cognitive behavioral therapy (CBT) to improve anxiety have shown some effectiveness in decreasing sleep terrors and can be used in both children and adults [7].

10.6 Sleepwalking

Sleepwalking, also referred to as somnambulism, differs from other parasomnias as it is associated with ambulation or other complex behaviors outside of the bed. Typically, sleepwalking follows a confusional arousal that occurs in the bed [1]. Sleepwalking is characterized by simple, usual behavior or complex, bizarre behaviors that occur during the first 15 min to 2 h of sleep. These behaviors may include wandering around the home or into someone else's bedroom, urinating or defecating in an inappropriate location, going outdoors, confusion, and incoherent responses or vocalizations. Parents or bed partners are sometimes unable to tell whether the individual is awake or asleep [5, 8]. Complex behaviors, such as driving a car, are rare but have been reported [8]. In an adult, inappropriate sexual activity with someone physically near them or themselves may occur during an episode. Ambulation may discontinue spontaneously, and the individual may lie down in an inappropriate area or may return back to bed while never becoming conscious at any point. Individuals who sleepwalk typically experience partial or complete amnesia of the event the following morning [1].

There is an increased risk for injury during sleepwalking episodes, which may result in falling down stairs, walking into traffic, going outside with inadequate clothing for the weather, or walking off a balcony [2, 8]. Fever and illness as well as sleeping with a full bladder can also trigger sleepwalking; thus, managing the illness and emptying the bladder prior to falling asleep can help decrease the possibility of occurrence [5]. Those sleeping in a different environment as well as situational stress or anxiousness can provoke sleepwalking. Medications such as lithium and withdrawal of medications like benzodiazepines or anti-tricyclics can increase slow wave sleep, thus further increasing the likelihood of sleepwalking [5].

Sleepwalking is typically diagnosed by a thorough history that involves clinical signs and symptoms by the bed partner or parent. Reviewing a home video can also be helpful to confirm sleepwalking. Polysomnography (PSG) is not necessary unless there are concerns for underlying sleep disorders causing sleep disruption in which a PSG should be obtained in order to diagnose and treat these disorders [2].

Reassurance and education should be provided given sleepwalking resolves typically by late adolescence. Ensuring safety of the individual is important so that they do not harm themselves or others during an episode. Installing high locks or hiding keys is helpful to prevent individuals from wandering outside. Encouraging the

family member not to disturb the individual during an episode will help prevent agitation during the episode [5]. Practicing good sleep hygiene, implementing a consistent bedtime routine, as well as avoiding caffeine can help ensure optimal quality and quantity of sleep [4]. Similar to sleep terrors, those sleeping in a different environment as well as situational stress or anxiousness can provoke sleepwalking. If episodes are frequent and dangerous, medications such as benzodiazepines (diazepam and clonazepam) and tricyclic antidepressants (clomipramine, imipramine) may be used to eliminate sleepwalking [4, 5]. Awakening the child 30 min prior to the anticipated time of sleepwalking has some effectiveness but could result in sleep disruption, further leading to daytime sleepiness [4]. Hypnosis and cognitive behavioral therapy to improve anxiety have shown some effectiveness in decreasing sleepwalking and can be used in both children and adults [7].

10.7 Sleep-Related Eating Disorder

Sleep-related eating disorder (SRED) or sleep eating is characterized by reoccurring events of involuntary eating and drinking during arousals at any time in the sleep cycle. SRED is most commonly associated with other sleep disorders such as restless leg syndrome, periodic limb movement disorder (PMLD), and obstructive sleep apnea (OSA). Sleepwalking, especially during childhood, is usually a predisposition to the development of SRED. Some medications such as zolpidem and a wide range of sedative hypnotics have been reported to lead to SRED as well as cessation of smoking, alcohol, and substance abuse [1]. Other medical conditions such as encephalitis, autoimmune hepatitis, and narcolepsy can prompt the occurrence of SRED. Eating disorders such as anorexia and bulimia as well as psychological stress can trigger SRED [1, 9]. If the individual has an eating disorder during the day, they do not conduct compensatory purging behaviors during the nighttime episodes [5]. Most reported cases are female (60–83%) with the average age of onset between 22 and 39 years of age [1].

Those with SRED consume foods that are typically high calorie, unusual forms, or combinations and can even be inedible or toxic substances (cleaning solutions, coffee grounds, raw ground meat, frozen potato fries). Subsequent injuries can occur while seeking out or cooking this food (lacerations from kitchen utensils, burns from ovens, poisoning from ingesting toxic substances). Partial or complete unawareness of the episode with impaired recall the following morning occurs, and episodes are not better explained by another disorder, substance use, or medication. Adverse health consequences related to SRED such as excess weight gain and dental caries can occur as a result of this binge eating. Obesity further can predispose those who have SRED to metabolic disorders such as diabetes and hypercholesterolemia. Depression can occur secondary to SRED from long-term feelings of failure due to the inability to control nighttime eating. As a result of these feelings, frequently, food restriction will then follow, and sometimes those with SRED may take part in potentially dangerous weight-loss regimens [1, 2].

SRED should be differentiated from night eating syndrome (NES), which is defined as excessive eating during wakefulness either between dinner and bedtime

or during the sleep period. Those with SRED do not partake in inappropriate compensatory behavior such as self-induced vomiting or purging during the event; however, those with SRED could have eating disorders, which further lead to this compensatory behavior during the day. Excessive weight gain that may occur can lead to fasting during the daytime or participation in excessive exercise to lose weight or prevent obesity. Some individuals with SRED may consciously eat before bedtime to try to suppress the urge to eat after falling asleep [1].

Disorders such as Kleine-Levin syndrome (KLS) should be ruled out as individuals with KLS can experience nocturnal eating, but it also occurs with other hallmark symptoms including periodic hypersomnia and hypersexuality that can last for days to weeks. Other medical neurologic disorders, such as hypoglycemic states, gastrointestinal disease (peptic ulcer disease and reflux esophagitis), and Kluver-Bucy syndrome, should be ruled out [1].

Diagnosis of SRED requires thorough clinical history taking inquiring about the timing, frequency, and description of foods ingested. History taking alone may be sufficient for diagnosis; however, if other sleep disorders like periodic limb movement disorder (PLMD) or obstructive sleep apnea (OSA) are suspected, a sleep study is warranted. If seizures are suspected, a full montage should be considered as well as placing food at the bedside to elicit an eating event [10].

Discontinuing the underlying drug eliciting the episodes of eating usually resolves SRED. If there are sleep disorders such as OSA, PLMD, or RLS that cause sleep fragmentation, these associated disorders should be treated. Continuous positive airway pressure (CPAP) treatment for OSA and dopamine agonists, such as pramipexole, for treatment of RLS, should be prescribed for treatment of SRED. When SRED is associated with sleepwalking, low-dose benzodiazepines such as clonazepam can be utilized to help resolve SRED. Serotonin reuptake inhibitors, like fluoxetine or sertraline, are considered first line of treatment for idiopathic SRED. If no resolution in symptoms, then topiramate can be an alternative treatment option. Combination therapy of medications for the underlying sleep disorder in addition to an SSRI may be considered if monotherapy alone does not resolve SRED [11, 12]. Behavioral therapies such as cognitive behavioral therapy and hypnosis alone have not shown any success in treating SRED [11, 13].

Given that age of onset for SRED is typically after adolescence, there are minimal transition considerations as the individual is likely diagnosed in the adult setting; however, pediatric providers who treat adolescents with eating disorders such as anorexia and bulimia should have increased awareness of SRED. Adult providers should frequently follow up after prescribing treatment for underlying sleep disorders or idiopathic SRED to monitor for resolution of related symptoms, weight changes, and drug-related adverse effects [11].

10.8 Sleep Talking

Sleep talking, also known as somniloquy, may occur during REM or NREM sleep and is defined as talking while asleep which can be understandable or incoherent. It is the most prevalent of parasomnias (66%) and remains stable from childhood

through adulthood [8, 14]. It can be idiopathic or associated with other parasomnias such as confusional arousals or REM sleep behavior disorder (RBD). Vocalizations associated with RBD have been reported to be loud, hysterical, and profane and are typically associated with the related dream [1].

Sleep talking is benign but can be disruptive to the family member or bed partner's sleep if it is loud and occurring frequently. Sometimes, the content may be offensive and can lead to sleep disruption for those who share sleeping spaces such as college dorms or fire stations. Sleep talking has not been shown to have any correlation with previous memories, and the individual mostly has no recollection of the episode the following morning [1].

Sleep talking is diagnosed based on clinical history and does not require any treatment; however, if it is associated with any other parasomnias such as sleep terrors or RBD, treatment of those parasomnias should be considered especially if the mental content is too violent or emotional [14]. PSG is not necessary unless there are concerns for underlying sleep disorders, causing sleep disruption in which PSG should be obtained in order to diagnose and treat these disorders [2].

10.9 Exploding Head Syndrome

Exploding head syndrome (EHS) is a painless sensation that occurs during the transition from either wakefulness to sleep or sleep to wakefulness (either from wake to N1 or from N1/N2 to wake) [15]. It is associated with a loud bang or crash that occurs with or without a flash of light. The patient perceives the sound originating from inside of the head. The duration is described as being less than a second. EHS often produces fear in the subject, resulting in physical symptoms of sympathetic activation such as tachycardia, shortness of breath, or muscle jerks. Insomnia may occur as patients can be disturbed by the phenomenon, further leading to fear of falling asleep.

The etiology of EHS is unknown; however, it has been hypothesized that it could be due to temporal lobe seizure activity, ear pathology, a gene mutation resulting in dysfunctional calcium channel activity, or neurological abnormalities [16]. EHS can be associated with sleep paralysis, hypnagogic or hypnopompic hallucinations, nightmares, and lucid dreams. Patients as young as 10 years of age have reported signs and symptoms of EHS; however, it often presents in the sixth decade of life. There is a higher incidence in female patients. The prevalence is estimated to affect approximately10% of the population; however, its true incidence is unknown as it is believed to be underreported. Diagnosis of EHS is made clinically with an appropriate history describing the event. Differential diagnoses include headache disorders and nocturnal seizures. Diagnostic testing or imaging is not indicated for EHS. Treatment often is focused on reassuring patients that EHS is a benign occurrence. Appropriate amounts of sleep and reducing stress can improve EHS. Case reports have shown that medical management with clomipramine, amitriptyline, topiramate, duloxetine hydrochloride, and calcium channel blockers can improve outcomes in patients with EHS [15].

10.10 Sleep-Related Hallucinations

Sleep-related hallucinations are a common parasomnia, occurring in approximately 30% of the population. These manifestations can be auditory, tactile, or kinetic in nature [17]. The most common of these is visual. Shapes, figures, and flashes of light have been reported. Images are often very defined and colorful in nature. Auditory hallucinations have been described as words, names being called, people talking, environmental noise, or animal sounds. Tactile sensations can include body distortion, pressure, or kinetic sensations such as flying or falling.

Hallucinations occur either from the transition from wakefulness to sleep, also known as hypnopompic, or from sleep to wakefulness, also known as hypnogogic. The hallucinations occur most frequently in teens and young adults. The incidence tends to decrease with advancing age. Sleep deprivation can increase the incidence of sleep-related hallucinations. This phenomenon can be associated with sleep paralysis or narcolepsy [1].

10.11 REM Sleep Disorders

Parasomnias that are associated with REM sleep include REM sleep behavior disorder, recurrent isolated sleep paralysis, and nightmare disorders. As sleep progresses through the night, the percentage of REM sleep in each cycle generally increases and becomes more dense REM sleep involves muscle atonia and contributes to 18–25% of the total sleep time in school-aged children, adolescents, and adults.

10.12 Nightmares/Nightmare Disorder

Nightmares are disturbing episodes that generally occur during REM sleep. Nightmare disorder is a clinical diagnosis in which nightmares are recurrent and cause significant impairment. The episodes occur typically during the latter half of the night in which the pressure for REM sleep is at its peak. Nightmares involve vivid experiences that are often negative in nature and frequently involve anxiety, fear, or terror. The episodes typically resolve upon awakening in which the person immediately is able to recall the episode.

Nightmares are very common in children with a prevalence of 60–75% [1]. About 10–50% of children will have nightmares severe enough that they disturb the caregiver. Recurrent nightmares may contribute to bedtime resistance in effort to avoid the fear of waking up with terror. If there is a clinical history of nightmares during childhood, then there is a higher risk of recurrent nightmares into adulthood [1]. About 2–6% of adults report having frequent nightmares [18]. There is a large population-based study from South Korea showing nightmare frequency increases in frequency with advancing age [19]. Adults over the age of 70 years demonstrated a threefold increase in prevalence of nightmares in comparison to adults 50–70 years of age.

Nightmare disorder often emanates from stress and/or trauma. It can be associated with posttraumatic stress disorder, anxiety, and acute stress disorder. Although by definition, nightmares are not considered pathologic, nightmare disorder is often a sign of underlying psychopathology. This includes depression, dissociative disorders, borderline personality disorder, anxiety, panic disorders, and schizophrenia [20]. With frequent nightmares, individuals are more likely to have suicidal ideation and may demonstrate self-harming behaviors [21, 22].

A vast number of pharmacotherapeutic agents can also be associated with nightmares. This includes those that affect neurotransmitters such as norepinephrine, serotonin, dopamine, acetylcholine, or gamma-aminobutyric acid (GABA). Certain antihypertensives, antimicrobials including antibiotics, and antivirals have also been known to contribute to nightmares. Withdrawal of particular medications that affect REM sleep is commonly known to produce nightmares. This is often due to an compensatory increase in REM sleep upon withdrawal of a REM sleep-suppressing agent. This may include alcohol, barbiturates, and benzodiazepines [23, 24].

Clinical history taking involves the description, frequency, and duration of the episodes and also a review of past and current medications to diagnose nightmares and nightmare disorder. Screening for psychiatric disorders may identify the etiology of nightmares. This includes screening for suicidal ideation as well as behaviors that may harm others. Assessment of sleep quality, sleep duration, and behaviors that are associated with the episodes is recommended. Self-reported questionnaires or diaries that monitor frequency of the episodes may help differentiate nightmares from general distress [25, 26]. A PSG is not indicated unless the clinical history is atypical and suggests that there are stereotypic movements, seizure-like activity, or other sleep disorders that could contribute to fragmented sleep or insufficient sleep.

Treatment for nightmares typically begins with reassurance for both pediatric and adult patients. Symptoms typically resolve over time without intervention. Best practice guidelines to treat nightmare disorder by the American Academy of Sleep Medicine (AASM) include medications such as prazosin and cognitive behavioral therapies for adults. Nightmare-focused cognitive behavioral therapies including image rehearsal therapy (IRT) have been shown to be effective [25]. IRT is a type of cognitive behavioral therapy (CBT) that involves recalling the nightmare and changing the distressing part of the dream to a more positive dream and then rehearsing the dream so that the unwanted part of the dream is displaced [25, 27].

In children, reassurance and education on adequate sleep hygiene as well as stress management are the first lines of treatment. CBT in children may include relaxation techniques and improving sleep hygiene. There are limited studies that support the use of IRT in children [28]. Adolescents who continue to have nightmares typically continue with cognitive behavioral therapy. However, when they reach adulthood and continue to have problems with maintaining sufficient amounts of sleep, then pharmacologic agents are typically initiated in conjunction to CBT. As they transition to adulthood, periodic screening for other sleep disorders, such as circadian rhythm disorders or sleep disordered breathing, which may contribute to insufficient sleep, is important.

10.13 Sleep Paralysis

Sleep paralysis is the inability to move after waking out of rapid eye movement (REM) sleep. This process can occur when falling asleep, also known as hypnogogic, or when awaking from sleep, also known as hypnopompic. Sleep paralysis occurs as humans become atonic during REM sleep [29]. This is due to the neurotransmitters glycine and GABA inhibiting skeletal motor function [30]. This process is beneficial as it prevents self-injury during REM sleep to inhibit a person from acting out dreams while in a dream state. During an episode of sleep paralysis, the patient is conscious but the patient is unable to move or speak. Sleep paralysis often provokes fear in the patient as they are aware their surroundings without the ability to move. The episodes can be accompanied by visual, such as a figure/intruder, or tactile hallucinations, such as a pressure on the chest. The duration of the episodes can last seconds to minutes. Sleep paralysis can occur as an isolated incident, or it can be recurrent. Sleep paralysis often presents during the teenage years but can begin later in life. Episodes can become more frequent with age. The prevalence is around 8% but has been estimated to occur in 5–40% of the population [29]. Sleep paralysis has a slight non-Caucasian predominance but no gender difference. Sleep paralysis is part of the narcolepsy pentad, along with sleep attacks, cataplexy, hallucinations, and sleep fragmentation. Patients presenting with sleep paralysis should be evaluated for narcolepsy.

Sleep paralysis can be associated with a variety of psychiatric disorders such as PTSD, anxiety disorders, bipolar disorder, and schizophrenia [30]. Medication use, family history, sleep-related leg cramps, insufficient sleep, an irregular sleep schedule, and supine sleeping have all been identified as risk factors for sleep paralysis. Treatment of sleep paralysis is non-specific but often involves reassurance to the patient. Improvements to sleep hygiene and obtaining adequate sleep time are often the basis of therapeutic management. CBT can improve sleep hygiene and insomnia, thus reducing sleep paralysis.

10.14 REM Sleep Behavior Disorder (RBD)

The ICSD-3 defines RBD as repeated episodes of sleep-related vocalization and/or complex motor behaviors that is documented to occur during REM sleep on PSG or there is a history of dream enactment. PSG demonstrates REM sleep without atonia, and the episode is not explained by another sleep disorder, psychiatric disorder, medication, or substance use. The dream enactment can be violent. Dream content may be associated with violent movements, but there is no memory recall of the violent behaviors. There is recall of the dream when awakened from the episode. Violent behaviors may include talking, kicking, screaming, punching, flailing of the extremities, or gesturing. Violent behavior during the day is not characteristic of RBD. Self-injury or injury to the bed partner is common and can be life-threatening. These episodes occur at least 90 min after sleep onset or sooner, particularly if there is a history of narcolepsy, as these patients have sleep onset REM periods.

The prevalence of RBD in the general population is about 0.5–1.25% [31]. RBD commonly occurs in males with the median age of onset of 50 years [1]. There are a few cases of RBD in adolescents and elderly adults. The presentation in younger ages involves less violent behaviors. RBD in adolescents is most commonly secondary to an underlying etiology such as medications, neurodevelopment abnormalities, and brainstem lesions [1, 32]. In adults, RBD can be secondary to central nervous system pathologies such as alpha-synuclein degeneration such as Parkinson's disease, Lewy body dementia, multiple system atrophy, non-synuclein disorders such as Alzheimer's disease, Huntington disease, myotonic dystrophy type 2, frontotemporal dementia or amyotrophic lateral sclerosis, structural pontine lesions, orexin deficiency such as in narcolepsy, or from medications [33, 34]. Medications that are commonly associated with RBD include venlafaxine, serotonin reuptake inhibitors, mirtazapine and other antidepressants, beta-blockers, and anticholinesterase inhibitors.

RBD can be associated with other sleep disorders such as periodic limb movements or narcolepsy with cataplexy. Approximately 50% of patients with narcolepsy have RBD [1]. Biomarkers for neurodegeneration are absent, and thus the physiology of RBD in narcolepsy involves the failure of orexin to stabilize REM sleep in contrast to the alpha synuclein neurologic disorders [35].

Overlap syndrome is characterized as RBD and either a disorder of arousal, sleep-related eating disorder, sexsomia, or rhythmic movement disorder. This presents more commonly in males and during childhood or adolescence. Neurologic conditions such as multiple sclerosis, rhombencephalitis, congenital Moebius syndrome, agrypnia excitata, brain tumors, psychiatric disorders, medications, as well as withdrawal of certain medications are associated with overlap syndrome.

Polysomnography along with clinical history is required to make the diagnosis of RBD. Increased amounts of sustained or intermittent loss of atonia with excessive phasic muscle twitch activity of the electromyogram (EMG) during REM sleep are demonstrated on PSG. Tachycardia and other signs of autonomic system discharge are absent in RBD, unlike disorders of arousals. Video monitoring with PSG will demonstrate abnormal, violent behaviors.

Treatment of RBD typically starts with maintaining safety for the patient and the bed partner. This includes counselling on safe sleep practices and practicing environmental precautions to avoid injury. Locking up firearms and removing sharp objects from the bedroom is also recommended. Patients are oftentimes asked to sleep alone in order to prevent injury to the bed partner. Removal of medications that exacerbate RBD should be discontinued and/or avoided [36].

High-dose melatonin is the first line of therapy for RBD in both children and adults [37, 38]. Melatonin aids in reducing the violent behaviors and is generally well tolerated [37]. Clonazepam is another first-line therapy for RBD that reduces the frequency of unpleasant dreams and violent behaviors [39]. Unfortunately, clonazepam helps with symptoms of RBD, but the side effects may be problematic, particularly in those with neurodegenerative conditions [40].

10.15 Enuresis

Nocturnal enuresis is diagnosed when unintended voiding during sleep occurs after 5 years of age. The etiology of enuresis is not fully understood. Nocturnal polyuria, detrusor overactivity, and high arousal threshold are all likely involved [41]. Nocturnal polyuria results from a decrease in the typical production of the antidiuretic pituitary hormone vasopressin (ADH). Glomerular filtration normally decreases by 30% during the night, and water reabsorption is increased via the arginine-vasopressin pathway. If ADH is not released in appropriate amounts, the decrease in urine production does not occur, resulting in polyuria [42]. The detrusor muscle can be overactive. This hyperactivity results in the bladder being compressed, reducing bladder capacity [42]. In children, constipation can result in distended bowel, further compressing the bladder and exacerbating detrusor muscle contraction. A full bladder and detrusor muscle contraction both can produce a strong arousal stimulus. These stimuli may not be adequate to wake a subject from sleep thus contributing to nocturnal enuresis.

Children who have nocturnal enuresis have increased nocturnal awakenings, increased sleep latency, and increased movements during sleep, including periodic limb movements [41]. These sleep changes suggest fragmented sleep, which is thought to lead to a higher arousal threshold, preventing the child from waking up when their bladder is full. Obstructive sleep apnea can also result in fragmented sleep, creating a higher arousal threshold [42]. If the body is unable to achieve enough of a wake stimulus, enuresis will result. Enuresis can occur during NREM or REM sleep (NREM> REM). Some data suggest that enuresis occurs during transitions in sleep (from N3 → N2 or N2 → N1) [42].

In pediatrics, enuresis is categorized into primary enuresis or secondary enuresis with primary defined as a child never achieving a period of time being dry at night and secondary being a child having been dry for a 6-month period and then begins to have accidents. Secondary enuresis can be associated with life stressors, traumatic experiences, or medical pathology. Warning signs for underlying pathology include excessive thirst, weight loss, fatigue, proteinuria, daytime incontinence, or urgency difficulties. Evaluation of secondary enuresis includes workup for urinary tract infections, constipation, diabetes, renal failure, and urologic abnormalities such as urethral valves. In children, 90% of cases are due to primary nocturnal enuresis. Primary enuresis is more common in males compared to female patients. Enuresis runs in families, and a family history of delayed nocturnal continence is common. Fifteen percent of children who continue to struggle with nocturnal enuresis will become dry in a year's time. The other 85% of children will continue with the diagnosis, which warrants medical intervention.

Treatment of nocturnal enuresis typically focuses on positive reinforcement to motivate the child. Studies have shown an 85% success rate with behavioral modifications. Limiting liquids before bedtime, voiding before going to bed, and double voiding, the process of going to the bathroom and then trying to void again, can be helpful. Waking the child 2–3 h after going to bed can help reduce accidents. Enuresis alarms, recommended after the age of 6 years of age, can help the child

awaken from sleep at the onset of voiding and help improve waking prior to the episode. Enuresis alarms have been shown to help improve enuresis in 50–80% of cases. It is recommended that once a child is dry for 14 consecutive nights, the alarm can be discontinued. Treatment with enuresis alarms is recommended for a 3–6-month period before success is expected to be achieved. Medications such as desmopressin, DDAVP, can be given intranasally or orally and can reduce rates of enuresis while the medication is being used. Relapse rates are high when the medication is terminated but can be helpful for short-term periods of desired continence.

Enuresis can persist into adulthood at an estimated prevalence of 2–3%. Incidence is higher in women with voiding dysfunction, adults with atypical development, and nursing home patients. In adults, there are three categorizations:

1. Persistent primary nocturnal enuresis—when a patient has never been dry.
2. Recurrent primary nocturnal enuresis—when a patient is dry for more than 6 months before recurrence during adulthood.
3. Secondary nocturnal enuresis—enuresis with no evidence of enuresis in childhood.

The most common form in adulthood is persistent primary nocturnal enuresis. Risk factors for adult enuresis include neurologic disorders, obesity, sleep apnea, psychiatric medication use, smoking, hypertension, benign prostatic hyperplasia, and outlet obstruction [43].

Treatment of enuresis in adults begins with behavioral modification techniques such as timed voiding or enuresis alarms. However, behavioral interventions are not as successful in the adult population when compared to the pediatric population. If these therapies fail, then medical management is recommended. Desmopressin is typically the first line of therapy. Desmopressin is typically effective but has the risk of increased seizure activity due to water intoxication and subsequent hyponatremia. If desmopressin is not an effective treatment therapy, then anticholinergics, such as imipramine, can be used. Monitoring for urinary retention and cardiac issues is necessary.

Enuresis is a distressing diagnosis for both children and adults. Patients who carry this diagnosis have a lower self-esteem, anxiety, depression, chronic fatigue, and difficulties in school or at work. Ensuring a proper medical evaluation and treatment plan is important to the global health of these patients.

10.16 Transition of Care for Patients with Parasomnias

Most parasomnias typically resolve by late adolescence; therefore, most pediatric patients with parasomnias do not require transitioning to adult care providers. For the small percentage of pediatric patients that need successful transition, an uninterrupted, coordinated, developmentally appropriate, and psychologically sound process is required [44]. There are many challenges for adolescents who are transitioning into an adult healthcare setting. Early on, caregivers are the leaders and decision-makers in their child's care especially when discussing the use of medication such as those utilized to control symptoms of RBD. Transferring the ownership of care

should be structured and carefully managed to ensure that the transition period is easily adaptable and maintained as the child matures to become an independent young adult.

Transitioning a young adult successfully from pediatric care to adult care is multifactorial. It requires collaboration with the caregivers, healthcare providers, and supporting staff. At each clinic follow-up visit, the pediatric provider should assess the readiness for transition. This can initially start by asking the patient to summarize their overall status of care or ask why they require medications and need to maintain safety during sleep.

Before transitioning to adult care, it is pertinent to ensure that pediatric records including diagnostic testing, such as polysomnography and electroencephalogram, as well as clinic notes are transferred to the adult provider. Parasomnias can present similarly to other disorders like nocturnal seizures; thus, understanding how the diagnoses were determined will help eliminate any unnecessary, repeated testing. Clinic notes are helpful in recognizing what previous treatment modalities or pharmaceuticals have been utilized in addition to their outcomes and adverse effects.

Most parasomnias increase in frequency with sleep deprivation or poor quality sleep; therefore, maintaining adequate sleep hygiene and a consistent bedtime routine should be reinforced even after transition to an adult provider. Re-emergence of such parasomnias like confusional arousals, sleep terrors, and sleep walking should trigger an evaluation by the adult provider to rule out other sleep disorders or causes of fragmented sleep, which include stress, anxiety, inadequate sleep hygiene, or new onset of sleep disorders.

When transitioning adolescents to adult care who have parasomnias, it is important for the pediatric and adult provider to ensure they have educated those that live with him/her about the diagnosis. This will help decrease distress during an episode and discourage abrupt awakenings during the episode. Safety precautions are implemented to avoid harm to the individual. A multidisciplinary approach to treatment in the adult setting with psychology should be considered if there is underlying psychiatric diagnoses, such as anxiety, as ongoing CBT and hypnosis may be utilized to help with management.

For young adults with ongoing sleep talking, the adult provider may recommend family members or bed partners towear noise cancellation devices such as ear plugs to help improve their sleep. However, they should use these with caution, especially if there are safety concerns associated with night terrors or RBD.

Adolescents who continue to have nightmares typically continue with CBT. However, when they reach adulthood and continue to have problems with maintaining sufficient amounts of sleep, then pharmacologic agents are typically initiated in conjunction to CBT. As they transition to adulthood, periodic screening for other sleep disorders such as circadian rhythm disorders or sleep disordered breathing that may contribute to insufficient sleep is important.

Given that the age of onset for SRED is typically after adolescence, there are minimal transition considerations. However, pediatric providers who treat adolescents with eating disorders such as anorexia and bulimia should have increased awareness of SRED to ensure timely diagnosis and treatment. Adult providers

should frequently follow up after prescribing treatment for underlying sleep disorders or idiopathic SRED to monitor for resolution of related symptoms, weight changes, and drug-related adverse effects [11]. Ensuring the individual is also following up with their managing provider for his/her eating disorder is also strongly recommended.

Adolescents with enuresis into adulthood should continue behavioral modification techniques such as timed voiding and enuresis alarms; however, if they have failed, medical management with desmopressin is the first line of treatment. Frequent follow-up with the adult provider is necessary to monitor for resolution or treatment failure. Frequent screening measures of mental health is important as these patients can experience depression and anxiety. Ongoing collaboration with psychology may be beneficial.

Having the adolescent meet the adult sleep provider with the pediatric sleep provider is recommended to ensure a smooth transition and allow time to encourage both the caregiver and patient to share fears and concerns about transitioning care. Coordination of care can be labor-intensive, and in order to ensure a timely and successful transition, social workers and nursing play a vital role with this process. This essential step will help close the loop of communication and begin to reinforce the care that was provided by the pediatric sleep provider to ensure a safe and reliable transfer of care.

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Movement Disorders: Diagnosis and Management

11

Denise Sharon and Lourdes M. DelRosso

11.1 Restless Legs Syndrome

Patient Report of RLS Journey

I remember discomfort in my hamstring area of both legs from an early age. My mother would massage my legs while I sat in a warm tub at 5 years of age. I developed the habit of taking the corner of my knuckles and hitting the side of both legs for relief from the discomfort I experienced. The sensations were classic RLS, not significantly painful, just annoyingly uncomfortable, which caused me to have to move my legs especially during rest. When I stood up, my symptoms ceased.

RLS symptoms from best memory:

- *Ages 5 to 15—two to three nights per week, would toss and turn and get 5–7 h of sleep*
- *Ages 16 to 25—three to four nights per week, 5–7 h of sleep*
- *Age 34—chronic, every night without exception and without medication, same now*

Movies, plays, and airline flights in the evening required me to stand on my back often.

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During high school, I would feel the sensations and would keep my left leg straight in the air while I sat in my desk. Classmates made fun of me, but I was doing it out of necessity.

I started seeing doctors in my 20s when they didn't know much. I tried many measures to gain relief: liquid quinine, many multilevel marketing products/potions, magnets, differing changes in vitamin regiments, iron supplements, or even putting soap between my sheets (still don't understand the science behind that idea). I tried meditation, yoga, re-birthing, pounding tennis racquet into the pillow while screaming, massage, chiropractic, and various other remedies.

Restless legs syndrome (RLS) is a chronic sensory-motor disorder that can affect sleep. Early accounts from Europe by Willis (England) in 1685, Astruc (France) in 1736, Wittmaak (Germany) in 1861, Xue Ji (China) in 1529 [1], and later Ekbom (Sweden) in 1944 [2] described RLS symptoms in adult patients, frequently in women. Only recently, Walters, Picchietti, Ehrenberg, and Wagner (1994) reported on five case histories and alerted to the occurrence of RLS in children and adolescents [3]. RLS can present itself differently in children and adults. An early RLS phenotype was described with onset in children and adults 45 years or younger, mostly familial. Early phenotype RLS symptoms generally tend to progress slower and seem to be milder. The late phenotype has an onset after the age of 45 years, and symptoms may progress quicker and be more severe [4].

Epidemiology and Pathophysiology

The prevalence of RLS is around 2% in the pediatric population and tends to increase with age through adolescence [5–8]. The female to male ratio is 1:1 in young children and gradually increases to 2:1 in adults [9]. RLS symptoms were reported as early as infancy [10]. Up to 40% of adult patients with RLS report a history of symptoms since childhood or adolescence [11].

Most children and adolescents with RLS have a family member with a sleep-related movement disorder (SRMD), frequently with RLS, periodic limb movement disorder (PLMD), or a history of growing pains [12–14]. Genes that have been associated with RLS include BTBD9, MEIS1, PTPRD, MAP2K5, SKOR1, and TOX3 [15]. These genes have also been associated with periodic limb movements of sleep (PLMS). PLMS occur in the majority of RLS cases [16].

Low brain iron is the single best documented biological abnormality of RLS [17]. Iron was reduced in the substantia nigra, basal ganglia, and thalamus of RLS patients [18]. In many but not all cases, large increases in peripheral iron could correct brain iron deficiencies, controlling RLS symptoms for several months. As indicated by several studies, nitric oxide, adenosine, and iron chelation triggered cellular hypoxic pathway activation in the microvasculature and peripheral tissues of RLS patients [19]. These alterations in iron management starting at the blood brain barrier are suggesting that RLS is a functional disorder of iron acquisition by the brain. Genetic or epigenetic factors carried by approximately one third of the population may contribute to the risk of developing RLS with this iron shortage [20].

In children, iron deficiency has been linked to impaired cognitive development and academic achievement, febrile seizures, breath-holding spells, stroke, and psychiatric disorders [21]. The prevalence of iron deficiency is higher in children than in adolescents and lower in adults, but increasing in the elderly [22]. Previous fasting, diurnal variation, and inflammation may affect iron levels differently in children, teenagers, and adults [23].

Diagnostic Features

The diagnosis of RLS is based on clinical evaluation. It is time-consuming and challenging especially in the younger, less verbal group. The current diagnostic criteria are based on the third edition of the International Classification of Sleep Disorders (ICSD) published in 2014 [24] and are listed in Box 11.1.

Box 11.1 RLS Diagnostic Criteria (Adapted from ICSD-Third Edition) [24]

Criteria A to C must be met:

(a) An urge to move the legs, sometimes accompanied by uncomfortable, unpleasant sensations in the legs:
- Triggered or worsened by rest or inactivity
- Partially or totally relieved by movement
- Circadian—occurring exclusively or predominantly in the evening or at night

(b) Not solely accounted for as symptoms of another medical, behavioral, or sleep-related condition

(c) Symptoms cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, or other important areas of functioning

Diagnosis notes:

1. The urge can be present without uncomfortable sensations and can affect arms or other parts of the body.
2. For children, the description of the symptoms should be in the child's own words.
3. When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.
4. As a result of severity, treatment intervention, or treatment-induced augmentation, the worsening in the evening might not be noticeable but must have been previously present.
5. For certain research purposes, Criterion C might be omitted, and this should be clearly stated in the report.

The essential feature of RLS is the urge to move the legs. The urge needs to be expressed by the patient, regardless of age. The urge to move the legs or also the arms is usually accompanied by uncomfortable and unpleasant sensations. The sensations are usually felt deep inside the limbs and can be associated with pain. However, pain is less frequent in children than in adults. The child should express the urge to move the legs and the sensations in his/her own words. Used descriptors include "twitchy," "ants crawling," "funny legs," "tickles," "oowies," "boo-boos," "fidgety," "too much energy," "cola running," "spider in the legs," or "restless" [10]. The urge is triggered or worsened by periods of rest or inactivity and at least partially relieved by movement for as long as the activity continues. These symptoms are worse in the evening or night than earlier in the day, even though school-aged children may experience symptoms after prolonged sitting in class. Clinically significant disease is defined by RLS symptoms causing distress, sleep disturbance, affecting performance, or interfering with quality of life.

Several features can suggest or support a diagnosis of RLS in pediatric patients. These features presented in Box 11.2 are not essential for RLS diagnosis but are closely associated with pediatric RLS and therefore should be noted [25].

Box 11.2 Clinical Features Supporting the Diagnosis of Pediatric RLS (Adapted from Simakajornboon et al. 2015 [25])

1. PLMS >5/h
2. Family history of RLS among first-degree relatives
3. Family history of PLMS>5/h
4. Family history of PLMD among first-degree relatives

Diagnosing RLS in children is challenging and requires a complete clinical history involving the patient and parent(s) or caretaker(s). Children should be encouraged to give their own report while avoiding the introduction of bias from parents' report or leading questions [13]. Younger children may not be able to use language to describe their symptoms. Children may not be familiar with the concept of "urge" and may use "need to," "have to," or "got to" move or "kick." Since children and adolescents tend to spend prolonged periods of time sitting in classrooms, daytime symptoms can be frequent [26]. Adolescents might be working or going out in the evening, limiting opportunities to sit, relax, and trigger the typical circadian pattern of RLS symptoms. The clinical presentation of RLS may develop gradually, and it may take several years for all diagnostic criteria to be met. Initially, RLS course can be waxing and waning with prolonged periods of partial or complete remission of symptoms [10].

Nonspecific symptoms such as growing pains, restlessness, restless sleep, insomnia, and daytime sleepiness can further confound RLS diagnosis. Common RLS "mimics" in children [11] and in adults [27] are presented in Table 11.1. A thorough physical and neurologic evaluation can rule out "mimics" and assess for

Table 11.1 Common RLS "mimics" in children and in adults (Adapted from Chokroverty 2015 [27])

Children	Adults
Positional discomfort	Positional discomfort
ADHD	Abnormal restlessness: akathisia, abnormal muscular activity (myokymia, essential myoclonus, tremor), ADHD, leg stereotypy disorder, anxiety
Growing pains	Nocturnal leg discomfort/pain: neuropathies, radiculopathies, varicose veins, myalgias, arthritis, delusional parasitosis)
Sore leg muscles, ligament sprain, tendon strain	Combined unusual motor activity and leg discomfort/pain: painful muscle cramps, painful legs and moving toes, muscular or cramp fasciculation syndrome, causalgia-dystonia syndrome, intermittent claudication
Chondromalacia patella	Nocturnal hypermotor activity: rhythmic movement disorder, PLMD, hypnagogic foot tremor, hypnic jerks, alternative leg muscle activation, propriospinal myoclonus
Osgood-Schlatter disease	
Dermatitis	

comorbidities such as attention deficit hyperactivity disorder (ADHD), anxiety, neuropathies, or arthritis. RLS by itself result in a normal examination.

Diagnostic polysomnography (PSG) can complement the diagnosis of RLS but is not routinely indicated. PSG can demonstrate sleep abnormalities frequent in RLS such as prolonged sleep latency, increased arousal index, and frequent PLMS with or without arousals. The presence and number of PLMS can significantly vary from one night to another in both children and adults. Periodic limb movements during relaxed wakefulness (PLMW) are a valid and reliable tool for RLS in adults and have been used in adolescents. Used for research, the Suggested Immobilization Test (SIT) and the Multiple-SIT are quantifying the PLMW and corroborating them with a sensory report such as a Visual Analog Scale (VAS) [28]. SIT has been used successfully with adolescents and more recently with older children. A specific protocol for children consisting of parental narratives, structural behavioral observations, and SIT [29] is currently studied in RLS and in growing pain patients.

The assessment of iron stores is part of the initial evaluation for RLS. It should include ferritin, transferrin, iron binding capacity (IBC), serum iron, and hemoglobin (Box 11.3).

Box 11.3 Iron Stores*

- Ferritin >50 ng/mL
- Transferrin saturation >45%
- IBC >300 ng/mL
- Serum iron >70 ng/mL
- Hemoglobin 11–18 gm/dL

*Should be performed early morning, in a fasting state (if possible)

Management and Treatment Options

The severity of RLS symptoms needs to be assessed in order to evaluate need, efficacy, and response to treatment [30]. Several severity scales, including the Johns Hopkins Severity Scale, the International RLS Severity Scale (IRLS), and its self-administered form, the sIRLS, have been validated for adult patients, but none was validated for the pediatric RLS patients [31–33]. The IRLS has been used successfully with adolescents and older children, and one can assume that the sIRLS could be used in a similar way. The Pediatric RLS Severity Scale (P-RLS-SS) is a questionnaire with 17 morning and 24 evening items. It was developed based on detailed input from children and adolescents with RLS and their parents and from clinical experts providing it with strong content validity [34].

The behavioral management of RLS starts with education about the disorder, its chronic course, and its potential impact on sleep, general and emotional health, and quality of life [35]. Patients are instructed in maintaining a regular sleep/wake schedule, regular exercise, and stretch schedule. Avoidance of caffeinated substances and of foods, substances, or medications that may trigger RLS symptoms is recommended. Mind-occupying activities to prevent RLS symptoms are discussed. These may include crossword puzzles, conversation, knitting, and handicraft. Symptomatic relief can be achieved with leisure walking, bicycling, soaking the affected limbs, leg massage, and pneumatic compression. In young adults, changes in work/school schedule and occupational counseling can be considered [36].

In cases with low iron stores, oral iron supplementation (Box 11.7) is recommended [37]. Intravenous (IV) iron is recommended for adult patients with RLS and has been successfully used in children and adolescents [37–40].

Box 11.4 Iron Treatment* for RLS or PLMD

- **Young children:**
  - 1–6 mg/kg/day of elemental iron divided into 2–3 daily doses; 1 h before or 2 h after feeds
- **Older children and Adults:**
  - 325 mg ferrous sulfate +100 mg Vit C, twice per day, or in one dose
- **IV** iron can be considered in those with contraindications or side effects to oral iron:
  - **Adults:** ferric carboxymaltose 1000 mg one dose or two doses, 500 mg each, 5–7 days apart
  - **Children and adolescents**: limited data—iron sucrose 3.6 mg/kg, ferric carboxymaltose 15 mg/kg for weight <50 kg or 750 mg for weight >50 kg

Medications listed in Box 11.5 might be considered in those RLS children and adults who are not candidate or are not responsive to behavioral management and to iron treatment [41]. There are currently no FDA-approved medications for the

management of RLS in children [42]. An attempt to investigate the pharmacokinetics of the rotigotine transdermal system in adolescents resulted in improvement of RLS symptoms and was well tolerated [43], and a follow-up study was planned.

The general consensus is to consider symptom management on an as-needed basis in both children and adults. If in addition to iron treatment chronic medication is required, the recommendation is to start at the lowest dose based on age and weight and titrate slowly and carefully in order to better control emerging side effects, including impulse control disorder and augmentation [44].

Box 11.5 Medication: In those RLS Children and Adults Who Are Not Candidate or Not Responsive to Iron Therapy and/or Behavioral Management*

Generally, consider PRN use; start low, and go slow:

- Clonidine 0.05–0.4 mg/day at bedtime in children 6 years and older, mostly for insomnia and pain
- Benzodiazepine such as clonazepam, mostly for sleep: 0.125–1.5 mg depending on age
- Alpha-2 delta ligands:
  - Gabapentin: 5–10 mg/kg at bedtime or 2 h before to 50 mg/kg for younger children
  - Gabapentin: 100–300 mg at bedtime or 2 h before for children 12 years and older
  - Gabapentin for adults: 100–2400 mg 2 h before bedtime, or in divided doses
  - Gabapentin enacarbil (FDA approved in adults): adults: 300–600(1200) mg/day at circa 5 pm
  - Pregabalin: no data in children; adults 50–450 mg/day, 1–3 h before bedtime
- Dopaminergic agent precautions: lowest effective dose; use intermittently if possible; ensure adequate iron stores, prefer longer acting
- FDA approved for adults with RLS:
  - Ropinirole: 0.25–4.0 mg/day, 1–2 h before bedtime
  - Pramipexole 0.125–0.75 mg/day, 2–3 h before bedtime
  - Rotigotine patch: 1.0–3.0 mg/24 h
- Non-FDA approved: carbidopa/levodopa: 10/100–25/250 for as-needed use
- Opioids are successfully used in severe cases, but are not FDA approved for RLS treatment:
  - Prolonged release oxycodone/naloxone 5.0/2.5–40/20 mg twice per day was approved by the European Union for the treatment of RLS in adult patients.

*Unless mentioned otherwise, treatments are not FDA approved for RLS

Summary

RLS is a familial, chronic, sensory motor disorder that can start in early infancy. It is a functional disorder of iron acquisition by the brain. One in three adult RLS patients report childhood or adolescence symptoms, frequently undiagnosed. Essential diagnostic features may develop gradually over years or decades and are similar for children and adults. The diagnosis is clinical, based on the reported urge to move the legs, triggered by rest and relieved by movement, having a circadian pattern, and causing concern or interfering with everyday life. Most RLS patients have PLMS, and many have sleep complaints. The clinician should be aware of age-specific vocabulary and of common RLS "mimics" in children and in adults. ADHD is a common differential diagnosis and comorbidity. Research on treatment modalities in children and adolescents is very limited. Behavioral modifications are usually recommended. Iron supplementation and IV iron emerged as the evidenced-based treatment approach.

11.2 Periodic Limb Movement Disorder

Initially described as nocturnal myoclonus by Charles Symonds (1953) [44], PLMD is characterized by periodic episodes of repetitive, highly stereotyped limb movements that occur during sleep and are causing sleep disturbance or impairment of functioning [24]. Even though the disorder is called periodic limb movement disorder, periodic limb movements during sleep (PLMS) occur most frequently in the lower extremities. The typical movement consists of an extension of the big toe combined with a partial flexion of the ankle, knee, or, less frequently, hip, occurring at periodic intervals during sleep A similar pattern can be seen in the upper limbs and in other areas of the body. The movements can be associated with arousals and sleep disruption and demonstrate significant night-to-night variability in frequency and pattern [45].

In some PLMD patients, PLMS have been associated with frequent cortical and autonomic arousals, resulting in non-restorative sleep [46]. This association is challenged by arousals that precede, coincide, or follow PLMS, or are totally dissociated.

In adults with the increased PLMS arousals, transient increases in blood pressure and heart rate were observed, suggesting autonomic and sympathetic system activation. This activation presents a possible mechanism for cardiovascular risk. Results from few studies in children support the need for a better understanding of the cardiovascular implications of the PLMS [47, 48].

PLMD is thought to be a rare disorder, similar in both children and adults. The prevalence and the pathophysiology of PLMD have been confounded by the observation and the study of PLMS either asymptomatic or in association with other

sleep disorders, mainly with RLS. Genetic and dopamine dysfunction have been implicated in the pathophysiology of PLMS in both PLMD and RLS [49].

Low brain iron as reflected by measurements of iron stores has been associated with RLS and also with PLMD. Replenishment of iron stores has been associated with improvement in clinical symptoms, reduced PLMS, and possible remission [50, 51].

Diagnostic Features

The diagnosis of PLMD is based on both clinical history and PSG (Box 11.6). During the clinical evaluation, the extent of sleep disturbance and the possible functional impairment are assessed. Sleep disturbances may include sleep onset difficulties, sleep maintenance problems, or reports of unrefreshing sleep. The resulting sleep deprivation may result in excessive daytime sleepiness, increased irritability, or excitability. Children with PLMD may present with problems with focusing attention and maintaining concentration, hyperactivity, learning deficits, and decreased school performance. Increased irritability, anxiety, mood disorders, increased aggressiveness, or social withdrawal and oppositional behaviors have also been reported. Mood alterations, inattention, reduced productivity, and absenteeism were noted in adults with PLMD [52, 53].

Box 11.6 Diagnostic Criteria for PLMD (All Must Be Met) (Adapted from ICSD-Third Edition [24])

1. Diagnostic polysomnography demonstrates PLMS as defined in the most recent version of the AASM manual for the scoring of sleep and associated events.
2. The frequency of the PLMS is >5/h in children or >15/h in adults.
3. PLMS cause clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.
4. PLMS and the symptoms are not better explained by another disorder: sleep, medical, neurological, or mental (limb movements occurring with apneas/hypopneas or are in sync with breathing should not be scored as PLMS).

PLMS and other limb movements during sleep are frequently noted during sleep studies and might be associated with other disorders that can cause sleep disturbance or functional impairment. Their significance and possible impact have yet to be clarified. Common differential diagnoses of PLMD are listed in Box 11.7.

Box 11.7 Differential Diagnosis of PLMS in PLMD

- Sleep starts: limb movements are limited to the transition from wakefulness to sleep and shorter, not periodic.
- Fragmentary myoclonus: limb movements are shorter and less periodic with lower EMG amplitude.
- Benign sleep myoclonus of infancy: limb movements are shorter and more frequent, with less periodicity; more in the arms.
- Nocturnal epileptic seizures: limb movements are not periodic and not limited to the legs.
- Sleep disorders: RLS, SRBD, narcolepsy, occasional in sleep-disordered breathing.
- Neurologic disorders: ADHD, Asperger syndrome, Williams syndrome, spinal cord injury, dystonias, neurodevelopmental disorders.
- Medical conditions: sickle cell disease, end-stage renal disease, congestive heart failure.

Management and Treatment Options

The management of PLMD is similar in children and adults. It starts with a thorough clinical and physical examination, including diagnostic PSG in order to establish the diagnosis and assess possible comorbidities. In children, PLMD might precede RLS.

Iron stores need to be assessed. Low brain iron can worsen PLMS, resulting in a worsening of PLMD symptoms. If iron stores are low, oral iron supplementation should be considered (Box 11.4).

Alas, the treatment of PLMD has not achieved research prominence. Attempts to control symptoms through changes in habits and behavior may serve as the first line of treatment for PLMD (Box 11.8).

Box 11.8 Behavioral Management for PLMD

- Patient education about the disorder
- Establishing and maintaining a sufficient and regular sleep routine
- Regular exercise in the early part of the day
- Avoid caffeinated beverages
- Review use of medications/supplements that may worsen PLMS

There is limited evidence-based data on the pharmacologic treatment of PLMD. Most research focused on improving sleep-related symptoms and reducing PLMS. It is important to note that there is no evidence that asymptomatic PLMS

need be treated. Considering the frequent association of PLMS with RLS, current medications used for PLMD (Box 11.9) are symptom directed and follow RLS treatment recommendations [49, 54]. Dopamine agonists tend to be effective in reducing PLMS with less need for higher doses.

Box 11.9 Medication: In Children and Adults with PLMD Who Did Not Respond to or Are Not Candidates for Iron Therapy and/or Behavioral Management (None Are FDA Approved for PLMD)

- Clonidine 0.1–0.4 mg at bedtime in children 6 years and older mostly for sleep complaints
- Benzodiazepine mostly for sleep complaints:
  - Clonazepam: 0.01–0.03 mg/kg at bedtime for children <10 years
  - Clonazepam: 0.25–0.5 mg at bedtime for children 10 year and older
  - Clonazepam: 0.5–1.5 mg at bedtime for adults
- Dopaminergic agent precautions: low dose, intermittent, ensure adequate iron store, longer acting, start low, go slow:
  - Ropinirole: 0.25–4.0 mg/day, up to 3 h before bedtime
  - Pramipexole 0.125–0.5 mg/day, up to 3 h before bedtime
  - Rotigotine patch: 1.0–3.0 mg/day
- Alpha-2 delta ligands:
  - Gabapentin: 5–10 mg/kg up to 2 h before bedtime up to 50 mg/kg for younger children
  - Gabapentin: 100–300 mg up to 2 h before bedtime for children 12 years and older
  - Gabapentin for adults: 100–2400 mg up to 2 h before bedtime, or in divided doses
  - Gabapentin enacarbil: no data in children; adults, 600 mg/day around 5 pm
  - Pregabalin: no data in children; adults 50–450 mg/day, up to 3 h before bedtime

Summary

PLMD is an uncommon, possibly underdiagnosed motor disorder that can profoundly affect sleep and daytime functioning. It can affect both adults and children, even infants. In some pediatric cases, PLMD progresses to RLS. PLMD is characterized by the presence of PLMS as established by diagnostic PSG and by reported sleep disturbance or impairment in functioning. PLMS can be asymptomatic or present in other disorders. Research focus on PLMS and confusion between PLMS and PLMD have hampered current understanding of PLMD, leaving clinicians scrambling for clinical and therapeutic insights.

11.3 Sleep-Related Bruxism

Sleep-related bruxism (SRB) presents different in children and adults. There are variations in risk factors, prevalence, and treatment options that are age dependent. The understanding of these differences is of utmost importance when transitioning patients with bruxism from a pediatric sleep center to an adult center. In this section, we will discuss the differences in bruxism across the various ages and some treatment options and transitioning considerations.

Diagnostic Features

AASM has established the diagnostic criteria for SRB, which includes regular tooth grinding during sleep and jaw pain, jaw locking, or temporal headache upon awakening [24]. The prevalence of SRB is highest during childhood, affecting up to 33% of young children with a slight higher prevalence in the school-age (6–12-year-old) group (35%) when compared to preschoolers (aged 3–5 years old) (31%) [55, 56]. Thereafter, the prevalence of SRB decreases with age, affecting up to 12% of adolescents and reaching a low 3% in older adults [57]. Bruxism in children younger than 12 years of age has been associated with second-hand smoking; disruption in sleep such as noise, light, and insufficient sleep; stress level and personality traits; and oral parafunctions such as clenching teeth or biting on non-food items [58–60]. The majority of parents of children with bruxism report that the amount of sleep is not affected, although in 29% of cases, sleep quality may be compromised [56]. Snoring, nightmares, sleep talking, and nocturnal agitation are also associated with bruxism in this age group [56].

Studies in adolescents with bruxism have shown that snoring every night has a strong association with SRB. Other associations include bad sleep hygiene, frequent headaches, tooth wear, jaw fatigue, daytime sleepiness, and difficulty waking up in the morning [57, 61]. Tooth wear has been reported in up to 51% of adolescents with bruxism [62]. Another important factor in adolescents is the strong association between SRB and depression [63]. The prevalence of depression found to be 5% in early adolescence increases to 20% in late adolescents [64]. And although a causal relationship cannot be established, identifying adolescents with depression in the dental setting is of utmost importance to ensure a prompt referral for evaluation and treatment. Smoking is also a moderate risk factor in adolescents [57].

A study in young adults between 18 and 30 years old, with bruxism, showed that the main symptoms in this age group were stress, fatigue, or anxiety in 76.3%, pain in the temporomandibular joint in 17%, and muscle pain in the region of the head, face, and neck in 25.7%. Tooth wear was also significant in this age group. In this study, smoking, alcohol consumption, sleep quality, biting nails, and acidic food consumption were not associated with bruxism [65].

Treatment Options

In general terms, treatment options for bruxism vary and include:

1. Intraoral: mandibular advancement appliances, occlusal adjustment, occlusal splints
2. Physiotherapy for masticatory muscles with electrical stimulus: biofeedback, transcutaneous stimulation, electrical stimulation
3. Drug therapy: antidepressants, antiepileptic, sympatholytic
4. Intramuscular injection: botulinum toxin A
5. Biofeedback: audible noise
6. Behavioral: relaxation techniques, sleep hygiene, cognitive treatment
7. Kinesiotherapy: masticatory muscles massage
8. Myofunctional therapy [66, 67]

In children, treatment options include occlusal splints, orthodontic treatment, psychological approach, pharmacological approach, physical therapy, and pharmacological treatments. Five medicines have been used in children. Trazodone at a dose of 0.5 mg/kg/day showed a significant reduction in bruxism frequency and morning pain after 2 and 4 weeks [68]. A single report using imipramine (25 mg/day) for 1 month reported improvement based on parental report [68]. Hydroxyzine was used at a dose of 25–50 mg at bedtime, showing decreased bruxism score more than the placebo [69]. Flurazepam was administered at the dose of 15 mg at bedtime with improvement in bruxism, parasomnias, and excessive movement during sleep [70]. Another study using diazepam at a dose of 2.5 and 5 mg in children 2–8 years old showed results were not statistically different between treatment group and placebo [71]. Occlusal splints have also shown reduction in self-reported bruxism in children by 76.7% along with reduction headaches and muscular discomfort [68]. Orthodontic interventions include fixed appliances and rapid maxillary expansion and have shown a reduction in self-reported bruxism improvement in headaches [6].

Summary

Bruxism prevalence decreases with age, but the consequences of tooth wear, headaches, maxillary pain, and daytime symptoms can persist and worsen if not adequately treated. There are limited treatment options for children and scarce data on medications. The treatment options increase when transitioning to adulthood particularly with the addition of intramuscular injections, physiotherapy, and a wider option of medications.

11.4 Sleep-Related Rhythmic Movement Disorder

Sleep-related rhythmic movement disorders (RMD) is commonly seen in young children, and in the majority of cases, RMD resolves by the age of 10; however, in some instances, it can persist into adolescence and adulthood. Although parental

reassurance may suffice for children with RMD, transitioning into adult care may have significant social implications for the young adult. In this section, we will discuss the diagnostic features and treatment options of RMD in both children and adults and some of the considerations when transitioning care of young adults with RMD.

Diagnostic Features

The identification of rhythmic movements is based on history and physical exam. Most patients with sleep-related rhythmic movements do not have any other complaints, and the course of the movements is benign and self-resolving. The International Classification of Sleep Disorders-Third Edition (ICSD-3) [24] has clear diagnostic criteria for sleep-related rhythmic movement disorder. Patients must present with rhythmic, stereotyped, and repetitive movements involving large muscle groups (especially neck and trunk muscles) that occur predominantly during drowsiness or sleep and with a complaint of sleep interference, impaired daytime function, or self-inflicted bodily injury while the movements are not better explained by seizures or another medical disorder [24]. The American Academy of Sleep Medicine Scoring Manual has further characterized the movements as having a frequency of 0.5–2 Hertz and with a minimum number of four clustered movements.

Although the majority of cases are seen in normally developing children, associations with children with neurodevelopmental disorders have been reported [72, 73]. When present in children, sleep-related rhythmic movements occur at sleep onset or in sleep stage transitions. When persisting into adulthood, the movements can occur in all sleep stages and can persist through the night. Furthermore, cases of RMD exclusively occurring in REM sleep have been reported. In these cases, REM atonia was preserved during REM periods without rhythmic movements [74, 75]. A case series of five adults with RMD showed that 81.4% of the rhythmic movements were triggered by a respiratory event, and in one case, RMD improved after CPAP [76].

An association between RMD and psychopathologies was suggested when RMD persisted beyond childhood. This association was refuted by Mayer et al. (2007) who demonstrated that the majority of adult patients with RMD did not have abnormal psychopathology [75].

Treatment Options

Currently there are no treatment guidelines for RMD in children or adults. In most cases, treatment might not be required. More research is needed on potential treatment options for RMD that causes a sleep disturbance. General recommendations include achieving adequate sleep, keeping a consistent bedtime routine, and taking safety measures. Patients with comorbidities that may result in arousals or

awakenings, such as sleep-disordered breathing, should be offered treatment for the primary disorder, as sleep consolidation may improve RMD [75]. Other treatment options used with varying degrees of success include benzodiazepines, antidepressants, melatonin, and hypnosis [77, 78].

Summary

RMD is common in childhood with spontaneous resolution but in a few cases can persist into adulthood. The diagnosis of RMD requires a history of rhythmic movements and sleep disruption, injury, or daytime sleepiness. Evaluation with polysomnography is not routinely done, unless a comorbid sleep disorder is suspected. Although most cases do not require medications, some with more persistent or disruptive rhythmic movements may benefit from a treatment trial. Small case series and individual cases reported treatment attempts with benzodiazepines, antidepressants, and melatonin.

11.5 Restless Sleep Disorder

Parents often bring their children to pediatric sleep centers for evaluation of restless sleep [79]. Questionnaire-based studies asking if sleep was thought to be "restless" have shown that a large percentage of children with restless legs syndrome (RLS) and children with periodic leg movements of sleep (PLMS) present with restless sleep [13]. Restless sleep has also been seen in adults, except most studies evaluating restless sleep in adults have been confounded by comorbidities. In this section, we will discuss restless sleep disorder and implications for transitioning into adult sleep centers.

Diagnostic Features

Restless sleep has commonly been defined as "persistent or recurrent body movements, arousals and brief awakenings that occur in the course of sleep," [80] but often, the definition is vague. Recently, a group of children with restless sleep and daytime symptoms that do not fit criteria for other sleep diagnosis have been characterized clinically and polysomnographically in comparison to children with RLS, PLMS, or sleep-disordered breathing (SDB). This condition has been called restless sleep disorder (RSD) [81]. The proposed diagnostic criteria for RSD include:

1. Motor sleep patterns characterized by movements involving large muscle groups persisting through the night, occurring almost every night, and comprising more than five movements per hour of sleep
2. Sleep latency and sleep time within expected range for age

3. The nocturnal movements result in perception by parent of restless sleep or impairment in daytime function (sleepiness, affected school performance, irritability, or hyperactivity)
4. The condition is not better explained by behavioral or medical disorders or medication effect [82].

The prevalence of RSD has been estimated to be 7.7% of children referred to a sleep center [79]. Diagnostic polysomnography is essential to diagnose RSD by identifying the large body movements and quantifying them to at least 5 per h and by excluding other sleep disorders such as PLMD or SDB. In adults, RSD is yet to be studied. Previous studies have identified adults with restless sleep, but associated comorbidities were also present. Depression, arthritis, and obstructive sleep apnea have been associated with restless sleep in adults [83–86]. To this date, there are no reports on video identification of movements during sleep in adults with restless sleep.

Treatment Options

Children with RSD had ferritin levels below 50 μg/L (mean 20.8) [79]. The low ferritin levels may indicate decreased iron stores, similar to patients with restless legs syndrome (RLS) [20]. Currently, there are no FDA-approved medications for the management of RSD in children. Iron supplementation has been suggested as an initial treatment [87]. In adults, treatment of the associated comorbidity has shown to improve restless sleep; for instance, in patients with SDB, using continuous positive airway pressure improved restless sleep [84, 88].

Summary

RSD has been identified in children, but the natural progression of the condition is still unknown. Therefore, we recommend following children with RSD periodically to reassess sleep symptoms and iron levels. Transition to an adult sleep center should include education of adult sleep specialists on RSD to appropriately identify potential symptoms. Similarly, adults with restless sleep should be thoroughly evaluated to identify potential comorbidities contributing to the sleep symptoms.

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Circadian Rhythm Disorders in Children and Adults

12

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12.1 Circadian Rhythm Across the Life Span

Circadian rhythm, or the rhythm of life, is an essential element in the control of sleep wake cycles. The term circadian comes from the Latin words *circa* = about and *dien* = day. Circadian rhythms are endogenous rhythms lasting about 24 h or a day. These rhythms are seen in many aspects of human physiology, including daily rhythms in body temperature, in hormone production and secretion, and even in cardiovascular function and platelet function. However, the circadian rhythm seen in sleep wake cycles is the most distinctive and apparent to humans.

12.2 Influence of the Circadian Rhythm on Sleep

A person's circadian rhythms are determined by both genetic and environmental factors. The intrinsic circadian system acts like an alerting signal to promote wakefulness. The homeostatic drive, or sleep debt, is the other factor that influences sleepiness. The drive to sleep is the most when the homeostatic drive is the highest and the circadian system signal is the lowest. After a full sleep period, the

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homeostatic drive is the least. Combined with a high circadian alerting system level, this results in wakefulness and alertness. As the day progresses, the sleep debt, homeostatic drive, increases. With an overall high circadian alerting signal however, wakefulness continues. As evening approaches and light decreases, the circadian signal lessens. This combined with an exceedingly high sleep homeostatic drive results in the onset of sleep.

The intrinsic circadian sleep wake cycle in the absence of environmental cues is about 24.5 h. It needs to be modulated to match the earth's 24-h day-night cycle. This regulation, or entrainment as it is called, is determined by many cues. The cues to entrain systems to the circadian rhythm are also known as *zeitgebers* (German for time-giver). The biggest *zeitgeber* is the presence of light [1].

Light is detected by melanopsin containing photoreceptors located in the retina. These receptors are different from the rods and cones present in the retina that participate in the visual pathway. Signals from the melanopsin-containing photoreceptors travel through the specialized retinal projection system called the retinohypothalamic tract. Projections from this tract terminate on the suprachiasmatic nucleus (SCN), which is located above the optic chiasma in the hypothalamus. The inherent rhythm of the body and the SCN without the light input is about 24.5 h. With the light input, this rhythm is entrained to the 24-h cycle. The effect of light on the SCN is dependent on the phase of the circadian rhythm and time of day. Light has the biggest influence during changes from light to dark and vice versa.

In addition, fibers of the retinohypothalamic tract terminate to the thalamic intergeniculate leaflet (IGL). Projections from the IGL to the suprachiasmatic nucleus exist and are known as the geniculo-hypothalamic tract (GHT). GHT provides a secondary indirect pathway for the light cue to reach the SCN. IGL also plays a role in the entrainment of the circadian system by cues other than light.

SCN additionally receives signals from the median raphe nucleus of the midbrain directly and again indirectly through the IGL. These projections also participate in the mediation of non-light cues to the circadian system regulation.

The output pathways from the suprachiasmatic nucleus innervate target areas in the diencephalon and basal forebrain, which in turn target the circadian system messages to the sleep-wake systems, autonomic and neuroendocrine systems.

12.3 Circadian Rhythm Through the Life Span

Circadian rhythms start during early infancy. Sleep rhythms are irregular during infancy and slowly consolidate over time. The phase of sleep onset and waking is earlier during childhood than during adolescence. During adolescence and puberty, there is a biological drive toward phase shifting, leading to delayed sleep onset and wake times. Most adults have a usual phase sleep cycle. Older adults, however, tend to again revert to an early phase circadian rhythm, possibly due to ageing of the circadian system [2].

12.4 Pediatric Sleep and Rhythm

The circadian rhythm starts at early stages in fetal development. Between 6 and 18 weeks' gestation, the suprachiasmatic nucleus, which is the central controller of the circadian rhythm, develops. During the fetal period, the rhythms seen within the fetus include day-night rhythms in heart rate and respiratory rate and production of adrenal hormones. However, it is found that the rhythmicity of the fetus matches the mother's and so may be driven by the mother's rhythm rather than the fetus. By gestational age 18 weeks, melatonin and dopamine receptors are present in the fetal SCN, suggesting a role for these, being the cues for circadian information reaching the fetus [3, 4]. Additionally, the mother's core body temperature variations, eating schedule, and cortisol release circadian rhythms probably influence the fetus' rhythm [5].

After birth, full-term infants show little circadian rhythm immediately but develop day-night differences in activity within the first 2 weeks of life. It is during this time that the infant moves from responding to internal cues to external cues such as light [6]. During this time, rhythms in hormone production also start developing with the diurnal variation in cortisol levels apparent by 3–6 months of age. Melatonin production starts by 12 weeks of age, and over the next few months, consolidation of periods of rest and activity starts to develop [7]. Around this time, almost 70% of children sleep for about a 5-h stretch at night [8]. Between 3 and 6 months of age, the infant usually has three sleep periods with two short naps in the morning and afternoon and a longer sleep period at night.

Sleep during childhood continues to transition to more sleep consolidation to the nighttime. By about 2 years of age, the morning nap is transitioned out, and by age 6, most children stop daytime naps and sleep during the night.

12.5 Sleep During Adolescence

During adolescence, with the onset of puberty, circadian rhythms start to delay as seen by changes in the time of sleep onset that starts to occur later in the night and a phase delay in melatonin rhythm as well [9]. This phase delay is dependent on the presence of gonadal hormones [4]. There is also an increased sleep requirement and more daytime sleepiness. This is because the intrinsic period or circadian length of adolescents becomes longer, up to 25 h or longer (as opposed to 24.5 h in adults) [10]. Additionally, environmental factors, such as electronics usage, social pressures, and removal of parental oversight on bedtimes, result in changes in the sleep timings and duration. Electronics usage in particular plays a big role as the light exposure from the devices during the late evening and night times leads to a suppression of melatonin secretion in adolescents. The sensitivity of the circadian system to influences of light seems to be more prominent during the adolescent phase of life [11].

12.6 Sleep During Adulthood and Later Life

Between the ages of 20 and 50, adults gradually shift from the delayed phase of adolescence to an earlier circadian phase. During this time, sleep wake cycles are greatly affected by environmental cues such as work and social responsibilities [12]. Childcare responsibilities also impact the sleep cycle and phase of adults. Extrinsic circadian rhythm disorders during adulthood include shift work disorder and jet lag disorder. Shift work, where the timing of the work schedule occurs during habitual nighttime, has been associated with an increased risk of cancer, heart disease, and depression [13].

Older people tend to sleep less and have poor-quality sleep. The circadian sleep phase tends to advance further. This may be due to a decrease in melatonin levels. Endogenous body temperature nadirs also occur 2 h earlier than in younger adults [14].

12.7 Circadian Rhythm Disorders

Circadian rhythm sleep-wake disorders (CRSWD) are defined by the International Classification of Sleep Disoders-3 to have the following general criteria [15]:

1. A chronic or recurrent pattern of sleep-wake disruption related primarily to an alteration of the endogenous circadian timing system of a misalignment between the endogenous circadian rhythm and sleep-wake schedule desired or required by an individual's physical environment or social/work schedules.
2. The circadian rhythm disruption leads to excessive sleepiness, history of insomnia, or both.
3. Sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.

Abnormalities in the circadian rhythm system at various levels can result in clinical disorders. Disorders of entrainment can occur if there is destruction of pathway bringing the light cue to the SCN. This can occur due to lesions in the retinohypothalamic tract or in the melanopsin-containing retinal cells. In blind persons with loss of rods and cones but intact melanopsin-containing cells, circadian rhythm entrainment persists. However, in those with complete destruction of the retina or the RHT tract, loss of entrainment results in a free-running circadian rhythm with a duration of about 24.5 h. This results in the sleep period being shifted by about 30 min each day. Problems with entrainment can also occur if individuals are exposed only to constant indoor lighting or darkness.

Damage to the SCN itself can also result in loss of a fixed circadian rhythm. These can be seen with anterior hypothalamus lesions or tumors.

The most common cause of circadian rhythm disorders is due to the endogenous clock or rhythm being out of sync with the external light-dark cycle. This can cause

the major sleep period to be prior to usual time of sleep based on light. This is known as advanced sleep phase disorder. Delayed sleep phase disorder occurs when the endogenous sleep phase occurs later than the usual sleep time. Extrinsic disorders of circadian phase occur due to asynchrony between the endogenous sleep wake cycle and external light dark timings due to travel (jet lag) or work schedules (shift work disorder).

Among children, the most common circadian rhythm disorders are delayed sleep phase disorder, free-running sleep phase disorder, or irregular sleep wake disorder.

12.8 Specific Circadian Rhythm Disorders

Delayed Sleep Phase Disorder

This disorder occurs when the circadian-driven sleep cycle is delayed and the sleep onset is after the desired bedtime. Sleep complaints of sleep-onset insomnia can occur if the patient tries to go to bed at the desired bedtime but the circadian rhythm cycles is delayed beyond that. If the wake time is set by societal requirements (e.g., work or school), then the person can get inadequate sleep and have symptoms of daytime sleepiness.

In infants and children, delayed sleep phase disorder can occur due to a limit-setting disorder. Lack of parental limits on sleep time and wake time can result in children having a later sleep onset.

Delayed sleep phase disorder is the most common circadian rhythm disorder seen in adolescents. In a Norwegian study of 1285 high-school students between the ages of 16 and 19, 17.2% reported difficulty falling asleep before 2 am at least three nights a week, and 27.3% reported difficulty awakening at desired time. 8.4% reported both symptoms and met the researchers' criteria for delayed sleep phase [16]. Those who met this criteria showed lower-than-average school grades, higher levels of depression and anxiety, and increased usage of tobacco and alcohol. A study of sleep schedules and daytime functioning in 3120 adolescents showed that up to 87% of adolescents studied felt that they needed more sleep than they got. Most tended to delay their sleep onset and awakenings on the weekends as compared to school days. The delayed circadian phase that is commonly seen in adolescents combined with the need to awaken earlier than desired due to early school times led to decreased total sleep time [17].

Advanced Sleep Phase Disorder

This disorder is seen when the circadian-driven sleep cycle is advanced such that sleep onset is before desired bedtime. The patient or parent can complain of early evening sleepiness prior to desired bedtime and also of early morning awakenings. Advanced sleep phase disorders are more common in the geriatric population. In children, the early morning awakening following an early bedtime occurs with

otherwise normal sleep quality and quantity. The consequences of ASPD are social if the child has to leave evening after-school activities early or is unable to complete homework.

Irregular Sleep Phase Disorder

Irregular sleep-wake pattern consists of disorganized and variable times of sleep and wake. The total sleep time is normal, but it is broken up into multiple irregular bouts of sleep. This pattern is normal in newborns and infants up to age 6 months. Beyond this age, this sleep pattern is considered abnormal. In children, it is commonly associated with neurologic impairment. In the elderly, especially those with neurodegenerative disorders like Alzheimer's disease, this irregular sleep phase pattern can occur.

Free-Running (Non-24 h) Sleep Wake Disorder

This disorder occurs when there is no entrainment to the light stimulus and 24-h cycle and is seen most commonly in blind people. The sleep-wake period is about 24.5 h without light entrainment, and therefore patients can have a shifting sleep schedule every day. A chronic pattern of delays in sleep onset and wake times can cause complaints of periodic insomnia followed by periodic excessive daytime sleepiness [18].

12.9 Circadian Rhythm Disorders in Neurodevelopmental Disorders

Circadian rhythm sleep disorders are seen in many neurodevelopmental disorders in children and adults. One of the most common neurodevelopmental disorders is ADHD (attention-deficit hyperactivity disorder). Children with ADHD report delays in sleep onset, eveningness preference, and poor sleep quality. They also show abnormal melatonin rhythms with phase delays and reduced amplitude [19]. Adults with ADHD can show delays in cortisol rhythm and decrease in the amplitude of their melatonin rhythms [20]. Sleep disorders are very common in children with autism spectrum disorders. Though a classic circadian rhythm disorder has not been defined in this subgroup of neurodevelopmental disorders, a decrease in evening melatonin levels has been found [21]. Administration of melatonin has been found to be helpful in treating children with ASD and sleep disturbances [22].

12.10 Circadian Rhythm Disorders in Neurodegenerative Disorders

Sleep disorders are more prevalent in elder individuals with neurodegenerative disorders such as Alzheimer's disease (AD) or Parkinson's disease (PD). Lower melatonin levels are seen as well as later sleep onset [23]. These sleep disorders may

precede other symptoms in PD and so may be a good early diagnostic finding. Sundowning is a common syndrome in patients with dementia in which increased restlessness, delirium, and agitation are seen in the early evening. Phase delay in sleep circadian cycles and decrease in body temperature rhythms correlate with the severity of sundowning symptoms [24].

12.11 Diagnostic Testing for Circadian Rhythm Disorders in Children and Adults

Detailed history taking is the most useful tool in determining if a circadian rhythm disorder is present. Details about sleep time and wake time, how long it takes to fall asleep, whether they are consistent or not, and how the pattern is on weekends and on holidays are useful questions to establish the pattern of sleep-wake cycle. If sleep patterns are irregular or out of sync with social and familial expectation, then a circadian rhythm disorder may be present [7].

A sleep log is helpful in determining the sleep schedule. Patients or caregivers are asked to record various parameters of sleep over a 2-week period, and this can be analyzed along with the sleep history to determine whether any circadian rhythm disorders are present.

Another diagnostic tool used to assess for circadian rhythm disorders is actigraphy. An actigraph is a watch-sized motion sensor usually worn on the wrist for a 2-week period. A sleep log is also kept by the patient during the same time. At the end of the recording, the data can be downloaded and analyzed to determine sleep onset time, wake time, time in bed, and duration of sleep. Actigraphy is recommended for use in both adults and children with circadian rhythm sleep wake disorders in the clinical guidelines for the use of actigraphy by the American Academy of Sleep Medicine [25]. Actigraphy is a useful tool especially in pediatrics to determine sleep patterns as children or adolescents may not be able to give a complete history or an accurate sleep log. Other diagnostic tests like polysomnogram (PSG) or MSLT (multiple sleep latency testing) are not required for the diagnosis of circadian rhythm disorders but may be useful in ruling out other sleep disorders.

12.12 Management of Circadian Rhythm Sleep Disorders in Children and Adults

The main management strategies in circadian rhythm sleep disorders include sleep hygiene, light therapy, melatonin therapy, and chronotherapy.

Sleep Hygiene

Good sleep hygiene principles include regular bedtimes and wake times on all days of the week, regardless of social and work schedules. Even if the patient has to stay up late on a few nights, the wake time should remain the same.

Light Therapy

Light therapy, or phototherapy, is the main management modality for DSPS in adults. Light has been long recognized to modulate circadian rhythm in humans [26]. The timing of administration of phototherapy is key to obtaining optimal therapeutic results. Light therapy administered after the temperature minimum (T_{min}), which is usually about 2 h before intrinsic habitual wake time, will result in a phase advancement of the circadian rhythm. If light therapy is administered before this T_{min}, then phase delay will occur.

Melatonin and Agonists

Melatonin has been used widely in the treatment of circadian rhythm disorders and insomnia. Melatonin is an endogenous endolamine produced in the pineal gland from the amino acid tryptophan. The secretion is regulated by the suprachiasmatic nucleus. Melatonin secretion starts at the onset of dim light (dusk) and in proportion to the duration of darkness [27, 28]. Melatonin activates melatonin 1 (MT1) and melatonin 2 (MT2) receptors in the SCN. When melatonin is given therapeutically, it acts as a hypnotic agent [29]. It's role as a chronotherapeutic agent is debated. However, it is established that administration of melatonin at the same time every day can help entrain the circadian rhythm especially in free-running form [30]. Tasimelteon is a new MT1 and MT2 receptor agonist with more affinity for MT2 receptors than MT1 receptors and therefore useful in the treatment especially of non-24-h free-running disorder.

Delayed Sleep Phase Syndrome

It is important to keep a set bedtime and wake time during all days of the week. Reverting to the intrinsic delayed sleep circadian rhythm on the weekends will cause the phase delay to persist. Avoiding electronics and bright lights in the evening is especially important in the treatment of this disorder. Bright lights from electronics can cause a further phase delay due to the response of the circadian system to light. Studies have shown that properly timed light therapy can cause a phase advance of circadian rhythm in patients with DSPS [31]. Light therapy should be administered in the mornings *after* the temperature nadir (Tmin). In order to clinically determine what the Tmin for the patient is, one would need to determine what the patient's intrinsic wake time is (e.g., what time the patient wakes on weekends or holidays without an alarm) [32]. Melatonin can be administered about 6 h before the desired time for sleep in both adults and children, with or without psychiatric comorbidities [32]. This causes a shifting of the endogenous melatonin secretion to an earlier time and helps with resetting the phase in DSPS. Chronotherapy, or progressively advancing sleep phase until desired sleep time is reached, may be useful for DSPS [33]. However, it is very

cumbersome for the patients to follow this therapy, which is required to be done over a few weeks.

Advanced Sleep Phase Syndrome

Treatment of advanced sleep phase syndrome is similar to that of DSPS but in the opposite time of administration of therapies. The child or adult with ASPS should be exposed to light therapy in the evenings, and melatonin administration should be early morning. In the morning, the room should be kept dark. Exercise in the evening can also be recommended.

Irregular Sleep-Wake Rhythm (ISWR)

In the treatment of ISWR, daytime bright light exposure may help. Multiple studies have shown a positive benefit of bright light exposure in nursing home patients with dementia [33]. The best management strategy for these patients, however, is a mixed modality strategy incorporating bright light exposure along with physical activity and other behavioral elements. Melatonin is *not* indicated for the treatment of ISWR in elderly patients with dementia but may be useful in treating children with ISWR and severe psychomotor retardation. Mixed modality therapy may also be useful for these children [33].

Free-Running (Non-24 h) Disorder (FRD)

As in the other circadian rhythm disorders, keeping a regular bedtime and waketime schedule is important in the management of this disorder. Morning light therapy may be useful to entrain sighted patients with FRD. In blind individuals, the use of external cues, other than light, are key for the patient to determine the time of day. Therefore, a regular schedule during the day, consisting of exercise, fixed mealtimes, and social activities, is useful to prevent napping during the day. Melatonin (commonly 3 mg dose) administered 1 h before desired bedtime is useful in establishing a regular sleep-wake schedule in sighted patients as well as blind patients with FRD [34, 35]. Tasimelteon, a potent dual-melatonin receptor agonist, has been the only FDA-approved drug for use in the treatment of free-running disorder [36].

12.13 Conclusion

Circadian rhythms are endogenous biological rhythms that last around 24 h and exist in all living organisms. The circadian rhythm starts to develop during the fetal period, and its physiology changes through an individual's life span. When there is a misalignment of a person's endogenous circadian rhythm with the desired

sleep-wake schedule, circadian rhythm sleep disorders emerge and can cause daytime sleepiness or insomnia. Circadian rhythm sleep disorders are common both in the pediatric age group and in adults and in the geriatric age group. The type of disorder, however, can vary with age. Additionally, what is normal sleep pattern at one age can be a disorder at another age, e.g., an irregular sleep-wake rhythm is normal in infants but abnormal when seen in older children and older adults. Similarly, a delayed sleep phase circadian rhythm is normal in most adolescents but can cause problems in adults. Advanced sleep circadian phase is seen normally in children but can be a disorder in older adults. The management of these disorders also varies from the pediatric age to adults to elderly. Transitioning care of patients from pediatric to adult medicine requires a good understanding of the normal circadian physiology and the various circadian sleep disorders.

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13 Transitional Care Aspects of the Diagnosis and Management of Narcolepsy and Other Primary Disorders of Hypersomnia

Brian J. Murray

13.1 Introduction

Transitional care is an emerging system model for helping adolescents reach adult care in a seamless transition. This model of care may help avoid lapses in care and improve health outcomes during the period of transition. This is particularly important for patients with narcolepsy and related disorders given the frequent presentation in this age range and the significant psychosocial implications of these disorders. This chapter will briefly review central hypersomnia conditions and describe general concepts of transitional care. Some practical strategies will be described to facilitate the successful transition of narcolepsy and hypersomnia patients to adult care. We will discuss an example of a transitional care model and outline important research needs for the future.

Narcolepsy

A complete review of narcolepsy is beyond the scope of this article but is well summarized in a recent review [1]. In summary, narcolepsy is a relatively common sleep and motor control disorder affecting approximately 1 in 2000 persons. Sleepiness is necessary for the diagnosis and can contribute to poor school performance. Type 1 narcolepsy is characterized by cataplexy—the loss of motor control precipitated by emotion, most commonly laughter. This finding is pathognomonic for the disorder

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and is seen in about 60% of patients with narcolepsy [2]. Cataplexy can be particularly dangerous in situations such as driving. Patients with narcolepsy can also have sleep onset hallucinations. Patients may be initially reluctant to describe this for concern over their perceived mental health. Sleep paralysis can occur; patients are briefly unable to move on waking, which can be frightening. This condition has a major impact on quality of life. Disrupted night sleep is also commonly noted.

Approximately 20 years ago, disrupted signaling of a novel neuropeptide—hypocretin, also known as orexin—was demonstrated to be critical for emergence of the disorder. Recent studies have noted an autoimmune destruction [3] of orexin/hypocretin following H1N1 [4] flu exposure. Onset of this condition is typically in teens or early 20s but can occur at any age.

Other Primary Hypersomnia Conditions

The International Classification of Sleep Disorders-Third Edition describes a number of other disorders of hypersomnolence [5, 6]. Idiopathic hypersomnia [7] is notable for sleepiness without REM sleep-associated features such as cataplexy or hallucinations. These patients can have significant difficulties waking/sleep inertia, prolonged sleep periods, and autonomic neurological symptoms. Klein-Levin syndrome is a condition characterized by episodic marked hypersomnolence and hypothalamic dysfunction characterized by hyperphagia and hypersexuality [8]. This condition often presents in adolescence [9] or early adult life.

There are many other causes of sleepiness. Insufficient sleep syndrome is a behavioral condition characterized by insufficient time in bed. Sleepiness can of course be related to other medical conditions, medications, and substance use, which might emerge as an issue around later childhood and early adult life.

Transitional Care

The distinction between pediatric and adult care is somewhat an artifact of historical organizational structures, and there is a significant movement to improve this care continuum in many conditions. A recent review outlines some of the important issues in transitional care in neurological disorders [10]. Some of the main considerations from this article include first acknowledging that transition of care usually has to happen. Families may be hesitant at first. Pediatric models of care typically are family based and comprehensive, whereas adult care tends to be patient centered and disease focused. Patients make their own decisions and take responsibility ultimately in an appropriate transition of care. Transfer of care simply refers to an adult system looking after pediatric patients once they reach an appropriate age. However, transition of care is more nuanced and provides a more graduated transition.

It is important to consider the potential benefits of a transitional care model. Examples from other disciplines outline why transition is important. Failure to

successfully transition has been suggested to lead to a decline in health and a cost to the healthcare system.

One study [11] looked to identify outcomes in transition care in multiple medical conditions and focused on population health, consumer experience, and utilization/costs of healthcare domains. In a literature review, 43 studies were identified, and 28 had statistically significant outcomes in at least 1 of these domains. Examples included the impact of transitional care on HBA1C values in diabetes, medication compliance, and quality of life. Satisfaction with care was also improved in transitional care models, and there was an increase in patients attending their first adult clinic visit as well as a decrease in hospital admissions. The most common outcomes studied were adherence to care plans and appropriate utilization of ambulatory care. Clearly defined structured interventions often lead to positive outcomes. It is likely that the lessons learned from general transitional care programs could be applied to narcolepsy, and we should aim to do so.

There is little written about transitional care in narcolepsy specifically. An example from the epilepsy literature [12] discusses basic biological, sociological, and psychological issues important in transitional care. Transition was found to be challenging for patients, family, and care teams. They identify several key factors including brain changes including an imbalance between risk-taking pleasure-seeking behavior and reduced frontal executive function compared with adults. Neuroendocrine changes involved in puberty, which may have implications for epilepsy, also likely influence sleepiness. Sexual onset occurs during the transition years, and adult sexual performance may be influenced by medications and underlying conditions such as sleepiness and cataplexy. Depression, anxiety, and other social factors are clearly important and should be identified and addressed. The authors also note the importance of considering the evolution of psychological development in this period of time, which will have implications for their independent care.

13.2 Diagnosis

Clinical Aspects

Sleep needs and structure vary over the life span [13, 14]. Children are often sleep deprived, with early school start times [15] and activities and distractions from friends including electronic devices and social media. As such, ensuring age-appropriate sufficient sleep opportunity is essential. Narcolepsy may be a double hit and can further present as difficulties in school related to impaired vigilant attention. Presentation of narcolepsy in childhood may be different than in adults [16] with attentional problems or poor school performance. Subjective tools for assessment of sleepiness require further validation in children of various ages [17]. There can be a considerable delay in diagnosis [18], which may reflect public awareness, as well as limited testing and expert assessment. Fortunately, there is some suggestion this delay in diagnosis is decreasing [19], likely due to increased public

awareness through access to information through the Internet and an increase in medical care for sleep disorders.

Cataplexy, when present, can be particularly striking but may lead to misdiagnosis including conversion disorder due to the emotional component of symptom provocation. Cataplexy may be subtle, and patients may present with hypokinetic or hyperkinetic movement disorders at disease onset [20]. We have noted in a retrospective study of 33 children with narcolepsy that the presence of facial hypotonia or tongue protrusion in the context of sleepiness was very common in narcolepsy and should raise clinical suspicion of the disorder [21]. This motor finding is generally not present in adults.

Weight gain and precocious puberty can also be noted [16]. Occasionally, cataplexy can be noted in uncommon pediatric disorders such as Prader-Willi syndrome, Niemann-Pick type C, and Norrie disease, among other conditions [22]. These conditions will be identified by other generally severe neurological presentations.

Neurophysiological Measures

Although imperfect, the most common clinical tests for narcolepsy in adults include the multiple sleep latency test (MSLT) [23, 24]. This test follows a polysomnogram and consists of a series of four or five naps, 2 h apart. The patient has 20 min to fall asleep, and if they fall asleep, there is a 15-min opportunity to see if the patient enters REM sleep. In the right clinical context, a latency to sleep on average of less than 8 min, with two or more sleep onset REM periods (SOREMPs), is suggestive of the diagnosis. In children, either a short sleep latency or multiple SOREMPs can be confirmatory in patients with type 1 narcolepsy [25]. Interpretation of the MSLT in the context of age is essential, as older children are noted to have fewer SOREMPs and an increased mean sleep latency [26].

Difficulties with Pediatric Normative Values for Neurophysiological Tests

Tests of alertness such as the multiple sleep latency test and maintenance of wakefulness test do not have well-defined normative values for all ages [6, 27]. There is a need to have better established normative age-specific information. At the point of transitional care, these tests may have better characteristics for clarifying the diagnosis.

Laboratory Testing

Spinal fluid levels of hypocretin/orexin can confirm a diagnosis of type 1 narcolepsy, although the test is not available in some countries [28]. Often patients with hypocretin/orexin deficiency have a specific immune haplotype—HLA DQB1*0602; this may provide further supportive information and can be helpful where there is clinical ambiguity, particularly in children.

Opportunities for Refining the Diagnosis in Transitional Care

It has been noted that transitional care is an ideal time to reflect on the diagnosis and consider repeat diagnostic testing [29]. It is likely that this particularly applies to narcolepsy. It is helpful to have another opinion and review the situation from a fresh perspective. New information may become available, and diagnoses may change. For example, neurological symptoms may emerge, and symptomatic multiple sclerosis might be responsible for symptomatic narcolepsy rather than the typical form. Similarly, a suspected idiopathic hypersomnia diagnosis may declare itself more formally as narcolepsy with the emergence of cataplexy over time. Patients may develop concurrent or new sleep disorders in the interim. For example, weight gain associated with narcolepsy [30] may lead to an additional diagnosis of obstructive sleep apnea, which may be amenable to treatment intervention. A critical review of the history may also identify new behavioral factors that may have emerged. For example, children may have had more regularly scheduled sleep and wake time at their parents' direction that dissolves in adolescence, and they may acquire insufficient sleep syndrome as a complicating factor. While this is a problem in many young adults, it is particularly complicating in narcolepsy and related disorders.

13.3 Management

Medications

Treatment of patients with hypersomnia disorders includes addressing alertness, as well as addressing cataplexy [31]. Stimulants such as methylphenidate or wake-promoting drugs such as modafinil are typically used. In pediatric populations, modafinil has to be carefully considered due to the possibility of severe drug rash [32] and has led to black box warnings in some jurisdictions such as Canada. Cataplexy is often treated with antidepressant agents, as well as sodium oxybate, which is highly effective. Many medications for central hypersomnia conditions are considered orphan drugs, and there is little formal approval from regulatory bodies for these agents, particularly in pediatric populations. Doses obviously need to be modified for pediatric populations due to the reduced volumes of distribution compared to adults and adjusted accordingly by growth.

Behavioral Management

Napping can be a particularly helpful adjunct to management [33]. Napping as needed through the day (and timing of medications) appropriate to individual attentional needs should be carefully considered.

Unfortunately, some patients avoid social interactions to avoid precipitating cataplexy. Early discussions around this are critical to normal social development. Educating supportive peers and friends can be impactful.

Eliminating concomitant sleep disorders, such as sleep apnea and insufficient sleep, is important in optimizing patient outcomes. I tell patients that having narcolepsy does not excuse them from needing good sleep habit—in fact, it is even more important.

General Management Issues in Transitional Care

Patients need to learn to accept responsibility for attending appointments as part of adult life. Electronic device reminders can be helpful in this regard.

It is important for patients to take responsibility for their medications. This includes ensuring that medication renewals are requested in a timely manner. Patients need to be informed not to withdraw medication suddenly, lest status cataplecticus occurs. Patients need to be educated about travel across international boundaries where medication rules and legality may differ. Keeping a note about the diagnosis in the patient's purse or wallet as well as a list of medications is helpful. It is particularly important to obtain adequate medication insurance to ensure patients can afford agents that they may rely on. Transitional care patients are particularly vulnerable as they may not have a job that can cover the insurance expense of the expensive medications that are emerging and may be coming off their parents' drug plan coverage.

Life Stage Considerations

Young women are often particularly relieved to know that fertility is normal and narcolepsy is generally not inherited. Most patients do well with pregnancy with very careful planning.

Sexual performance can be impaired in about a quarter of patients [34] and is influenced by sleepiness and a number of medications. Anticholinergic anticataplectic drugs can be particularly problematic. Baseline sleepiness or cataplexy may interfere with normal adult relationships.

For young women, the menstrual cycle may contribute to iron loss, which can contribute to fatigue and cyclic symptoms of hypersomnia. Some cyclic hypersomnia in women may be amenable to hormonal interventions.

Birth control should carefully be considered. Modafinil can have a drug interaction with the birth control pill. Several agents for alertness and cataplexy are teratogenic. Young women should be off modafinil several months prior to trying to conceive. Many young women come off all their medications during pregnancy. However, some agents such as antidepressant-anticataplectic drugs can be used with acknowledged risks. I have found many young women choose to come off medications during pregnancy. This requires coordination of restricted driving activities as well as accommodations at work.

A high-risk obstetrician should be engaged if a young woman with narcolepsy becomes pregnant. Cataplexy could interfere with the physical birth process and be problematic.

Many psychoactive agents come out in breast milk, so this should also be considered when breastfeeding.

Infant care can be problematic if the mother has cataplexy. Additional support should be available, particularly around bathing the child. The author has noted that women with narcolepsy often do very well during pregnancy. Whereas young mothers without narcolepsy are less accustomed to polyphasic sleep, it has often become a way of life for patients with narcolepsy. As such, the contrast in adapting to infant care is not as stark and most readily adapt.

Housing

In some locations, optimal treatments might not be possible. For example, college dormitories may be a risky environment for the use of sodium oxybate given the potential for abuse. Some adapt to this with trusted roommates and a safe to store medications.

Accidents occur in about a third of patients with narcolepsy [35] and include concerns with basic household tasks such as ironing. Patients with narcolepsy are also at a higher risk of parasomnias, and some of the medications can precipitate parasomnias. The bed environment should be safe without sharp furniture corners, easy access to stairways, or glass structures. An extra key at the desk of the hotel or dormitory or leaving one with a trusted friend could also be helpful in case they wander out of their rooms and end up locked out. Positioning furniture in front of the door could be useful, for example, when traveling.

Driving

Many patients with narcolepsy have fallen asleep driving, and some have had cataplexy in this scenario [36]. Many jurisdictions have different rules around driving permission. Even within a country such as Canada, rules vary between provinces. In Ontario, conditions that threaten an individual's safety to drive need to be reported to the government ministry of transportation. There is considerable variability among care providers for assessing readiness to drive in adolescents with narcolepsy [37]. In my practice, we typically optimize care prior to applying for driving privileges. The patient needs to be alert and free of cataplexy. If there is any question around alertness, we may do a maintenance of wakefulness tests to ensure objective sleepiness has been successfully managed [38]. I do not permit any cataplexy that involves motor hand control. Some patients state that they may have

cataplexy only with intense emotions but do not in a driving environment. This should be interpreted cautiously. For example, if a car suddenly appears, this could be surprising and could represent a triggering event.

Education

Schools may be unaware of these conditions, but increased campaigns to raise attention to these disorders will help with management of central disorders of hypersomnolence in educational settings. Once aware of the condition, schools are often quite supportive of accommodations for patients with narcolepsy. Examples of accommodation should be quite specific as many organizations will not know what is required and the accommodations could be very individualized. For example, extra time during examinations may be helpful. Nap opportunities or adjustment of the timing of examinations might need to be suggested.

Work

Patients with narcolepsy may have reduced performance at work and fear of job loss [36]. Work environments may be less accommodating given economic motivators. Driving might not be possible, which further complicates some career choices. Shift work is problematic for most people and is generally difficult for patients with narcolepsy, but some patients may adapt quite readily. Letters of advocacy can help patients get the accommodations that may be required at work. It is helpful to discuss career plans on an ongoing basis to help facilitate a realistic career trajectory. Sometimes, medications have to be adjusted to facilitate different lines of work. Most can accomplish their goals with careful management. I've had examples of patients with cataplexy who have been able to pursue surgical careers once symptoms were fully controlled. I've also had examples of individuals who have not been able to achieve their career plans, such as emergency response work, out of problematic cataplexy management. Newer agents will likely help more people achieve their path.

Substance Use

Medications can interfere with diagnostic testing [39], and even withdrawal of medications can contribute to diagnostic uncertainty. Toxicology screens should be routinely obtained with MSLT. Patients should be counseled around avoiding agents such as cannabis, which can compound problems of sleepiness. Recreational use of street drugs can be problematic as it may also interfere with safe prescribing of stimulants or raise concerns among prescribers. Caffeine, however, may be considered as an adjunct to prescription therapies [40], given a favorable safety profile.

Comorbid Conditions

Patients with narcolepsy can gain weight related to reduced activity. Along with metabolic changes of adult life, it is important to ensure inadequate physical activity is not contributing further to problems. One study [41] evaluated the association between depressive symptoms, sleepiness, and physical activity in a cross-sectional study of patients aged 10–18 with narcolepsy. The study showed that greater mood impairment was associated with poor sleep quality, sleepiness, and lower self-reported physical activity. This may represent a potential intervention target.

13.4 How Transitional Care Works in Toronto, Canada

At the University of Toronto, the Hospital for Sick Children has an excellent multidisciplinary sleep clinic and adolescent medicine program. For adult care, Sunnybrook Health Sciences Centre has expertise on neurological sleep disorders. The collaboration between the adult care and childcare physicians has been a key feature of successful transitions here. Occasionally, consultation is arranged with the adult care physicians when the patient is quite young in unusual circumstances or to obtain a second opinion. Visits are arranged early to establish comfort. This may take time. For example, one patient in our transitional clinic was seen at a young age and did not speak a single word. Several years later, he returned to the team for ongoing care and was able to participate actively. Communication and flexibility are key. A transfer of records occurs early on, with the results of neurophysiological testing, HLA typing, etc. We plan visits early so that there will be less chance for a gap in care between pediatric and adult care. At a formal new patient visit, a considerable amount of time is left for the initial consultation. Parents are often present in early visits but gradually encouraged to back away when appropriate, to facilitate independence of the young adult. Our transitional care program continues to learn ways to improve care as part of a learning healthcare system.

13.5 Strategies to Improve Transitional Care

One important step in creating a transitional care plan is to plan. First, a discussion of the anticipated transition should be held with patients by teenage years if developmentally appropriate. Next, there should be an assessment of self-management skills. Life stage-specific considerations need to be addressed at each visit.

Patients and families may be reluctant to let go. Identifying the next caregiver is important. It may be difficult to identify an appropriate care provider. The adult care provider may need education about uncommon pediatric or rare conditions. Development of networks for this type of transitional work is helpful.

While the examples in the literature from narcolepsy are limited, there is some emerging literature from epilepsy, which shares many similar issues. Many patients

with childhood-onset epilepsy require ongoing care, have episodic events, take psychoactive medications, and even have sleepiness or driving issues, for example. In fact, patients with narcolepsy tend to have even more significant psychosocial difficulties compared to patients with epilepsy [42]. One paper outlined care gaps in young adults with epilepsy. The study looked at 130 patients on anti-seizure medication within 2 years of their 18th birthday and found that only 31% had "transition" discussions. Identifying barriers to delivery of transition care is important for remediating care gaps and building effective ongoing care [43].

If the patient does not transition in care, they still must learn how to manage their own care wherever possible. There should be a move to interview patients separately and encourage independence. Even if the adolescent is driven to the appointment, the parents can wait in the waiting room, which is helpful to address sensitive issues. Consent must be obtained from patients to speak with parents once reaching the age of majority.

Adolescents are prone to emotional, mental, physical, and social difficulties. A literature review revealed 49 articles in epilepsy transition and established risk factors that could lead to interventions [44]. Multidisciplinary transition care for adolescents was widely recognized as useful, but only a few transition clinics have been established in the epilepsy community. There are considerably fewer in narcolepsy. There was a lack of evidence for quality and cost-effectiveness of these programs, and the authors note that this represents a useful future research direction. The authors make particular note that attention should be paid to the risk of psychosocial problems during transition. This is particularly important given the psychosocial burden of patients with narcolepsy [45].

It should be noted that the family unit may or may not function well with a member with narcolepsy. One study [46] had the objective of evaluating family functioning using a family impact module called the PedsQL. The tool encompasses parent health-related quality of life, daily activities, family relationships, communications, and worry. In this study of 30 adolescents with the mean age of 13.8 years, families were noted to be impaired similar to families of adolescents with chronic pain. Teams should ask about concerns and challenges related to caring for adolescents with narcolepsy and provide resources and support as needed.

One author notes that the transition from pediatric adult epilepsy care is particularly challenging [29]. The three main areas identified include diagnosis and management, mental health and psychosocial needs, as well as financial, community, and legal supports. There were no systematic studies on the outcome of transition programs and epilepsy. Teenagers at risk of poor transition should be identified early. Coordination between pediatric and adult specialists should occur before transfer. The article noted that transitional care was an ideal time to reflect on the diagnosis and consider repeat diagnostic testing.

There may be a delay in transitional care, and this can lead to lapses in medication renewals or derailing a plan that was already in progress. It helps to have close interaction between pediatric and adult specialists in order to ensure there's no significant gap in care. Planning early helps in this regard.

A number of excellent resources are freely available to help structure transition care programs. The website gottransition.org has a remarkable set of freely available resources for various scenarios that could rapidly be adapted to narcolepsy. For example, there are transfer letter templates. This website outline six core elements of care including the transition policy, transition tracking and monitoring, transitional readiness, planning, transfer of care, and follow-up with transfer completion assessment. The Transition Readiness Assessment Questionnaire (TRAQ) [47] assesses whether the patient will need additional assistance in transition. Examples of domains assessed include managing medications, appointment keeping, tracking health issues, capacity to talk with health providers, and issues around managing daily activities.

Woody Allen once noted that 80% of success is just showing up. This is particularly relevant in transitional clinical scenarios. Some adolescents may drop out of supportive care and not be able to refocus their lives. It is so particularly helpful to have regular contact with a supportive clinician to help patients with narcolepsy achieve the best possible outcomes.

13.6 Future Directions

Narcolepsy and Other Primary Hypersomnia Conditions

Neurophysiological diagnostic assessment continues to improve, and this will benefit transitional care patients. Hidden information in the overnight polysomnogram can provide further diagnostic information [48]. Similarly, the neurophysiological criteria for narcolepsy were adapted recently to include the counting of a sleep onset REM period in the overnight polysomnogram in the requirements of two sleep onset REM periods typically identified in the MSLT [6]. Diagnostics in narcolepsy are likely to be improved with the use of machine learning and artificial intelligence [49].

There are several new agents available for the treatment of impaired alertness as well as cataplexy [50]. Pitolisant, a histamine H3 receptor inverse agonist, is available in several markets. Solriamfetol, an agent with dopaminergic and noradrenergic activity, and extended-release formulations of sodium oxybate, should be available shortly. Novel orexin agonist therapies are under development and represent specific therapies with significant potential [51].

Transitional Care in Central Hypersomnolence

It is likely we will further see the emergence of transitional care models in central hypersomnia conditions. Care gaps specific to narcolepsy should be identified, as these may be directly amenable to interventions to improve care and the quality of experience. Economic analyses should also evaluate the impact of transitional care models. The effects of addressing exercise and metabolic factors will continue to provide a target for improved outcomes particularly in this age group.

13.7 Summary

Dr. Francis Peabody [52] noted, "One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient." By paying attention to the gradual development of the patient as a person, we can more carefully direct patients to optimal care, rather than adhering to artifactual care structures. The development of transition care programs represents a significant opportunity to improve individual outcomes but also provides opportunities to better understand narcolepsy biology. While there are few programs specifically addressing this care gap in narcolepsy, there are excellent general transitional tools available from multiple sources that can be implemented. I encourage programs around the world to learn from other transitional care programs and implement successful interventions, in the goal of improving quality care of these patients.

Conflicts of Interest None.
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14 Transition of Sleep Care in Patients with Neuromuscular and Neurodegenerative Disorders

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Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AChR	Acetylcholine receptor
AD	Autosomal dominant
ADHD	Attention-deficit hyperactivity disorder
AR	Autosomal recessive
BMD	Becker's muscular dystrophy
CDM	Congenital myotonic dystrophy
CLA	Congenital lactic acidosis
CMD	Congenital muscular dystrophy
CMS	Congenital myasthenic syndromes
CNM	Centronuclear myopathies
CP	Cerebral palsy
DM	Myotonic dystrophy
DM1	Diabetes Mellitus type 1
DM2	Diabetes Mellitus type 2
DMD	Duchenne's muscular dystrophy
DS	Downs syndrome
EDS	Excessive daytime sleepiness
GERD	Gastroesophageal reflux disorder
ID	Intellectual disabilities
KSS	Kearns-Sayre syndrome
LS	Leigh syndrome
MD	Muscular dystrophy

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MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
MERRF	Myoclonic epilepsy with ragged red fibers
MIDD	Maternally inherited deafness and diabetes
MNGIE	Mitochondrial neuro-gastrointestinal encephalopathy
mtD	Mitochondrial diseases
mtDNA	Mitochondrial DNA
NARP	Peripheral neuropathy, ataxia, and retinitis pigmentosa
nDNA	Nuclear DNA
NIV	Noninvasive ventilation
NMD	Neuromuscular diseases
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PDC	Pyruvate dehydrogenase complex deficiency
PEO	Progressive external ophthalmoplegia
PLMS	Periodic limb movements of Sleep
PSG	Polysomnograms
REM	Rapid eye movement
SCCMS	Slow-channel congenital myasthenic syndrome
SD	Sleep disorders
SDB	Sleep-disordered breathing
SMA	Spinal muscular atrophy
TNMG	Transient neonatal myasthenia gravis
XLMTM	X-linked myotubular myopathy

Sleep disorders (SD) are commonly associated with neurodegenerative and neuromuscular disorders such as Down syndrome (DS), cerebral palsy (CP), and disorders of the anterior horn cell, neuromuscular junction, and muscles. In this chapter, we will highlight important disease-specific SD in the above-mentioned patients with focus on management and transition of care.

14.1 Neurodegenerative Disease

Several studies have confirmed an increased prevalence of SD in patients with intellectual disabilities (ID) who live at home. Richdale et al. found that SD were more frequent in children with mild-to-profound ID (57.7%) than their non-disabled peers (16%) [1]. Sleep problems include excessive daytime sleepiness (EDS), frequent awakenings, early awakenings, and parasomnias such as teeth-grinding and night terrors [2]. Sleep disturbances are reported more frequently in children and adults with Down syndrome (DS) and cerebral palsy (CP). As these patients also experience neurodegeneration, their brain could be at increased risk to the additional negative effects of obstructive sleep apnea (OSA) such as lower IQ and

behavioral disorders, as OSA appears to have a negative impact on brain function and structure [3].

Down Syndrome (DS)

DS is the most common chromosomal disorder caused by trisomy of chromosome 21 with an incidence of about 6000 births each year [4]. Throughout the years, medical interventions have resulted in increasing their life span from an average of 12 years in the 1940s to an average of 57.8 years for women and 61.1 years for men [5]. Many age-related changes such as reduced DNA repair, increased biological aging, and mortality occur at an earlier age than those without this disorder [5]. In addition to ID, individuals with DS have craniofacial abnormalities such as midface hypoplasia, micrognathia, macroglossia, narrow nasopharynx, small larynx, and hypotonia, leading to floppiness of the upper airways and an increased risk of sleep-disordered breathing (SDB), particularly OSA [6]. OSA is present in 30–55% of children with DS, rising to more than 90% of adults with DS [7, 8]. As discussed earlier, other sleep-related problems occur more frequently in patients with ID including frequent awakenings, difficulty initiating and maintaining sleep, Excessive daytime sleepiness (EDS), and parasomnias.

Screening for sleep disorders and management of comorbidities contributing to OSA should be done throughout childhood and into adulthood. Polysomnograms (PSG) remain the gold standard for diagnosis of OSA and are recommended for all patients with DS by 4 years of age, regardless of symptom history. Marcus et al. found overnight PSGs to be abnormal in 100% of children with DS including OSA (63%), hypoventilation (81%), and desaturation (56%) [7]. Because children and adults with DS do not present with typical signs and symptoms of OSA, screening for SDB should be done annually.

Treatment of should be individualized based on patient's age, developmental status, comorbid conditions, and acceptance to treatment. Options include positive airway pressure (PAP), upper airway surgery (most often tonsillectomy and adenectomy), dental appliances, nasal steroids, oral leukotriene modifiers, and weight-reduction strategies. Tonsillar adenectomy is the mainstream treatment for children with OSA. Unfortunately, almost two-thirds of children with DS have residual OSA after undergoing adenotonsillectomy [9]. This emphasizes the need for postsurgical PSG and possibly evaluation of the upper airway via drug-induced sleep endoscopy.

Cerebral Palsy

CP is one of the most common childhood disabilities with an occurrence rate of 2–2.5 per 1000 live births [10]. It encompasses a group of permanent, non-progressive disorders of movement, posture, and muscle tone, resulting from cerebral damage. Although it is not a progressive disorder, clinical expression of the disease can change with time as the nervous system matures. Even though it is

primarily a motor abnormality, there are a variety of other symptoms including altered sensation or perception, ID, behavior and language difficulties, seizure disorders, and musculoskeletal complications [11].

SD are commonly found in children with CP (23–46%) when compared to typically developing children (20–30%) [12]. These include difficulty initiating and maintaining sleep, sleep-wake transitions, SDB, sleep bruxism, nightmares, sleep talking, and EDS [11]. Additionally, sleep deficiency due to pain, mobility impairment, uncontrolled seizures, and gastroesophageal reflux disorder (GERD) are common [13]. Visual loss commonly seen in CP causes dysregulation of melatonin production, leading to abnormalities in their sleep-wake cycles. This not only negatively affects the child's emotional, cognitive, and physical well-being but also has extensive impact on their families and caregivers.

Early recognition and treatment of SD are imperative in improving their quality of life, cardiopulmonary consequences, seizure control, and neurobehavioral consequences [14]. PSG remains the gold standard for diagnosing OSA with treatment options similar to the general population with PAP, dental appliances, upper airway surgery, and medical management with nasal steroids and leukotriene modifiers. In treating dyssomnias, providers should not overlook other comorbidities such as pain. Some tricyclic antidepressants (amitriptyline, nortriptyline, trimipramine) and serotonin modulators (trazodone) have been studied and proven effective in treating both chronic pain and SD. Gabapentin and pregabalin are also often used to treat CP and dyssomnias [15].

Neuromuscular Disease

Neuromuscular diseases (NMD) are a group of acquired or hereditary disorders caused by a defect in a portion of the lower motor neuron-anterior horn cell, peripheral nerve, neuromuscular junction, or the muscle. These disorders have varying anatomic distribution of weakness, patterns of muscle weakness, rate of progression, and age of onset. Many are multisystem disorders causing abnormalities in the skeletal muscles, smooth muscles, myocardium, brain, and ocular systems. Children often present with infantile floppiness or hypotonia, delayed motor milestones, feeding and respiratory difficulties, frequent falls, or abnormal gait. Adults often present with muscle cramps, loss of strength and endurance, fatigue, breathing difficulties, or bulbar symptoms, relating to speech and swallowing difficulties.

SDB is commonly found in NMDs due to weakness in their respiratory and diaphragmatic muscles, increased risk for obesity starting earlier in life due to loss of ambulation, and other comorbidities such as GERD. Although the rate of respiratory failure varies from disease to disease, physiological changes occurring in rapid eye movement (REM) sleep (intercostal inhibition, loss of accessory muscle tone, reduction in ventilatory drive, and diminished arousal response) result in REM-related SDB, before appearing in non-REM sleep. Most commonly hypoventilation occurs due to decreased tidal volume, but nocturnal desaturations may also present

secondary to sleep-related hypoventilation, apneas, or hypopneas. SDB, including OSA and sleep-related hypoventilation, in NMD is found in 27–62% of children and 36–53% of adults [16]. If not recognized and addressed early, nocturnal ventilatory failure leads to daytime ventilatory failure, causing significant morbidity and mortality.

In addition to respiratory muscle, other factors contribute to disruptive sleep including upper airway and craniofacial weakness, impaired cough mechanism, difficulty with secretion clearance, and limitation of posture causing discomfort due to weakness [16]. Not only is sleep subjectively disrupted, alteration in objective PSG findings includes a decrease in total sleep time, sleep efficiency, and REM sleep with increased sleep fragmentation, arousals, and stage 1 sleep [16]. Depending on the type of NMD, they may present with other comorbidities associated with sleep disorders such as ID, learning disabilities, seizure disorders, and accompanying environmental and psychosocial stressors.

Disorders of the Anterior Horn: Spinal Muscular Atrophy (SMA), Types 1–4

SMA is an autosomal recessive (AR) disorder characterized by degeneration of the motor neurons in the anterior horn cells due to a mutations of the survival of motor neuron gene (SMN1) on chromosome 5. There are four different phenotypes based on severity of disease, age of onset, and maximum motor function achieved (see Table 14.1) [17]. Introduction of new disease-modifying treatments in the pediatric population has reshaped the natural history of the disease, care pathways, and outcomes associated with SMA in adulthood. Ongoing research is needed to develop guidelines for standard of care and advance health policy to ultimately reduce the burden associated with adult SMA.

Sleep disorders in SMA have had increasing attention over the last decade with past research porting sleep apnea and sleep-disordered breathing found commonly in this population. Patients were also found to have abnormal sleep architecture with reduced arousal in those with SMA 1 and SMA 2.

Table 14.1 Classification of SMA [17]

Type	Age of onset	Survival	Maximum muscular function
SMA type 1 (severe)	Before 6 months	Ventilation by 2 years of age	Severe hypotonia and unable to sit or roll
SMA type 2 (intermediate)	6–18 months	Survival until adulthood	Proximal muscle weakness
SMA type 3 (mild)	Early childhood—Early adulthood	Normal	May lose ability to walk
SMA type 4 (adult)	Adulthood (20–30 years of age)	Normal	Mild motor impairment

14.2 Neuromuscular Junction Disease

Currently, we have a very good understanding of how autoimmune processes and genetic disorders affect the neuromuscular junction. In infants and children, they can be either acquired or congenital, causing fluctuating muscle weakness, hypotonia, and fatiguability, either transiently or permanently. Other symptoms are respiratory distress, feeding difficulties, and flaccid tone following delivery.

Neonatal Myasthenia Gravis

Maternal IgG autoantibodies against acetylcholine receptor (AChR) can freely cross the placenta and cause transient neonatal myasthenia gravis (TNMG) in 21% of infants born to mothers who have clinical myasthenia gravis [18, 19] and in some cases may have no symptoms or are in remission [20, 21]. Passively transferred AChR antibodies in some infants did not cause myasthenic symptoms [18], and one case described delayed-onset hypoxia [20]. Usually, the symptoms are transient and resolve after maternal antibody clearance generally after 2–4 weeks. Neonates may manifest difficulties in sucking, swallowing, and respiration, which predisposes them to aspiration and respiratory compromise. Polyhydramnios can also be a sign antenatally [22].

TNMG should be highly suspected in infants with myasthenic symptoms born to a mother with known myasthenia gravis or in remission after successful treatment. In the setting where maternal status is uncertain, a challenge of an acetylcholinesterase (AChE) inhibitor, usually neostigmine and in some cases pyridostigmine [23], may be attempted in an appropriate clinical setting, after which, clinical response is assessed. There are suggestions that repetitive motor nerve stimulation may be a much more reliable diagnostic tool than acetylcholinesterase challenge, especially in the setting of hypoxia and poor respiratory effort [23, 24].

A multidisciplinary supportive approach is of benefit, which includes nasogastric and orogastric feedings and assisted ventilation when necessary. Neostigmine can be given prior to feedings, though side effects such as diarrhea, oropharyngeal secretions, and weakness limit its use. In rare cases, plasma exchange has been used [22] as well as IV immunoglobulins. Disease course may be monitored by nerve studies and serum levels of AChR antibodies. Majority of affected infants will recover with early diagnosis and prompt treatment.

Congenital Myasthenic Syndrome

Unlike the autoantibody nature of TNMG, congenital myasthenic syndromes (CMS) are a rare heterogeneous group of disorders brought about by genetic mutations of proteins in the presynaptic, synaptic, and postsynaptic regions of the neuromuscular junction or defects in protein glycosylation and serine peptidases involved in post-translational protein modification [25]. As a result, there is dysfunction in

neuromuscular transmission, leading to muscle weakness, which is worse with sustained exertion. Most symptoms such as hypotonia, variable eyelid ptosis, bulbar weakness, dysphagia, and respiratory distress are evident during birth, but mild forms may cause symptoms during adulthood. Feeding difficulties and respiratory failure are of concern. Severe episodic apnea has been reported as well as sudden death and anoxic brain injury [26, 27].

The advent of low-cost massively parallel and next-generation DNA sequencing resulted to rapid discovery of the 30 genes currently implicated to CMS [28, 29]. Almost all cases of CMS are inherited through AR pattern, except the autosomal dominant (AD) classic form of slow-channel congenital myasthenic syndrome (SCCMS) [30]. Prevalence in the UK is 9.2 cases per million under 18 years of age [31]. Initial diagnosis includes fatigable exertional weakness pronounced on ocular and cranial muscles, pediatric onset, negative autoantibody testing, and supportive electrophysiologic data [32].

Fortunately, treatment for most CMS are available currently, though extra care should be exercised since some treatment for a certain genetic type may be ineffective and/or detrimental to another such as using pyridostigmine in DOK7, acetylcholinesterase deficiency, and SCCMS. Present approach to therapy is to determine which CMS is responsive to either cholinergic agonists, long-lived open-channel blockers of the acetylcholine receptor ion channel, and beta-adrenergic agonists [32, 33]. Such approach will be dependent on accurate genetic testing. When there is decreased synaptic response to acetylcholine (ACh), pyridostigmine, an AChE inhibitor, and 3,4-diaminopyridine (3,4-DAP) increase ACh in the synaptic cleft. In SCCMS with increased synaptic response to ACh, fluoxetine and quinidine are used as long-lived open channel blockers of the AChR. Beta-adrenergic agonists like salbutamol and ephedrine are adjunctive treatment for CMS due to glycosylation defects, fast channel syndrome, AChR deficiency, and choleacetyltransferase deficiency. Respiratory support, such as noninvasive ventilation, may be needed as all CMS forms can cause hypoventilation. Unlike in TNMG, there is no role for immunotherapy or plasma exchange.

14.3 Disorders of the Muscle

Muscular Dystrophy

Muscular dystrophies (MD) are a group of genetic conditions characterized by muscle weakness and atrophy, each affecting different muscle groups and presenting with onset of symptoms at varying times. In addition to SDB, MDs are strongly associated with SDs including periodic limb movements (PLMS), central hypersomnia, and REM sleep dysregulation, including high REM density and a narcoleptic-like phenotype [34]. In this section, we will discuss Duchenne's muscular dystrophy (DMD), Becker's muscular dystrophy (BMD), congenital muscular dystrophy (CMD), and myotonic dystrophy (DM) (see Tables 14.2 and 14.3).

Table 14.2 Muscular dystrophy [35]

Type	Age of onset	Progression	Affected muscles	Symptoms
Congenital muscular dystrophy (CMD)	Infancy or early childhood (<2 years)	Variable. Can shorten life span	Voluntary muscles	Muscle weakness with possible joint stiffness
Becker's muscular dystrophy (BMD)	2–16 years old. Up to 25 years of age	Slowly progresses Can live into adulthood	Arms, legs, and spine. Can affect cardiac muscles	Weak muscles. Affects males only
Duchenne's muscular dystrophy (DMD)	2–3 years of age	Worsens rapidly. Life expectancy into 30s–early 40s	Proximal muscles then distal muscles. Legs then arms	Muscle weakness Ambulatory stage: Preschoolers who are clumsy, can't climb stairs, run Children: Walk on their toes, waddling gait Early non-ambulatory stage. Wheelchair by 12 years Late non-ambulatory stage. Teens with weakness of arms, legs, and trunk. Require mechanical support Death: 20s–early 30s
Myotonic dystrophy (DM)	DM type 1 ages 0 years to adulthood DM1, mild DM1, adult onset DM1, early childhood DM1, congenital	Slow progression. Decreases life expectancy	Myopathy early adulthood and disabling at age 50 years. Can also affect the central nervous system DM type 1: Facial and distal muscle weakness. Grip myotonia DM type 1, variation (congenital myotonic dystrophy): Global hypotonia, clubfoot	Stiffing and spasms of the muscles. Prolonged muscle contractions (myotonia) and are not able to relax muscles after use Insomnia: Prominent
	DM type 2: 8–60 years	Milder than DM1with normal life expectancy	Proximal muscle weakness. Variable mild grip myotonia	Myotonia present <50% Muscle weakness onset at age 50–70 years. Respiratory muscle weakness is exceptional Insomnia: Infrequent

Table 14.3 Muscular dystrophy and associated sleep disorders [34, 36–38]

Type	Age of onset (years) [37]	Clinical manifestation	Progression	Respiratory and sleep disorders
Congenital	Birth	Birth: Severe hypotonia, respiratory distress/failure, clubbed feet, feeding difficulties Childhood: cognitive defects, motor developmental delay, muscle weakness (distal>proximal), muscle atrophy [37]	Mortality of 30–40% in neonatal period from respiratory failure [39] Mean life expectancy: 45 years [37]	Muscular weakness causing respiratory distress/failure at birth [37] Impaired central respiratory control leading to SDB (OSA, CSA) Hypersomnolence and fatigue
Childhood	1–10	Facial weakness Generalized muscle weakness Recurrent infections (weak cough) Myotonia (first decade of life) Muscular atrophy Cognitive defects Psychosocial issues Incontinence [37]	Mortality: Similar to adult onset Mean life expectancy: 60 years [37]	EDS (50%) in childhood [38] Hypersomnolence and fatigue Features of adult-onset subtype present in adulthood: SDB (OSA, CSA, hypercapnia, hypoxemia) RLS and Periodic Limb Movement of Sleep (PLMS) (38% have PLMS >5/h on PSG [38] REM sleep dysregulation [36] – Increased density and frequency of REM sleep – Narcoleptic-like phenotype with increased Sleeponset Rapid Eye movement Periods (SOREMPs) during time [34]

(continued)

Table 14.3 (continued)

Type	Age of onset (years) [37]	Clinical manifestation	Progression	Respiratory and sleep disorders
Adult-onset	10–30s	Myotonia Muscle weakness Cataracts Conduction defects Insulin resistance Respiratory failure [37]		EDS (70–80%) [Hilton] Hypersomnia (HLA haplotype DRW6-DQW1) [34] SDB (OSA, CSA, hypercapnia, hypoxemia) RLS and PLMS (61.1% had PLMS >5/h on PSG [34] REM sleep dysregulation [36] – Increased density and frequency of REM sleep – Narcoleptic-like phenotype [34] with increased SOREMPs during Multiple Sleep Latency Test (MSLT)
Mild/late onset	20s–70s	Mild myotonia Cataracts [37]		

Congenital Muscular Dystrophy

CMD infants usually have dystrophic features (hypotonia, arthrogryposis, and contractures) within the first few months of life. There are more than 30 different disorders affecting various muscle groups with different ages of onset, severity of disease, and inheritance patterns. Muscle weakness may improve, remain stable, or worsen with time. Some forms of CMD are associated with ID, seizure disorders, and cardiac dysfunction. As disease progresses, all types of CMD develop respiratory failure, and some may be severe at birth. Management for CMD must be individualized to help treat specific symptoms, and ongoing multidisciplinary care is required for optimization of care.

Duchenne's and Becker's Muscular Dystrophy

DMD and BMD are X-linked recessive disorders found exclusively in males. They are caused by reduction or absence of function in the dystrophin protein, particularly in the cardiac and skeletal muscles, leading to muscle weakness. Although they present with similar signs and symptoms, they vary in age of presentation, severity, and rate of progression. DMD is the most common form of MD in childhood with a

prevalence of 4.78 per 100,000 males [40]. Compared to BMD, they present earlier in childhood with signs and symptoms of difficulty walking, calf hypertrophy, and progressive muscle weakness, which rapidly progresses to loss of ambulation and premature death. BMD has a milder in presentation with a prevalence of 1.53 per 100,000 males worldwide [40].

Duchenne's Muscular Dystrophy

Previous studies report SDB (frequency of 31%) in patients with DMD with OSA (31%) in the first decade of life and sleep-related hypoventilation (32%) in the second decade of life [41]. Despite prolonged survival with corticosteroid therapy and noninvasive ventilation (NIV), the major cause of death is respiratory failure, with one quarter of deaths occurring unexpectedly during the night [42]. Patients with DMD also have high rates of ID (17–27%), learning disabilities (26%), autism spectrum disorder (15%), attention-deficit hyperactivity disorder (ADHD) (32%), and anxiety (27%), which are all associated with SDs [43]. Daily care, including the need to be turned by a career associated with immobility, muscular-skeletal pain, medications, and behavioral and psychological problems, also affects their quality of sleep [44].

Evaluation of sleep problems includes assessing for symptoms of fatigue, morning headache, frequent awakening, hypersomnolence, tachycardia, and frequent nightmares. According to the American Thoracic Society consensus statement on respiratory care of patients with DMD (2004), patients should be evaluated by a physician specializing in respiratory care once between ages 4 and 6 years and before they are wheelchair bound. Baseline pulmonary function testing should be obtained, and anticipatory guidance regarding respiratory complications of DMD should be offered. Simple oximetry can be used in the home to screen for sleep-related oxyhemoglobin desaturations, but annual awake CO_2 monitoring and evaluation for SDB should also be performed with PSG and capnography. In areas where PSG with capnography is not available, continuous pulse oximetry and CO_2 monitoring can help provide limited information regarding nighttime gas exchange. Because disorders of maintaining and initiating sleep (30%) are often a side effect of steroid use and disorders of excessive somnolence (11%) are common, a comprehensive clinical assessment of sleep should be obtained at every patient encounter [44].

Interventions for SDB and sleep-related hypoventilation include nocturnal assisted ventilation (preferably NIV) with a backup rate. Assisted daytime ventilation is added when despite nocturnal ventilation, daytime pCO_2 are >45 mmHg or symptoms of dyspnea while awake are present. To decrease the risk of SDB, clinicians should create ongoing nutritional plans to help maintain an ideal body weight. Adaptation of the dosage of steroids should be considered if sleep initiation or maintenance insomnia is present. Medications with central nervous system depressant effects should be avoided due to potential further respiratory compromise. As a replacement, melatonin, in particular the slow-releasing form, may be considered for sleep initiation and maintenance disorders [45].

Myotonic Dystrophy

Myotonic dystrophy (DM), an AD progressive myopathy with myotonia, is divided into two clinically distinct diseases (type 1 DM and type 2 DM), both caused by a repeat expansion mutations. Although there is limited research on DM type 2 (DM2), we know it presents as a milder form of DM type 1 (DM1), with proximal rather than distal weakness and less prominent muscle wasting. Additionally, DM1 includes facial weakness, ptosis, respiratory insufficiency, and a congenital form, which are generally absent in DM2.

DM1 is the most common form of MD in adulthood, affecting about 1 in 8000 people worldwide presenting with varying phenotypes including congenital, early childhood, adult onset, and late/asymptomatic onset [46]. Although adult onset is well understood, congenital and childhood phenotypes require further investigation to help optimize outcomes and develop standards of care. DM1 has prominent propensity to SD including SDB, resulting in nocturnal hypoxia and hypercapnia, PLMS, REM sleep dysregulation, and EDS [34, 47].

Classic adult-onset DM1 is a relatively slow progressing disease with primary symptoms of fatigue. EDS, and SD including PLMS, SDB, and REM sleep disturbances. Prior studies suggest selective loss of serotoninergic neurons of the dorsal raphe nucleus and low cerebrospinal fluid orexin A levels. This may directly affect sleep regulatory circuits in the CNS, causing sleep dysregulation and abnormality in central control of ventilation. As a result, symptoms of EDS that are out of proportion to degree of SDB, fatigue, and REM sleep dysregulation are present. Patients also present with symptoms similar to idiopathic hypersomnia with long, nonrestorative sleep and diurnal sleep episodes [36]. REM sleep dysregulations have been described with sleep-onset REM periods frequently with short sleep latencies found on MSLT and hypocretin CSF deficiency to support the diagnosis of narcoleptic-like phenotype [36]. Like other NMDs, SDB is commonly found with associated nocturnal hypoxemia, sleep-related hypoventilation, OSA, and CSA [34].

Congenital myotonic dystrophy (CDM) is considered the severe early form of "classic" DM1 with a biphasic course, whereby symptoms stabilize in surviving neonates before adult-type symptoms present [37]. Individuals present at birth with severe hypotonia, clubfoot, respiratory weakness, cerebral atrophy, and ventricular enlargement with a high mortality rate from respiratory failure. Those individuals who do survive show gradual improvement in motor function with almost all CDM children having the ability to walk, swallow, and independently ventilate until the third and fourth decade of life, when cardiorespiratory complications arise [48, 49]. Like those who survive CDM, early childhood DM presents first with cognitive deficits and learning abnormalities and then with progressive muscular weakness in early adulthood. EDS is the most common non-muscular-related sleep symptom and reported in 50% of children with DM1 [38]. Patients with mild-/late-onset DM generally have minimal clinical manifestations with myotonia, weakness, and EDS rarely present [37].

Myotonic Dystrophy Type 2

Scarce research has been done on DM2; therefore, little is known regarding the occurrence of SD in these patients. The most common symptom mentioned is pain-induced nocturnal awakenings, and in contrast with DM1, fatigue, not EDS, is a prominent clinical feature of DM2 [50]. The clinical spectrum of DM2 includes similar but milder form of sleep problems as seen in DM1, including SDB, PLMS, RLS, insomnia, and REM sleep dysregulations. More research is needed to help understand the prevalence and pathophysiology of this disease.

Management of DM1 and DM2 emphasizes having a multidisciplinary team to provide supportive care, reduce complications, and optimize health and quality of life [37]. Although muscle weakness in DM1 is rarely progressive in childhood, it is important to provide ongoing therapies to limit and manage complications such as contractures, pain, and scoliosis and to maximize muscle function [39]. Diagnosis of EDS is the same for the general and DM population with thorough assessment using questionnaires, actigraphy, MSLT, and a maintenance of wakefulness testing. Evaluation for SDB includes overnight pulse oximetry testing and PSG with capnography, and treatment remains standard with NIV (continuous PAP or bilevel PAP) with a backup rate. Management of DM2 is similar to DM1 but with less need for supportive care and respiratory needs.

Congenital Myopathy

Congenital myopathy defines a heterogeneous group of congenital muscle disorders characterized by genetic defects affecting skeletal muscle fibers, resulting in generalized muscle weakness, poor muscle tone and bulk, hyporeflexia, and dysmorphic features, with intelligence mostly intact. Symptoms may present subtly or profoundly at birth, in early life, and in rare cases adulthood [51, 52]. The abnormal genes code for proteins, making up the sarcomere or involved in Ca^{2+}-mediated myofibrillar contraction. Different forms are based on predominant pathologic features such as presence of rods or nemaline bodies, oxidation-deprived cores, abnormally located central nuclei, and type I fiber hypotrophy [53]. These may overlap, making classification challenging. Creatine kinase levels are usually normal, though maybe mildly elevated. Electromyography and nerve conduction studies are normal most of the time, except in severe disease. Muscle biopsy is done in specialized centers along with light and electron microscopy for identification of specific subtypes [54]. Genetic testing using parallel, whole exome, and genomic sequencing currently is needed for accurate diagnosis and guide management [55].

Nemaline Myopathy

This group of congenital myopathies is identified microscopically by distinct Z line-derived red rods against a blue-green myofibrillar background with modified

Gomori trichrome staining. Various clinical phenotypes exist and may occur at birth or later during childhood with some reported cases presenting as respiratory failure in adults [51, 52]. Severe congenital cases may manifest as profound generalized weakness and hypotonia in bulbar regions and in muscles of respiration, contractures and fractures at birth, and swallowing difficulties. Childhood-onset symptoms are commonly delayed motor milestones, gait abnormalities, and poor exercise tolerance. A North American and Australian clinical study of 143 patients from infancy to adults reported 17 out of 23 deaths from respiratory failure in infants, 12 of which were ventilator-dependent until death and 30% of surviving group requiring mechanical ventilation during first few months of life [56]. During the same study, ventilatory failure was associated with mortality in the first year of life, but not after. Conflicting electromyography results from patients with nemaline myopathy were reported, showing normal-to-mild myopathic changes in action potentials [57].

At least 12 genes have been identified, and some are still being under investigation due to increasing use of parallel sequencing methods and whole exome and genome sequencing. Inheritance may be either AR or AD, and associated features reported were presence of cores, zebra bodies, fiber-type disproportion, actin accumulation, excess connective tissue, ophthalmoplegia, arthrogryposis, and cardiomyopathy, among many others [58].

No current treatments exist, but patients will benefit from a multidisciplinary approach involving muscle strengthening, mobility exercises, physiotherapy, and regular respiratory assessment and care.

X-Linked Myotubular Myopathy

X-linked myotubular myopathy (XLMTM) is one of the forms of the genetically heterogeneous group of centronuclear myopathies (CNM) whose distinct pathologic features involve one or more centrally placed nuclei, instead of the usual peripheral location brought about by the absence of myofibrils. It has been described as a disorder of muscle development as a result of the expression of pathogenic variants in the MTM1 gene. In an investigation of nine CNM patients, there was persistence of fetal cytoskeletal proteins vimentin and desmin, as well as intracytoplasmic dystrophin, indicating evidence of maturation arrest [59].

While other forms of CNM have AD or AR pattern of inheritance, XLMTM occurs almost in males, is much more common, and has severe phenotypes. Estimated incidence is at 1 in 5000 live male births [60]. The multicenter RECENSUS study reviewed 112 XLMTM patients in 6 sites. They reported a mortality of 44% with 90% of patients requiring respiratory support at birth, spending 35% hospital stay, and requiring an average of 3–4 surgeries during the first year of life [61].

Reduced fetal movement and polyhydramnios are signs of antenatal onset. Infants appear with macrosomia, cryptorchidism, elongated facial features, high-arched palate, and ophthalmoplegia. An Italian cohort during 2010–2014, involving 352 CNM patients, reported 15 patients with the pathogenic MTM1 gene variant. The patients' age ranges from a month old to 45 years old. All except one had

respiratory issues at birth with three requiring tracheostomy during the first year of life and two requiring noninvasive ventilation. Almost all had feeding problems and hypotonia at birth, with about half developing delayed motor milestones and extraocular muscle abnormalities [62].

Clinical characteristics at birth warrant a muscle biopsy showing histopathologic features as well as genetic confirmation of the pathogenic MTM1 variant. As with other congenital myopathies, there is currently no treatment, and care should be focused on optimizing functional capacity and managing medical complications through a multidisciplinary team.

Mitochondrial Disease

Mitochondrial diseases (mtD) comprise a group of inherited or spontaneous nuclear (nDNA) and mitochondrial DNA (mtDNA) mutations, causing defects in oxidative phosphorylation, resulting in impaired adenosine triphosphate production. It is known that proteins of the oxidative phosphorylation must be translated before being imported to the mitochondria and finally inserted into the mitochondrial membrane. Any mitochondrial and nuclear gene mutations may cause defects in the mitochondrial respiratory chain. Additionally, defects in the mitochondrial membrane phospholipid bilayer as well as in the mitochondrial movement, fusion, and division cause failure of the respiratory chain [63–65].

Epidemiological studies in childhood approximate the prevalence of mtDNA disease and minimal risk of developing mtD to be greater than 1 in 5000 and estimate prevalence of pathogenic nDNA mutations at 1 in 35,000 [66]. Primary mtD are the most common inborn errors of metabolism.

PSG changes, periodic movements, and SDB have been observed [67, 68]. Muscular weakness and decreased ventilatory drive to $PaCO_2$ have been elucidated in various case series and case reports as causes of SDB in patients with mtD [69–71]. The prevalence of SDB in patients with mtD has not been clearly defined. A retrospective chart review by Mosquera et al. of 18 patients with mtD aged 1.5–18 years showed SDB in 56% of the sample [68]. Hypotonia ($P = 0.043$) and being overweight and obese ($P = 0.036$) were shown to be significantly associated during the same study.

Manifestations vary and can be limited from isolated myopathy, exercise intolerance, fatigue, or diplopia to more serious multisystem involvement, which can be fatal. High-energy-demand organs such as skeletal, cardiovascular, renal, and endocrine are usually affected, but virtually any organ system may exhibit findings (Fig. 14.1) [72]. Some degree of overlap exists between and among the known phenotypes (Table 14.4) [73]. A retrospective, multicenter cohort in Austria and the Czech Republic consisting of 75 pediatric patients who had either biochemically or molecularly diagnosed mitochondrial disease revealed a predominance of nonspecific encephalomyopathy and Leigh syndrome [74].

The diagnosis of mtD is complicated by varying clinical phenotype, dual genomic origins, and symptomatology as well as the lack of a definitive biomarker. Maternal

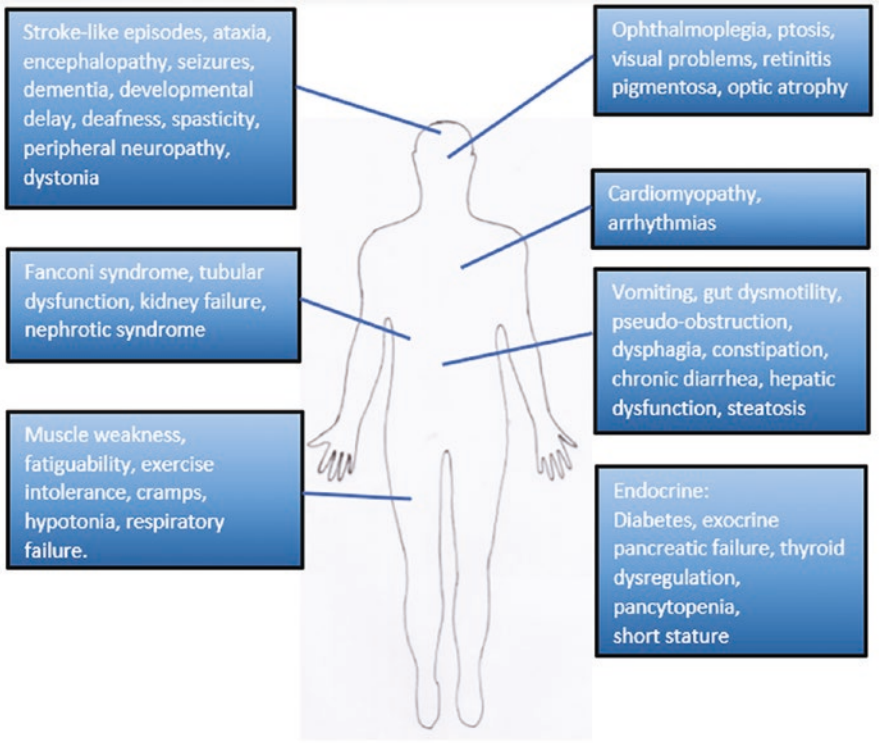

Fig. 14.1 Clinical systemic presentations of mitochondrial disease

pattern of inheritance is a clue that a provider should not miss since the disease is mainly transmitted by females, though diagnostics may not be evident in heteroplasmic mutations. The approach is different between patients who present with classic versus a non-classic phenotype. It is of prime importance to gather an extensive family history that spans 3–4 generations. For multisystem involvement, high-energy-demand organs are prone to be affected though atypical presentations and single-organ disease can range from usual fatigue, exercise intolerance to abnormal eye movements, retinopathy, and cardiomyopathy, among many others. Generally, noninvasive tests such as genetic testing should be considered initially and muscle biopsy be reserved for equivocal genetic testing results or when ruling out other differential diagnosis. In 2014, a consensus statement from the Mitochondrial Medicine Society on the diagnosis and management of mitochondrial disease was released [75].

Next-generation genetic sequencing techniques have revolutionized the way we identify specific mutations underlying mitochondrial dysfunction, which is by far the gold standard for diagnosis as it can test for deletions and duplications of the mitochondrial genome [76]. Although equivocal results of genetic studies necessitate the need for muscle biopsy analysis, the invasive nature of performing open muscle biopsy over percutaneous route is limiting but useful in confirming

Table 14.4 Clinical phenotypes of mitochondrial diseases including pattern of inheritance and signs and symptoms

Clinical phenotype	Pattern of inheritance	Onset	Signs and symptoms
Alpers syndrome	Autosomal recessive	Youth	Neurodegeneration Seizures Hepatopathy
Congenital lactic acidosis (CLA)	Multiple etiologies	Youth	Lactic acidosis Seizure Infection Organ failure
Kearns-Sayre syndrome (KSS)	Sporadic, maternal, autosomal dominant, or autosomal recessive, mtDNA and nDNA	Youth	Retinitis pigmentosa External ophthalmoplegia Short stature Cerebellar ataxia
Leber's hereditary optic neuropathy	Maternal (mtDNA)	Young men	Bilateral acute loss of central vision
Leigh syndrome (LS)	nDNA and mtDNA	Infancy or early childhood	Seizure Blindness External ophthalmoplegia Psychomotor regression Hearing loss Dementia Ataxia Hypotonia Lactic acidosis
Maternally inherited deafness and diabetes (MIDD)	Maternal (mtDNA)	Third and fourth decade	Insulin dependence Sensorineural hearing loss
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)	Maternal (mtDNA)	Variable	Stroke-like episodes Seizures Migraines Diabetes Hearing loss Psychiatric problems Dementia
Mitochondrial neuro-gastrointestinal encephalopathy (MNGIE)	nDNA, autosomal recessive	First to fifth decade	Early satiety Nausea Dysphagia GERD Postprandial emesis Episodic abdominal pain Diarrhea Neuropathy
Myoclonic epilepsy with ragged red fibers (MERRF)	Maternal (mtDNA)	Childhood	Dementia Generalized epilepsy Ataxia Myopathy Optic atrophy

(continued)

Table 14.4 (continued)

Clinical phenotype	Pattern of inheritance	Onset	Signs and symptoms
Peripheral neuropathy, ataxia, and retinitis pigmentosa (NARP)	Maternal (mtDNA)	Youth	Sensory neuropathy Seizures Dementia Lactic acidosis
Progressive external ophthalmoplegia (PEO)	Maternally (mtDNA)	Any age	Bilateral ptosis
Pyruvate dehydrogenase complex deficiency (PDC)	nDNA, X-linked, autosomal recessive	Youth	Hypotonia Psychomotor retardation Seizures Lactic acidosis

diagnosis and ruling out other causes. Histochemical stains, traditionally Gomori trichrome stains, aid in visualizing the subsarcolemmal and intermyofibrillar accumulation of mitochondria, which appears as bright red masses, coined "ragged red fibers," against a blue background of muscle fibers. Other stains such as SDH, NADH-TR, COX, and SDH/COX combination are being utilized by different institutions depending on their availability and operator experience.

In 2014, a systematic review of 1335 abstracts published in the Cochrane Database concluded no clear evidence supporting the use of any intervention in mtD [77]. Management remains as symptomatic interventions and supportive treatment. Noninvasive positive-pressure ventilation is a life-sustaining modality for those suffering from chronic respiratory failure and sleep-disordered breathing [78]. Acute treatment of stroke and seizures is a priority especially in patients with MELAS. A multidisciplinary approach that includes speech, physical and occupational therapy, genetic counseling, and nutritional support needs to be coordinated [73, 79, 80].

14.4 Conclusion

With the advancements in medicine, individuals with neurodegenerative and neuromuscular disorders have longer life expectancy leading to a larger population of adults with health issues related to their premature aging, neurocognitive disabilities, and neuromuscular weakness. This highlights the importance of future research, aiming to further evaluate neurocognitive outcomes, characterize OSA, and improve treatment efficacy for these patients. There is a need to provide ongoing evidence-based, specialized care to this vulnerable population, who are at risk for medical conditions at an early age that are otherwise low risk to the general population.

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Cystic Fibrosis: A Successful Model of Transition of Care and Lessons Learned

15

Taylor Baumann and Tara Lynn Barto

15.1 Introduction

Cystic fibrosis (CF) is a life-limiting disease caused by a defect in the functioning of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Dysfunction in this protein leads to a multisystemic disease, leading to lung remodeling, recurrent infection, respiratory failure, pancreatic insufficiency, diabetes, hepatobiliary dysfunction, gastrointestinal obstruction, and reduced fertility. When first described in 1938 by Dr. Dorothy Hansine Andersen, children diagnosed with cystic fibrosis rarely survived beyond early childhood [1]. Today, advances in antimicrobial medicine, protein modulation, and supportive measures allow individuals diagnosed with cystic fibrosis to lead full lives.

15.2 Epidemiology

Cystic fibrosis is the most common autosomal recessive life-limiting disease among individuals of northern European descent. Approximately 1 in 30 Caucasian persons are carriers of dysfunctional CFTR gene, leading to approximately 1 incidence of CF in every 3000 live births [2]. According to the CF Foundation 2018 Annual Data Report, 93% of individuals with CF were White, 5% were African American, 9% were Hispanic, and 4% were other races (answers were not mutually exclusive) (Table 15.1).

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Table 15.1 The Cystic Fibrosis Foundation (CFF) is a large nonprofit organization, which currently supports a network of over 130 accredited CF care centers throughout the United States [3]. As part of this membership, CF care centers contribute information on the health status of their patients to the Cystic Fibrosis Foundation Patient Registry (CFFPR), which is then used to further research, care guidelines, and quality improvement throughout the cystic fibrosis community [3]

CF by the numbers			
	2008	2013	2018
People with CF	25,286	28,030	30,775
Newly diagnosed individuals	1140	1048	852
Detected by newborn screening (%)	43%	60%	62%
Individuals with first CF event at less than 60 days after birth (%)	56%	70%	71%
Mean age at diagnosis for all people with CF	3.6	3.8	4.2
Median age at diagnosis for all people with CF	5	4	3
Mean age (years)	18.9	20.2	22.2
Median age (years)	16.9	17.9	19.8
Adults 18+ years (%)	46%	50%	55%

Data taken from [4]

15.3 Genetics

First identified in 1985, the cystic fibrosis transmembrane conductance regulator protein gene codes for a cAMP-activated ion channel protein mainly expressed in the airway, gastrointestinal tract, sweat glands, and genitourinary system. The CFTR protein serves two main functions through the transport of chloride and bicarb. First, CFTR chloride secretion plays an important role in maintaining hydration along the internal surfaces of tracts within the GI, sinopulmonary, and genitourinary systems. Second, CFTR bicarbonate secretion maintains pH in airway epithelium, which serves an important role in innate immunity [5]. The consequence of a dysfunctional CFTR protein therefore leads to dehydrated, viscous mucus as well as impairments in mucociliary clearance and microbial defense [6].

Although over 2000 mutations to the CFTR protein have been identified, each dysfunction has been grouped into six classes, which roughly correlate to the severity of the phenotypic presentation and are not mutually exclusive [4, 7]. Mutation classes I–III result in an absent or completely dysfunctional CFTR protein, leading to more severe symptomatic presentations of the disease. In contrast, CFTR mutation classes VI–VI result in a partially functional but inefficient protein. F508del is the single most common mutation, with at least one mutation present in 85% of CFFPR participants and a homozygous F508del noted in 44% [4].

15.4 Pathophysiology

Pulmonary System

Lung disease is the main source of morbidity and mortality among individuals with cystic fibrosis [2]. Within the Lung, CFTR dysfunction leads to pH

imbalance, the accumulation of thickened mucus, and an inability to conduct mucociliary clearance [6]. This creates an environment ideal for bacterial growth and propagation while hampering the individual's ability to clear pathogens from the respiratory tree. The immune response to bacterial overgrowth attracts both inflammatory cell products and proteases, which leads to airway wall inflammation. Over time, recurrent cycles of infection and inflammation cause the progressive development of an irreversible bronchiectasis, which further inhibits the body's ability to mitigate new and recurrent lung infections. Ultimately, approximately 90% of patients with cystic fibrosis will die from respiratory failure, unless they receive a lung transplant [7].

Bacterial colonization and infection drives the progression of lung disease in cystic fibrosis. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, MRSA, *Haemophilus influenzae*, *Achromobacter*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia* are the most common bacteria grown for cystic fibrosis airway. *S. aureus* is the most prevalent bacteria in younger individuals; however, *P. aeruginosa* becomes increasingly common as individuals age with worsening bronchiectasis [4] (Fig. 15.1). The mucoid morphotype of *P. aeruginosa*, a pathogenic strain that has uniquely adapted to living in CF airways, is particularly important in chronic CF bronchiectasis. Although relatively avirulent, the chronic inflammatory response caused by mucoid *P. aeruginosa* is disproportionately responsible for lung remodeling with earlier infection correlating with the severity of future lung disease [8, 9]. The presence of nontuberculous mycobacterium (NTM) such as *M. avium complex* and *M. abscessus* has also been associated with a more severe lung disease [10]. Although relatively uncommon a decade ago, the prevalence of reported NTM has dramatically increased in the past decade to approximately 14% among patients with cystic fibrosis [4] (Fig. 15.2).

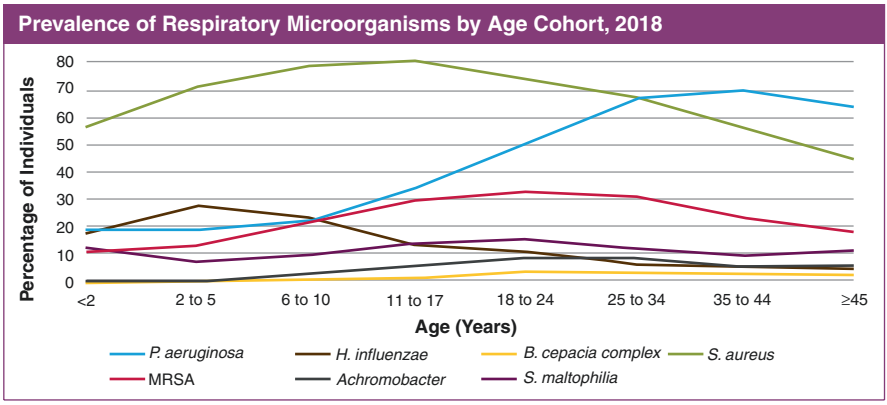

Fig. 15.1 Graph demonstrating the prevalence of specific microorganisms in relation to age cohort in 2018. (Reproduced from reference [4])

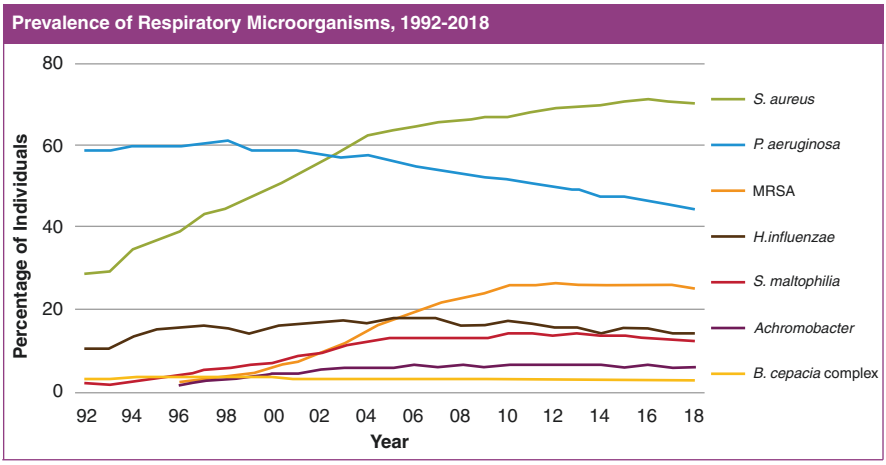

Fig. 15.2 Graph demonstrating the changes in the microbiome in cystic fibrosis patients over the previous 25 years. (Reproduced from reference [4])

Gastrointestinal System

Pancreas

When cystic fibrosis was first described in 1938, severe malnutrition due to pancreatic insufficiency was the main unifying feature of the disease [1]. Dysfunction of the CFTR protein leads to dysfunction in the hydration of secretions within pancreatic ductal lumens. This causes thickened secretions, which cause ductal obstruction, leading to the pooling of exocrine pro-enzymes within the pancreatic ductal network. Over time, local irritation from pro-enzyme accumulation leads to progressive scarring and fibrosis, hampering both the exocrine and endocrine functions of the pancreas [11].

Disruption of the exocrine function of the pancreas leads to malnutrition due to an inability to appropriately digest complex proteins, carbohydrates, and lipids. Although almost all individuals with cystic fibrosis experience some degree of pancreatic dysfunction, overt pancreatic insufficiency is seen in approximately 85% of cases and is associated with the more severe class I–III CFTR genotypes [12].

Endocrine function of the pancreas is primarily manifested as CF-related diabetes (CFRD).

Although CFRD is typically uncommon in children, abnormal glucose tolerance is seen in 40% of patients by 10 years of age [13]. CFRD prevalence rises throughout adolescents with approximately 50% of patients meeting diagnostic criteria as adults [14]. Although adults do not generally die from DKA or macrovascular consequences related to CFRD, the associated hyperglycemia and increased catabolic state caused by diabetes lead to a pathogen-promoting environment that significantly contributes to pulmonary complications of CF [14].

Hepatobiliary

CFTR dysfunction within the bile ducts of the liver leads to scattered areas of decreased bile flow, ductal obstruction, and chemokine upregulation throughout the hepatobiliary tree. These areas of multifocal inflammation can eventually lead to a peribiliary fibrosis described as CF liver disease (CFLD). The continuum of liver disease associated with CFLD includes a progression of focal biliary cirrhosis to multilobular biliary cirrhosis and eventually pulmonary hypertension [11].

Due to the variable dispersion of fibrosis throughout the liver, the diagnosis of CFLD is difficult to make. The most widely accepted definition requires a 12-month period including two or more of the following features: hepatomegaly, abnormal liver function tests, ultrasonic evidence of liver dysfunction, or portal hypertension [15, 16]. Although as many as 40% of individuals with CF demonstrate abnormalities in liver function testing, only 5–10% of patients develop CFLD [12].

Bowel

Within the bowel, chloride and bicarbonate are essential for the formation of the loose, well-hydrated mucus, which assists with conducting stool throughout the GI tract. As a result, CFTR dysfunction leads to the formation of the dense stool associated with meconium ileus, distal intestinal obstruction syndrome (DIOS), and constipation [17, 18].

Meconium ileus occurs when thick, dense meconium physically obstructs the intestinal tract during the neonatal period. Typically occurring on either side of the ileocecal junction, the obstructing meconium leads to proximal small bowel distention, which is complicated by volvulus, ischemic necrosis, perforation, or peritonitis in approximately 50% of cases [12]. Due to its neonatal presentation, meconium ileus is often the first presenting symptom of CF, occurring in approximately 15% of CF births, with very few cases occurring in babies without cystic fibrosis [19]. Although occurring later in life, DIOS also presents as an acute ileocecal obstruction with a similar mechanism to meconium ileus. The risk of DIOS increases with age, with a lifetime prevalence of approximately 15% in adult patients and a high risk for recurrence at approximately 50% [20].

15.5 Reproductive Health

Cystic fibrosis affects the fertility of both men and women, although by different mechanisms. In men, CFTR dysfunction leads to approximately 98% infertility rate due to obstructive azoospermia from a congenital bilateral absence of the vas deferens (CBAVD). In men with CF who are born with the vas deferens intact, alterations in ejaculate pH create an additional hurdle to conception by altering sperm motility [21].

Although women with CF typically have normal reproductive anatomy, reduced CFTR function causes concentrated, thick cervical mucus, which impedes the traversal of sperm in the reproductive tract [21]. In addition, decreased bicarbonate secretion lowers the pH within the uterine cavity, further hampering sperm motility.

Even so, it is estimated that up to 50% of women with cystic fibrosis can conceive a child by natural means [22]. Once conceived, the majority of pregnancies result in a successful birth with conflicting data suggesting a potential increased risk for low birth rate or prematurity correlating with the severity of the mother's lung disease [23, 24].

15.6 Cystic Fibrosis Transitions of Care

Transition Concepts

Healthcare transition is the process of moving an adolescent's healthcare from a pediatric-oriented care setting to an adult-oriented care setting [25, 26]. This includes supporting each young adult through the process of engaging in their own healthcare through transition preparation, the transfer of care, and integration in an adult-oriented healthcare system. During these stages, the young adult gains increasing responsibility for self-care through treatment adherence, communicating with the healthcare team, and maintaining appointments [27]. This educational period begins prior to adolescents and continues until they are able to assume full responsibility for their own care [28].

In contrast, the transfer of care refers to the actual event or series of events through which adolescents move their care from a pediatric model to an adult model of care. The goal of a transition program is to prepare a young adult for the transfer of care and to support the individual with uninterrupted healthcare that is patient centered, developmentally appropriate, flexible, and comprehensive [28].

Why Is Transition Medicine Important to Cystic Fibrosis?

As recently as the 1980s, the life expectancy for an individual diagnosed with cystic fibrosis rarely extended past early adulthood [29]. In the past 40 years, advancements in pharmacology, surgical interventions, healthcare systems, and psychosocial support have led to a steady increase in both the quality of life and the longevity that a person with cystic fibrosis can hope to enjoy. According to Cystic Fibrosis Foundation Registry data, the population of adults with cystic fibrosis first exceeded the population of children with cystic fibrosis in 2014 [30]. This same data set predicts that babies with cystic fibrosis born between 2014 and 2018 will have an average life expectancy of 44 years [31]. As a result, most individuals with cystic fibrosis will require healthcare within an adult-oriented healthcare system at some point in their life.

For many chronic diseases, the beneficial outcomes associated with transition are well known. Although there is limited data on the medical benefits associated with CF transitions, patients within an established CF transition program showed no decline in function during the transfer from pediatric to adult care [32]. Patients and families also consistently report improved healthcare experience when transitioned

appropriately and effectively [33]. In recognition of the importance of facilitating appropriate transitions, the CF Foundation requires an established transition process between pediatric and adult providers in order to obtain accreditation as a cystic fibrosis center [34].

Models of Transition

In 2011, three major primary care organizations (AAP, AAFP, and ACP) produced a joint clinical report updating prior guidelines pertaining to transitions of care for patients with chronic medical conditions. They identified six core elements to a successful transition and suggested a timeline for initiating each step, intended to provide practitioners with a flexible framework for approaching transitions of care in a variety of care settings [35] (Fig. 15.3).

In addition, the Cystic Fibrosis Foundation has mandated that all CFF-accredited cystic fibrosis centers follow one of four models for transition to adult-oriented care (table below) with the expectation that >90% of patients past their 21st birthday will be transferred to an adult program [29] (Table 15.2).

Challenges During Transition

Healthcare transitions are inherently complicated, occurring within the context of other important adolescent milestones including the progression toward independence in social, educational, and financial aspects of life. In addition to these challenges, the several other key complicating barriers commonly experienced by individuals with CF are discussed below.

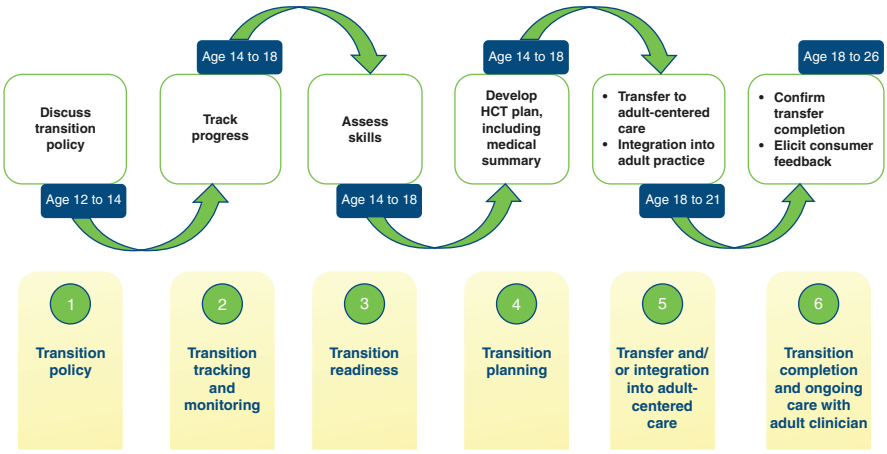

Fig. 15.3 Six core elements to a successful transition in the context of a suggested timeline. (Data taken from reference [35])

Table 15.2 Proposed models of adult CF care by the CF Foundation. (Modified from reference [36])

Models for Adult CF Programs	Primary care provider	CF-specific care provider	Location of outpatient clinic	Role of program director	Inpatient location
1	All adult patients have an adult care PCP	CF care is provided by local CF center team	Adult patients are cohorted to adult specific clinics	Programs with >20 adult patients should identify an adult care provider to attend clinic	Age-appropriate setting is encouraged
2	Adult program physicians provide inpatient and outpatient care to all patients in the adult program	CF-center team has adult experience and routinely interacts with adult program physicians	Outpatient care is provided in adult or pediatric clinics, but adult patients are cohorted	Adult program director should see patients for sick visits and receive telephone calls	Adult hospital or adult inpatient unit
3	Same as for model 2 except there is a separate coordinator for the adult program				
4	Same as for model 2 except there is (1) separate adult team and coordinator and (2) outpatient care is provided in the adult outpatient department				

Complexity of Health History

Remembering and understanding lifelong medical histories with multiorgan complications and the involvement of multiple subspecialty providers is a challenging task for anyone and often leads to significant reliance on parental assistance and a potential for parental dependence. It can especially be difficult for parents to "let go" and allow their children to find their own routines for care [37].

Unclear Responsibilities of Co-managing Providers

The majority of individuals with cystic fibrosis identify their pulmonologist as their "main doctor," even though they have established a primary care provider. However, less than 40% of these individuals reported counseling on sexual health, mental health, tobacco use, alcohol use, or safety from either provider within the past year [38].

Time and Financial Burden of Treatment Regimens

In one survey, individuals with CF reported spending an average of 108 min on treatment activities each day [39].

Financial Stressors

A majority of adolescents with chronic diseases report gaps in their insurance coverage or extended periods without insurance [40]. Medication price has specifically

been noted by adolescents with CF as a significant barrier to adherence to treatment regimens [41].

Social Impact of Illness

Conflicts or perceived threats to relationships with parents, other family members, or friends have been cited as significantly detrimental for medical adherence [37].

Sexual Health Disparity

Adolescent women with CF report a lack of routine counseling regarding sexual and reproductive health [42]. These individuals are also less likely to have ever used contraception or have been tested for STDs when compared to the general population, suggesting potential gaps in sexual healthcare [43]. In addition, many CF providers note significant discomfort or a lack of training in addressing sexual health [44].

Peer Group Limitations

Peer support is noted to be particularly important to adolescents with chronic illness during the process of establishing independence in their healthcare routines [37]. However, opportunities for face-to-face peer interactions are limited in cystic fibrosis due to the risk of transferring resistant organisms among patients. However, many online communities have formed to provide virtual peer-to-peer support.

Additional Resources

Cystic Fibrosis Foundation

A large, well-funded, non-profit organization that supports the cystic fibrosis community while funding research and advancing healthcare related to CF (https://www.cff.org/).

Got Transition/Center for Health Care Transition Improvement

A cooperative agreement between the Maternal and Child Health Bureau and The National Alliance to Advance Adolescent Health focused on improving the transition from pediatric to adult healthcare (https://www.gottransition.org/).

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Sickle Cell Disease: Lessons Learned

16

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16.1 Introduction

There is a national focus on transition from pediatric to adult healthcare as a major healthcare issue. Most of these efforts are guided by general health and development models focused on patient, provider, and healthcare system level change, such as the biopsychosocial model [1, 2] bioecological model [3], and transtheoretical stages of change model [3, 4]. In addition, models focused on transition to adult healthcare have been developed, such as the social-ecological model of adolescents and young adult readiness for transition (SMART) [5–8]. While these models provide clear foundations for the development of individual programs, they do not provide guidance for developing and assessing the progress specific fields make in developing, evaluating, disseminating, and implementing healthcare transition programming. Also, the application of these models has resulted in the development of an array of transition programs that are often site-specific. This limits programs' applicability; results in limited distribution, application, or evaluation across healthcare settings; and ultimately hinders the field's development of clear transition program standards.

We describe a framework for guiding individual fields as they systematically plan and evaluate transition research. The framework can be used by researchers,

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Fig. 16.1 A conceptual framework for guiding research agendas on transition from pediatric to adult healthcare as represented in three sequential phases of research. Phase 1 (pre-program development) supports Phase 2 (program development and evaluation), which leads to Phase 3 (program dissemination and implementation)

clinicians, healthcare administrators, and policymakers and focuses on outlining a field's research trajectory, culminating in widespread program implementation and dissemination. Our framework (Fig. 16.1) is organized as a set of sequential and interconnected transition research activities organized into three phases: (1) pre-program development, (2) program development and evaluation, and (3) program dissemination and implementation. We then apply the model to critically discuss the current state of the literature on transition from pediatric to adult healthcare for individuals with SCD, with a focus on lessons learned and appropriate next steps for the field.

16.2 Sickle Cell Disease Overview

SCD is a group of inherited red blood cell disorders affecting 100,000 individuals in the United States, primarily of African ancestry [9]. Worldwide, SCD is prevalent in sub-Saharan Africa, the Mediterranean, the Middle East, India, Central and South America, and the Caribbean [10]. It is estimated that globally 300,000 babies per year are born with sickle cell anemia, with the majority of births occurring in Nigeria, the Democratic Republic of the Congo, and India [11]. Individuals with SCD have an abnormal hemoglobin molecule (hemoglobin S), which distorts red blood cells into a crescent or sickle shape [12]. These abnormal blood cells die prematurely and can adhere to each other, impeding the flow of oxygenated blood to parts of the body. This results in a host of symptoms, including anemia, debilitating pain, progressive organ damage, and early death, with the hallmark symptom being recurrent vaso-occlusive pain episodes. Disease-modifying treatments include

medications, regular blood transfusions, and hematopoietic stem cell transplantation. Since 2017, the US Food and Drug Administration approved three new medications for the treatment of SCD: Endari (L-glutamine), Oxbryta (voxelotor), and ADAKVEO (crizanlizumab). Prior to this, hydroxyurea was the only established medication for SCD [13]. Blood transfusions can ameliorate and prevent stroke, but iron overload and poor transfusion reactions can limit its benefits [14]. Stem cell transplantation is the only curative option to date for SCD; however, it is costly and has potential for toxicity, and few individuals have a suitable donor [15]. Gene therapy and gene editing approaches have the potential to cure SCD with clinical trials ongoing [16–19].

Historically, only half of children with SCD survived into adulthood [20, 21]. Medical advances, such as prophylactic penicillin and hydroxyurea therapy, have improved survival. SCD is no longer a pediatric illness but a chronic disease with the burden of the disease shifting to adulthood [21]. For this reason, it is necessary for patients to transition to adult healthcare. This period of transition is critical; young adult patients aged 18–30 years have the highest rates of initial and re-hospitalization compared to other age groups [22]. Transitioning patients receive less treatment-related care (e.g., transfusions, hydroxyurea, iron chelation) and have higher healthcare costs than pediatric patients [23]. Furthermore, mortality rates sharply increase from adolescence to young adulthood: 0.6/100,000 for ages 15–19 years to 1.4/100,000 for ages 20–24 years [24]. As patients age, end-organ damage and more comorbidities emerge, increasing the need for disease knowledge and self-management skills and accessible and affordable healthcare [25]. Therefore, transition programs have been created to support adolescents and young adults (AYA) during the transition process. The following sections discuss activities associated with each phase focused on transition programming for individuals with SCD.

16.3 Phase 1: Pre-program Development

The purpose of Phase 1 transition research agenda activities is to (1) gather stakeholder perspectives about the transition process and goals, (2) evaluate existing transition practices, and (3) conduct behavioral research to define transition mechanisms and targets and investigate factors that influence the transition process and programming. The majority of SCD transition research has focused on obtaining stakeholders' unique perspectives on the barriers of successful transition and priorities for transition preparation and programming. AYAs with SCD often report feeling unprepared to transition due to a lack of perceived knowledge and skills [6, 26–31]. They are required to navigate the healthcare system; communicate effectively with physicians in emergency departments, inpatient settings, and outpatient settings; educate others (including healthcare providers) about SCD; schedule and coordinate healthcare appointments; refill prescriptions; and adhere to medications. AYAs also report a reluctance to leave trusted pediatric providers due to a mistrust of the healthcare system and fears about adult providers and adult healthcare settings [32–34]. Results from a qualitative study of adults who had recently

transitioned from pediatric to adult care found that many participants felt "surprised" and "abandoned" when they were approached about transition [33]. Studies using validated transition readiness assessments indicate an inadequate level of preparation for transition to adult healthcare [27]. Patients report wanting more information and education about the transition process, particularly using technology-based health education platforms [31, 35–41].

Many caregivers also share concerns about their child's disease knowledge and self-management skills and treatment received by new providers who may not be familiar or comfortable treating SCD [34, 42–44]. Caregivers describe an inability to "let go" or to let their child assume more responsibility in their care management. A survey study found that 44% of caregivers reported concerns about their child taking over their healthcare responsibilities, independent of the caregiver [45]. In a descriptive study of AYA-parent dyads examining perceptions of transition readiness [30], parents reported "often" being responsible for their child's care and that the AYAs were not at all responsible for scheduling specialty or primary care appointments or refilling prescriptions. The researchers found that parental involvement was negatively correlated with AYA perceived readiness to transfer to adult care and called for interventions directed at decreasing parental involvement and increasing AYA's responsibility for self-management [30].

Consistent evidence has shown that many adult healthcare providers feel ill-equipped to manage the care of patients with SCD [45, 46]. A 2017 study of adult providers found 66% were unaware of the 2014 SCD guidelines, the most recent guidelines at the time of the study [47]. The American Academy of Pediatrics (AAP) has identified training and clinical learning experiences in care transition as key gaps to be addressed [48]. There is no standard practice for transition care in the United States, and most comprehensive SCD centers do not have established transition programs [31, 33, 49]. A 2011 survey of pediatric SCD providers [50] found that 77% of respondents reported having a transition program, though many had not been established for longer than 2 years. Providers reported challenges with finding an appropriate adult SCD provider for patients and identified a need for more transition resources, including assessment of transition readiness, and more rigorous program evaluation. These challenges are particularly salient in rural areas, where many AYAs with SCD lack access to appropriate medical and psychosocial support services [3, 32].

It is important to recognize the socio-racial context of transition for AYAs with SCD, who are primarily African American and disproportionately come from lower socioeconomic backgrounds [9, 10]. Chronic illness research has demonstrated that traditionally underserved communities experience greater healthcare barriers. As such, non-Hispanic black youth are less likely to discuss changing healthcare needs, plan for these changes, or discuss transitioning care to adult providers with their pediatric providers than non-Hispanic white youth, highlighting racial disparities in transition [51]. Further, poor patient-provider relationships have been documented, with providers viewing patients with SCD as drug-seeking when receiving treatment for pain [52, 53]. As a result, it is important for programs to recognize these

challenges, include provider training concerning these issues and how to address them in culturally sensitive ways, and design culturally tailored programs to educate and empower AYAs.

16.4 Phase 2: Program Development and Evaluation

The focus of Phase 2 transition research agenda activities is to (1) develop programs and program components; (2) conduct clinical trials to evaluate feasibility, safety, and efficacy of programs and program components; and (3) conduct clinical trials to compare effectiveness of empirically supported transition programs. SCD researchers and clinicians have a number of sources to guide transition program development, including research on stakeholder perspectives about the transition process and transition goals, health and developmental theories, and national guidelines.

One of the first published accounts of a SCD transition program was of the Children's Regional Sickle Cell Program, part of CHRISTUS Santa Rosa Children's Hospital and the University of Texas Health Science Center in San Antonio [54]. The program was informed by a review of the literature on adult healthcare needs of individuals with childhood-onset illnesses. This two-part program emphasizes the importance of disease education and management skills early on and throughout the care continuum by starting at the newborn's initial visit at the pediatric healthcare system. Families are informed that care is provided to the patient until age 18 and given a binder with SCD and treatment information and related SCD care items and materials. Families engage in activities to learn about the disease and become actively involved in care (e.g., quarterly newsletter with educational information, medication index cards to remember medications and dosages). At age 13, patients receive a preparation for transition binder with skills checklists, appointment tracking sheets, pain management plans, and educational materials that are reviewed with the caregiver and patient on a regular basis. At age 14–16 years, patients participate in an activity to develop communication and advocacy skills for when they are in the emergency department.

At the national level, Got Transition/The National Center for Health Care Transition Improvement was founded to guide the development of transition programs for clinical practices. Got Transition developed the Six Core Elements of Health Care Transition in clinical practice to serve as best-practice guidelines to improve transition practices and programs for AYA with chronic conditions [55]. These guidelines define the key components of a model transition program: (1) establishment of transition policy, (2) transition tracking and monitoring, (3) assessment of transition readiness, (4) transition planning, (5) transfer of care, and (6) transfer completion [55]. Got Transition has published numerous resources and self-assessment tools on gottransition.org, including transition readiness assessments, transfer checklists, and post-transfer feedback surveys.

Virginia Commonwealth University's SCD Transition Intervention Program (TIP) was developed based on Got Transition's Six Core Elements [56]. It is a

multidisciplinary transition program that begins transition programing at age 15. The program's primary goal is to successfully prepare and then transfer patient care at high school graduation, with a first visit to an adult provider within 6 months of graduation. The TIP includes a 3-year curriculum delivered by an educational coordinator and clinical psychologist that addresses knowledge, skills, attitudes, and confidence about transition. It also includes individual and group education sessions alongside targeted support during regular transition visits. Transfer success is indicated by completion of the initial visit with an adult SCD provider within 6 months of high school. Prior to implementation of TIP, 50% of patients completed their initial visit with an adult SCD provider within 6 months of graduation. Evaluation of TIP demonstrated that 78% of patients who completed their initial adult provider visit within 6 months of their high school graduation continued to receive care in the adult clinic [56].

Also, at the national level, the Health Resources and Services Administration (HRSA) funded the Sickle Cell Disease Treatment and Demonstration Program (TDP) to support collaborative learning and improvement science across five dimensions of SCD care, including healthcare transition [57]. TDP's purpose was to enhance the prevention and treatment of SCD through service delivery coordination, training of health professionals, and other related efforts. TDP grantees (pediatric and adult comprehensive SCD centers, SCD community organizations, and federally qualified health centers) collaborated with the HRSA Sickle Cell Disease for Newborn Screening Program and the National Initiative for Children's Health Quality to develop the SCD Transition Curriculum. Based on current research, it was designed as a reference for healthcare practitioners, patients, and parents by patients' age (e.g., 12–14-year-olds, 15–17-year-olds, and 18–25-year-olds) in three domains (i.e., medical, social, academic) [58]. No published transition programs have acknowledged being based on these guidelines.

Regarding program evaluation, nearly 30 articles have been published describing and presenting evaluation data on SCD transition programs [59]. Programs vary in delivery, methods, content, and personnel involvement from center to center. The primary components noted include facility tours [39, 49], specialized transition clinics [60–62], education-based interventions [34, 41, 63–67], technology-based interventions [68, 69], and patient navigators [35, 40]. Of note, there is a lack of published results from randomized controlled trials (RCTs). However, a search of clinicaltrials.gov yielded three currently recruiting RCTs. One study is incorporating peer mentoring with young adults with SCD as coaches in the intervention arm [70]. Another study is comparing usual care to a transitional care program with patient and family education, individual psychological care, and group education [2, 71]. The third study is testing the efficacy of a telehealth adaptation of a cognitive remediation intervention to prepare adolescents for transition [72]. These RCTs are examining a variety of outcomes including healthcare utilization, transition readiness, transition satisfaction, medication adherence, health-related quality of life, cognitive functioning and neuroimaging and program feasibility.

16.5 Phase 3: Program Dissemination and Implementation

The final phase of the transition research agenda framework is focused on (1) distribution of program materials/components to the larger field and (2) adoption and integration of evidence-based programs into different settings. Dissemination and implementation efforts are focused on shortening the time lag between research establishing evidence-based practices and the integration of evidence-based practice into routine clinical practice—estimated to be 17 years [73]. Dissemination aims to distribute program materials and components to the larger field. This can be accomplished in numerous ways, such as through articles, workshops, manuals, and websites. Implementation aims to facilitate adoption and integration of evidence-based practices into real-world settings. This can be accomplished by studying "real-world" clinical settings, identifying barriers and facilitators to program adoption and integration, and systematically deploying strategies to alter the setting and aspects of programs to enable adoption and integration while maintaining program effectiveness. The implementation process should take into account how different settings vary in resources, challenges, and population characteristics.

Despite the lack of empirical evidence for most SCD transition programs, some of these activities—primarily dissemination—have begun. The majority of dissemination activities have used peer-reviewed articles to distribute information on program components and provide details on program structure. Two programs have disseminated program materials via websites: the SCD-Age Based Curriculum (SCD-ABC) transition program [67, 74] and the St. Jude Children's Research Hospital (St. Jude) Transition to Adult Care Program for SCD [75, 76]. In this section, we will focus on the most disseminated transition programs and program components for individuals with SCD.

SCD-specific assessments for transition readiness have been created to guide program development, assess the progress of participants' pre- and post-intervention, and evaluate program effectiveness. Two SCD-specific assessments have been published in peer-reviewed journals: the Transition Intervention Program-Readiness for Transition (TIP-RFT) measure [77] and the Sickle Cell Transition Intervention Program Skills Checklists [3, 28]. The TIP-RFT is a 22-item self-report survey with 4 subscales assessing independent living skills, healthcare knowledge and skills, education and vocational planning, and social support. Items were developed after a review of the transition literature, refined based on feedback from patients with SCD and their providers, and then empirically evaluated and revised using two samples of 170 transition-age patients (ranging from 14 to 26 years) with SCD at different sites [77]. The Sickle Cell Transition Intervention Program Skills Checklists is a collection of eight self-report surveys focused on knowledge skill sets (i.e., healthcare skills, educational and vocational skills, health benefits, social support, and independent living skills) and psychological functioning (i.e., feelings about transition, sickle cell stress, and SCD self-efficacy) [3]. Results from a study of 33 transition-aged patients (aged 18–23 years) with SCD indicated that the psychological functioning surveys have good internal consistency (Cronbach's alphas >0.70),

while the knowledge skills sets demonstrated moderate-to-poor internal consistency (Cronbach's alpha <0.70) [28].

The American Society of Hematology (ASH) also released a transition toolkit [78] that includes a self-report SCD Transition Readiness Assessment as well as a SCD-specific Medical Summary Form. The Readiness Assessment is a 29-item self-report survey assessing patients with SCD's confidence in managing their healthcare and their health and healthcare knowledge (i.e., disease knowledge, medication management, appointments, insurance, and healthcare privacy). The SCD Medical Summary form is a four-page document to be completed by the pediatric provider, pediatric patient, and their family to gather clinical information to be communicated to the adult provider during the transition process. It is based on a non-disease specific assessment and medical summary template created through a collaborative initiative led by the American College of Physicians (ACP). ASH then developed working groups to tailor the forms for general hematology, hemophilia, and SCD patients. The toolkit is available on the ASH website but has not been empirically tested. Of note, there are currently no disseminated caregiver-report SCD transition readiness assessment tools.

As for disseminated programs, the SCD-ABC transition program [74] developed at Children's Healthcare of Atlanta consists of (1) monthly teen clinics for 13–18-year-olds and their families, focused on age-based transition preparation (e.g., SCD knowledge, steps for transitioning to adult care, finances, health insurance, and college); (2) quarterly transition events for 17- and 18-year-olds and their families to meet adult providers, tour the adult clinic, and meet in gender-specific mentor-provider-led groups; and (3) an annual Sickle Cell Education Day for patients and their families, which includes a graduation ceremony for 17- and 18-year-olds who have completed the program. The manual, "Stepping Up to Adult Care" (available at SCInfo.org) [74], provides detailed information for setting up and managing the clinics, transition events, and the annual education day. It also includes staffing models, recommendations for billing, lists of activities and goals, quality improvement procedures, and program evaluation tools. Program development details and preliminary evidence for program efficacy are provided in a peer-reviewed journal article [67]. Results from a study of 55 adolescents with SCD (aged 13–19 years) who regularly attended the teen clinic indicated that clinic attendance significantly increased SCD knowledge over time. Also, at the time of the publication, 350 adolescents had been eligible to attend transition day events, but only 135 participated. Post-event survey results from 100 attendees found that 97% reported the program to be helpful in preparing them for transition, 100% reported the gender-specific provider-mentor-led groups to be helpful, and 88% indicated they intended to or were comfortable with transitioning.

The St. Jude Transition to Adult Care Program for SCD is detailed in a peer-reviewed journal article [76], with program components available on St. Jude's "Sickle Cell Disease Treatment" webpage [75]. The program is a series of comprehensive, interconnected interventions for 12–25-year-old patients with SCD that map onto the Got Transition Six Core Elements. Program components consist of:

1. Pediatric and adult transition policies
2. A clinical database to track transition benchmarks and outcomes
3. Transition readiness assessments paired with disease education and self-management skills trainings
4. Supports for planning for adult care (i.e., a teen support group, academic planning and support, and periodic neurocognitive screenings)
5. Transfer activities (e.g., tour of the adult clinic and scheduling of the first adult appointment)
6. Co-location of the pediatric and adult providers

Results based on 568 patients who have participated in the program indicate that the program reduces the likelihood pediatric patients discontinue care, decreases transition time, increases the likelihood patients attend their first adult care visit, and increases the likelihood patients continue adult care visits after transfer.

Program components of the St. Jude program that have been disseminated via their website include their disease education skills training program—the Sickle Cell Transition E-Learning Program (STEP) for Teens with Sickle Cell Disease [79]—and additional educational resource booklets [80]. STEP contains six educational modules consisting of 5–7-min educational videos paired with interactive pre- and post-video quizzes. The videos cover information on SCD knowledge, healthy living habits, pain, infection, other SCD complications, genetics, and self-advocacy. Patients are also encouraged to print their quiz results and discuss them with their healthcare provider as part of the transition process. Of the 183 patients offered access to the STEP program, only 29% (53 patients) completed at least one module [66]. A study of 39 adolescents (aged 12–15 years) who completed at least one STEP module and evaluation surveys demonstrated the number of modules completed was positively related to patient's disease knowledge, but not related to patients' self-management confidence.

Educational resource booklets available on the St. Jude website include the "Health Smart Transition Booklet: Teens with SCD Moving from Pediatric to Adult Care" booklet and the "Taking Control: Teens with SCD" booklet [80]. The "Health Smart Transition" booklet is an information guide for adolescents preparing or in the process of transitioning, which consists of pictures of actual adolescent patients asking transition-related questions with a corresponding answer on the next page. The "Taking Control" booklet is centered on the message that self-management is central for successful transition and focuses on providing information to promote self-management. Beyond the overall program evaluation, there is no supporting data for the booklets.

In contrast to dissemination activities, implementation activities for existing transition programs for individuals with SCD are non-existent. The SCD-ABC Transition program [74] manual includes a sample budget and suggestions for implementing the program at different sites, including the need to engage stakeholders to identify and discuss site and population barriers to transition and to assist with the pre-planning and implementation process. Also, Smith and colleagues [56] detailed implementation issues they encountered while developing and

implementing their SCD transition program: funding to support team members (particularly clinicians and administrative staff) to construct the program, sustaining the program over years given staff turnover, differences in pediatric and adult care models, and the scarcity of psychosocial resources during the transition period. However, there are no published implementation trials for SCD transition programs.

16.6 Future Directions, Opportunities, and Lessons Learned

Using the Framework for Transition from Pediatric to Adult Health Care Research Agenda, the weaknesses and gaps of the current research on SCD transition programs are clear. Many of the Phase 1 pre-program development work has been completed, with a focus on gathering stakeholder perspectives and evaluating existing transition practices. Less work has been focused on conducting behavioral research to define transition mechanisms and targets, as well as contextual factors that may influence the transition process and future programming. That work will be essential for evaluating, disseminating, and implementing effective transition programming. A barrier to this research is the absence of a national patient registry to better understand access to care and disparities, variations in treatment and outcomes, and factors that impact quality of life during the transition period. The Centers for Disease Control and Prevention (CDC) established the Registry and Surveillance System for Hemoglobinopathies (RuSH), a SCD surveillance program, in 2010, to collect information on diagnoses, treatments, and healthcare access for seven states [81]. The Sickle Cell Disease Implementation Consortium (SCDIC), established in 2016, also aims to establish a SCD Registry to gather patient information across eight sites [82]. Though positive steps forward, a nationwide registry would provide a more comprehensive understanding of SCD patient-related issues, as well as acting as an invaluable resource for researchers interested in conducting observational studies in SCD.

Phase 2 activities are currently being conducted, with a focus on program development and evaluation through retrospective and single-arm pre-/post-designs. Research has demonstrated issues with uptake of transition program components as evidenced by low rates of participation for any one program component. However, because components are integrated across clinical services, youth may be receiving the information and training they need within other aspects of the program. The lack of RCTs to rigorously evaluate the efficacy and effectiveness of programs and program components continues to be a limitation. However, the current RCTs underway are promising. Also, the ASH SCD Clinical Network is an initiative to facilitate the conduct of future clinical trials across sites and engage and educate the SCD community to promote clinical trial recruitment [83]. Utilizing a centralized data repository and coordination among sites will facilitate sharing of results and best practices for the larger SCD research community.

Relatedly, rigorous SCD transition research may be hampered by measurement issues. Across populations, there is a lack of consensus on the definition of successful transition and limited identification of outcomes and appropriate clinical

endpoints [84]. This is consistent with the lack of SCD-specific transition measures. Only three SCD-specific measures are available; they are not consistently used across studies, and only the TIP-RFT has undergone formal psychometric analysis for reliability and validity [77]. In the few studies attempting to address transition outcomes, outcome measurement has been simplified, examining aspects such as pre- and post-transition SCD knowledge [41], the completion of an initial visit to an adult care provider and healthcare utilization [39, 49, 61, 85], and satisfaction with the transition process [67]. However, when viewing transition through a biopsychosocial lens, outcomes such as medication and treatment adherence, health navigation skills, self-efficacy, quality of life, and socioemotional and behavioral functioning must be considered [86, 87]. With other chronic illnesses (e.g., cystic fibrosis, diabetes, and HIV), the primary outcomes for transition programs tend to be clinical data, such as pulmonary function, metabolic control, and viral load [88–90]. Because the definition of SCD disease severity is complex and not agreed upon, there is not a definitive medical indicator that may be used as an overall clinical transition outcome measure. Thus, it is critical to identify and test suitable measurable transition outcomes specific to SCD.

Phase 3 dissemination and implementation efforts for SCD transition programs are limited. Part of the limitations in this area are due to the lack of empirically supported programs. However, as the field prepares to move forward, we should pull from dissemination and implementation theory and the rising empirical evidence bases to guide future Phase 3 activities. Several SCD transition programs have been implemented within individual institutions and medical centers; therefore, work to increase dissemination and implementation across sites of transition practices and programs is critical to improve the quality of care and overall quality of life of AYAs with SCD. The SCDIC aims to conduct needs assessments among stakeholders and multimodal interventions to improve healthcare utilization among adults and adults with SCD [82]. Beyond the registry mentioned above, one of the consortium's aims is to provide training in dissemination and implementation science to design research studies to address issues identified from a consortium-wide needs assessment. These studies will then be conducted across multiple sites to promote widespread implementation.

Programs and transition practices also need to be designed and tailored for global dissemination and implementation, as transition presents challenges in not only high-income countries but also middle-income and low-income countries. A 2020 review published recommendations for transition from a global perspective with a multi-country task force of experts from the United States, Europe, the Middle East, and Africa [91]. Although the largest SCD burden is in sub-Saharan Africa and India, there are no formalized transition guidelines for those countries, and many countries are unprepared for the increasing numbers of adults living with SCD. Low- and middle-income countries have implemented a healthcare strategy known as "task sharing, task shifting" (TSTS), where tasks typically completed by physicians are passed on to allied health professionals, such as non-physician clinicians and community health workers [91]. US-based transition programs that use patient and nurse navigators may be adapted to use these allied health professionals that are

already integrated into the healthcare setting, thus, allowing for the adoption and integration of evidence-based programs into middle- and low-income global settings.

Lastly, related to implementation, most transition activities are not reimbursable; therefore, cost and compensation must be determined to financially sustain programs [76]. Got Transition and the AAP have created the 2022 Coding and Reimbursement Tip Sheet for transition from pediatric to adult healthcare. The payment tip sheet lists transition-related CPT codes, corresponding Medicare fees, and relative value units (RVUs), including clinical vignettes with recommended CPT and ICD coding. It also provides categorized codes based on provider type and whether the service can be delivered face to face or non-face to face and a letter template to be customized and sent to payers to recognize transition-related CPT codes [92].

In summary, to move the field of transition from pediatric to adult healthcare for individuals with SCD and other chronic illness groups, there needs to be a clear framework to guide that work. The framework outlined and applied in the current chapter is a useful tool for guiding transition research agendas and evaluating their progress. When applied to transition research in SCD, it highlighted significant gaps related to measuring transition readiness and success; evaluating existing and future transition programs, with a need for more RCTs; and working to promote dissemination and implementation across US healthcare settings and globally.

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