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Michael J. Thorpy
S.R. Pandi-Perumal
Editors

Narcolepsy

A Clinical Guide

Second Edition

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To our families who continue to support us selflessly and unreservedly in this and all our personal and professional endeavors

Preface

We are delighted with the popularity of the first edition of *Narcolepsy: A Clinical Guide*. The fast pace of research in the field of sleep medicine, especially narcolepsy research, has motivated us to update our volume with a second edition. While essentially similar to the first edition, the second edition includes updated chapters, references, figures, and information reflecting the development within the field. Because many readers are familiar with the layout of the first edition, we have tried to change it as little as possible. Here is a summary of the main changes:

Various surveys in Europe have reported an increase in the incidence of narcolepsy after administration of adjuvanted vaccine for influenza. These findings, reported in this book, have implications for the administration of vaccinations in individuals generally and especially those who have a family history of narcolepsy.

The most recent ICSD and DSM-V diagnostic criteria of narcolepsy are discussed in detail.

New data on the evidence of comorbidities pose further challenges in managing the treatment of narcolepsy under complex conditions. The AWAKEN survey illustrated a gap in knowledge among professionals regarding narcolepsy, and another survey showed a lag of 8–10 years from the onset of symptoms and diagnosis of narcolepsy. These data further reinforce the idea of more educational initiatives directed toward physicians and also the general public, thus improving the quality of care provided to patients.

More information on improved treatment modalities and the exciting new discovery of the hypocretin/orexin system and its role in the etiology and treatment option in narcolepsy is now available, thus alleviating the misery and suffering for most patients with this disorder. It is noteworthy that research is in progress on the hypothesis that narcolepsy may be an autoimmune condition. Furthermore, development in the area of gene therapy and non-pharmacological management of narcolepsy are also discussed.

Recent studies showing the effects of medications during pregnancy and the importance of managing narcolepsy during and after pregnancy are discussed. These findings reinforce the complexity of managing narcolepsy and the importance of providing appropriate treatment to patients in special conditions.

The substantial economic and personal burden of having narcolepsy in the USA corroborates the findings in Europe. New data show low QOL in narcolepsy compared to the general population. The QOL in children is also

affected because of narcolepsy. The discussion on the positive effect of social support on the well-being of patients as well as the presentation on dreams and hypnagogic hallucinations further elucidates the complexity of managing narcolepsy and the importance of comprehensive management of this condition by a team of specialists. The latest studies on quality of life are more sophisticated in research design and statistical methodology and lend further credence and specificity to the deleterious effects of narcolepsy on QOL.

The definition of disability in narcolepsy, the rights of the disabled, and eligibility criteria for obtaining disability benefits are discussed along with case reports. The effect of the Affordable Care Act 2013 on healthcare delivery system is a major area of interest and concern to professionals as well as patients and is discussed in this volume. The involvement of other qualified professionals such as physician's assistants, nurses, social workers, and psychologists is likely to reduce costs and provide better follow-up and comprehensive care, thus enabling professionals to provide the highest quality of care that patients deserve.

In light of these new developments, this second edition of *Narcolepsy: A Clinical Guide* covers current thoughts and trends on narcolepsy. We have provided a disease-focused and patient- and family-centered approach to narcolepsy, in an attempt to provide a multidimensional management strategy. This book will benefit primary care physicians, sleep professionals, neurologists, psychiatrists, pediatricians, as well as psychologists, social scientists, and nurses—professionals who are interested in gaining knowledge about the clinical and the QOL issues derived from cutting-edge research in narcolepsy. Professionals will have up-to-date information with which to diagnose, treat, and make appropriate referrals. Researchers in the field of narcolepsy will have access to recent evidence-based research and pertinent literature on narcolepsy. Moreover, this book will appeal to patients who often inquire about support groups, new methods of managing their narcolepsy, and improving the quality of their lives.

Bronx, NY — Meeta Goswami
Bronx, NY — Michael J. Thorpy
Toronto, ON — S.R. Pandi-Perumal
June 22, 2015

Credits and Acknowledgments

A project such as this one represents not the work of one, but of the community of scholars, and this is especially true of this volume. In preparing this second and enlarged edition of *Narcolepsy: A Clinical Guide*, we gratefully acknowledge the contributions of those who were instrumental in the production of this revised volume.

We would like to express our deep appreciation to all the contributors for their scholarly contributions that facilitated the development of this book. The expertise of contributors to *Narcolepsy: A Clinical Guide* reflects the broad diversity and knowledge concerning narcolepsy research, which has continued to grow over the last several decades. These authors represent the cutting edge of basic and applied narcolepsy research and provide the most recent information regarding how such knowledge can be used in clinical settings. Their informed opinions and insights have significantly contributed to our scientific understanding of narcolepsy and have provided important interpretations regarding future research directions.

The highly talented people of Springer USA made this project an especially rewarding one. We are grateful for the professional and highly enthusiastic support of Mr. Richard Lansing, Executive Editor, Springer USA, without whom this volume would not have been possible.

We gratefully acknowledge the support and guidance provided by Gregory Sutorious, Senior Editor, Clinical Medicine, through the entire project. Greg was always available to provide information and direction as needed.

During the evolution of this project, we have benefited from the guidance and assistance of Tracy Marton, Developmental Editor at Springer, who supported us from the start to finish. Her gentle reminders, gracious communication, and rigorous follow-up greatly facilitated the task of compiling this edition. Many thanks to Tracy Marton.

It was also a pleasure to work with the entire production team of Springer. Their technical expertise and commitment to excellence were invaluable.

Finally, we are grateful to our families for their understanding, encouragement, and loving support.

Meeta Goswami
Michael J. Thorpy
S.R. Pandi-Perumal

Contents

Editors

Meeta Goswami, BDS, MPH, PhD has been the director of the Narcolepsy Institute and an assistant professor of neurology at the Albert Einstein College of Medicine. She graduated with a dental degree from Bombay, India, and received a PhD in sociomedical sciences and a master's in public health from Columbia University in New York. Dr Goswami is a member of the American Academy of Sleep Medicine, Sleep Research Society, and the National Sleep Foundation (USA); she is also a member of the medical advisory board of the Narcolepsy Network, the national association for people with narcolepsy. Since its inception in 1985, the Narcolepsy Institute was funded by New York State to provide psychosocial support services to individuals with narcolepsy and their families.

Meeta Goswami, with Michael J. Thorpy and others, edited the first book on *Narcolepsy and Psychosocial Issues 1992*; she has coauthored, with Michael J. Thorpy, the *Narcolepsy Primer 2006 Second Edition*, developed a video on narcolepsy, and publishes a semiannual newsletter *Perspectives* on narcolepsy. She has published several papers on narcolepsy and has presented her papers nationally and internationally.

She has received awards for her professional contributions including the Lifetime Achievement Award, from the US Narcolepsy Network, and, recently, the Mahatma Gandhi Pravasi Samman Award in 2013, presented in the House of Lords, London, for outstanding achievements, services, and contributions. Dr Goswami is committed to integrating the social and medical sciences and applying this knowledge to improve the quality of care and the quality of life of those who have narcolepsy. As the director of the Narcolepsy Institute, Montefiore Medical Center, for almost 30 years, Dr Goswami learned that patients benefit most when their medical care for narcolepsy is integrated with comprehensive psychosocial support at the individual level and in group sessions and has observed the improvement in patients' mood, demeanor, self-esteem, organization of daily activities, and productivity levels when patients avail themselves of the support services at the Narcolepsy Institute.

S.R. Pandi-Perumal is the president and chief executive officer of Somnogen Canada Inc, a Canadian corporation. He is a well-recognized sleep researcher both nationally and internationally and has authored many publications in the field of sleep and biological rhythms. His general area of research interest

includes sleep and biological rhythms. He has edited nearly 25 volumes related to sleep and biological rhythms research. Further details about his academic credentials can be found at http://pandi-perumal.blogspot.com

Michael J. Thorpy, MD board-certified in sleep disorders medicine, is the director of the Sleep-Wake Disorders Center at the Montefiore Medical Center, Bronx, New York. Both a clinician and a well-published researcher, Dr Thorpy serves as professor of clinical neurology at the Albert Einstein College of Medicine. In addition, Dr Thorpy served on the National Sleep Foundation (NSF) Board of Directors and founded and directed the NSF's National Narcolepsy Registry, which was located at Montefiore Medical Center. He is past chairman of the Sleep Section of the American Academy of Neurology.

Dr Thorpy was born in New Zealand and earned his medical degree from the University of Otago in 1973. He has published extensively on narcolepsy, insomnia, and sleep disorders. His seven books include *The Encyclopedia of Sleep and Sleep Disorders*. He has published more than 50 peer-reviewed articles, including publications in journals such as *The New England Journal of Medicine*. Dr Thorpy's Sleep Medicine Home Page is one of the major sleep sites on the Internet, and his computerized textbook on sleep medicine, SleepMultiMedia (available on DVD-ROM), is the only one of its kind.

In 1993, Dr Thorpy was awarded one of the sleep field's highest honors: The Nathaniel Kleitman Award from the American Sleep Disorders Association.

Dr Thorpy is frequently quoted in the media, including *The New York Times*, *The Washington Post*, and *Good Housekeeping*. He has appeared on the "Today Show," "20/20," and "Donahue," and given more than 100 television, radio, and print interviews.

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Part I

Etiology

The Genetics of Narcolepsy

1

Shahrad Taheri

Introduction

While familial cases of narcolepsy have been described, including some early descriptions of the disorder [1], narcolepsy is not a simple genetic disorder [2]. Early familial clustering observations may have exaggerated the heritability of narcolepsy by mistaken inclusion of cases of sleep apnoea. Although there is a 20–40 times higher risk than the general population, first-degree relatives of patients with narcolepsy have about a 1–2 % narcolepsy risk. Also, only 25–31 % of monozygotic twins have been observed to be concordant for narcolepsy [2, 3]. Some symptoms associated with narcolepsy can be genetically transmitted [4]. For example, sleep paralysis has been observed in some cases to have an autosomal dominant transmission [5]. Furthermore, relatives of patients with narcolepsy can have higher frequency of individual narcolepsy symptoms [3]. Sleep paralysis also shows a greater concordance in monozygotic compared to dizygotic twins.

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The majority of human cases of narcolepsy are sporadic, but genetic approaches in both humans and naturally occurring and experimental animal models have been instrumental in our understanding of the pathophysiology of narcolepsy and in particular type 1 narcolepsy characterised by cataplexy [6, 7]. In humans, a key finding has been the identification of an association between human leukocyte antigen (HLA) markers and narcolepsy [2], which has suggested a significant, yet unconfirmed, autoimmune aetiology. Several human studies have examined associations between narcolepsy and single nucleotide polymorphisms, suggesting the involvement of multiple genes. These studies have been recently augmented by genome-wide association studies that have further supported an autoimmune aetiology for narcolepsy. In animals, the canine model of narcolepsy and gene manipulation studies of rodents have helped identify the hypocretin (orexin) system as the key dysfunctional neuropeptidergic system in narcolepsy [8]. This chapter reviews the genetic contribution to narcolepsy and to the understanding of its pathophysiology and pathogenesis.

Animal Models of Narcolepsy

Canine narcolepsy occurs in both sporadic (like human cases) and genetic forms. Sporadic forms have been observed in several breeds. The genetic form occurs in an autosomal recessive manner

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with full penetrance by a single gene called *canarc-1* and was initially observed in Doberman pinschers and Labrador retrievers. A genetic canine narcolepsy breeding colony was set up at Stanford in the 1970s. The canine genetic model of narcolepsy has key similarities to human narcolepsy. Neurophysiologically, canine narcolepsy homozygotes display short sleep latency and fragmented sleep. Behaviourally, the dogs demonstrate cataplexy that is triggered by emotions including presentation with wet food and playing. Indeed, the food-elicited cataplexy test (FECT) has been used to examine the impact of different drugs on cataplexy [2]. Initial linkage studies in the Doberman suggested a link between *canarc-1* and immune system genes such as the dog leukocyte antigen (DLA), which suggested similarities with sporadic human cases, where an autoimmune mechanism was suspected. However, these genetic associations proved to be some distance away from the affected gene. Genome walking using a bacterial artificial chromosome (BAC) library constructed using the DNA of a Doberman pinscher heterozygous for *canarc-1* led to key observations. An exon for the canine orthologue of Myo 6 was identified in a BAC end-sequence mapping to the canine chromosome 12 by fluorescence in situ hybridization (FISH). The canine chromosome 12 also includes the DLA gene but at some physical distance from the key region. Examination of polymorphic markers from more than 150 dogs and physical mapping studies identified the susceptibility region to an ~800 kb segment containing the hypocretin receptor-2 (HCRTR2) gene [9]. Mutations in this gene were observed in three autosomal recessive canine narcolepsy breeds. Hypocretin (also called orexin) neurons originate in the lateral perifornical hypothalamus and project to multiple regions in the brain [8, 10–12]. Hypocretin neurons produce two key neurotransmitter peptides (hypocretin-1 [orexin A] and hypocretin-2 [orexin B] derived from preprohypocretin) that act through two G protein-coupled receptors (hypocretin receptor-1 [HCRTR1] and hypocretin receptor-2 [HCRTR2]). Thus, hypocretin receptor gene mutations in dogs suggested a key role for the hypocretin neuropeptidergic system in narcolepsy [13]. In Labradors and Dobermans, exon-skipping mutations in the HCRTR2 gene were observed, while in a multiplex dachshund family, a point mutation was identified. Exon-skipping mutations were associated with a dysfunctional truncated receptor. In the dachshund, the point mutation in N-terminal region was associated with normal membrane localization, but a loss of ligand binding and significantly reduced post-receptor calcium mobilisation.

Preprohypocretin gene null mice were generated to study the physiological role of the hypocretin system with the expectation that they would have a feeding phenotype. It was, however, observed that null mice displayed episodes that initially appeared seizure-like, but proved to be abnormal transitions into in rapid eye movement (REM) sleep [14]. Because the null model removed the gene early, ataxin-3 expression was induced in hypocretin neurons in mice to confer a gradual toxic disappearance of these neurons [15]. Ataxin-3-expressing mice developed a selective loss of hypocretin neurons that was evident by 12 weeks of age and also demonstrated a narcolepsy-like phenotype. HCRTR2 gene knockout mice demonstrate a greater narcolepsy phenotype than HCRTR1 gene knockout mice, suggesting a greater role for HCRTR2 in narcolepsy as observed in dogs [16]. The double receptor gene knockout mice demonstrate a similar phenotype to preprohypocretin gene (ligand) knockout mice [17]. Therefore, abnormalities in both the hypocretin peptide (preprohypocretin) and hypocretin receptor genes in animals are associated with a narcolepsy phenotype. Furthermore, the sporadic canine and human models are associated with hypocretin deficiency as observed through measurements of hypocretin-1 levels in the cerebrospinal fluid [18].

Hypocretin System Genes in Human Narcolepsy

Only one human case associated with a preprohypocretin gene mutation has been described [19]. This case was associated with early-onset

narcolepsy (6 months old) with a typical narcolepsy-cataplexy phenotype and absence of hypocretin-1 peptide in the cerebrospinal fluid and no HLA association (see below), which commonly occurs in typical sporadic human narcolepsy. A mutation in the region for the preprohypocretin signal peptide (G to T substitution, switching a Leu to Arg) was associated with abnormal peptide trafficking in vitro. No mutations/polymorphisms in the hypocretin system genes (preprohypocretin gene and hypocretin receptor genes) have been observed in sporadic canine narcolepsy, which, like human type 1 narcolepsy, is associated with hypocretin deficiency in the brain and cerebrospinal fluid. No functionally important mutations in hypocretin system have been reported in human narcolepsy [20, 21]. Human narcolepsy with cataplexy is associated with selective loss of hypocretin neurons in the hypothalamus that translates to reduce hypocretin-1 levels in the cerebrospinal fluid. The cause of the selective loss of hypocretin neurons is unknown, but genetic studies, discussed below, suggest an autoimmune aetiology.

Narcolepsy and Immune-Related Genes

The human leukocyte antigen (HLA) system maps to the short arm of chromosome 6 (6p21.31). Glycoprotein products of several HLA class I and II genes are intimately involved in antigen processing and presentation to cytotoxic and regulatory T lymphocytes, respectively. Class I genes code for an alpha polypeptide chain that combines with a non-polymorphic beta chain ($beta_2$ microglobulin) whose gene is on chromosome 15. The resulting cell surface molecule is present on all nucleated cells. The highly polymorphic HLA class II genes, normally expressed by immune cells (B and T lymphocytes, macrophages and dendritic cells and thymic epithelial cells), code for alpha and beta polypeptide chains of HLA-DR, HLA-DQ, and HLA-DP. The A designation in HLA (e.g. HLA DQA1*102) refers to genes for alpha chains, while the B designation (e.g. HLA DQB1*0602) refers to genes for beta chains. The numbers following * (e.g. HLA DQB1*0602) refer to the gene variant. The alpha and beta chains form heterodimers on antigen-presenting cells and present foreign antigens to T lymphocytes by engaging the T-cell receptor resulting in mobilisation of the immune response.

Several autoimmune disorders are associated with specific HLA class II antigens. Strong HLA associations with type 1 diabetes mellitus (DR3, DR4, DQB1*0302, DQB1*0201, DQB1*0602), rheumatoid arthritis (DR4), seronegative arthritides (B27), multiple sclerosis (DR2, DQB1*0602), coeliac disease (DQA1*05, DQB1*02), and pemphigus vulgaris (DRB1*0402) have been observed. In autoimmunity, susceptible HLA class II antigens associated with foreign antigen presentation trigger an autoimmune response in conjunction with auto-antigens, resulting in specific cellular destruction by the immune system, e.g. pancreatic beta cells in type 1 diabetes mellitus.

Narcolepsy with cataplexy has been observed to have a close association with specific HLA alleles. This association was first observed in the Japanese population with DR2 and DQ1 [22, 23] and confirmed in other populations [24, 25]. Although this finding was confirmed in European populations, it was more variable in African Americans [26]. The most significant association with narcolepsy is with HLA DQB1*0602 (a subtype of DQ1/DQ6) in all ethnic groups [27]. In Europeans and Japanese, the HLA DQB1*0602 allele occurs with HLA DQA1*102 on a haplotype with HLA DRB1*1501. This is not the case in African Americans where HLA DQB1 and HLA DQA1 alleles occur with distinct HLA DRB1 haplotypes such as HLA DRB1*1503, HLA DRB1*1501, HLA DRB1*1101, and HLA DRB1*806 [28, 29]. HLA DQB1*0602 is in almost complete linkage disequilibrium with HLA DQA1*102, but HLA DQA1*102 by itself does not increase narcolepsy risk. While some 90 % of narcolepsy cases are associated with HLA DQB1*0602, this allele is common in the general population (12 % in Japanese to 38 % in African Americans), suggesting additional factors in the aetiology of narcolepsy [2]. HLA DQB1*0602 is a low penetrance susceptibility

factor with relatives sharing the same HLA susceptibility only rarely developing narcolepsy. HLA DQB1*0602 homozygotes have 2–4 times greater risk for narcolepsy compared to heterozygotes [30–33]. This is further supported by the observation that HLA DQB1*0602 homozygote status is associated with greater white cell DQB1*0602 mRNA and protein expression.

Apart from HLA DQB1*0602, additional HLA predisposition has been observed with high relative risks across several ethnic groups observed for HLA DQB1*0301 [31, 32]. HLA DQB1*0301 predisposition occurs in the face of multiple DQA1 haplotypes, suggesting that the beta chain has the greatest effect for antigen binding or alters immune cell engagement independent of alpha and beta chain pairing. An important observation is that HLA DQB1*0601 is protective for narcolepsy, but has a very similar structure to HLA DQB1*0602, suggesting that only small variations in HLA antigen-presenting region can have profound effects [2]. Lesser protection is conferred by DQA1*0103-DQB1*603 [31].

Recently, other HLA gene susceptibility and protective loci have been identified by several studies [34, 35]. In a genome-wide association study, a protective variant of HLA-DQA2 was observed. This variant was strongly linked to HLA DRB1*03-DQB1*02 and HLA DRB1*1301-DQB1*0603. Narcolepsy cases almost never carried a trans HLA DRB1*1301-DQB1*0603 haplotype. With the observation of the association between upper respiratory infection (such as influenza A H1N1 [36, 37]) and narcolepsy, using a case control approach with matching for HLA-DR and HLA-DQ, a recent study observed protective effects for HLA DPA1*0103-DPB1*0402 and HLA DPA1*0103-DPB1*0401. Protective effects were observed for HLA DPA1*0103-DPB1*0402 and HLA DPA1*0103-DPB1*04:01. While one study has reported that class II antigens (DQ1) are the key marker for narcolepsy in Europe [38–40], another study reported HLA class I susceptibility effects for HLA A*1101, HLA B*3503 and HLA B*51:01 [35]. These alleles suggest additional roles for HLA markers in autoimmunity triggered by infection. Indeed, previous work had observed changes in HLA associations after the 2009 H1N1 pandemic.

The tight and highly reproducible HLA association with narcolepsy, low disease concordance in monozygotic twins, and young peri-pubertal age of disease onset have instigated the hypothesis that narcolepsy is an autoimmune disease. However, unlike most autoimmune diseases, which have a female preponderance, narcolepsy is equally distributed between the two genders, and few immune abnormalities in narcolepsy have been noted. Interestingly HLA DQB1*602 status may also be associated with sleepiness and alterations in sleep architecture, suggesting neurophysiological effects [41].

To date, no sufficiently convincing evidence to directly support autoimmunity in narcolepsy has been observed. However, a role for the immune system in narcolepsy has been further supported by genome-wide association studies. The T lymphocyte cell receptor consists of alpha and beta chains. A role for polymorphisms (especially rs1154155) in the TRA@ (T-cell receptor alpha) locus (on chromosome 14q11.2) has been observed; this association was unique to narcolepsy compared to other autoimmune diseases [42]. Using a custom genotyping array (ImmunoChip) to identify additional risk factors to HLA DQB1*0602 [43], importance of TRA@ was confirmed, while two additional loci (cathepsin H [CTSH] and tumour necrosis factor (ligand) superfamily member 4 [TNFSF4/OX40L]) were also identified. CTSH is a cysteine protease important in peptide processing, a key aspect of antigen presentation. TNFSF4/OX40L is also found in antigen-presenting cells and has been implicated in T-cell regulation. In another report, a single nucleotide polymorphism (rs4804122) has been reported to be associated with HLA DQB1*0602 narcolepsy compared to HLA DQB1*0602-positive controls. This polymorphism is downstream on purinergic receptor subtype 2Y11 (P2RY11) gene on chromosome 19p13.2, which has high linkage disequilibrium with PPAN (peter pan), P2RY11, EIF3G (eukaryotic translation initiation factor 3) and DNMT1 (DNA (cytosine-5-)-methyltransferase 1) genes [44]. Purinergic signalling plays an important role in immune

cell regulation, chemotaxis, proliferation, and apoptosis. In a further study, the disease-associated EIF3G allele (rs3826784) was associated with increased EIF3G expression. The association between EIF3G, located between P2RY11 and DNMT1, has been observed across three ethnic groups [45]. Interestingly, EIF3G expression correlated with expression of PPAN and PRY11, suggesting shared regulatory mechanisms. A Japanese study has identified a role for chemokine receptors (CCR1/CCR3) important in monocyte migration [46]. A polymorphism (rs3181077) located upstream of CCR1 and CCR3 was associated with narcolepsy. Furthermore, expression of CCR1 and CCR3 was lower in narcolepsy patients.

Several studies have reported the presence of Tribbles 2 homology (Trib2) autoantibodies in sera from early-onset narcolepsy with cataplexy. The role of these antibodies in disease pathogenesis is unclear, but a recent study reported on a potential pathogenic effect of these antibodies on hypocretin neurons [47]. An infectious trigger has been suggested by the relation between narcolepsy and upper respiratory infections (influenza A H1N1 2009 variant and *Streptococcus pyogenes* [48, 49]) and seasonal variation in narcolepsy incidence. The potential relation between narcolepsy, infectious disease, and vaccination has suggested that molecular mimicry and bystander activation may also result in damage to hypocretin neurons.

Nonimmune System-Related Genes in Narcolepsy

Cataplexy is considered to be pathognomonic of narcolepsy. However, it has rarely been observed in several other disorders, which are usually associated with some degree of hypothalamic dysfunction. These disorders include Prader-Willi syndrome (PWS) [50–52], Norrie disease, Niemann-Pick disease type C [53], and diencephalic tumours. Prader-Willi syndrome (PWS) is a genetic disorder associated with abnormalities in chromosome 15q11-q13 inheritance, occurring in 1:10,000–1:25,000 live births. PWS is characterised by hypotonia, respiratory distress, postnatal failure to thrive, short stature, small hands and feet, hypogonadism, mental retardation, behavioural problems, and hyperphagia associated with obesity. Cataplexy-like symptoms associated with cerebrospinal fluid hypocretin deficiency have been described with PWS [52]. Sleep apnoea secondary to obesity, however, is more common in PWS than narcolepsy. Norrie disease is an X-linked recessive dysmorphic syndrome, which has also been associated with cataplexy. Abnormalities in monoaminergic neurotransmission in this condition suggest a role for this neurotransmitter system in narcolepsy [54]. Catechol-o-methyltransferase (COMT) is a key enzyme involved in catecholamine breakdown. The COMT gene may confer gender-specific effects on sleepiness [55]. Women with narcolepsy and high-COMT activity fall asleep faster than those with low levels, while the opposite is true for men.

Familial cases of narcolepsy have suggested a role for several genes in narcolepsy pathogenesis. Observations have included a missense mutation in MOG (myelin oligodendrocyte glycoprotein), a member of the immunoglobulin superfamily and a potential target for autoimmune attack [56]. MOG gene null mice, however, have not been observed to display a narcolepsy phenotype, suggesting that the mutation observed could be a gain in function mutation. Autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN) are associated with low cerebrospinal fluid hypocretin-1 levels. Narcolepsy progresses to deafness, ataxia, and dementia [57, 58]. Other associated findings are peripheral neuropathy, optic atrophy, and psychosis. These cases are associated with DNMT1 mutations [59].

Several early studies of polymorphisms associated with narcolepsy have not been confirmed by recent genome-wide association studies. Genome-wide association studies in narcolepsy have identified several susceptibility loci. In one of the first studies from Japan, rs5770917, a single nucleotide polymorphism located between CPT1B and CHKB and that may regulate these genes, was linked with narcolepsy [60, 61]. Both CPT1B and CHKB may have roles in sleep regulation. CPT1B regulates beta-oxidation of

long-chain fatty acids, while CHKB is an enzyme involved in choline metabolism, which is key to acetylcholine neurotransmitter production. Another GWA study was combined with database search confirming the association with TRA@, but also noting associations with NFATC2 (nuclear factor of activated T cells), SCP2 (sterol carrier protein 2), CACNA1C (calcium channel, voltage-dependent, L-type, alpha 1C subunit), POLE [polymerase (DNA directed), epsilon, catalytic subunit] and FAM3D (family with sequence similarity 3, member D) genes [62]. In one study, variant rs12425451 in the vicinity of the transcription factor TEAD4 (TEA domain family member 4) was observed to be associated with age of cataplexy onset. TEAD4 has been associated with nerve cell survival [63].

Conclusion

Genetic approaches to narcolepsy have resulted in significant advances in our understanding of this unique sleep disorder. A key finding has been the establishment of abnormalities in the hypocretin neuropeptidergic system as central to narcolepsy. Loss of hypocretin neurons, observed in human brain postmortem studies and reflected by low cerebrospinal fluid hypocretin-1 levels, is key to narcolepsy with cataplexy. How hypothalamic perifornical hypocretin neurons are lost in narcolepsy is still unclear, but genetic studies have identified a key role for the immune system supporting the hypothesis invoking an autoimmune aetiology. A key association is with HLA class II antigens involved in antigen presentation. This combined with alterations in the T-cell receptor could trigger immune mechanisms that ultimately lead to hypocretin neuron loss. Other genes involved in this process include those with roles in peptide processing, antigen presentation, cell metabolism, and neuronal cell survival. Autoimmunity could be triggered by upper respiratory infections in susceptible individuals through molecular mimicry and bystander activation.

The precise role of the currently identified nonimmune system genes in narcolepsy pathogenesis remains to be elucidated. These genes could also provide clues to other disorders associated with excessive sleepiness such as narcolepsy without cataplexy and other hypersomnias. More advanced gene sequencing approaches could identify additional genes in the pathophysiological pathway for narcolepsy. Next steps will also include the use of the increased genetic understanding of narcolepsy in disease prevention, reversal, delay, and treatment.

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Orexin (Hypocretin) and Narcolepsy

2

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Discovery of Orexin (Hypocretin)

Neuropeptides orexin-A and orexin-B (hypocretin-1 and hypocretin-2, respectively) were initially reported in 1998 independently by two laboratories. Sakurai et al. identified these peptides as endogenous ligands for two orphan G-protein-coupled receptors (GPCR) [1]; GPCRs for which endogenous ligands are unknown are referred to as "orphan" GPCRs. Since intracerebroventricular (ICV) injection of these peptides in rats acutely stimulated food consumption, they were named orexin-A and orexin-B after the Greek word *orexis*, meaning "appetite." Orexin-A and orexin-B are produced by cleavage of prepro-orexin, a single precursor polypeptide. Mammalian orexin-A is a 33-amino-acid peptide with two intrachain disulfide bonds that undergo pyroglutamylation and amidation at its N- and C-terminals, respectively, while orexin-B is a 28-amino-acid linear peptide that undergoes C-terminal amidation (Fig. 2.1a).

De Lecea et al. previously identified 38 rat mRNAs selectively expressed within the hypothalamus. They found that one of those mRNAs, the clone 35, was expressed exclusively by a bilaterally symmetric structure within the posterior lateral hypothalamus [2]. The gene from which this clone derived encoded a polypeptide identical to prepro-orexin and named the putative mature peptides hypocretin-1 (orexin-A) and hypocretin-2 (orexin-B). Although the initial estimated structures of hypocretin-1 and hypocretin-2 were not the same as those of orexin-A and orexin-B, the terms "orexin" and "hypocretin" are currently used as synonyms in many papers.

The actions of orexins are mediated by two G-protein-coupled receptors, named orexin 1 (OX1R) and orexin 2 (OX2R) receptors (also known as HCRTR1 and HCRTR2) [1] (Fig. 2.1a). OX1R has a one-order higher affinity for orexin-A than for orexin-B, while OX2R binds orexin-A and orexin-B with similar affinities. Both receptors are coupled to the $G_{q/11}$ subclass of G-proteins and have caused strong excitatory effects on neurons examined thus far [3], except in one study that reported the direct inhibitory action of orexin receptors on suprachiasmatic nucleus (SCN) neurons at night [4]. When overexpressed, OX2R has also been reported to couple to $G_{i/o}$ in a neuronal cell line, suggesting that OX2R could exert inhibitory action in some neurons [5].

Neurons expressing orexins (orexin neurons) are distributed within an area consisting of three contiguous hypothalamic regions: the lateral hypothalamus (LH), perifornical area (PFA),

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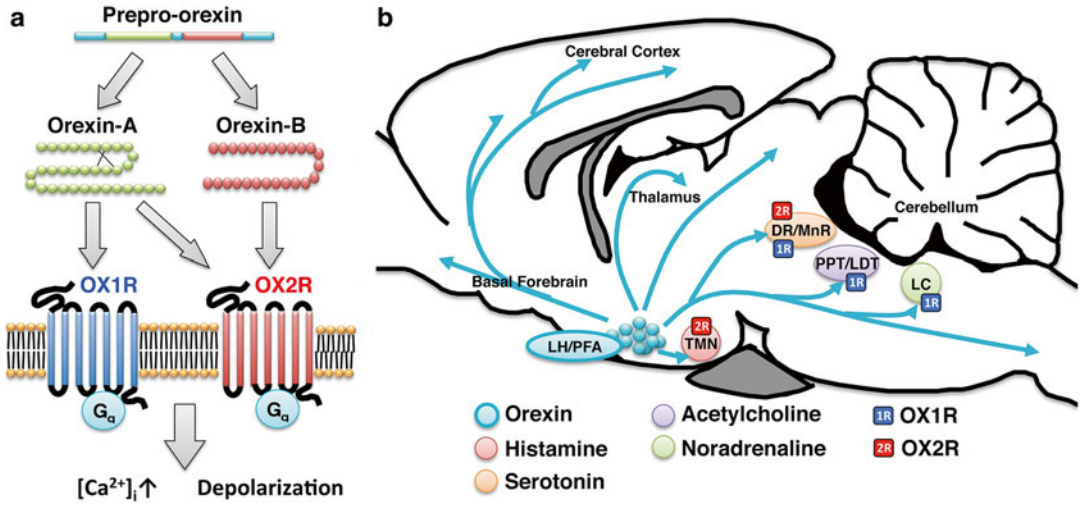

Fig. 2.1 The orexin system. (**a**) Orexin and orexin receptors. Orexin-A and orexin-B are derived from prepro-orexin, a common precursor peptide. The actions of orexins are mediated by two G-protein-coupled receptors: the OX1R and OX2R receptors. OX1R is selective for orexin-A, whereas OX2R shows similar affinities for both orexin-A and orexin-B. Both receptors are coupled to the $G_{q/11}$ subclass of G-proteins and cause strong excitatory effects on neurons. (**b**) Schematic drawing showing main projections of orexin neurons, through which the former may promote wakefulness. Circles show regions with strong receptor expression and dense orexinergic projections. Orexin neurons originating in the lateral hypothalamic (LH) and perifornical (PFA) areas regulate sleep and wakefulness and the maintenance of arousal by sending excitatory projections to the entire central nervous system, excluding the cerebellum, with particularly dense projections to monoaminergic and cholinergic nuclei in the brainstem and hypothalamic regions, including the locus coeruleus (LC), which contains noradrenaline; the tuberomammillary nucleus (TMN), which contains histamine; raphe nuclei (raphe), which contain serotonin; and pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), which contain acetylcholine. OX1R and OX2R show differential distributions in these brainstem cholinergic/monoaminergic neurons

and dorsomedial hypothalamic nucleus (DMH) (Fig. 2.1b) [1, 2, 6–8]. The number of these neurons has been estimated to be from 3000 to 4000 in rat and 70,000 in human brains [9, 10]. In contrast to the restricted localization of their cell bodies, orexin neurons send projections throughout the central nervous system (CNS), including the cerebral cortex, limbic system (such as the amygdala, bed nucleus of stria terminalis [BST], and hippocampus), hypothalamus (such as the arcuate nucleus [ARC] and tuberomammillary nucleus [TMN]), and brain stem area (such as the central gray, locus coeruleus [LC], and raphe nuclei) [6–8, 11]. Consistent with the broad projections of orexin neurons, OX1R and OX2R show partly overlapping but distinct distributions of their mRNA throughout the CNS [12, 13]. Concerning the nuclei implicated in the regulation of sleep and wakefulness, the LC, laterodorsal tegmental nucleus (LDT), and pedunculopontine tegmental nucleus (PPT) mainly express *OX1R* mRNA, while the TMN almost exclusively expresses *OX2R* mRNA (Fig. 2.1b).

Disruption of the Orexin System Causes Narcolepsy–Cataplexy

Human narcolepsy is a debilitating neurological disease that affects approximately 1 in 2000 individuals in the United States [14–16]. Onset of the condition is usually during adolescence (approximately 12–14 years old). A cardinal symptom of the disorder is excessive daytime sleepiness (EDS, an insurmountable urge to sleep), which manifests itself primarily when the subject falls asleep at inappropriate times ("sleep attacks"). When normal individuals fall asleep, a certain period of non-rapid eye movement (NREM) sleep (approximately 90 min) precedes rapid eye move-

ment (REM) sleep. However, the latency of REM sleep is markedly reduced in narcolepsy patients. REM sleep is sometimes observed immediately after wakefulness (sleep-onset REM period, or SOREMP). Nocturnal sleep is also fragmented in patients and often accompanied by hypnagogic hallucinations, vivid dreaming, and sleep paralysis, which usually occur near sleep onset. Narcolepsy patients often suffer from a condition called "cataplexy," which is characterized by a sudden weakening of muscle tone (muscle atonia), ranging from jaw dropping and speech slurring to complete bilateral collapse of the postural muscles. These attacks are often triggered by emotional stimuli such as laughter, excitement, and pleasure. Consciousness is preserved during cataplexy. Around 10 % of narcolepsy patients do not suffer from cataplexy, although they experience excessive daytime sleepiness. Therefore, narcolepsy with cataplexy is sometimes referred to as "narcolepsy–cataplexy" to stress the occurrence of cataplexy. *The International Classification of Sleep Disorders, Third Edition* (ICSD-3) classifies narcolepsy as either type 1 or type 2. Type 1 narcolepsy (narcolepsy with cataplexy) is defined as EDS that persists for at least 3 months, accompanied with at least two of the following: clear-cut cataplexy, a positive result on the Multiple Sleep Latency Test (MSLT, mean sleep latency is shorter than 8 min and two or more SOREMPs), or low levels of orexin in CSF. Type 2 narcolepsy (narcolepsy without cataplexy) is diagnosed as EDS that, in the presence of normal levels of orexin, persists for at least 3 months and scores a positive result on the MSLT.

The symptoms of narcolepsy can be divided into two independent pathological phenomena [17, 18]. One is the inability to maintain a consolidated awake period, characterized by abrupt transitions from wakefulness to NREM sleep (i.e., dysregulation of NREM sleep onset). This phenomenon manifests clinically as excessive daytime sleepiness or sleep attacks. The other phenomenon is the pathological intrusion of REM sleep or REM atonia into wakefulness or at sleep onset (i.e., dysregulation of REM sleep onset). It is during these periods that patients may experience cataplexy, hypnagogic hallucinations, and sleep paralysis.

Soon after the discovery of orexins, two independent studies using forward genetics with canines and reverse genetics with mice, respectively, elucidated a causal linkage between disruption of orexin signaling and narcolepsy–cataplexy. For decades, a Stanford University group has established and maintained canine breeds with autosomal recessive inheritance of a narcolepsy syndrome [19]. This canine model of narcolepsy displays emotionally triggered cataplexy, fragmented sleep patterns, excessive daytime sleepiness, and a higher frequency of SOREMP. In 1999, Lin et al. identified functionally null mutations in the *OX2R* gene responsible for canine narcolepsy by positional cloning [20].

Around the same time, Chemelli et al. reported that prepro-orexin knockout mice (*orexin*$^{-/-}$) exhibit a phenotype strikingly similar to human narcolepsy [21]. They exhibit frequent sudden collapses during the dark phase, the portion of the circadian rhythm during which there is the most time awake and spent in activity. These attacks resemble human cataplexy attacks. Electroencephalogram/electromyogram (EEG/EMG) recordings correlated these attacks with direct transitions from wakefulness to REM sleep, suggesting that they are homologous to cataplexy. Quantitative sleep state parameters in *orexin*$^{-/-}$ mice revealed significantly decreased waking time, increased NREM and REM sleep time, decreased REM sleep latency, and, most importantly, a markedly decreased duration of waking episodes during the dark phase (i.e., inability to maintain a long awake period). Consistent with a presumed critical role of orexin in the regulation of sleep and wakefulness, orexin-immunoreactive nerve terminals were observed on neurons implicated in arousal regulation, including LC noradrenergic neurons, raphe serotonergic neurons, TMN histaminergic neurons, and PPT/LDT and basal forebrain cholinergic neurons. Subsequently, orexin receptor subtypes turned out to be expressed in these regions with different expression patterns, implying their differential role in the regulation of sleep and wakefulness (Fig. 2.1b) [12, 13].

Shortly afterward, disruptions of the orexin system in human narcolepsy were confirmed.

In contrast to normal control individuals, approximately 90 % of narcolepsy with cataplexy patients have low or undetectable levels of orexin neuropeptides in the cerebrospinal fluid (CSF) (<110 pg/mL) [22, 23]. Drastic reductions of *orexin* mRNA and immunoreactivity in postmortem brains of narcoleptic patients were also shown [24, 10]. A recent finding revealing the concomitant loss of dynorphin, neuronal activity-regulated pentraxin, and orexin, all of which colocalize in orexin neurons, strongly indicates a selective loss of orexin neurons in narcolepsy, instead of the selective inhibition of *orexin* gene expression [25]. Because narcolepsy is closely associated with *HLA-DQB1*06:02*, polymorphisms in the T-cell receptor α and *P2RY11* genes, and the pandemic anti-H1N1 vaccination, narcolepsy is likely to be caused by a selective autoimmune degeneration of orexin neurons [14, 26–29]. An increasing number of patients with a milder form of typical narcolepsy (type 2 narcolepsy), which involves EDS and SOREMPs yet without cataplexy, are being recognized [16]. In contrast to narrowly defined narcolepsy by the presence of cataplexy, most people (>75 %) diagnosed with narcolepsy without cataplexy have normal CSF orexin-A concentrations [22].

In addition to the evidence described above, the selective degeneration of orexin neurons has been demonstrated to cause narcolepsy with cataplexy in mice and rats [30–32], while sporadic canine narcolepsy has been associated with substantially decreased concentrations of orexin-A (hypocretin-1) in the CSF and brain [33]. Collectively, these studies established that the disruption of the orexin system causes narcolepsy–cataplexy.

Importantly, narcoleptic symptoms of animal models can be prevented by the replacement of orexins. Chronic overproduction of orexin peptides from an ectopically expressed transgene prevented the development of narcolepsy syndrome in orexin neuron-ablated mice [34]. Furthermore, acute ICV administration of orexin-A maintained wakefulness, suppressed sleep, and inhibited cataplectic attacks in these mice [34]. These results indicate that orexin neuron-ablated mice retain the ability to respond to orexin neuropeptides and that spatially targeted secretion of orexin is unnecessary in preventing narcoleptic symptoms. A similar result was also obtained by Fujiki et al., who demonstrated that orexin-A administered intravenously in an extremely high dose induced a very brief anticataplectic effect in an orexin-deficient narcoleptic canine [35]. Unfortunately, constitutive production of orexin peptides from a prepro-orexin transgene in mice caused fragmentation of NREM sleep episodes in the light period, when mice spend the most time asleep [34, 36]. These results indicate that orexin neurons should be turned on and switched off to maintain consolidated wakefulness and NREM sleep, respectively. Thus, orexin receptor agonists with half-lives of several hours (<12 h) would be of potential value for treating human narcolepsy–cataplexy. Such agonists might also be useful in the treatment of other conditions of excessive daytime sleepiness in humans.

Conversely, orexin receptor antagonists might be useful as safe hypnotics. For instance, suvorexant (Belsomra, Merck), an orally available antagonist of OX_1R and OX_2R, has been reported to increase subjective and objective electrophysiological signs of sleep in humans [37], approved for sale by the US Food and Drug Administration (FDA), and is now available in US and Japan.

The Regulation of Sleep and Wakefulness by Orexin Peptides

Sleep and wakefulness are controlled by a complex network of neurotransmitters and neuromodulators [38, 39]. Monoaminergic neurons, including LC noradrenergic, dorsal and median raphe (DR and MnR) serotonergic, and TMN histaminergic neurons, project diffusely to the cerebral cortex, thalamus, and brainstem, as well as are thought to promote arousal. They are active during wakefulness, reduce their firing rates during NREM sleep, and nearly cease discharge during REM sleep. By contrast, GABA/galaninergic neurons in the preoptic area (POA) of the hypothalamus, including lateral, median, and ventrolateral preoptic nuclei, are active during sleep, especially

during NREM sleep, and considered to be a sleep center. POA neurons and monoaminergic neurons are thought to reciprocally inhibit each other [38].

Orexin neurons send their projections densely to nuclei involved in the regulation of sleep and wakefulness, including LC noradrenergic neurons, DR/MnR serotonergic neurons, TMN histaminergic neurons, and cholinergic neurons in the pontine (PPT/LDT) and basal forebrain (BF) (Fig. 2.1b) [8, 21]. In accordance with the innervation, neurons in these nuclei express OX1R and/or OX2R in different combinations [12, 13]. ICV administration of orexin-A in rodents reduces REM and NREM sleep, as well as increases wakefulness [13, 40]. Furthermore, optogenetic excitation of orexin neurons results in reduced latencies to wakefulness from either NREM or REM sleep [41], while optogenetic silencing of these neurons induces NREM sleep in mice [42]. Similarly, pharmacogenetic modulation of orexin neurons using designer receptors exclusively activated by designer drugs (DREADD) alters states of sleep and wakefulness [43]. The application of orexin-A directly into the LC [44], TMN [45], BF cholinergic area [46, 47], and LDT [48] has also been reported to increase wakefulness. In vitro slice electrophysiology studies have shown that orexin-A and orexin-B increase firing rates of monoaminergic neurons in the LC [49, 50], DR [51, 52], TMN [53–55], and cholinergic neurons in the BF and LDT [56, 57]. These observations suggest that orexin neurons stabilize wakefulness by regulating these monoaminergic and cholinergic neurons. In addition, orexin neurons activate themselves directly and indirectly via local glutamatergic neurons, forming positive feedback circuits that may stabilize the activity of the orexin neuron network [58, 59].

Considering symptoms of narcolepsy, orexin neurons are expected to be active during wakefulness and to be silent during sleep, as observed in wake–active monoaminergic neurons. In vivo single-unit recordings have confirmed this wake–active firing pattern of orexin neurons [60–62]. Importantly, firing rates of orexin neurons are much higher during active waking with movement than in quiet waking, suggesting that these cells are activated during emotional and sensorimotor conditions similar to those that trigger cataplexy in narcoleptic animals. Indeed, extracellular orexin level is linked to emotion and social interaction in humans [63].

Differential Involvement of Deficient OX1R- and OX2R-Mediated Pathways in the Pathophysiology of Narcolepsy

The fact that functionally nullmutations in the *OX2R* gene were found in two independent lines of familial narcoleptic canines suggests that OX2R may play a critical role in the regulation of sleep and wakefulness [20]. Studies of orexin receptor-deficient mice (*OX1R*$^{-/-}$ and *OX2R*$^{-/-}$ mice) further elucidated the differential roles of OX1R and OX2R in detail (Fig. 2.2). First, *OX1R*$^{-/-}$*;OX2R*$^{-/-}$ mice demonstrate narcoleptic phenotype nearly similar to that in *orexin*$^{-/-}$ mice, implying that these two receptors are sufficient to mediate the regulation of sleep and wakefulness by orexins [18, 64]. The deletion of *OX1R* produces no measurable effect on states of sleep and wakefulness in the baseline condition [18, 64]. However, *OX2R*$^{-/-}$ mice have clear characteristics of narcolepsy, although their behavioral and EEG phenotypes are less severe than that found in *orexin*$^{-/-}$ mice [18, 65]. In infrared videophotographic studies, during the dark phase, *OX2R*$^{-/-}$ mice showed abrupt cataplexy-like behavioral arrests, and the frequency of such arrests was far less in *orexin*$^{-/-}$ mice (31-fold lower frequency in *OX2R*$^{-/-}$ mice than in *orexin*$^{-/-}$ mice). By contrast, *OX2R*$^{-/-}$ mice showed a distinct variety of behavioral arrests with more gradual onsets (gradual arrests). Moreover, *orexin*$^{-/-}$ mice also exhibited gradual arrests with a frequency similar to *OX2R*$^{-/-}$ mice, in addition to plenty of abrupt arrests. A detailed characterization of behavioral, pharmacological, and electrophysiological features of *orexin*$^{-/-}$ and *OX2R*$^{-/-}$ mice defined abrupt and gradual arrests as the presumptive mouse correlates of cataplexy and sleep attacks in human narcolepsy, respectively [65].

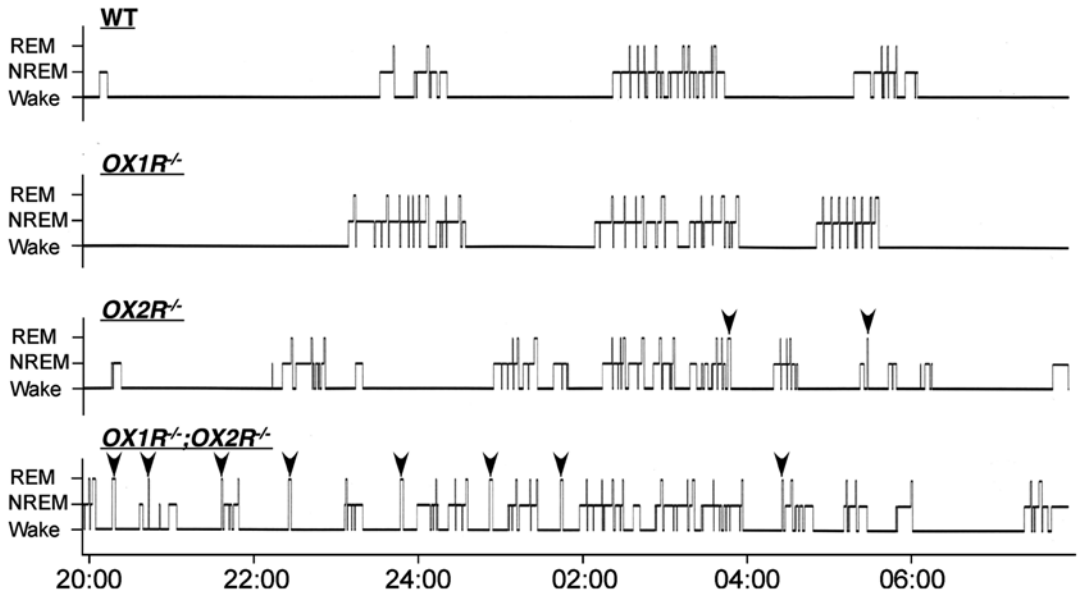

Fig. 2.2 Sleep state abnormalities in orexin receptor knockout mice. Representative 12-h dark period (20:00–08:00) hypnograms for wild-type (WT), *OX1R*$^{-/-}$, *OX2R*$^{-/-}$, and *OX1R*$^{-/-}$*;OX2R*$^{-/-}$ mice, all on a C57BL/6J background, are shown. The different levels above the baseline indicate states of sleep and wakefulness (e.g., REM, NREM, and wakefulness) of mice at the time. Episodes of direct transition from wakefulness to REM sleep are shown by arrows. Note the greater awake and NREM sleep episode fragmentation and reduced duration of wakefulness in the hypnograms of *OX2R*$^{-/-}$ and *OX1R*$^{-/-}$*;OX2R*$^{-/-}$ mice compared with WT and *OX1R*$^{-/-}$ mice. Episodes of direct transition from wakefulness to REM sleep were not observed in *OX1R*$^{-/-}$ mice and were hardly observed in *OX2R*$^{-/-}$ mice, though they were frequently observed in *OX1R*$^{-/-}$ and *OX2R*$^{-/-}$ mice (modified from [18])

In addition to gradual behavioral arrests, *OX2R*$^{-/-}$ mice exhibit fragmentation of wakefulness, another sign of sleepiness, to an extent similar to that of *orexin*$^{-/-}$ mice (Fig. 2.2) [65]. These results of reverse genetic studies with mice suggest that the normal regulation of wakefulness and NREM sleep transitions depends critically on OX2R activation, whereas the profound dysregulation of REM sleep control unique to narcolepsy emerges from loss of signaling through both OX1R- and OX2R-dependent pathways.

The substantially lower frequency of cataplexy in *OX2R*$^{-/-}$ mice than in *orexin*$^{-/-}$ mice appears to be inconsistent with the fact that mutations of the *OX2R* gene are solely responsible for an inherited canine model of narcolepsy, which demonstrates a frequent occurrence of cataplexy as well as excessive sleepiness [20]. This circumstance may result from species difference (e.g., the precise expression patterns of two orexin receptors) and/or selection bias. However, even in canines, the absence of orexin peptides may cause severe narcoleptic symptoms as compared to *OX2R* mutation. Early studies of narcoleptic Dobermans and Labradors found that these canines were 30- to 80-fold less severely affected with cataplexy than poodles with sporadic narcolepsy, which manifested in literally hundreds of attacks per day [66], an effect previously attributed solely to differences in breed and breed size.

In an experiment complementary to behavioral studies and baseline sleep/wakefulness recordings of *OX1R*$^{-/-}$ and *OX2R*$^{-/-}$ mice, the arousal effects of ICV orexin-A administration were compared between wild-type, *OX1R*$^{-/-}$, and *OX2R*$^{-/-}$ mice [13]. The effects of orexin-A on wakefulness and NREM sleep were significantly attenuated in both knockout mice as compared to wild-type mice, with substantially larger attenuation in *OX2R*$^{-/-}$ than in *OX1R*$^{-/-}$ mice. These results suggest that, although the OX2R-mediated pathway plays a pivotal role in the promotion of

wakefulness, OX1R also plays additional roles in promoting arousal.

By contrast, the suppression of REM sleep via orexin-A administration was slightly and similarly attenuated in both *OX1R*$^{-/-}$ and *OX2R*$^{-/-}$ mice, which suggests a comparable contribution of the two receptors to REM sleep suppression [13]. The supplementary role of OX1R in the suppression of NREM sleep is consistent with the fact that *OX2R*$^{-/-}$ mice on a C57BL/6J genetic background show less fragmented wakefulness than *orexin*$^{-/-}$ mice and *OX1R*$^{-/-}$ and *OX2R*$^{-/-}$ mice [18, 67, 68] but show similarly fragmented wakefulness on a C57BL/6J-129/SvEv-mixed background, as described above [65], which suggests that OX1R is indispensable for the maintenance of wakefulness in the absence of OX2R.

Effector Neural Circuits That Stabilize Wakefulness Downstream to Orexin Neurons

Although the application of exogenous orexins has been shown to excite many types of neurons [3], neurons activated by the pharmacological application of exogenous orexin may not necessarily be essential to the endogenous mechanisms by which orexin neurons regulate sleep and wakefulness in a physiological condition. Thus, neurons directly downstream to orexin neurons in physiological conditions (i.e., neurons influenced by endogenous orexins that mediate their wake-promoting and REM-suppressing effects) have remained uncertain. Several reports have suggested that histaminergic neurons in the TMN play an important role in the arousal-promoting effect of orexin, which is supported by the facts that the effect of ICV orexin-A administration is both markedly attenuated by the histamine H1 receptor antagonist pyrilamine [55] and is absent in *H1 histamine receptor* knockout mice [45]. Accordingly, the TMN abundantly expresses OX2R [12, 13], the subtype whose absence causes the narcoleptic phenotype in mice and canines [20, 65]. Mochizuki et al. produced a mouse model in which a *loxP*-flanked gene cassette disrupted the production of OX2R, though normal OX2R expression could be restored by Cre recombinase [67]. They showed that targeted Cre expression (i.e., focal restoration of OX2R expression) in the TMN and adjacent regions rescued the fragmentation of wakefulness in their mouse model, which further suggest that the orexin signaling mediated by OX2R in the TMN (and possibly its surrounding area in the posterior hypothalamus) is sufficient to prevent sleepiness caused by systemic OX2R deficiency.

However, this hypothesis remains controversial. Mice lacking both OX1R and histamine H1 receptors demonstrate no abnormality in sleep or wakefulness [64]. Moreover, a recent optogenetic study showed that orexin-mediated sleep-to-wakefulness transitions do not depend on histamine [69].

Recently, in order to identify neurons directly activated by endogenous orexins and that mediate their wake-stabilizing effect in a natural context, we searched for monoaminergic and cholinergic nuclei in which the focal rescue of orexin receptor expression in *OX1R*$^{-/-}$*;OX2R*$^{-/-}$ mice by recombinant AAV vectors ameliorates their narcoleptic phenotype [68]. The targeted restoration of orexin receptor expression in the DR and LC of these mice differentially inhibited cataplexy-like episodes and the fragmentation of wakefulness (i.e., sleepiness), respectively. The suppression of cataplexy-like episodes correlated with the number of serotonergic neurons restored with orexin receptor expression in the DR, while the consolidation of fragmented wakefulness correlated with the number of noradrenergic neurons restored in the LC. Furthermore, the pharmacogenetic activation of these neurons using DREADD technology ameliorated narcolepsy in mice that lacked orexin neurons. These results suggest that DR serotonergic and LC noradrenergic neurons may play differential roles in the regulation of sleep and wakefulness by orexin neurons.

The suppression of cataplexy-like episodes by DR serotonergic neurons, but not by LC noradrenergic neurons, was quiet unexpected [68], since LC noradrenergic neurons have been considered to be a candidate to prevent cataplexy, according to various pharmacological and

electrophysiological studies. For example, cataplexy in humans and canines is strongly suppressed by drugs that increase noradrenergic tone and is worsened by drugs that block noradrenergic signaling [19, 70]. In addition, LC neurons cease firing during cataplexy in canines [71]. Nevertheless, our abovementioned observations have never conflicted with the importance of the noradrenergic system in the pathophysiology of cataplexy, yet simply indicate that the sole regulation of LC noradrenergic neurons by endogenous orexins is not sufficient to suppress cataplexy in narcoleptic mice. It is also likely that non-LC noradrenergic neurons play an important role in the suppression of cataplexy by the pharmacological augmentation of systemic noradrenergic tone.

As described earlier, the disruption of both OX1R- and OX2R-mediated pathways is required for the frequent occurrence of cataplexy [18]. This fact is consistent with the contribution of orexin signaling in DR serotonergic neurons since most DR serotonergic neurons express both OX1R and OX2R [13]. DR serotonergic neurons greatly reduce firing rates during cataplexy in canines [72]. These neurons, as well as LC noradrenergic neurons, have also been implicated in the suppression of REM sleep by inhibiting REM-on cholinergic neurons in the PPT/LDT and/or by activating REM-off GABAergic neurons in the ventrolateral periaqueductal gray (vlPAG) and adjacent lateral pontine tegmentum (LPT), also known as dorsal deep mesencephalic reticular nuclei (dDpMe) [39, 73]. Indeed, we observed dense projections of DR serotonergic neurons to these brain areas, as well as to the amygdala [68], which suggests that DR serotonergic neurons may coordinately control multiple brain regions involved in the regulation of REM sleep and emotion.

Restoration of orexin receptor expression in the LC noradrenergic neurons significantly consolidated wakefulness to an extent comparable to that in *OX2R*$^{-/-}$ mice [68]. As described above, the fragmentation is less severe in *OX2R*$^{-/-}$ mice than in *orexin*$^{-/-}$ mice and *OX1R*$^{-/-}$*;OX2R*$^{-/-}$ mice on the same C57BL/6J genetic background [18, 67], which suggests that OX1R plays an important role in the maintenance of wakefulness in the absence of OX2R [13]. In conjunction with the fact that LC noradrenergic neurons exclusively express OX1R in wild-type mice [13], these neurons are likely to be responsible for the contribution of OX1R to the maintenance of wakefulness, while another OX2R-mediated mechanism, most likely mediated by TMN histaminergic neurons, is required for the normal regulation of wakefulness duration. Recent optogenetic studies have demonstrated a causal relationship between the firing of LC noradrenergic neurons and transitions from sleep to wakefulness [74] as well as showed that the inhibition of these neurons blocked the arousal effects of the stimulation of orexin neurons [75], which further supports the importance of the orexinergic regulation of LC noradrenergic neurons in the consolidation of wakefulness.

Links among Emotion, Narcolepsy, and Orexins

As mentioned previously, cataplexy is most often triggered by positive emotions. The amygdala, which is important for processing emotions, may be a structure relevant to this characteristic of the pathophysiology of cataplexy [76]. Moreover, the amygdala and orexin neurons form reciprocal connections [8, 77, 78]. A recent study demonstrated that levels of orexin-A in the amygdala of humans are maximized during positive emotion, social interaction, and anger [63]. The amygdala sends inhibitory projections to the brainstem monoaminergic nuclei and to regions in the pons that suppress REM sleep and atonia [79], as well as non-GABAergic projections to REM-on neurons of the sublaterodorsal nucleus, which indirectly inhibits motor neurons [80]. In addition, many neurons in the amygdala of freely behaving narcoleptic canines increase activity during cataplexy [81]. A study using single-photon emission CT (SPECT) indicated hyperperfusion in several brain areas, including the right amygdala, during human cataplexy [82]. Humorous pictures reportedly also elicit enhanced amygdala response in patients [83]. Two studies have reported abnormal amygdala responses to emotional stimuli in

people with narcolepsy, with increased amygdala response to positive rewards and decreased amygdala response to aversive stimuli [84, 85]. Finally, amygdala lesions significantly reduce cataplexy in *orexin*$^{-/-}$ mice [79]. Altogether, positive emotions may trigger the weakening of muscle tone through the amygdala, which is antagonized by orexin neurons in healthy people, by enhancing the activity of neural circuits that inhibit atonia and by reducing the activity of the amygdala [76].

Regarding the roles of orexins in the function of the amygdala, two recent studies reported the importance of the orexinergic activation of the noradrenergic pathway from the LC to the amygdala in the formation of fear memory [86, 87]. These results are consistent with studies in human narcolepsy patients, who are impaired in acquiring a conditioned threat response and show reduced amygdala activity as compared to controls when exposed to aversively conditioned stimuli [85, 88].

Conclusions

Identification of the orexin system has allowed a huge step forward in understanding the pathophysiology of narcolepsy as well as in understanding the physiology of the normal regulation of sleep and wakefulness. Future studies using multiple approaches with the orexin system and its afferent and efferent pathways promise to further elucidate the whole picture of neural mechanisms underlying the physiology and pathophysiology of sleep. By targeting the orexin receptors or by replacing orexin expression, novel therapies for narcolepsy are also expected to become available in the near future.

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Precipitants of Narcolepsy: Vaccines and Infections

3

Birgitte Rahbek Kornum

Precipitants of Narcolepsy

Genetic data have taught us two important things about narcolepsy with hypocretin deficiency. One is that there must be an involvement of the immune system in the pathogenesis, and the other is that it is not a purely genetic disorder. Even in monozygotic twins, concordance rate is only about 20–35 %, which tells us that there must be important environmental factors shaping the occurrence of the disease. This chapter will describe what is known about infectious agents (bacteria and viruses) and vaccinations in association with narcolepsy. Epidemiological population-based studies and case series will be covered, as well as case–control studies measuring biomarkers of infection in biosamples from narcolepsy patients. To date, several findings support an association between certain infections and vaccinations and narcolepsy onset, but it is important to stress that so far no studies have proved any causality in this regard. Important missing pieces are proof of autoreactive immune mediators and data showing that the autoreactivity is actually induced/activated by infection/vaccination. There also still is no published autoimmune mouse model of narcolepsy, a tool that could greatly advance research.

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Upper Airway Infections Increase the Risk of Narcolepsy

Epidemiological Evidence

Epidemiological studies have suggested that upper airway infections have an effect on narcolepsy susceptibility. A population-based case–control study from King County, Washington, reported a 5.4-fold increased risk of narcolepsy in subjects with a history of a physician-diagnosed streptococcal throat infection before the age of 21 [1]. The study adjusted for race and family income. Little or no association was found between narcolepsy and other childhood infectious diseases, such as mononucleosis, pneumonia, or hepatitis, or with vaccinations or head trauma. In the same study, it was also observed that an increased risk (5.1-fold) of narcolepsy was associated with passive smoking in childhood [2]. Since exposure to environmental tobacco smoke through passive smoking in childhood is associated with serious bacterial infections and with altered immunity, this latter finding could also point toward upper airway infections being implicated in the development of narcolepsy. In a case–control study from

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California, unexplained fevers and flu infections in the year preceding onset were also associated with increased disease risk (3.9-fold and 1.8-fold increased risk, respectively) [3].

A significant association between birth order and narcolepsy has been reported, with higher birth order more prevalent in cases than in controls. Being the third child or higher was associated with a 2.5-fold increase in risk [4]. In the same study, no association was seen with sibling number, sibling gender, number of children, and children's gender. The association of disease with birth order has been observed in other autoimmune diseases, and it is thought to reflect effects of environmental factors, specifically exposure to early life infections [5, 6].

Narcolepsy has also been suggested to be associated with season of birth. This is however still controversial. A study from Germany of 555 narcolepsy cases suggested that a birth in spring gave the highest risk of narcolepsy, while a reduced risk was seen with a fall birth [7]. A study from the Netherlands in contrast did not find an effect of birth month on the occurrence of narcolepsy with cataplexy in a study of 307 cases after adjusting for changing birth patterns in the general population [8].

Seasonal effects have also been shown regarding disease onset. Data from China shows 6–7-fold more frequent onset in the late spring/early summer versus late fall/early winter. The study was a retrospective analysis of narcolepsy onset dates in 629 patients (69 % children) diagnosed from September 1998 to February 2011 at the People's Hospital, Beijing University, China. In this population, onset of narcolepsy often occurs abruptly at an early age, allowing for documented month of onset information [9]. To date, this is the only study tracking month of onset in a large cohort, and replication in another cohort will be important as the study design has limitations that could lead to inclusion bias. However, as an unbiased population-based design would have needed ascertainment of >3 million individuals to reach a similar sample size, this is not an easy thing to do.

Despite limitations, the data from China are important and support the concept that winter infections are associated with the onset of narcolepsy in a temporal manner. Lifelong risk may potentially be increased after having suffered from *Streptococcus pyogenes* or influenza H1N1, or an upper airway infection may simply precipitate narcolepsy in subjects who would have developed the disorder later and with a slower and less abrupt onset.

Streptococcus pyogenes

Streptococcus pyogenes belong to the group of beta-hemolytic streptococci and are also known as group A *Streptococcus*. The bacterium is the causative agent in a wide range of noninvasive or invasive infections. The noninvasive infections are more common and less severe, the most common being streptococcal pharyngitis (strep throat) and impetigo (localized skin infection). Raised levels of serum antibodies against proteins specific to *Streptococcus pyogenes* can indicate past or present infection, and such antibodies have been measured several times in narcolepsy patients.

In 1989, two small studies suggested increased titers of antibodies against streptolysin O (ASO) and streptodornase B (also called DNaseB, ADB) in a small number of narcoleptic patients regardless of disease duration [10, 11], but a third bigger study could not replicate this finding [12]. Mueller-Eckhardt et al. compared 100 narcolepsy with cataplexy patients to 57 patients with other sleep disorders and 107 healthy controls and found ASO values above background in 48 % of the narcolepsy patients, 30 % of other patients, and 36 % of healthy controls. For ADB, the numbers were 9 % in patients, 2 % in patients with other sleep disorders, and 11 % in controls. The increased number of narcolepsy patients with ASO antibodies was not significant, and the authors concluded that streptococcal infections were not implicated in the pathogenesis of narcolepsy. However, the publication did not give any clinical details on disease duration, which could be a serious confounder. This lead Aran et al. to speculate that a possible infectious trigger would not be detectable long after onset of narcolepsy, thus explaining these variable results [13].

It was therefore hypothesized that if streptococcal infections were indeed a trigger for narcolepsy, it would be best detected in patients, which had a recent onset. Indeed, their data showed that titers of antistreptococcal antibodies were present in more patients with newly diagnosed narcolepsy ($n=200$) compared to age-matched, healthy controls ($n=200$) for both ASO (34.5 % vs. 18.5 %, $P=0.0003$) and ADB (28 % vs. 16 %, $P=0.005$). Further stratification by disease duration revealed higher titers only in cases with onset within 3 years, when compared to controls. 65 % of patients with disease onset within a year were positive for ASO or ADB antibodies. Recent onset patients also had significantly higher titers compared to subjects with long-standing disease. Of importance, Aran et al. analyzed if the presence of DQB1*06:02 affected the result, as all patients were DQB1*06:02 positive, while only 28.5 % of the controls were HLA positive, as expected from a largely Caucasian sample. Presence of ASO did not differ between DQB1*06:02 positive and negative controls, while ADB was slightly higher in the HLA positive controls compared to HLA negative controls. The difference in % ADB between recent onset patients and age-matched controls was however still as significant when controlled for HLA status. Increased titers of ASO in narcolepsy patients have lately been confirmed in a study of 38 narcolepsy cases with H1N1 vaccination-related disease onset up to 2 years earlier. The same study also showed some evidence of increased T-cell responses to *Streptococcus pyogenes* antigens among patients [14].

Neurologic disorders with a hypothesized autoimmune etiology such as rheumatic heart fever and Sydenham chorea have long been known to be associated with streptococcal infections [15, 16]. In the more controversial syndrome, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), child patients develop obsessive compulsive disorder, tics, and sometimes other neurologic abnormalities acutely following an infection with *Streptococcus pyogenes*. The patients almost always have high ASO titers, and plasma exchange and intravenous immunoglobulin have been found to be effective in lessening the neuropsychiatric symptom severity [15].

Although the mechanism by which narcolepsy or other diseases could be triggered by *Streptococcus pyogenes* is unknown, streptococcal infections can stimulate autoimmunity via the release of toxins (small proteins) that cross-link the T-cell receptor with antigen-presenting MHC molecules independently of antigen presentation. This causes activation of a large number of T cells and massive cytokine production and has led to the description of these as superantigens [17]. It might thus be possible that the observed narcolepsy-associated T-cell receptor polymorphisms may reflect involvement of streptococcal superantigens in narcolepsy. Streptococcal infections may also increase narcolepsy risk through nonspecific effects such as a general activation of immunity (known as bystander activation) or an increased permeability of the blood–brain barrier to autoreactive T cells, caused by inflammatory agents or fever [18, 19].

Influenza A Virus

Infections Precede Narcolepsy Onset

After the pandemic in 2009–2010 caused by the H1N1-type influenza A virus, several reports have suggested an association with an increase in narcolepsy (with hypocretin deficiency) incidence. This is mainly driven by H1N1 vaccination as will be described later, but infection with the virus seems also to be associated with increased risk of developing narcolepsy. The first report of post-H1N1 narcolepsy came in 2010, where a paper described 16 patients who developed narcolepsy on average 7.4 weeks after exposure to H1N1 either as a vaccine or by infection with the virus [20]. In 2011, Han and coworkers described a clearly increased incidence of narcolepsy in China following the winter of 2009–2010. There was an overall threefold increased incidence of narcolepsy, which was observed 5–7 months after the peak of the

pandemic in 2009 [9]. Importantly, narcolepsy incidence in China returned back to prepandemic levels in later years, supporting a contributing role of pandemic H1N1 virus infection in the development of narcolepsy [21]. Only few of the patients recalled having a H1N1 vaccination, so this finding has been attributed to infection with the influenza virus. However, these studies were purely epidemiological, and no microbiological verification of H1N1 infection in the study subjects was included. The peak in incidence in 2010 in China has also been observed in data from another sleep center [22]. Data from South Korea however failed to provide supportive evidence for the role influenza infection (or vaccination) in the etiology of narcolepsy [23]. This could be explained by different pandemic influenza disease burden or different epidemiology of the infection in China and South Korea.

The 1918 Spanish Flu and Encephalitis Lethargica

Historically, neurological disturbances including narcolepsy-like symptoms have also been associated with H1N1 infections, most notably in the context of the 1918 Spanish flu pandemic, an epidemic that killed over 100 million individuals. Coincident with the Spanish flu, a smaller epidemic, that of encephalitis lethargica, affected tens of thousands of individuals worldwide as described by von Economo [24, 25]. Encephalitis lethargica is characterized by hypersomnolence and posterior hypothalamic lesions and has been suggested to bear some resemblance to narcolepsy, even though this is still debated [26]. Encephalitis lethargica was a very polymorphic disorder, associated not only with somnolence but also more occasionally with psychosis, insomnia, or movement disorders. The disease has largely disappeared, but cases are still occasionally reported and interestingly were found to be associated with high ASO titers [16, 27]. It is therefore possible that a whole range of CNS disorders, including narcolepsy, may occasionally be precipitated or caused by upper airway infections and subsequent autoimmune reactions.

H1N1 Vaccination

The H1N1 Vaccine Pandemrix Is Associated with Narcolepsy Onset in Children

The first reports of a possible association between onset of narcolepsy and H1N1 Pandemrix vaccination came from Finland and Sweden in the summer 2010 [28, 29]. This was quickly followed up by epidemiological studies. In Finland, the narcolepsy incidence increased from 0.31 (95 % CI 0.12–0.51) to 5.3 (a 17-fold increase) per 100.000 person years in children and adolescents below age 17 [30, 31]. In the same age group in western Sweden, the diagnostic incidence increased from 0.2 to 6.6 (a 25-fold increase) per 100.000 person years [32]. In Norway, the incidence increased from 0.5–1 to 10 (10–20-fold) per 100.000 in vaccinated children [33]. In Ireland and the UK, an association between H1N1 vaccination and narcolepsy has also been found in children and adolescents, and disease risk (based on odds ratio) was calculated to have increased by 14.4-fold following vaccination [34]. In France, the risk of developing disease was approximately 6.4-fold higher in children vaccinated with Pandemrix compared to matched healthy controls [35]. No increase in incidence was seen in countries like the Netherlands and Italy in the same period, which most likely is explained by the fact that these countries vaccinated much fewer children or did not use the Pandemrix vaccine [36]. Of course numbers like these have some uncertainty to them, as they depend on accurate clinical assessment of the disease and a low prevalence of undiagnosed disease. Especially pre-vaccination estimation of incidence is difficult because of lack of awareness and long diagnostic delays.

A large study attempted to get more precise estimates of the increase in risk with H1N1 Pandemrix vaccination by carefully determining the background rates of narcolepsy in Europe based on large linked automated health-care databases in six countries: Denmark, Finland, Italy, the Netherlands, Sweden, and the UK. This was a retrospective analysis covering the

years 2000–2010. Overall, 2608 narcolepsy cases were identified in almost 280 million person years of follow up. The pooled incidence rate was 0.93 (95 % CI: 0.90–0.97) per 100,000 person years [36]. It is important to note that this study reports the incidence of narcolepsy diagnosis and not onset of disease, and the data could thus be misleading if there has been a shift in public awareness and a lowering of diagnostic delay in the time period covered. The increase in incidence rates following the H1N1 Pandemrix vaccination campaigns was however so large that it is unlikely to be a false signal caused by imprecise estimates. Overall, the data presented here shows a consistent and strong association between onset of narcolepsy and preceding vaccination with the H1N1 Pandemrix vaccine.

An important question that was raised early on is whether infection with the actual H1N1 virus preceding or coinciding with vaccination could have played a role in the increase in narcolepsy incidence. Finnish investigators discovered that most individuals infected with the pandemic H1N1 virus (A/Finland/554/09 similar to A/California/7/09) developed antibodies against the nonstructural protein 1 (NS1). This response was not seen following the Pandemrix vaccine. They developed a test where NS1 proteins from recombinant influenza A/Finland/554/09 (H1N1) viruses were purified and used in Western blot analysis to determine specific antibody responses in human sera. Using this test, they saw titers above 600 in 12 out of 28 patients who had confirmed pandemic H1N1 infection. In the same test, only 4 out of 45 postvaccination narcolepsy cases had titers above 600, while 15 out of 50 healthy age-matched controls responded [37]. From these data, it can be concluded that the infection rate with A/Finland/554/09 virus was at least not higher and likely lower in the group of children who developed narcolepsy following H1N1 Pandemrix vaccination compared to children who did not develop the disease.

Curiously, a later study from Finland did find antibody responses to NP protein in serum from most Pandemrix vaccinated children using a different method [38]. The difference could be attributed to methodological differences or antigenic differences as the response in the later paper was shown to be linked to DQB1*06:02. Future studies should address this.

Still despite these discrepancies, and taken together with the clinical report from the same patient group that influenza-like illness was found only in a minority of patients and other symptomatic upper respiratory tract infection such as sore throat were not observed at all [31], it is unlikely that H1N1 pandemic virus infection itself caused the sudden increase in the incidence of childhood narcolepsy observed in Finland in 2010.

The H1N1 Vaccine Pandemrix and Narcolepsy in Adults

There is still some controversy regarding whether H1N1 Pandemrix vaccine also increased risk of narcolepsy in adults. In the initial reports, no significant signal was seen in adults, but this could have been a false-negative as the symptoms in adults have been less severe than in children, and the onset also more gradual, which may have caused diagnostic delay and masked an actual increase in incidence. Later reports have suggested a 2–5-fold increased risk in adults aged less than 30 years [39, 40]. A French case–control study also found an association in adults [35]. More studies are needed to fully address this question.

Pandemrix-Associated Narcolepsy Versus Spontaneous Narcolepsy

It has been speculated whether H1N1/Pandemrix-associated narcolepsy is the same disease as spontaneous narcolepsy. This has been based on case reports of a phenotype with a more dramatic onset and more psychiatric symptoms. Two studies so far have addressed this more systematically. Pizza et al. compared clinical features of two groups of childhood narcolepsy cases. One group consisted of 27 Finnish patients with post-H1N1 vaccination narcolepsy, and the other group consisted of 42 Italian patients with sporadic narcolepsy onset

before the H1N1 pandemic. Overall, anthropometric, clinical (EDS, cataplexy, sleep paralyses or hallucinations, and aggressive behavior or irritability), hcrt-1 deficiency, and polysomnographic data did not differ among groups. Post-vaccine cases showed slightly shorter mean sleep latency in the multiple sleep latency test (MSLT) compared to pre-H1N1 cases and more disrupted nocturnal sleep. This was however not to an extend where it was clinically significant [41]. A case-series study from Finland comparing H1N1-vaccine-related and sporadic narcolepsy cases arrived at the same conclusion regarding clinical and polysomnographic measures [42], and it is thus likely that it is indeed the same disease regardless of triggering mechanism.

Vaccine Composition Matters

Following the emergence of the pandemic H1N1 strain in 2009, a multitude of vaccines were approved for use in humans. In Europe alone, eight influenza A pandemic H1N1 strain vaccines were licensed: Cantgrip (Cantacuzino), Celvapan (Baxter), Celtura (Novartis), Fluval P (Omnivest), Focetria (Novartis), Pandemrix (GSK), Panenza (Sanofi Pasteur), and PanvaxH1N1 (CSL). So far, data on narcolepsy disease onset has only shown an association with the Pandemrix vaccine [43]. Pandemrix was the only vaccine used in Europe containing the AS03 adjuvant. AS03 differs from the more commonly used MF59 adjuvant by containing α-tocopherol, whereas both adjuvants contain squalene. It should be mentioned that the World Health Organization encouraged the use of adjuvants as an antigen-sparing strategy to make more vaccines available from the scarce supply of global pandemic vaccine antigen. About a third of the H1N1 pandemic vaccines used adjuvants including AS03 and MF59. MF59 had been used in seasonal influenza vaccines since 1997, and more than 45 million doses had been distributed with no substantial safety concerns [44]. AS03 had not been used before in licensed vaccines, but had a clinically acceptable safety profile in clinical trials, as has also later been shown in children [45].

Interestingly in Canada and Brazil, the only other AS03-containing H1N1 vaccine was used (Arepanrix), but so far no increase in narcolepsy incidence has been reported from these countries [46]. Detailed characteristics of the two vaccines can be found in Barker and Snape [46].

The risk of narcolepsy conferred by Pandemrix is therefore likely related to some specific characteristics of Pandemrix not present in Arepanrix. Obviously, all pandemic H1N1 vaccines contained antigen from the same virus. However, there could easily be small differences in protein sequence resulting from the use of slightly different derivatives of the A/California/7/2009 strain. Manufacturing process could also significantly change antigenicity of the vaccine and thus shape the induced immune response. Two studies have addressed this question.

Jacob et al. used a qualitative mass spectrometry approach and studied in detail the protein composition of the two vaccines including post translational modifications such as glycosylation [47]. The overall conclusion from that study was that the two vaccines were mostly similar. Interestingly, Jacobs et al. found that HA1 146N (residue 129N in the mature protein) displayed a tenfold higher deamidation in Arepanrix versus Pandemrix, a difference that could affect antigenicity of the corresponding epitope. The study was however only based on a single vaccine batch from each of the two vaccines and should thus be replicated with more vaccine batches.

Vaarala et al. used a functional approach and studied serum antibody responses to different vaccine antigens using samples from vaccinated Finnish children, half of whom developed narcolepsy, while the other half remained healthy [38]. It was observed that children with narcolepsy showed higher levels of IgG antibodies binding to the Pandemrix H1N1 antigen suspension than did vaccinated healthy children from the general population. This binding could be inhibited by Pandemrix H1N1 viral antigen but only to a lesser extent by Arepanrix H1N1 antigen indicating antigenic differences between the protein components of Arepanrix and Pandemrix. Once such difference was suggested to be the presence of structurally altered nucleoprotein (NP) from

H1N1 in higher amounts in Pandemrix. It was also demonstrated that children with narcolepsy had higher levels of IgG antibodies to Pandemrix-derived NP compared to healthy children.

All pandemic and seasonal flu vaccines administered after 2009 contained antigens from the pandemic H1N1 virus, but still the only vaccine associated with narcolepsy was Pandemrix. It is critical for the understanding of this to study antigenic differences between vaccines, and more studies are needed to substantiate the findings described above. The suggestions of immunologically important differences in the H1N1 antigens of Arepanrix and Pandemrix could explain the difference observed in the vaccine-attributable risk of narcolepsy in these two AS03 adjuvanted H1N1 vaccines. The role of AS03 could therefore be minor, but it could also still have been indispensable as a booster of the immune response or as an inducer of strong cross-reactive T-cell responses against viral antigens as has been shown for the AS03 adjuvanted H5N1 vaccine [48].

Could an Infection Trigger Narcolepsy with Hypocretin Deficiency?

Infections are increasingly recognized as playing a role in the pathophysiology of autoimmune diseases [49]. From the studies described above, it is clear that there indeed is an association between onset of narcolepsy and infection with *Streptococcus pyogenes* and infection/vaccination with the pandemic influenza A H1N1 virus. The possible causality of this still remains to be shown. Curiously, so far studies have failed at detecting increased levels of general inflammatory markers (C-reactive protein, cytokines, and chemokines) even very close to disease onset arguing against infection as a triggering mechanism. It is however still possible that there is a temporal association with recent infections and narcolepsy, but that the delay between the infection and onset of narcolepsy is so long that general inflammatory markers have returned to basal levels. Potentially, upper airway infections increase lifelong risk of narcolepsy in genetically susceptible individuals, or an upper airway infection may simply precipitate narcolepsy in subjects who would have developed the disorder later with a slower and less abrupt onset.

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Part II

Clinical Considerations

Epidemiology of Narcolepsy

4

Lauren Hale, Stanford Guan, and Erin Emanuele

Narcolepsy Has a Variable Phenotype

First described by Gelineau in 1880 and Westphal in 1887, narcolepsy refers to a sleep disorder characterized by excessive daytime sleepiness and episodic weakness [1]. This episodic weakness later became known as cataplexy. In the 1950s, Yoss and Daly described the classic tetrad of narcolepsy symptoms: excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic (at the onset of sleep) or hypnopompic (on awakening) hallucinations [2]. Other symptoms of narcolepsy include disturbed nocturnal sleep and rapid eye movement (REM) sleep behavior disorder [3].

Excessive daytime sleepiness, or hypersomnia, refers to when patients suddenly feel overwhelmingly tired and become unaware of their environment during the day. This sleepiness occurs regardless of the amount or quality of nocturnal sleep [4] and tends to be heightened in sedentary or boring environments [5]. For narcolepsy patients, even short sleep is refreshing upon awakening.

Cataplexy refers to episodic bilateral muscle weakness without loss of consciousness and occurs in 60–80 % of patients diagnosed with narcolepsy [6–9]. Cataplexy usually occurs after the onset of daytime sleepiness; however, in rare cases, cataplexy may occur first or be the only symptom of narcolepsy. Attacks of cataplexy range from a slight slackening of the facial muscles to total collapse on the ground. Often attacks of cataplexy only affect certain muscle groups, such as those in the neck or face [3]. A cataplexy attack can last up to a few minutes, during which the patient is unable to move, despite maintaining consciousness. If the attack is prolonged, sleep may occur. Positive emotions such as exhilaration and surprise tend to trigger these attacks [5]. Yet other emotions, including anger, embarrassment, or sexual arousal, can also prompt an attack, though less frequently [10]. Frequency of cataplexy attacks ranges from 1 to 2 episodes per year to 12 or more per day [11, 12]. Generally, frequency of cataplexy attacks remains stable as the patients age [13, 14], but some patients may adapt to their illness over time and avoid situations in which cataplexy attacks may occur [14].

Sleep paralysis refers to an inability to move one's head or limbs during the transition to sleep

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or wakefulness. Sleep paralysis can accompany hypnagogic/hypnopompic hallucinations, which are vivid auditory or visual experiences. These symptoms may be difficult to recognize, especially in children, where they may resemble nightmares. Narcoleptic patients tend to have dreams involving flying, being chased, and crawling into a tube more than non-narcoleptic patients [5].

Additional symptoms include disrupted nighttime sleep and participating in automatic behavior while sleeping, but having no memory of doing things (e.g., talking, eating, putting things away) [5]. Abnormal REM sleep includes persistence of muscle tone, excessive twitching, and periodic leg movements while sleeping.

Difficulties with Diagnosis Complicate Epidemiological Estimates

Given the variable phenotype for narcolepsy, there is no gold standard for the diagnosis of narcolepsy since many of the symptoms overlap with non-narcoleptic patients. Moreover, there remains some controversy over whether cataplexy need be an essential feature of narcolepsy. Generally, a specific diagnosis of narcolepsy with cataplexy requires the combination of the relatively common symptom of excessive daytime sleepiness with the uncommon symptom cataplexy. Symptoms can vary in their nature and severity, which complicates diagnosis and could lead to misdiagnosis. Indeed, both excessive daytime sleepiness and cataplexy-like symptoms can be reported in non-narcoleptic patients with other sleep disorders and even in healthy patients [5]. In addition, before diagnosing a patient, physicians need to rule out other potential causes for excessive daytime sleepiness, including inadequate sleep hygiene, use of medications or illicit drugs, sleep-disordered breathing, and delayed sleep phase syndrome. Further, hypersomnia can disguise other neuropsychiatric conditions, such as depression [15, 16].

Due to the potential for misdiagnosis and people not seeking treatment right away, it is estimated that less than 50 % of patients with narcolepsy have been diagnosed [11]. Among those who are diagnosed with narcolepsy in the UK, the median interval between symptom onset and diagnosis is 10.5 years [17]. A sample among narcolepsy patients in southern China reveals a mean time to diagnosis of 16 years [18]. Similarly, results from the European Narcolepsy Network reveal a mean diagnostic delay of 14.6 years, which is typically longer in women than men [19].

Diagnostic criteria have been updated to three categories of narcolepsy: narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy due to another underlying condition. Diagnosis is based on a clinical presentation along with both night and daytime polysomnographic (PSG) testing. In narcoleptic patients, sleep latency is low, and there is the presence of sleep-onset REM periods. Patients are usually diagnosed for narcolepsy using the multiple sleep latency test (MSLT), which assesses the degree of sleepiness and timing of REM sleep onset. The MSLT is performed by allowing five opportunities for the patient to nap at 2-h intervals throughout the day, as described elsewhere [20]. Sleep-onset REM sleep indicates that REM occurs within 15 min of sleep onset, while sleep latency refers to the time from lights out to stage I sleep, for each nap. The mean sleep latency (MSL), which is the arithmetic mean for all naps, provides an index of the severity of sleepiness. Patients with narcolepsy usually have an MSL of less than 8 min. However, low MSL can occur in up to 15 % of the population, so this is not enough to diagnose narcolepsy. When a patient has a combination of sleep-onset REM and an MSL of less than 5 min, the MSLT has a sensitivity of 70 % but a specificity of 97 % for narcolepsy [21].

Laboratory tests for human leukocyte antigen (HLA) and cerebrospinal fluid (CSF) hypocretin-1 (110 pg/mL or less) analysis also can be helpful diagnostic tools. The majority of narcolepsy patients with cataplexy are carriers of the HLA DQB1*0602 gene [22, 23]. In addition, animal and human studies show a connection between a deficiency in the hypothalamic orexin/hypocretin system and the pathogenesis of narcolepsy with cataplexy [24–27].

Prevalence and Incidence Estimates Vary by Methods and Populations

Most of the early literature on narcolepsy was based on case reports. A series of case reports collected by physicians at the Mayo Clinic details many early experiences with the disorder [1]. Yet while these studies were important, they did not provide any information on the prevalence of narcolepsy in the population. As with many rare diseases, prevalence varies depending on the study methods and population, ranging from 0.2 per 100,000 people in Israel [28] to 590 per 100,000 people in Japan [29].

Longstreth et al. [1] provides a table summarizing narcolepsy prevalence estimates and other details from 30 studies around the world. Generally, for more intensive screening, the prevalence of narcolepsy with cataplexy falls between 19 and 56 per 100,000 people in the USA and Western Europe [2, 3, 9, 30], with a similar rate of 22 per 100,000 people in Norway [31].

In a review article, Longstreth et al. identified a set of 12 studies in which patients are more intensively screened for narcolepsy [1]. For example, Ohayon et al. [2] conducted a representative population-based sample of nearly 19,000 Europeans from five countries (the UK, Germany, Italy, Portugal, and Spain) and diagnosed narcolepsy according to the International Classification of Sleep Disorders (ICSD). Their results are within the range of other estimates at 26–47 per 100,000 people, for moderate to severe narcolepsy. Another analysis of the entire population of Olmsted County in Minnesota has a range of 36–56 per 100,000 people, depending on whether the definition requires the symptom of cataplexy or not [9]. Additionally, an analysis of residents with "physician-diagnosed" narcolepsy with cataplexy of King County Washington has a range of 19–25 per 100,000 people and typically higher among African-American women [32]. The lowest prevalence estimate among the sample of more intensively screened epidemiological studies [1] is 1.08 per 100,000 people in a survey of providers and pharmacies in Singapore [33]. This number may be low due to under diagnosis or low reporting to the Singapore General Hospital. Elsewhere, the prevalence rates for narcolepsy in regions in Eastern Asia vary from 15 per 100,000 people in South Korea [34] to 34 per 100,000 people in Hong Kong [35]. One study in Saudi Arabia reports prevalence rates as low as 4 per 100,000 people [36].

Prevalence of narcolepsy symptoms range from 204 per 100,000 in a population of adults in southern France [37] to 30,586 per 100,000 people in Sivas, Turkey [38]. Thus, the symptoms of narcolepsy are much more common than the diagnosis with cataplexy. Other studies show that daytime sleepiness is prevalent in approximately 8–15 % of adults [2, 39].

Incidence of narcolepsy, which is less frequently studied, is estimated at 0.74 per 100,000 person-years for those with narcolepsy and cataplexy and 1.37 per 100,000 person-years for narcolepsy with or without cataplexy (1.72 per 100,000 person-years for men and 1.05 per 100,000 person-years for women) [9]. These incidence rates are similar to those of multiple sclerosis and motor neuron disease.

Age of Onset Generally Begins in the First Two Decades

Age of onset for narcolepsy usually starts in the second decade of life. For instance, the median age of onset in the Czech Republic is 18 [6]. Similarly, in Olmsted County, the age of onset had a median of 16 with a full range between 4 and 56 where age of onset was unrelated to sex or HLA type [9]. Several studies reveal a bimodal distribution of age of onset, with the first peak at age 15 and the second peak at age 35 [18, 40, 41]. In Southern China, the bimodal patterns were observed even after separating the sample into males and females and cataplectic and non-cataplectic. The only difference was that the ages of the peaks in females came earlier than that for males [19], which may be related to puberty [18].

An analysis of 57 narcoleptic patients in Switzerland shows that only 5 % of the sample started having symptoms of narcolepsy before age 10 and only 8 % after the age of 40 [5]. Those with a family history tended to have earlier

ages of onset, whereas the disease arrives at a later age in those without a family history [40]. Retrospective studies suggest that about half of adults with narcolepsy had the onset of symptoms in their youth [42, 43]. However, the pediatric literature has paid scant attention to the disorder, and it may be a key to understanding the disease [44, 45]. Parents may not recognize excessive daytime sleepiness in a child under five and not know how to report it. Daytime sleepiness in school-aged children and adolescents is relatively common at 17–21 % [46]. Once children start attending school, however, parents and teachers may become more aware of the frequent napping behaviors of narcoleptic children. Another reason it may be hard to diagnose young children is that they may also experience the episodes of sleepiness differently than adults [44]. Further, childhood narcolepsy may not be indicative of developing cataplexy later in adulthood [7].

At the other end of the age spectrum, narcolepsy prevalence data in the elderly are not available [47]. Secondary forms of narcolepsy can occur at any age and are typically due to intracerebral disease such as brain tumors or head trauma [48].

Narcolepsy Without Cataplexy Is More Common Among Men Than Women

Several studies that have looked at gender and narcolepsy do not see large differences by gender with regard to narcolepsy [3, 18]. Yet, in Olmsted County and in the Mayo Clinic case series, narcolepsy appears to be more common in men than in women [1, 9]. Analyses from the Wisconsin Sleep Cohort Study show that the gender difference is larger in those without cataplexy [49].

Narcolepsy Has Few Links to Lifestyle Characteristics

Given the rarity and complications with diagnoses, it is difficult to compare estimates across studies to look for ethnic differences, but some comparisons suggest that there is as much as a 2500-fold difference in ethnic predisposition to narcolepsy [35]. As cited previously, Japanese populations have much higher rates of narcolepsy than Israeli Jews. But these dramatic differences may be in part due to differences in stringency of the definitions for narcolepsy.

With regard to lifestyle, very few studies show that lifestyle and behavioral characteristics are associated with narcolepsy [1]. The Longstreth review [1] refers to studies that show an association between narcolepsy and excessive alcohol consumption. Small studies during the 1970s revealed that narcoleptics ate more snacks throughout the day than controls, but in the end narcoleptic patients consumed fewer total calories [1]. One investigation shows that there are no increased eating disorders among patients with narcolepsy [50]. Early studies showed that narcoleptic cases were more likely to be overweight, which was associated with non-insulin-dependent diabetes mellitus. Additionally, obesity appears to be present in the early stages of the disease, even when the disease begins in childhood. However, it is not clear whether the symptoms of narcolepsy precede the onset of the weight [51].

Narcolepsy Has Both a Genetic and Environmental Link

The genetics of narcolepsy is complex. In humans, narcolepsy is more common among first-degree relatives, but it is less common than one would expect based on normal inheritance patterns [52]. Concordance among monozygotic twins is only 25–31 %, emphasizing the importance of environmental factors [23]. As with many other conditions, there is likely a genetic susceptibility to an environmentally controlled event [22, 23].

Genetically, narcolepsy has associations with multiple genes including HLA DQB1*602 (which is present in approximately 25 % of the population), with other interacting alleles [22]. Over 85 % of narcoleptic patients with cataplexy have this allele compared to no more than 38 % in the general population, depending on the population. In Israel, for example, less than 7 % of a sample of 252 healthy controls had HLA

DQB1*602, which suggests this population has a lower percentage of genetic susceptibility to narcolepsy. This finding is consistent with large epidemiological studies showing a very low prevalence of narcolepsy in Israel [53, 54]. In individuals who are positive for HLA DQB1*602, there is evidence that higher birth order increases risk for narcolepsy [55].

Furthermore, while the role of environmental factors is not clearly understood, there is growing evidence of an environmental link. Coincidence with other diseases (such as autoimmune diseases) and the presence of stressful environmental factors (such as a death in the family, divorce, abortion, or sexual violence) are suggested as possible triggers for the manifestation of narcolepsy [56, 57].

Seasonality of Birth Gives Clues to Environmental Origins of Narcolepsy

Some research has further investigated the environmental origins of narcolepsy by specifically examining seasonality of birth. Narcolepsy is more common among patients who were born in March (with a peak odds ratio of 1.45), with the lowest prevalence of narcolepsy occurring for those born in September (with a trough odds ratio of 0.63) in a study using data from France, Canada, and the USA [58]. In Southern China, narcolepsy prevalence peaks for those patients with births in January (OR = 3.0 with 95 % confidence interval = 1.4–6.4) [18]. This seasonal pattern suggests that exposure in utero may have an increased risk of the disease, but this does not explain why concordance between monozygotic and dizygotic twins is not higher. Differences in environment could include in utero nutrition, sunlight, toxins, infectious agents, and temperatures. For example, children born in certain months may be more likely to get an infection after birth that may lead to a future risk of narcolepsy. However, a recent study of 307 cases from the Netherlands refutes the association between seasonality of birth and narcolepsy with cataplexy [59].

Looking Ahead: The Future of Epidemiology of Narcolepsy

With rapidly improving ability to test and treat sleep disorders, awareness about the diagnosis and prevalence of narcolepsy has increased dramatically. Thus, knowledge about the predictors and consequences of narcolepsy at the population level is growing. Understanding the epidemiology of the disease should help scientists focus in on the social, behavioral, genetic, and environmental pathways and consequences of the disease.

Even with the increased understanding, however, narcolepsy remains rare enough that many people do not know about the disorder nor know when or where to get treated. At the clinical level, individual concerns are primarily about quality of life and daily functioning. The public health implications of the disease relate to public safety, because patients with narcolepsy are at a heightened risk of falling asleep while driving. With regard to social disparities, to the best of the scientific knowledge, the disease does not affect certain socially vulnerable populations more than others. However, due to high rates of non-diagnosis, misdiagnosis, or delayed diagnosis, there is a concern that people who do not have access to health care are not receiving adequate treatment or diagnosis. In addition, due to the social and occupational difficulties with the disease, people with narcolepsy may be more prone to fall through the cracks. Disadvantaged populations, particularly the unemployed who do not have as much access to healthcare, should be considered at a higher risk for having undiagnosed cases of narcolepsy. Through better epidemiological research on narcolepsy, the scientific and medical community can improve causes, awareness, early recognition, and treatment of the disease.

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Diagnostic Criteria and Delay in Diagnosis of Narcolepsy

5

Michael J. Thorpy

Narcolepsy, a chronic neurologic disorder resulting from dysregulation of the sleep-wake cycle, frequently has an early age of onset. However, a long delay until diagnosis has been consistently reported in the literature across countries [1]. Most reports indicate a delay of up to 8–15 years, with individual cases of >60 years, although there is a trend over time toward a shorter diagnostic delay. The factors associated with this delay have been identified with the most likely underlying reason being a lack of symptom recognition, often resulting in misdiagnosis prior to reaching the narcolepsy diagnosis. Some medical and psychiatric disorders have symptoms that overlap with narcolepsy. The mean age of onset of narcolepsy is typically at age 16 years, and children often can be misdiagnosed with behavioral or psychiatric disorders. Part of the difficulty in diagnosis is due to a lack of understanding of the symptoms of narcolepsy, and unfortunately, the diagnostic criteria largely rely on objective testing once the diagnosis is suspected, rather than symptom recognition.

The current diagnostic criteria, mainly used by sleep specialists, are contained in the third edition of the *International Classification of Sleep Disorders* (ICSD-3), produced by the American Academy of Sleep Medicine, and published in 2014 [2]. In 2013, the American Psychiatric Association (APA) published the revised version of the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V)* which includes a section entitled "Sleep-Wake Disorders" which also includes narcolepsy diagnostic criteria similar but not identical to that of the ICSD-3 [3]. The presence of two competing narcolepsy diagnostic criteria may produce confusion, especially for health insurance companies and for epidemiological research.

APA DSM-V Narcolepsy Diagnostic Criteria

The DSM-V diagnostic criteria include a category called hypersomnolence disorder which includes symptoms of excessive quantity of sleep, deteriorated quality of wakefulness, and sleep inertia. A diagnosis is made if there is a 3-month history of excessive sleepiness, despite a main sleep period of at least 7 h, in the presence of significant distress or other impairment, and it is not due to another sleep disorder. Objective documentation is not required. This general category of sleepiness can be coded along with other mental, medical, and sleep disorders. A hypersomnolence disorder diagnosis might cause a delay in a diagnosis of narcolepsy, if an additional evaluation is not performed.

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Narcolepsy is defined as recurrent episodes of sleep that occur for at least 3 months along with one of three additional features, such as cataplexy, hypocretin deficiency, or polysomnographic features which include either a sleep onset REM period (SOREMP) on a nighttime polysomnogram (PSG) or a multiple sleep latency test (MSLT) showing a mean sleep latency less than 8 min and 2 or more SOREMPs [3, 4]. So narcolepsy can be diagnosed by DSM-V criteria if just sleepiness occurs for 3 months and there is a SOREMP on the nocturnal PSG. This has the potential of leading to errors in diagnosis as other disorders including obstructive sleep apnea syndrome (OSA) can produce similar findings. Five narcolepsy subtypes are specified in DSM-V according to the presence or absence of hypocretin deficiency; autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCADN); and autosomal dominant narcolepsy, obesity, and type 2 diabetes (ADNOD) or secondary to another medical condition.

ICSD3 Narcolepsy Diagnostic Criteria

In the ICSD-3, there are two forms of idiopathic narcolepsy: type 1 and type 2. Type 1 is consistent with hypocretin reduction or loss and requires the presence of cataplexy or reduced csf orexin/hypocretin [2]. Type 2 does not have cataplexy or hypocretin reduction, but polysomnographic findings are essential. The polysomnographic criteria in the DMS-V may only require a SOREMP on the nighttime PSG, whereas the ICSD-3 requires both a PSG and MSLT. A SOREMP on the PSG may count as one of the two required for diagnosis according to the ICSD-3. Type 2 narcolepsy is more difficult to diagnose because the pathognomonic symptom of cataplexy is not present. A detailed clinical history is essential to rule out other possible causes of chronic sleepiness [5]. The multiple sleep latency test is the most important measure, and prior sleep deprivation, shift work, or circadian disorders should be excluded by actigraphy or sleep logs. Although sensitivity is low, on polysomnography, a short REM sleep latency (≤15 min) can aid in the diagnosis of narcolepsy without cataplexy. Hypocretin levels can be helpful, as levels are low to intermediate in 10–30 % of narcolepsy without cataplexy patients [6].

Delay in Diagnosis

The five main symptoms of narcolepsy are sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and disturbed nocturnal sleep. Approximately 70 % of the US general public know about narcolepsy, but no one in the general population can identify all 5 symptoms [7]. It ranks lowest in awareness relative to other chronic diseases requiring long-term treatment. In 2012, only 7 % of primary care physicians in the USA could identify all 5 main narcolepsy symptoms [7].

A narcolepsy diagnosis is less likely to be missed by clinicians if narcolepsy is included in the differential diagnosis of the complaint of sleepiness. As other comorbid sleep disorders are commonly seen in narcolepsy, the clinician has to consider that more than one sleep disorder may be present [8]. Questions about frequency of sleepiness, sleepiness while sedentary, dreaming during naps, and the age of onset of sleepiness will help in the diagnosis. The symptom of cataplexy should be explored on more than one occasion as many patients fail to recall the symptom when first asked, and the symptom has great variability. The ancillary symptoms, when present, of sleep paralysis, hypnagogic hallucinations, automatic behavior, and frequent and vivid dreaming all help establish the clinical diagnosis.

Recent studies have indicated that narcolepsy is typically associated with a delay in diagnosis of approximately 8–15 years [1]. The diagnosis may be more delayed in females [9]. An analysis of 1000 patients with narcolepsy of all ages showed a median onset of 16 years and a median age of diagnosis of 33 years [1]. The reason for the delay in both sexes appears to be related to numerous causes such as mildness of initial symptoms, gradual onset, lack of recognition of the condition by the patient or clinician, mistaken diagnosis due to alternative disorders of sleepiness such as sleep deprivation or obstructive

sleep apnea, and misdiagnosis due to psychiatric disorders such as attention deficit disorder or depression [1, 10].

Clinical Features

Cataplexy, the pathognomonic symptom of narcolepsy, when obvious such as when a person laughs and falls to the ground, often leads to a rapid diagnosis, but even cataplexy can be misdiagnosed as a drop attack or a psychogenic symptom. However, most patients do not have falls associated with cataplexy but have more subtle symptoms such as facial, head, or limb weakness, which may be more difficult to diagnose. The manifestations of cataplexy are often very different in children when the disorder usually begins. However, sleepiness is the most common feature of narcolepsy and also usually the most disabling.

In children, the initial presentation of abnormal sleepiness can be increased total sleep during the 24 h [11]. The sleepiness is present everyday although can be better on some days, but the patient is never free of sleepiness. Typically, the sleepiness is most evident when the patient is sedentary or inactive such as when watching television, reading, or sitting quietly or when as a passenger in a car. The sleepiness may be momentary sleep, and the patient can continue wakeful activities such as driving, but memory formation may be impaired, thereby leading to episodes of so-called "automatic behavior" for which the patient has no memory. The patient is capable of acting appropriately but has no recall for the activity.

Cataplexy in adults is mainly precipitated by positive emotions such as laughter, elation, or happiness, although it can be precipitated by negative emotions such as anger [12]. In children, the cataplexy may be precipitated by exhaustion, tiredness, and stress and can be described as the child having "puppet-like" movements, but it usually evolves into the more typical form of cataplexy as the child ages [11]. Although the knees may buckle leading to falls, sometimes cataplexy may be an abnormal sensation felt in the muscles with emotion. Facial weakness with the inability to smile or drooping of the eyelids or head and facial twitching or grimacing can occur. Objects may be dropped from the hands, or stumbling or incoordination can cause falls. Often the features of cataplexy are considered to be a form of epilepsy, or parents may think that the child has a psychogenic symptom.

Vivid dreams at sleep onset are a common feature and often can occur prior to falling asleep leading to "hypnagogic hallucinations" that are usually visual but can be auditory. Frequent dreams, nightmares, and lucid dreams are common [13, 14]. Dreams upon awakening "hypnopompic dreams" occur but are less specific to narcolepsy. Delusional dreams in which the patient after awakening believes the activity really occurred are more common in narcolepsy [15]. A partial manifestation of REM sleep, "sleep paralysis," leading to an inability to move for seconds or minutes, can occur in the transition from sleep to wakefulness or from wakefulness to sleep, often in association with dreams or hallucinations. However, sleep paralysis occurs frequently in healthy individuals and so may not raise a suspicion of narcolepsy.

Disturbed nocturnal sleep is characterized by sleep fragmentation, increased lighter sleep, and reduced deep sleep with disrupted REM sleep and sometimes features of REM sleep behavior, which is dream-driven activity that occurs while asleep [16]. There are fragmented, frequent, brief, nightly awakenings with difficulty returning to sleep and overall poor sleep quality. The sleep disturbance may be a major concern of the patient and can lead to specific treatment. Some patients have been misdiagnosed as having insomnia which has delayed a narcolepsy diagnosis.

Narcolepsy is associated with weight gain for many patients which may lead to a misdiagnosis of obstructive sleep apnea syndrome if the patient has some mild features of sleep apnea. Studies have shown increased BMI and leptin levels indicating altered energy homeostasis in hypocretin-deficient narcolepsy patients [17].

Psychiatric disorders especially depression are also common in narcolepsy patients [18]. A common misdiagnosis for patients with narcolepsy is a psychiatric diagnosis.

Diagnostic Tests

Subjective scales include the Epworth Sleepiness Scale (ESS), an eight-question questionnaire that asks about the chance of doing in everyday situation such as when watching television or when reading. The ESS can aid the clinician in determining the presence of abnormal sleepiness and the severity. A score greater than 10 out of 24 indicates abnormal sleepiness, and patients with narcolepsy typically score approximately 18 [19]. Anyone who scores over 15 on the ESS should be considered a high risk of having narcolepsy, although sleep apnea and sleep deprivation can produce similar values.

The most definitive test for narcolepsy is the measurement of csf hypocretin levels which, when <= 110 pg/ml, or less than one third of baseline levels, is diagnostic for narcolepsy in the presence of typical clinical features [2]. Unfortunately, a national assay for hypocretin is not available, and testing is restricted to research facilities. Although the HLA DQB1*0602 is found in most patients with narcolepsy/cataplexy, a negative result does not exclude the diagnosis, and 26 % of normal patients are positive, so a positive result is supportive but not diagnostic for narcolepsy.

When narcolepsy is suspected, all patients should undergo electrophysiological testing by means of sleep studies that involve not only a nighttime polysomnogram (PSG) but also a daytime Multiple Sleep Latency Test (MSLT). The overnight sleep study should demonstrate an adequate amount of sleep for the age of the patient, including REM sleep, and may show the characteristic features in narcolepsy of reduced sleep efficiency, short sleep latency, and, in 50 % of patients, a short REM latency. The PSG will also rule out other causes of sleepiness such as sleep apnea or frequent periodic limb movements of sleep. The MSLT, performed the next day, will show a reduced mean sleep latency of 8 min or less and two or more sleep onset REM periods (SOREMPs) during the 4 or 5 nap test. However, the MSLT may be falsely negative especially if the patient is anxious or highly aroused, and therefore, a repeat MSLT at a later date may be necessary to confirm the diagnosis.

Conclusion

The long duration between symptom onset and diagnosis indicates that many patients with narcolepsy remain undiagnosed. This delay is a major barrier to the timely and appropriate management of patients. The delay most likely results from lack of recognition of the diagnostic features of narcolepsy, since the symptoms may be suggestive of other conditions for which there is greater awareness, especially within the pediatric population.

Education initiatives to enhance the recognition and diagnosis of narcolepsy should focus on symptom description and also on the impact that symptoms have on patients as the impact may be more readily recognized than the actual symptoms. It is important that referral is made to an appropriate specialist for diagnostic testing, as early referral combined with greater symptom awareness may reduce the time between symptom onset of narcolepsy and its accurate diagnosis.

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Narcolepsy in Childhood

6

Shalini Paruthi and Suresh Kotagal

This chapter provides an overview of narcolepsy in childhood.

Historical Notes

Westphal published the first good description of the disease in 1877 as "strange attacks of falling to sleep" using the term "epileptoid" [1]. In 1880, Jean Baptiste Gélineau wrote of a patient who was experiencing as many as 200 sleep attacks per day, some probably cataplectic [2]. Gélineau believed that he was dealing with a disorder that was distinct from epilepsy and hence proposed the term "narcolepsy." He wrote of "a specific neurosis, characterized by the twofold criterion of drowsiness and falling or astasia" [2, 3]. Schenck indicates that in June of 1930, Janota and Skala presented a paper at the Neurological Society of Prague which described the successful treatment of narcolepsy with ephedrine sulfate, but the work was not formally published [3]. A series of 147 patients with narcolepsy was published by Luman Daniels from the Mayo Clinic in 1934 [4]. A distinction was made between idiopathic and symptomatic forms of narcolepsy, but Daniels questioned the relevance of classifying them separately. The term "cataplexy" was first used by Adie [5]. It was defined by the Oxford dictionary of the early twentieth century as a "temporary paralysis or hypnotic state in animals when shamming death." *Cataplessa* in Greek means to strike down with fear or the like [2, 5]. In the early 1930s, a neurologist at the Mayo Clinic, upon seeing a patient in an attack of cataplexy, made the following vivid observation: "he looked like a patient with myasthenia gravis for 30 s, then normal" [4].

Introduction

Childhood narcolepsy is evaluated and diagnosed in a manner similar to adults. The *International Classification of Sleep Disorders—Third Edition* (ICSD-3) provides two classifications of narcolepsy, including narcolepsy type 1 (narcolepsy with hypocretin deficiency, previously narcolepsy with cataplexy) and narcolepsy type 2 (narcolepsy without hypocretin deficiency or narcolepsy without cataplexy) [6]. The diagnostic criteria apply to both adults and children (see Table 6.1). No new studies or trials using this new diagnostic classification in children have yet been published at time of writing. Most of the studies referenced in this chapter were based on criteria from the prior ICSD edition. The main difference

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now is the clear understanding that hypocretin deficiency is a key underlying mechanism in narcolepsy–cataplexy.

Adults and children may have similar clinical presentations. Disabling hypersomnia is always present. A study of 148 patients with narcolepsy (31 children) investigated differences in children and adults with narcolepsy. There was no difference in the high sleepiness scores or in the results of the multiple sleep latency test (MSLT), with both groups having short mean sleep latencies and increased mean number of SOREMPs. Additionally, children and adults with narcolepsy with cataplexy both showed over 90 % presence of histocompatibility antigen (HLA) DQB1*0602. Further, in the case of narcolepsy without cataplexy, children were more likely than adults to be HLA DQB1*0602 positive [7]. It thus suggests a potential for evolving into narcolepsy–cataplexy at a later date.

Table 6.1 Diagnostic criteria are the same for children as for adults

Narcolepsy type 1
1. Daily periods of excessive sleepiness for at least 3 months
2. One or both of the following
a. Cataplexy and a multiple sleep latency test (MSLT) with a mean sleep latency of ≤8 min and two or more sleep onset REM periods (SOREMP). A sleep onset REM period within 15 min of sleep onset on the preceding overnight polysomnogram may be considered toward the SOREMP on MSLT
b. CSF hypocretin-1 concentration is ≤110 pg/mL or less than 1/3 of mean values obtained in normal patients with the same standardized assay
Narcolepsy type 2
1. Daily periods of excessive sleepiness for at least 3 months
2. A multiple sleep latency test shows a mean sleep latency of ≤min and 2 or more SOREMPs. A sleep onset REM period within 15 min of sleep onset on the preceding overnight polysomnogram may be considered toward the SOREMP on MSLT
3. Absence of cataplexy
4. CSF hypocretin-1 concentration is >110 pg/mL
5. The sleepiness and/or MSLT findings are not better explained by another sleep, medical, neurologic, or other disorder or medication

Generally, the tetrad of excessive daytime sleepiness, hypnagogic or hypnopompic hallucinations, sleep paralysis, and cataplexy is present for at least 3 months. This tetrad may not be fully apparent in younger children, but over time, these symptoms become more easy to document. It is difficult to know whether this is due to insufficient history from relatively nonverbal younger children or whether there is indeed a gradual evolution of these symptoms over time. The additional complaint of disrupted nocturnal sleep completes the pentad of narcolepsy.

The diagnosis of narcolepsy is particularly challenging in children given the variability in clinical presentation, limited descriptive ability of the child, and variations in reliability of the parents as historians.

Prevalence

The prevalence of narcolepsy is estimated at 0.05 % globally. Variation exists due to the inconsistency of clinical diagnostic criteria [8], such as requiring coexistence of cataplexy, and characterization by frequency and intensity of cataplexy. Some epidemiologic studies have exclusively evaluated children. For instance, Honda queried school children aged 12–16 years in Fujisawa, Japan, by questionnaire and estimated a prevalence of 160/100,000 or 0.16 % for narcolepsy with cataplexy [9]. In contrast, Han found a prevalence of 40/100,000 or 0.04 % among 70,000 consecutive children evaluated in China in a pediatric neurology clinic by screening questionnaire, polysomnogram (PSG), MSLT, and human leukocyte antigen (HLA) typing [10]. No new large prevalence studies have been completed with the recent reorganization of diagnostic criteria from ICSD-3.

Other epidemiologic studies include wider age ranges of adults and children. In the United States, prevalence and incidence were analyzed through the records-linkage system of the Rochester Epidemiology Project in Olmsted County, Minnesota. Silber et al. found the overall prevalence of narcolepsy to be 0.056 %, with an incidence of 1.37 per 100,000 persons per year

(1.72 for men and 1.05 for women) [11]. Approximately 36 % of prevalence cases did not have cataplexy. Further examination of data by age groups of 0–9 years and 10–19 years showed a prevalence rate of narcolepsy with cataplexy of 4/16,074 and 15/15,112, respectively. These figures were slightly higher for cases without cataplexy. Incidence was calculated as 1.01 for the 0–9-year age group and 3.84 for the 10–19-year age group [11].

The typical age of onset of narcolepsy is also disputed [8, 12–14]. For example, Silber et al. found a median age at diagnosis of 16 years in the Olmsted County population, with a range of teens to early 1920s [13]. On the other hand, Dauvilliers et al. found a bimodal distribution in Canadian and French subjects, with peaks at age 14.7 and 35 years of age ($n=519$) [14]. Aran noted in over 100 children 40 % reported symptom onset prior to age 15 years and 2.1 % had onset prior to age 5 years [15].

It is well known that a lag often exists between symptom onset and the correct diagnosis of narcolepsy in adults and children. Misdiagnoses include emotional disturbance, normal maturation behaviors, infection, epilepsy, and other sleep disorders [15]. Similarly, vasovagal syncope or drop attacks may mimic narcolepsy with cataplexy [16]. Other children have been misdiagnosed with clumsiness, malingering, or conversion disorder [17]. Hypothyroidism has also been diagnosed in patients with narcolepsy due to hypotonia [18]. A long delay to diagnosis was associated with poor school performance and the need to repeat a grade [19].

The combination of symptoms of inattentiveness, excessive night awakenings, daytime sleepiness, and bizarre hallucinations can lead to psychiatric misdiagnosis such as depression or schizophrenia. This clearly emphasizes the need to gather a complete psychiatric history including depression or mood changes to distinguish mental health disorders from consequences of narcolepsy. Some children will have both, narcolepsy and a mental health disorder. In a report of 51 children found to have narcolepsy, all children presented at least once during follow-up with depressive symptoms as a response to their disease [20].

Clinical Presentation

Preschool-Age Children

Narcolepsy is rare in preschool-age children, with rates ranging from 4.6 % (235 patients) [21] to 11.7 % (85 patients) [22] diagnosed by age five. In general, diagnosing narcolepsy prior to age four or five is difficult as physiologic napping still commonly occurs in this age group. See Table 6.2. Additionally, the ability to verbalize history of cataplexy, sleep paralysis, and hypnagogic hallucinations is limited. Judicious use of family history, sleep diaries, actigraphy, HLA typing, and cerebrospinal fluid (CSF) hypocretin-1 measurement, and polysomnography can aid in early diagnosis of suspected narcolepsy in this age group.

Narcolepsy–cataplexy at this age can mimic atonic seizures (Kotagal, clinical observation). Nevsimalova described a boy that she has followed for years who was noted to have cataplexy at 6 months, found to be HLA DQB1*0602 negative, and subsequently diagnosed with hypocretin-deficient narcolepsy due to a mutation in the hypocretin-1 gene. He suffered severe bulimia in early childhood, predominantly at night. Postpuberty he developed hypnagogic hallucinations, sleep paralysis, disrupted night sleep, automatic behavior, and behavioral disorders. He was the only child to

Table 6.2 Key features of childhood narcolepsy: difficult diagnosis

• Narcolepsy is a pediatric disorder, with a peak incidence in the mid- to late teenage years
• Accuracy of the history is limited by expressive ability of the child or parent report of cataplexy, sleep paralysis, or hypnagogic hallucinations descriptions
• Daytime napping is physiologic in preschool-age children; thus the multiple sleep latency is not applicable below the age of 6 or 7 years
• The MSLT may need to be repeated serially if there is a high suspicion of narcolepsy without sleep onset REM periods on nap opportunities
• CSF hypocretin may also be obtained to confirm the diagnosis in young children, children on medications that cannot be safely stopped, and children without sleep onset REM periods on MSLT
• Video clips from parents may help to document cataplexy

Table 6.3 Daytime sleepiness in children

• Reemergence of napping in middle of first decade
• Naps can be of variable length and not necessarily refreshing
• Sleepiness may lead to behavioral and cognitive dysfunction and impair academic function

present with the full tetrad of narcolepsy in her case series of 23 children [17, 23]. Additionally, Sharp and D'Cruz described a 12-month-old with hypersomnia which was later confirmed to be narcolepsy [24].

School-Age Children

School-age children are better able to describe the common signs and symptoms of narcolepsy. These include excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, hypnopompic hallucinations, and sleep paralysis. Additionally, children with narcolepsy experience poor school functioning, behavior problems, and decreased quality of life. These will be further described here and are listed in Table 6.3.

Excessive daytime sleepiness is the most universal and disabling characteristic of narcolepsy. School-age children are likely to present with daytime sleepiness, including sleep attacks (an irresistible urge to nap) during sedentary activities such as sitting in a classroom or reading. The consequences of sleepiness include impaired memory consolidation, decreased concentration, impaired executive functioning, and emotional disorders [25, 26]. Automatic behaviors (performing behaviors without recall) and mood swings have also been described [25, 26].

Excessive daytime sleepiness may manifest as reemergence of napping in a child who had previously stopped napping. Most children stop napping between the ages of 5–6 years, particularly with entrance into kindergarten; thus the MSLT has not been validated in this younger population. Naps in children with narcolepsy are often longer than those seen in adults (30–90-min duration), and in contrast to adults, children do not uniformly experience a refreshed feeling after the nap [26, 27].

Table 6.4 School problems reported in children with narcolepsy

• Falling asleep
• Poor grades/academic performance despite normal IQ
• Interpersonal conflicts with teachers and peers
• Conduct and emotional problems
• Difficulty making friends
• More absences from schools

Parents may not recognize daytime sleepiness until it starts affecting the child's mood, behavior, or academic performance. See Table 6.4. Moreover, daytime sleepiness can manifest as behavioral problems or poor performance in school. Teachers may mistake sleepiness for laziness. Sleepiness in children may mimic attention deficit hyperactivity disorder (ADHD) [28], oppositional behavior, or disruptive conduct disorder. It is important to recognize that young children may actually exhibit increased motor activity and disruptive behavior as a consequence of sleepiness in an attempt to stay awake [29].

Cataplexy is the most specific feature and the second most common manifestation of narcolepsy after excessive sleepiness. It is associated with hyperpolarization of spinal alpha motor neurons, active inhibition of skeletal muscle tone, and temporary absence of tendon reflexes. It was identified in 80.5 % of idiopathic narcolepsy and in 95 % of symptomatic narcoleptic patients by Challamel et al. [22]. Classic cataplexy in adults and children is similar, i.e., muscle atonia in response to emotional triggers such as laughter, surprise, anger, or fright. Cataplexy occurred within 3 months of onset in 85 % of 51 children [15]. However, children may also exhibit atypical cataplexy or atonia in situations not associated with an emotional trigger, such as tongue thrusting, and cataplectic gapes (weakness of jaw) may occur near onset of narcolepsy [30]. Another study found that some children will initially manifest persistent hypotonia and prominent facial involvement that will gradually develop into the more classic adult phenotype [31]. A study followed 39 patients with narcolepsy with video recordings while the children were watching funny videos. These move-

ments could be classified as "negative" if they included head drops, falls, tongue protrusion, and persistent facial or generalized hypotonia and "positive" if there was raising of the eyebrows, perioral and tongue movements, facial grimaces, swaying of head/trunk, stereotyped motor movements, and dyskinetic or dystonic movements. Near the onset of narcolepsy, an increase in all negative and positive motor movements, except for facial grimacing, occurred in the children with narcolepsy compared to a group of control children. Control children had an increase in the positive motor movements while watching the funny videos [31, 32].

Cataplexy in children can be subtle such as a head bob, jaw dropping open, and minor buckling of the knees, or it can be more pronounced with the child falling to the floor. The severity of cataplexy may be rated empirically on a Cataplexy Severity Rating Score: (1) moderate weakness (head drop/jaw drop), (2) maintain posture with external support, and (3) loss of posture and falls to ground [33]. Children may develop defense mechanisms to minimize the impact of cataplexy on their lives—some may avoid attending fun-filled and exciting events like birthday parties, whereas others may attend a birthday party but try to avoid smiling or laughing. These behaviors may over time impact the development of peer relationships (authors' opinion).

It is also difficult for children to provide a description of cataplexy, given its unusual nature and the embarrassment they may feel because of it. For example, Kotagal describes a 6-year-old girl with proven narcolepsy who denied any episodes of weakness, yet she would repeatedly fall whenever she jumped on a trampoline [34].

In most children with narcolepsy, cataplexy is more frequently observed close to disease onset. Since cataplexy is a defining hallmark of narcolepsy, when interviewing the child and parent, it is most important to ask open-ended questions to elicit a complete description of the first episode of cataplexy. This helps to distinguish true cataplexy from "weakness" or other vague answers to yes/no type questions regarding weakness or cataplexy. With the widespread use of smartphones, parents may bring in videos of their child having cataplexy events.

Hypnagogic or hypnopompic hallucinations are noted in 50–60 % of narcoleptic patients and are described as vivid, sometimes frightening, dreamlike images. They can be auditory or visual in nature. There is no difference in the presence of hypnagogic/hypnopompic hallucinations in children with narcolepsy with cataplexy versus the children with narcolepsy without cataplexy [35].

Sleep paralysis is described as an inability to move or speak when falling asleep or awakening from sleep. Both can be normal, but the child with narcolepsy is more likely to describe them as occurring regularly or on a daily basis.

Children may complain of disrupted nocturnal sleep. Sleep fragmentation is common in narcolepsy patients. This may be intrinsic to narcolepsy or due to periodic limb movements of sleep (PLMS) which are more frequently reported in narcolepsy patients. Sleep fragmentation may occur with or without electroencephalographic evidence of cortical arousal. (See earlier chapter for further discussion of PLMS in narcolepsy.) Another interesting manifestation of narcolepsy–cataplexy is the development of REM sleep without atonia or actual REM sleep behavior disorder [35].

Common concurrent sleep disorders include obstructive sleep apnea (OSA), restless legs syndrome, REM sleep behavior disorder, or periodic limb movements during sleep.

At least one sleep comorbidity (OSA, restless legs syndrome, REM sleep behavior disorder, or periodic limb movement during sleep) was present in 40 % of 31 children with the proportion rising up to 85 % for the group on patients older than 60 years [7]. In a study of patients ranging 12–80 years of age, total periodic limb movements during sleep were highest in patients with idiopathic RLS, and next highest in patients with narcolepsy with cataplexy and RLS, with PLMS equally distributed in NREM and REM sleep. RLS may be seen in 15 % of patients with narcolepsy with cataplexy [36].

In a study of 44 children with narcolepsy, only four (9 %) had a PLM index >5/h. A total of 16 (36 %) had a PLM index >0, with a mean PLM

index of 1.3/h [37]. It has been suggested that PLMS frequently occur in narcolepsy due to the dopaminergic pathway dysfunction. Children with any PLMS in this study were found to have a higher arousal index and shorter sleep latency on the MSLT nap opportunities [37]. Additionally, Young and colleagues describe PLMS in five of eight children with narcolepsy [38].

Behavioral, Psychosocial, and School Problems

Information is becoming available regarding behavioral manifestations in childhood narcolepsy. An example of a well-validated tool is the Conners Rating Scale, primarily used to assist with a diagnosis of ADHD but can also provide information on the consequences of sleepiness in children with suspected narcolepsy.

Multiple researchers, including Teixeira et al. have investigated the psychosocial problems at school as recalled by adults with narcolepsy [29]. One half of the 45 respondents recalled falling asleep in class. A third or more of respondents noted achieving less than capable performance, interpersonal conflicts with teachers, embarrassment due to symptoms, or inability to use their qualifications. Eleven percent recalled difficulty making friends and taking frequent days off [29]. Stores et al. assessed the psychosocial difficulties of 42 children with narcolepsy (mean age 12.4, range 7.3–17.9), 18 subjects with excessive daytime sleepiness unrelated to narcolepsy (EDS; mean age 14.2, range 5.1–18.8), and 23 unaffected controls (mean age 11.3, range 6–16.8) [39]. They found significantly higher scores on the Strengths and Difficulties Questionnaire in the narcolepsy and EDS groups. The domains of this questionnaire included peer problems, hyperactivity, conduct problems, emotional problems, and adverse impact on the family. As compared to healthy controls, both the narcolepsy and EDS group scored higher on the Child Depression Inventory. Children with narcolepsy and EDS also had more absences from school (means 6.4 and 5.3 days, respectively) as compared to controls (mean 1.3) and showed more problems on a composite educational difficulties score, suggesting that sleepiness in general, rather than narcolepsy per se, adversely influences the psychosocial and emotional health of the patients [39].

Academic performance may suffer in children with narcolepsy with cataplexy. For example, in a sample of 13 children with narcolepsy with cataplexy, seven children reported academic failure. After comprehensive neuropsychological testing, all 13 children had a normal full IQ with a mean of 104 (range of 87–115) according to the Wechsler Intelligence Scale for Children [40]. No particular neuropsychological pattern was identified in the children with narcolepsy [40]. School absenteeism was higher in obese children with narcolepsy. They also had more school difficulties [19].

Quality of Life

Quality of life was further investigated in a study of 117 subjects divided into children and adolescent categories. The narcoleptic children had lower health-related quality of life, vitality, general well-being, poorer self-image, less contact with parents, and lower school performance, when compared to control children. Narcoleptic adolescents also had lower quality of life index, lower physical well-being, and fewer friends and leisure activities than control children. Depression was the factor that most affected quality of life. Interestingly, however, there were no differences in health-related quality of life when comparing treated versus non-treated narcoleptic patients [19].

Metabolic Disturbances

Prominent weight gain has been reported in children following the onset of narcolepsy [15, 31]; up to 86 % of 51 children gained at least 4 kg within 6 months of onset [15]. Furthermore, obesity may occur in at least 25 % of all narcoleptic children [15]. In a study of 117 children with narcolepsy (81 % with cataplexy), 60 % were found to be obese. Obese children were younger at disease onset and at time of diagnosis of narcolepsy than nonobese children [41]. There was no difference in sleepiness severity or cata-

plexy between obese and nonobese children. There was an increased tendency toward night eating in the obese group [41]. Additionally, precocious puberty has also been identified in children with narcolepsy; in a series of 21 children, 3 (14 %) were observed to have precocious puberty [31]. In another study with 44 children with narcolepsy, 31 (74 %) of children were obese, with 25 (60 %) having a large increase in weight temporally related to the onset of narcolepsy. Twenty-two children showed signs of puberty, and 7 of the 21 (32 %) children were diagnosed with precocious puberty; nine (41 %) children had accelerated pubertal development. The authors note a younger age at onset of the first sign/symptom of narcolepsy is a predictor of precocious puberty [42].

Twin Studies in Narcolepsy

A combination of the genetic predisposition and acquired stress seems to trigger most cases of narcolepsy [43]. Case series of monozygotic twins provide the strongest evidence for an environmental trigger, with high discordant rates of up to 13/20 (65 %) [44–47]. For example, Honda describes a pair of twins, with one child developing narcolepsy–cataplexy at age 12 and the other twin developing narcolepsy at age 45 after suffering from emotional stress and sleep deprivation [46].

Secondary Narcolepsy

While the majority of narcolepsy is idiopathic, structural lesions of the diencephalon and rostral brainstem can precipitate secondary narcolepsy in those who are biologically predisposed. Case reports have documented the development of secondary narcolepsy in cerebellar hemangioblastomas, temporal lobe B-cell lymphoma, pituitary adenoma, third ventricular gliomas, craniopharyngioma, head trauma, viral encephalitis, ischemic brainstem disturbances, sarcoidosis, and multiple sclerosis [48–55]. Neurogenetic/metabolic disorders that can be associated with narcolepsy–cataplexy include Niemann–Pick disease type C, Coffin–Lowry syndrome, and Norrie disease. In general, children with these three conditions show severe brain dysfunction and other more specific neurologic findings (see differential diagnosis).

Role of Infections in Triggering Narcolepsy

A number of children diagnosed with narcolepsy have high prevalence of streptococcal throat infections, showing high levels of serum antibodies against streptolysin O [15, 56] or other infections. Additionally in China, there was increase in narcolepsy with cataplexy following the winter of 2009–2010 attributed to the H1N1 influenza pandemic. In early 2010, an increased incidence of narcolepsy was also detected in Finland and Sweden. A study showed an association between the pandemic H1N1 vaccination and narcolepsy with cataplexy by an odds ratio up to sixfold in children <18 years of age. Many of these children received the Pandemrix vaccine with the adjuvant ASO3 [56]. A similar increase in incidence in narcolepsy following the 2009 influenza vaccination efforts was not reported in the United States, likely because of use of a different influenza vaccine called Medimmune. It is possible that in individuals who were genetically susceptible to narcolepsy–cataplexy (on the basis of HLA DQB1*0602 positivity), the 2009 influenza infection or Pandemrix vaccine served as triggers for an immune-mediated disturbance that precipitated narcolepsy–cataplexy. This is still a hypothesis and has not been definitively proven.

Physical Examination

Most children with narcolepsy will have a normal physical examination. The child may be obese [15, 57, 58]. In addition, if observing a child during an episode of cataplexy, deep tendon reflexes should be absent or diminished. Determination of Tanner staging is useful to assist with interpreting MSLT results [59]. This can be done by questionnaire or visual inspection. Mental status examination may reveal impairments in digit span (indicative of a short attention span) and in recall of information.

Diagnosis

The diagnosis of narcolepsy is established on the basis of history and corroborated by testing, principally with the gold standard of a nocturnal PSG immediately followed by the MSLT [60]. With the change in diagnostic criteria, tools such as HLA typing or CSF hypocretin determination are becoming increasingly important. Additional tests are described in this section.

Polysomnography and Multiple Sleep Latency Test

The overnight PSG is used to screen for other potential sleep disorders such as OSA or PLMS and to ensure the child obtained adequate sleep the night before the MSLT [61, 62]. Prior to the overnight sleep study, patients should discontinue central nervous system acting medications, hypnotics, antidepressants, or other psychotropic drugs when medically safe, for approximately 2 weeks (or five half-lives) in order to minimize drug-induced changes in sleep architecture. With some medications such as fluoxetine that have a very long half-life, a 3- to 4-week medication-free interval would be appropriate. The child should attempt to maintain a regular wake-sleep schedule during at least the week prior to testing; this can be verified by sleep diaries or actigraphy. A urine drug screen can be performed when the child completes the overnight testing prior to MSLT.

The overnight PSG may show a sleep onset REM period (SOREMP) within the first 15 min of sleep onset, increased stage N1 sleep, and increased periodic limb movements [38, 63]. A shortened REM latency may also be seen. The recent changes in ICSD-3 note that a SOREMP occurring during the overnight PSG may be counted toward the requirement of two SOREMPs between the PSG and MSLT [6].

The MSLT provides quantitative and qualitative information on the degree of sleepiness and nature of the transition between wake and sleep stages, such as wakefulness directly to REM sleep, which is characteristic of narcolepsy. Nap opportunities should be started 2 h after the final morning awakening. The MSLT consists of five 20-min nap opportunities, provided at 2-h intervals in a dark, quiet room [64]. Measures should be taken to keep the patient from accidentally falling asleep between nap opportunities, such as playing a board game with the parent and keeping the child out of bed. The recruitment of parents in assisting with conduct of the MSLT thus becomes quite important. The American Academy of Sleep Medicine has published an evidence-based review that provides guidelines for the MSLT in childhood [65].

The MSLT has been validated for narcolepsy in adults when the mean sleep latency is less than 8 min and there are two or more SOREMPs [66]. Similar validation does not exist for the pediatric population. Generally accepted values in children with narcolepsy include a mean sleep latency of less than 5–8 min, with the presence of two SOREMPs. Chronic sleep deprivation and delayed sleep phase syndrome may masquerade as narcolepsy as patients may show short sleep latencies and multiple SOREMPs.

In a study of 27 prepubertal children, 3 (15 %) did not have a positive MSLT [15]. Serial MSLTs can be used to objectively follow patients with hypersomnia in whom the diagnosis of narcolepsy is uncertain initially but becomes gradually more apparent over time [6, 67].

The mean sleep latency on MSLT correlated with performances of alertness tasks for auditory and visual stimuli during neuropsychological testing in 13 children with narcolepsy with cataplexy [40].

Sleep Logs

Sleep logs or sleep diaries are helpful to quantify sleep and assess distribution of sleep. They should be completed a minimum of 1 week prior to the MSLT test.

Histocompatibility Antigen and Other Loci

The association between narcolepsy and HLA DR2 was reported in 1984 by Juji and coworkers in Japan [68]. As in adults, HLA typing is a useful diagnostic tool in children. In 2001, Mignot demonstrated a strong association of narcolepsy with HLA DQ antigens, specifically DQB1*0602 and DQA1*0102, which are present in >90 % of narcoleptic patients, as compared to a 12–38 % prevalence in the general population [69].

Patients who are negative for HLA DQB1*0602 are unlikely to exhibit low CSF hypocretin-1 levels. Correlation of narcolepsy with and without cataplexy and spinal fluid hypocretin-1 levels indicates that low levels of hypocretin are seen in those having narcolepsy with cataplexy [70, 71].

HLA typing is expensive and may not be covered by insurance carriers. More recently, three loci outside the HLA region were significantly associated with narcolepsy disease, including a strong signal in the T-cell receptor alpha [72]. This is yet to be further specifically investigated in children.

CSF Hypocretin Deficiency (Also Known as Orexin Deficiency)

Narcolepsy was shown to be tightly associated with hypocretin-1 (also known as orexin) deficiency in 2000. Nishino and others have shown that a CSF level less than 100 pg/mL carried a diagnostic sensitivity of 84.2 % and was almost always found in patients who are HLA DQB1*0602 positive and had narcolepsy with cataplexy [73]. In the absence of cataplexy, a patient may choose to undergo further testing for CSF hypocretin deficiency as seen in narcolepsy type 1, without the clinical presentation of cataplexy. The CSF hypocretin-1 assay should be considered in HLA DQB1*0602-positive cases when MSLT data may be difficult to obtain or interpret (such as preschool-age children) and when the patient is receiving REM-suppressant medications like selective serotonin reuptake inhibitors (SSRIs) or tricyclic agents (TCA) that cannot be stopped safely. Other circumstances include suspicion of insufficient sleep or other confounding sleep disorders. Currently, CSF hypocretin-1 measurement is limited to a few select centers nationwide. To date, studies have not been able to elicit consistent results from blood testing for hypocretin-1 levels.

Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI)

Imaging by CT or MRI evaluates for the presence of brain tumors or structural abnormalities as narcolepsy is especially rare in preschool or early school children.

Questionnaires for Assessing Sleepiness

Several questionnaires can be used to evaluate sleepiness in children including the Epworth Sleepiness Scale and Stanford Sleepiness Scale [60]. In addition, in children, a picture sleepiness scale has been validated in 345 children ages 4–7 years by Maldonado [74]. Other questionnaires also exist, such as the Cleveland Adolescent Sleepiness Questionnaire (CASQ), the School Sleep Habits Survey, and the Pediatric Daytime Sleepiness Scale (PDSS) [75–77]. The CASQ and PDSS have however been validated only in children with sleep-disordered breathing and not primary hypersomnias like narcolepsy. Nevertheless, they are easy to use and provide some measure of quantification. The Stanford Center for Narcolepsy Sleep Inventory is a validated questionnaire predictive of cataplexy and also evaluates for the other symptoms of narcolepsy; it can be completed by parent, child, or together [78].

Maintenance of Wakefulness Test (MWT)

The first study to utilize the MWT assessed the efficacy of medication in 10 children with narcolepsy (six with cataplexy). They found a median mean sleep latency of 16 min (range 5.8–40 min)

on 13 tests; only six tests showed a mean sleep latency >20 min. Additionally three patients had SOREMPs. In seven children, results of the MWT influenced medication changes [79].

Actigraphy

Actigraphy may be a supplemental tool for the assessment in narcolepsy. Two studies have demonstrated the ability to distinguish between non-medicated patients with narcolepsy and control patients. Additionally, actigraphy can be helpful to assess insufficient sleep, which is included in the differential diagnoses of narcolepsy [80].

Differential Diagnoses

Insufficient nocturnal sleep is by far the most common cause of daytime sleepiness in the adolescent [81]. Sleep length is often influenced by circadian factors such as the physiologic delay in dim light melatonin release in teenagers and the resulting postponement in sleep onset time to 10:30–11:00 p.m. [82]. On most school days when the child has to awaken by 5:30–6:30 a.m., this leads to sleep deprivation and daytime sleepiness [81, 82]. Carskadon and coworkers have documented SOREMPs during MSLTs in 12 of 25 healthy adolescents [81, 82].

Inadequate sleep hygiene, such as cell phone use, text messaging, playing video games, and watching television, leading to shifted bedtimes and wake times can worsen sleepiness [83]. In addition, *the use of illicit drugs*, stimulants, prescription medications, over-the-counter hypnotics, and sedating antihistamines should also be considered when evaluating sleepiness.

In narcolepsy, patients frequently experience concurrent weight gain and increasing BMI with a higher likelihood of developing diabetes and OSA. The spectrum of non-apneic *obstructive hypoventilation* may be considered. Additional medical and metabolic disorders should be considered including anemia or thyroid evaluations.

When cataplexy is noted, clinical conditions that should be considered include Niemann–Pick disease type C, Norrie disease, Prader–Willi syndrome, or Coffin–Lowry syndrome. Niemann–Pick disease type C is a neurovisceral storage disorder which presents with dystonic gait abnormality, motor incoordination, downward gaze paresis, and cataplexy [84]. Norrie disease is an X-linked recessive disorder characterized by retinal atrophy, microphthalmia, blindness, and severe mental retardation [85]. Cataplexy is a minor manifestation of the disorder, which is due to almost complete absence of monoamine oxidase. Coffin–Lowry syndrome is associated with X-linked mental retardation, hearing loss, pugilistic nose, large ears, tapered fingers, hypertelorism, and anteverted nares [86]. See Table 6.5.

Table 6.5 Differential diagnosis of narcolepsy in children

• Inadequate sleep hygiene
• Insufficient sleep
• Delayed sleep phase syndrome
• Depression
• Structural brain lesions leading to hypersomnolence
• Idiopathic hypersomnia
• Obstructive hypoventilation

Management

Given that narcolepsy is a lifelong disorder that often requires multiple medications, it is imperative that the diagnosis be accurate. It is important to individualize therapy by targeting the symptom(s) most bothersome to the patient. The key management strategies are listed in Table 6.6.

Behavioral strategies include regularizing sleep–wake schedules, taking planned daytime naps when sleepiness peaks, exercising regularly, and remaining engaged in after school sports. One or two 30-min planned naps (or longer) per day may help to offset sleepiness [87] but are rarely sufficient to completely treat sleepiness. Parents should monitor their child closely for signs/symptoms of depression. Emotional support through counseling is suggested for most patients given the rarity and complexity of the disease and its lifelong nature. Driving should be

Table 6.6 Management strategies in children

• Assist the child in developing coping strategies
• Provide emotional support
• Encourage a regular sleep–wake schedule, including strategic timing of naps
• Sit in the front row of the classroom
• Use exercise to counter sleepiness
• Medications to enhance alertness
• Medications to treat cataplexy
• Discuss safety precautions—child should avoid activities which may trigger cataplexy and injury to them, such as climbing monkey bars or cooking
• Screen for and treat coexisting depression
• Screen for and treat precocious puberty. Management in adolescents suggested edit MG
• Limited, well-supervised driving
• Avoid alcohol
• Vocational guidance to assist in choice of a profession

discussed with adolescent patients. In general, limited driving may be allowed on a strict, case-by-case basis in appropriate conditions. In the series by Broughton et al. [88] and Leon-Munoz et al. [89], 66–72 % of adults reported falling asleep driving. An additional 16–28 % of those surveyed reported experiencing cataplexy when driving.

Prepubertal children's symptoms may be managed by monotherapy, whereas peri- and postpubertal children often require more than one medication to adequately control symptoms [15]. First-line medications include methylphenidate, venlafaxine, modafinil, and sodium oxybate, all on off-label basis. See Table 6.7.

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or sertraline may be indicated when emotional and behavioral problems are superimposed on cataplexy. Caution should be used with SSRIs in children, given the "black box" warning for increased suicidal thinking and behavior during short-term treatment of children and adolescents with major depressive disorder and other psychiatric disorders [90].

Table 6.7 Medications commonly used ("off label") to treat narcolepsy and comorbidities in childhood

Symptom	Drug (trade name)
Daytime sleepiness	Modafinil (Provigil)
	Armodafinil (Nuvigil)
	Methylphenidate hydrochloride
	Ritalin
	Ritalin SR
	Ritalin LA
	Methylin (oral solution)
	Concerta
	Metadate CD
	Metadate ER
	Daytrana (skin patch)
	Dexmethylphenidate hydrochloride
	Focalin
	Focalin XR
	Dextroamphetamine (Dexedrine, Dextrostat)
	Methamphetamine (Desoxyn)
	Amphetamine/dextroamphetamine
	Mixture (Adderall)
	Adderall XR
	Lisdexamfetamine (Vyvanse)
	Sodium oxybate (Xyrem)
Cataplexy and emotional problems[a]	Venlafaxine (Effexor)[a]
	Fluoxetine (Prozac)[a]
	Sertraline (Zoloft)[a]
	Clomipramine (Anafranil)
	Imipramine (Tofranil)
	Protriptyline (Vivactil)
	Sodium oxybate (Xyrem)
Periodic leg movements	Elemental iron
	Gabapentin (Neurontin)
	Clonazepam (Klonopin)
	Ropinirole (Requip)
	Pramipexole (Mirapex)

[a]Antidepressant medications are associated with increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorder
Stimulant medications are not recommended in children under the age of 6 years as the safety and efficacy in this age group have not been established

Pharmacotherapy of Daytime Sleepiness The objective is to enhance alertness to the point of effective daytime functioning in the classroom, home, and the social setting with a minimum of side effects. Currently there is no Food and Drug Administration (FDA)-approved medication to treat the hypersomnolence of children with narcolepsy under age 16 years. In adults, there have

been several studies that support the efficacy of traditional stimulants in the treatment of narcolepsy [91]. Drugs commonly used on an "off-label" basis are shown in Table 6.7. Modafinil, stimulants like methylphenidate, various preparations of amphetamines [90–94], and sodium oxybate (Xyrem) [95] are most commonly used to enhance alertness. Modafinil has not been systematically studied in the pediatric setting. Small case series of children with narcolepsy or other conditions causing hypersomnia show that children tolerate modafinil well, with improvement of daytime sleepiness [96–98]. The half-life is about 15 h; it can be given in a single dose upon awakening or divided among two doses. Common side effects include headache and nausea. On rare occasions, Stevens–Johnson syndrome may also develop. Modafinil can lower the potency of concurrently administered oral contraceptives, thus counseling of young women with narcolepsy in this regard is important. With regard to efficacy, the open-label study of Ivanenko et al. [96] provides Level 4 evidence about utility of modafinil in childhood narcolepsy/idiopathic hypersomnia. In 13 children, treatment with modafinil led to subjective improvement in sleepiness as reported by the parents. There was also objective improvement on the MSLT, with the mean sleep latency rising from a baseline of 6.6 +/− 3.7 min to 10.2 +/− 4.8 min on treatment with modafinil.

There have been no head to head studies comparing the efficacy of modafinil to the traditional psychostimulants, which are salts of methylphenidate or dextroamphetamine [90]. Some degree of tolerance may develop over months to years to the alertness-enhancing effects of methylphenidate and dextroamphetamine, necessitating gradual dose escalation. The general side effects of stimulants range from loss of appetite, poor weight gain, nervousness, tics, headache, and insomnia. In general stimulants are not recommended in children less than age three. Safety below age six has not been established in amphetamine preparations of Dexedrine®, Dextrostat®, Adderall®, or Vyvanse®. These amphetamine derivations are also not recommended in children with known structural cardiac defects. The half-life varies depending on age, 9 h in children aged 6–12 years and 11 h in children aged 12–17 years, which will affect dosing [90]. Methylphenidate preparations including Ritalin®, Concerta®, Metadate®, and Daytrana® carry similar warnings, with additional data suggesting slowing of growth rate. Half-life is typically 2–4 h. Daytrana® comes with a potential advantage as it is a skin patch formulation.

Pharmacotherapy of Cataplexy Mild cataplexy that is not leading to falls or socially embarrassing situations may not need therapy. Cataplexy that is bothersome to the patient can be treated with SSRI agents, selective noradrenergic reuptake inhibitors (SNRI), and TCA [90]. However, no antidepressant has been FDA-approved for treating cataplexy. These agents might also ameliorate hypnagogic hallucinations and sleep paralysis. The side effects of TCA drugs include daytime sleepiness, orthostatic hypotension, weight gain, anorexia, dry mouth, and diarrhea. In adults, sodium oxybate reduces cataplexy, daytime sleepiness, and nocturnal sleep disruption. Black et al. showed that modafinil and sodium oxybate have a synergistic relationship in controlling sleepiness and cataplexy when compared to placebo or each medication individually [99]. Sodium oxybate may increase slow wave sleep and consolidation of sleep, with many patients reporting refreshed sleep upon awakening. The safety and effectiveness have not been established in patients below 16 years of age. Caution is warranted with the use of sodium oxybate owing to its abuse potential. It is tightly regulated with only one central pharmacy across the United States. Exacerbation of concurrent sleep apnea, depression, enuresis, constipation, and tremor are potential adverse effects. Due to the short half-life of 0.5–1 h, the preparation of sodium oxybate must be given in two doses, the first one immediately before bedtime, with typically an alarm set to awaken the patient to take the second dose 2.5–3 h later [99]. Sodium oxybate has been successfully used in children in small series [33, 100]. These studies show sodium

oxybate decreased the frequency and severity of cataplexy. Side effects occurred in 6 (40 %) of the 15 children. Academic improvement was observed in 11 (73 %) of the children while taking sodium oxybate [100]. Before prescribing sodium oxybate, it is important to ensure strong family/parental support and low potential for drug abuse/diversion. A multicenter, prospective study on the safety and utility of sodium oxybate in children with narcolepsy–cataplexy is now being launched.

Temazepam

In a case report of two children and five adults with narcolepsy with cataplexy, temazepam was prescribed in an effort to decrease arousals and consolidate sleep. This resulted in a decreased Epworth Sleepiness Scale score in one child. Additionally, one child reported improvement in the frequency of cataplexy [101].

New drugs on the horizon include histamine receptor inverse agonists/antagonists which may enhance alertness, such as pitolisant [102, 103]. In a preclinical study, ATC 0175, a melanin-concentrating hormone antagonist has been suggested as possibly being able to counter sleepiness and cataplexy [104]. Intranasal administration of human recombinant hypocretin-1 might also hold some promise. Baier et al. found that it reduced REM sleep percentage and the number of transitions from wakefulness into REM sleep [105].

Immunotherapy

Owing to possible underlying dysregulation of the immune system, narcolepsy–cataplexy subjects have been treated with intravenous immunoglobulin G soon after the diagnosis has been established. Lecendreaux et al. treated a 10-year-old boy [106], while Hecht et al. treated an 8-year-old boy [107]. From the long-term standpoint, however, the results of intravenous IVIG have been mixed and inconclusive. In three of the four subjects treated in an open-label manner by Dauvilliers et al. [108], there was improvement in cataplexy but not in sleepiness [109]. The limitations of the immunotherapy studies include the small sample size, open-label design, and placebo effect.

With treatment and over time, it is likely the signs/symptoms of narcolepsy may gradually improve over decades. For example, Honda and colleagues followed 329 patients up to 40 years, observing spontaneous improvement with a little over half of 133 patients noting no further cataplexy [110]. Similar percentages were provided for hypnagogic hallucinations and sleep paralysis.

Lastly, education is a tool which can help the patient learn to manage their disease with the least amount of disruption to their daily lives. For example, the Narcolepsy Network (www.narcolepsynetwork.org) is a private, nonprofit resource for patients, families, and health professionals. There is also the National Narcolepsy Registry. More information can be found at www.ninds.nih.gov/disorders/narcolepsy.

Conclusions

While many aspects of childhood narcolepsy resemble those of adults, some differences that standout include the subtle and somewhat nonspecific initial manifestations of hypotonia, fatigue, mood swings, inattentiveness, weight gain, and the limited reliability of the history. Why some children show significant cataplexy and SOREMPs right at the onset while others manifest a gradual progression of intrusion of REM sleep phenomena onto wakefulness over months remains unknown. Also not known is the long-term difference if any between the outcome of those who are HLA DQB1*0602 positive versus those who are negative for this haplotype. Molecular mechanisms underlying the loss of hypocretin secreting neurons from the hypothalamus are being rigorously studied. Hopefully, spinal fluid hypocretin-1 assays will become more easily available. Large pharmacokinetic, safety, and efficacy studies of drugs used to treat sleepiness and cataplexy in children are needed.

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Narcolepsy in the Older Adult

7

Natalie Cornay-Manalo and Hrayr Attarian

Introduction

Narcolepsy is generally considered an illness of youth because its incidence peaks around the second to third decade of life. In an Olmsted County-based epidemiological study, the median age of onset was found to be 16 years, with a range from 4 to 56 and a 90th percentile of 33.4 years [1]. Another study comparing two large populations in Quebec and France found the mean age of onset at approximately 24 years with a bimodal distribution of incidence. The first peak was at age 14 and the second peak at age 35 [2]. There have been a handful of cases that reported onset after age 35 and well into the seventies.

Narcolepsy is still not as well recognized a syndrome as it should be, given its incidence (0.05 % in Western Europe [3] compared to 0.07 % worldwide prevalence for multiple sclerosis (MS), a much better known entity) [4]. There is a significant delay in diagnosis of an average of 6.5–22 years from the onset of symptoms with a range of <1–60 years [5]. Not all cases, therefore, diagnosed with narcolepsy after age 35 are due to late onset of symptoms; some are also due to delay in diagnosis. A third, smaller group of late-onset narcolepsy consists of cases referred to as symptomatic narcolepsy or narcolepsy-like symptoms due to other medical conditions.

As narcolepsy is a chronic illness and we are an aging population, more and more people over the age of 40 have been living with this condition. According to a multination European study, 43.4–48.7 % of subjects with narcolepsy were over the age of 45 [6]. It is, therefore, important to recognize the clinical challenges age confers on the diagnosis and treatment of this disease.

This chapter presents narcolepsy cases with onset after age 35 or diagnosis after this age despite an earlier onset of symptoms, as well as some of the reasons behind delays in diagnosis. We also summarize the different medical problems that have secondarily caused narcolepsy and conclude with the treatment challenges facing older adults with the condition and their physicians.

Narcolepsy Onset After Age 35

Rye et al. reported seven patients, as part of a series of 41 diagnosed later in life, whose symptoms started after age 40. All seven had narcolepsy without cataplexy [7]. Unfortunately, the

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above paper does not mention the total number of narcolepsy patients diagnosed at the center over the same 3-year period during which these 41 patients were presented. Population studies from different areas show extremely rare incidence of narcolepsy starting after age 40. In the Olmsted County study by Silber et al., there was only one patient with narcolepsy and cataplexy out of 72 (1.4 %) who had onset of symptoms after age 40; this patient was in his mid-fifties [1]. In a study comparing two populations in Montpelier, France, and Montreal, Canada, only a few cases out of a total of 519 had their symptoms start after age 35 and none after age 40 [2]. Other population studies concur with the above finding, showing that the incidence of narcolepsy with or without cataplexy after age 40 is about 2–6 % [8–10].

There are also sporadic case reports of narcolepsy with the onset of symptoms after the age of 40. The earliest such case was reported in 1987 in the UK by Kelly et al. They reported two cases: one who had narcolepsy with cataplexy starting at age 72 and the other who had narcolepsy without cataplexy starting at age 85 [11]. Both cases were initially misdiagnosed as having complex partial seizures and treated with antiepileptic drugs (AEDs). In both the cases, obstructive sleep apnea (OSA) was also suspected because of their age despite the classic presentation of sleep attacks and cataplexy. In 2005, Chen et al. published another case of narcolepsy with cataplexy with the onset of symptoms at age 60, in which the patient was also misdiagnosed as having temporal lobe epilepsy and treated with AEDs [12].

In 2006 we reported the oldest case of new-onset narcolepsy with cataplexy with symptoms starting at age 74 [13]. This patient was also erroneously treated with AEDs and underwent testing to rule out OSA and was even given a therapeutic trial of empiric CPAP. In 2014 Panda and Krishnamurthy et al. independently reported two cases of narcolepsy with severe cataplexy (the first was described as status cataplecticus) both with onset in the 6th decade [14, 15]. The severe cataplexy in these cases is unusual because with most cases of later onset narcolepsy, the EDS and cataplexy are milder [16].

Interesting parallels can be seen among many of these cases. Several were treated with AEDs prior to diagnosis, and several were thought to have OSA, in addition to possible seizures. Interestingly, children under 10 presenting with narcolepsy are also often misdiagnosed as having seizures [17].

These parallels highlight the fact that narcolepsy in the older individual is still not considered in the differential diagnosis despite clear, textbook descriptions of cataplexy and sleep attacks in many of the cases. It is important to keep an open mind when evaluating older patients (and children under 10) with new-onset daytime sleepiness with or without "unusual spells" because despite the age it still could be narcolepsy.

Case 1

A 65-year-old man started having episodes of brief knee weakness when excited and persistent EDS in his mid- to late 20s. He thinks both symptoms started simultaneously but is not absolutely sure. Shortly afterwards, he developed infrequent episodes of sleep paralysis especially when napping along with auditory hypnopompic hallucinations. It took him a couple of years to seek medical attention. For the next 10 years, he was unsuccessfully treated for anxiety and depression. The falls were attributed to his preexisting congenital spinal stenosis. He finally was referred to a sleep center where he underwent an overnight sleep study without a MSLT and the next day was diagnosed with narcolepsy. He was started on methylphenidate 20 mg slow release in the morning and then another two tablets of 10 mg immediate release methylphenidate as needed in the late morning and every afternoon. Up until 6 years ago, this was enough to control his EDS. His cataplexy remained under partial control with protriptyline 10 mg tablets five times per day. He was content with the control as long as he was able to ride his motorcycle without falling. Over the past 6 years, he developed loud snoring, nocturia, and severe back pain which led him to not be as physically active and to put on weight. His cataplexy also got a bit worse with his worsening EDS.

When he presented to our sleep center, he was sleeping from 10:30 p.m. to 7:00 a.m. every day and taking two to three brief 5- to 10-min naps. His Epworth sleepiness scale score was 23/24. His sleep paralysis and hypnopompic hallucinations were no longer bothersome and occurred very rarely. He also was drinking four to five 12 ounce cups of coffees a day.

In addition to his narcolepsy medications, he was taking omeprazole for gastroesophageal reflux, gabapentin for low back pain, and a statin for his hyperlipidemia.

On examination, the remarkable findings were a body mass index of 30.2 kg/m^2, blood pressure of 140/95 mmHg, and an antalgic gait because of back pain. Otherwise, the complete physical and neurological examination was normal.

An overnight sleep study was performed 2 weeks later that revealed moderate obstructive sleep apnea (OSA), with an apnea/hypopnea index of 20.2/h and a nadir oxyhemoglobin saturation of 84 %. He had early REM sleep. He was treated with CPAP and a pressure of 7 cm of H20 completely controlled the OSA.

Two months of using CPAP only modestly improved his EDS. He was due to come in to have his medications adjusted but suffered angina and was admitted to the hospital and underwent two vessel coronary bypass graft complicated by transient ischemic attack and arrhythmias. The latter was attributed to protriptyline so his dose was reduced to 20 mg a day, which did not control his cataplexy at all so it was discontinued altogether. He recovered from his surgery quite well and was started on Xyrem at 3 g a night. He had nausea with it and had no control of his cataplexy which started occurring multiple times a day even when only minimally excited. Xyrem dose was increased to 4.5 g and then to 6 g a night, and although his nausea subsided and the cataplexy only marginally improved, his blood pressure which was under good control on lisinopril started creeping up. Xyrem was discontinued, and the blood pressure control improved once more. His methylphenidate was also tapered off after his surgery, and he was started on modafinil. At 200 mg three times per day, his EDS was well controlled. For his cataplexy he was tried on sertraline, and at 75 mg a date his cataplexy was reduced by 50 % but still not enough for him to ride his motorcycle which was his main hobby after retirement. Higher dose of sertraline caused sexual dysfunction with no improvement of his cataplexy. Clomipramine was introduced at 25 mg once-a-day dosing. The goal was to taper him off sertraline once clomipramine reached a therapeutic dose, but on 50 mg of clomipramine and 75 mg of sertraline and 600 mg of modafinil and his CPAP, both his EDS and cataplexy came under excellent control. At his last visit, to which he rode his motorcycle, his symptoms were under control for over a year on the above regimen.

Delayed Diagnosis

One of the major reasons a good proportion of narcolepsy sufferers present later in life is because of delayed diagnosis. The mean number of years from onset to diagnosis has been reported to be 15 with a range of 1–61 in one UK study [18], 17 years in a Canadian study [19], and 9.9 ± 10.1 years with a range of 0–59 years in a Japanese study [20]; an Austrian paper reported a mean of 6.5 year and a range of 0–39 [5], and a few US papers have cited 10–14 years as the mean [21, 22]. Only about 15–30 % of people with narcolepsy are diagnosed and treated, and nearly half first present for diagnosis after the age of 40 years [7, 23]. According to a landmark paper published in 1994, approximately 85 % of narcolepsy patients go through life undiagnosed [24].

Factors that influence the delay are (1) the year of presentation to a medical professional with the initial complaint, since in the 1980s there has been more awareness about the condition among physicians, leading to a more timely diagnosis; (2) the onset of symptoms, with those presenting before teens and after age 30 less likely to be diagnosed in a timely fashion; and (3) the lack of cataplexy or ancillary symptoms [17, 23]. The severity of symptoms may also hasten proper diagnosis, and some patients with long-standing mild daytime sleepiness may seek medical attention after developing a comorbid disorder that increases the severity of daytime sleepiness [23].

Cultural variables also play a role in shaping the presentation of the syndrome, especially when it comes to daytime sleepiness. Depending on the cultural background, different people may complain more of fatigue or malaise than sleepiness, and this could also delay diagnosis. Gender may also affect time to diagnosis. A 2014 single-center study found that despite similar presentations most men were diagnosed within 16 years of symptom onset compared to 28 years for most women [25].

Interestingly, in a recent retrospective study in Japan, 58 % of patients reported that they first became aware of the concept of narcolepsy not from their doctors but from the media [20]. Only 22 % of patients were initially told about the condition by their physician. With the Internet now becoming an important source of medical information for patients, awareness among patients themselves may lead to earlier diagnosis. The Awareness and Knowledge of Narcolepsy (AWAKEN) survey queried a 1000 US adult lay people, 300 primary care physicians, and 100 sleep medicine specialists (36 board certified). Overall 70 % of the lay public had heard of narcolepsy. Only 22 % of sleep specialists (7 % of PCPs) could identify all five major symptoms of narcolepsy from a list of symptoms, and only 42 % of sleep specialists felt confident to make the diagnosis of narcolepsy [26].

Another important variable is the impact of age on the results of objective testing which may make the diagnosis of an older individual more difficult. The Multiple Sleep Latency Test (MSLT) is the gold standard for the diagnosis of narcolepsy, and since 2005 a mean sleep latency of less than 8 min with two or more sleep onset REM periods (SOREMPs) is considered diagnostic of it [27]. Prior to 2005 the pathognomonic mean sleep latency was considered to be less than 5 min. These numbers are based on studies that primarily included narcolepsy patients in the typical age group of late teens to early 30s. Dauvilliers et al. showed that there was a significant progressive decrease in the number of SOREMPs with age and a progressive increase in the mean sleep latency on the MSLT as a function of age [28] (see Fig. 7.1).

The former, however, was not associated with changes in REM latency at night, in contrast with the classic decrease of REM latency in the non-narcoleptic aging population [28]. Nevsimalova et al. in 2013 found no significant difference in MSLT sleep latency or number of SOREMPs between children and adults with narcolepsy; they state, however, that the higher portion of patients with narcolepsy without cataplexy in the childhood group may account for this lack of difference as a higher number of SOREMPs and shorter sleep latency is associated with narcolepsy with cataplexy [29]. In general there is also a progressive decrease in cataplexy attacks with age [28, 30] and a decline in the severity of sleep paralysis and hypnagogic hallucinations [30].

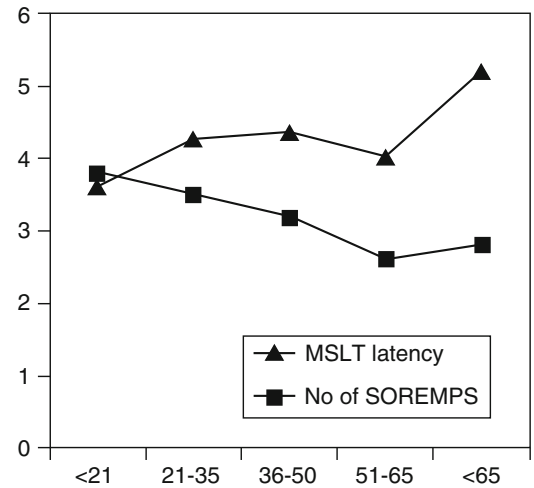

Fig. 7.1 Age groups vs. MSLT latency in minutes and number of SOREMPs (Adapted from Dauvilliers et al. [28])

Subjectively, however, there is no real difference in the degree of excessive daytime sleepiness (EDS) across the age spectrum [6, 30]. Nor is there any difference in the cognitive problems primarily related to attention or in the sleep disruption at night [6]. Another symptom of narcolepsy that often goes undiagnosed is dream-enacting behavior or REM sleep behavior disorder (RBD). RBD tends to occur in about one-third of narcoleptics and may have a higher incidence in the 40 plus age group [31] though a more recent study did not find a significant difference in incidence between age groups [16].

These "atypical" diagnostic features may be yet another reason why older adults with narcolepsy are less likely to receive a timely diagnosis.

Case 2

A-53-year-old woman presented to the sleep center, referred by her neurologist for 30-year history of excessive daytime sleepiness (EDS). She first presented to her primary care physician's office at age 25 with a 2-year history of EDS. After a preliminary workup was negative, she was sent to a sleep center for evaluation. A polysomnogram revealed mild, primarily positional obstructive sleep apnea (OSA) with an apnea hypopnea index (AHI) of 5.4/h. She was titrated on CPAP and compliantly used it for a year, but because there was no change in her symptoms, she stopped using it.

About a year ago, she developed frequent episodes of dream-enacting behavior during one of which she punched her husband. She also endorses long-standing sleep paralysis and hypnopompic hallucinations, although these occur less frequently now than they used to in the past. She does not recall having any cataplexy-like episodes. Her Epworth Sleepiness Scale is 20/24. Physical exam and a brain MRI (done for headaches by her neurologist) are both normal. Repeat PSG shows resolution of her OSA (she has lost 20 lbs recently) with an AHI of 1.0/h and elevated muscle tone in REM sleep or REM sleep without atonia (RSWA). Multiple Sleep Latency Test (MSLT) showed a mean latency of 5.6 min with 3 sleep onset REM periods (SOREMP).

Treatment was instituted with armodafinil 250 mg a day and 3 mg of melatonin at bedtime for the REM sleep behavior disorder. Follow-up visit revealed a satisfactory control of symptoms.

Symptomatic Narcolepsy

Over the years there have been several case reports of narcolepsy or narcolepsy-like syndromes occurring in a variety of illnesses. Some of these are in people of age 40 and above.

The most well-recognized association is with head trauma. One study found a narcolepsy prevalence of 6 % in a group of traumatic brain injury patients. The mean age of those with sleep problems was 43.05 years. There was no correlation between the presence of a sleep problem and the severity of the trauma [32]. In a meta-analysis by Mathius and Alvaro, 21 studies that included 1706 patients with TBI were analyzed. The authors comment that it is difficult to determine the true prevalence of sleep disorders post-TBI because of different methodologies of studies, but they estimate that 50 % of TBI patients had sleep disturbance and 25–29 % had a diagnosis of sleep disorder made after their TBI. Narcolepsy was diagnosed in 4 % and daytime sleepiness was reported in 27 %. The age of those diagnosed with narcolepsy was unavailable, but the mean age among the total number of participants in whom data on age was available was 35.3 [33].

Another reported association is with Parkinson disease (PD) and other neurodegenerative disorders. PD and other synucleinopathies are well-known causes of EDS and RBD, two entities commonly seen in narcolepsy. In a recent study patients with probable Lewy body dementia (a synucleinopathy) were found to have low CSF hypocretin concentrations versus patients with Alzheimer's type dementia and non-demented controls [34]. Another study showed a significant deterioration of the hypocretin neurons in patients with progressive supranuclear palsy [35]. Weinecke et al. compared sleep laboratory tests of patients with Parkinson's disease with that of patient's with narcolepsy with cataplexy and with matched controls. They found that nocturnal sleep efficiency was worse in patients with

Parkinson's disease than in controls or narcoleptics. While excessive daytime sleepiness was most severe in narcoleptics, objective measures of sleepiness were correlated with decreases in CSF hypocretin in PD patients suggesting that hypocretin cell loss may contribute to excessive sleepiness in PD patients [36]. There are numerous case reports of patients with a history of PD developing narcolepsy late in life.

Sleep disturbances including some with features of narcolepsy (especially EDS) are also prevalent in Alzheimer's disease (AD) [37]. Fronczek et al. investigated hypocretin neuron loss in patients with Alzheimer's disease (AD). They quantified the total number of hypocretin-1 immunoreactive neurons in postmortem hypothalami of AD patients and found them to be decreased by 40 % compared with controls. They also examined the postmortem spinal fluid of 25 patients with AD and 24 controls and found that the levels of hypocretin 1 were lower in patients with AD (by 14 %). Two patients in the AD group that had symptoms of severe EDS had especially low CSF hypocretin-1 levels. They concluded that the hypocretin system is affected in AD and may explain some of the sleep disorders seen in AD [38].

Other conditions associated with late-onset secondary narcolepsy (either with MSLT evidence or low CSF hypocretin) have been elegantly summarized in a 2005 paper by Nishino and Kanbayashi and include a case of hypothalamic tumor (age of onset 65), two brain stem infarcts (ages 40–45), two of encephalitis (ages 40 and 65), two of MS (ages 43–45), three paraneoplastic syndromes (ages 38–67), a 65-year-old with Hashimoto's encephalopathy, and a 38-year-old with acute disseminated encephalomyelitis (ADEM) [39]. Since 2005 there have been several additional case reports as well and these include the following: Whipple's disease with narcolepsy in a 45-year-old man [40], a pontine stroke in a 67-year-old man followed by isolated cataplexy and RBD [41], and a 55-year-old man with a Ma1 and Ma2 paraneoplastic syndrome due to a tonsillar carcinoma [42]. None of these had hypocretin levels checked. Other reported cases of symptomatic narcolepsy include neurocysticercosis in a 54-year-old man [43]; a case of brain stem encephalitis with a mediotegmental lesion in a 30-year-old man [44], both with normal CSF hypocretin levels; and MS in a 37-year-old woman with low CSF hypocretin levels [45].

Recently, there have been reports of an association between narcolepsy and N-methyl-D-aspartate receptor (NMDAR) antibody positivity. Tsutsui et al. examined 5 patients with narcolepsy with severe psychosis and found 3 of the 5 to be positive for anti-NMDAR. The first of these was a 58-year-old man with 15-year history of PD who presented with EDS since age 55 along with hypnagogic hallucinations followed 2 years later by delusions and auditory hallucinations. He had an abnormal MSLT and a low CSF hypocretin. The two other anti-NMDAR patients were women. Psychosis followed the onset of their narcolepsy symptoms by 3–30 years. The authors unfortunately do not specify the age of onset of narcolepsy. Ten patients with narcolepsy but without psychosis were also checked for antibody positivity and 2 out of 10 were found to be positive for anti-NMDAR. None of the antibody-positive patients had symptoms typical of encephalitis (seizures or autonomic dysfunction) [46].

Iatrogenic narcolepsy has also been described in a few older individuals. Dempsey et al. described a 60-year-old man who developed atypical cataplexy (not triggered by emotion but occurring spontaneously) and EDS two weeks after completing radiotherapy for a pituitary adenoma. A MSLT confirmed the diagnosis of narcolepsy with a mean sleep latency of 6.4 min and two SOREMPs. His CSF hypocretin levels were normal [47].

Two other cases of radiotherapy-induced narcolepsy were reported as part of an eight case series of secondary narcolepsy in 2001. Both had typical cataplexy, and one had MSLT-confirmed narcolepsy. No information is available on their age of onset or hypocretin levels although only one out of all the 18 cases was above 35 years of age (45) at the time of diagnosis [48].

Another example of iatrogenic narcolepsy with cataplexy was described by Nissen et al. in a 55-year-old woman who presented with EDS and typical cataplexy after discontinuation of the

Table 7.1 Symptomatic narcolepsy cases

Primary condition	Age	Gender	MSLT	Hypocretin	Reference
Radiation for pituitary adenoma	60	M	Abnormal	Normal	Dempsey [47]
Effexor withdrawal	55	F	Abnormal	Normal	Nissen [49]
Hypothalamic tumor	65	F	Abnormal	Low	Nokura [53]
Pontomedullary infarct	40	M	Abnormal	Normal	Bassetti [54]
Thalamic infarct	45	M	Abnormal	Normal	Nokura [53]
Rasmussen's encephalitis	40	M	Abnormal	Low	Lagrange [55]
Limbic encephalitis	65	M	Not done	Low	Yamato [56]
Anti-NMDAR-associated encephalitis	55	M	Abnormal	Low	Tsutsui et al. [46]
Anti-NMDAR-associated encephalitis	37	F	Abnormal	Low	Tsutsui et al. [46]
Neurocysticercosis	54	M	Abnormal	Normal	Watson [43]
PD	69	M	Abnormal	Normal	Overeem [57]
PD	64	M	Abnormal	Normal	Overeem [57]
PD	52	M	Abnormal	Normal	Overeem [57]
PD	43	M	Abnormal	Low	Maeda [58]
PSP	74	M	Abnormal	Low	Hattori [59]
MS	45	F	Not done	Low	Kato [60]
MS	43	F	Not done	Borderline	Nozaki [61]
MS	37	F	Borderline	Low	Vetrugno [45]
ADEM	38	F	Abnormal	Low	Gledhill [62]
Whipple's disease	54	M	Abnormal	Not checked	Maia [40]
Hashimoto's encephalopathy	65	M	Not done	Low	Castillo [63]
Paraneoplastic Anti-Ma-associated encephalitis with germ cell tumor of testes	45	M	Not done	Low	Overeem [64]
Paraneoplastic Anti-Ma-associated encephalitis with germ cell tumor of testes	38	M	Not done	Low	Overeem [64]
Paraneoplastic Anti-Ma-associated encephalitis with adenocarcinoma of the lung	67	F	Not done	Low	Overeem [64]
Paraneoplastic Anti-Ma-associated encephalitis with tonsillar carcinoma	55	M	Abnormal	Not checked	Adams [42]

antidepressant venlafaxine. She had MSLT-confirmed narcolepsy with normal hypocretin level. The symptoms resolved after restarting venlafaxine [49].

In addition, in 2010 doctors in Finland and Sweden reported a rise in incidence of narcolepsy among children and adolescents immunized with the HINI ASO3-P pandemic vaccine. The European Medicines Agency has confirmed this association, and since then the association has also been found in England, Ireland, France, and Norway [50]. In France there was an increased incidence of narcolepsy in both children and adults [51]. The increased incidence among children but not adults in some of these studies may be related to differences in vaccination recommendations in the different age groups or earlier presentation of symptoms in a susceptible population (children) due to autoimmunity induced by the vaccine [52].

Table 7.1 summarizes these cases.

Not all cases of narcolepsy comorbid with immunological disorders are necessarily secondary narcolepsy. Among a group of 156 narcolepsy patients, 16.6 % had some form of immunopathological disorder including idiopathic thrombocytopenic purpura, multiple sclerosis, systemic lupus erythematosus, psoriasis, Crohn's disease, ulcerative colitis, autoimmune thyroid disease, Peyronie's disease and idiopathic recurrent facial palsy, atopic dermatitis, allergic asthma, and allergic rhinitis. The symptom onset was on average 9.3 years earlier in this subset with immunological comorbidities, and cataplexy was more severe [65].

Case 3

A 47-year-old woman presented to the sleep clinic for reevaluation of her narcolepsy. She started having EDS at age 21 followed by cataplexy a few years afterwards. She also developed rare sleep paralysis and hypnopompic hallucinations. A PSG and MSLT done when she was 30 showed a normal overnight sleep and a mean sleep latency of 0.5 min and 3 SOREMPs. She failed to respond to modafinil or methylphenidate. Around the same time as her diagnosis of narcolepsy, she started having shortness of breath, and a chest X-ray revealed bihilar lymphadenopathy. The biopsy of a plaque on the skin under the chin confirmed the diagnosis of sarcoidosis.

On examination she was noticed to have left upper extremity mild weakness and a mild left facial droop. A MRI of the brain demonstrated nodular leptomeningeal enhancement in multiple areas but particularly along the hypothalamus. CSF hypocretin levels were borderline at 164 pg/ml. Twice-a-day dosing of 20 mg extended release amphetamine/dextroamphetamine modestly controlled her daytime sleepiness, and sertraline 25 mg controlled her cataplexy. She was also started on methotrexate and prednisone for the sarcoidosis.

Implications of Narcolepsy in the Older Adult and Therapeutic Challenges

Narcolepsy patients in general have more impairment of attention and some executive functions such as verbal fluency despite intact memory compared to controls. These cognitive impairments were similar to those encountered in people who are chronically sleep deprived [66]. In the narcolepsy population of over 40 years of age, these cognitive problems become more pronounced [7]. There is also a significant reduction in health-related quality of life (HQoL) scores [67], indicating that patients with narcolepsy, in addition to cognitive impairment, have a reduced quality of life. Older people, in general, have lower HQoL scores because of multiple other medical issues that become more prevalent as one ages [68]. The longer the daytime sleepiness goes without treatment, the greater is the psychosocial impairment from both of these factors. There is also good evidence that treatment will reverse the impairment and that symptomatic relief in narcolepsy is associated with good psychosocial adjustment [69]. The cognitive and psychosocial impairments inherent to untreated individuals, therefore, become magnified in older individuals; hence, it is extremely important to recognize the symptomatology of narcolepsy early in the course of the illness to prevent the complications mentioned above. Narcolepsy is also associated with higher mortality across all age groups compared to those without narcolepsy. The overall standardized mortality ratio is 1.5 with women with narcolepsy having a SMR of 1.3 and men a SMR of 1.8 compared to those without narcolepsy. The cause of this is still unknown [70].

A common comorbidity among older adults is hypertension. Research in narcolepsy patients has shown altered control of heart rate and a "non-dipper" blood pressure (loss of the normal dip in blood pressure during non-REM sleep) and exaggerated increase in blood pressure during REM sleep compared to controls [71]. It is unclear what the long-term implications of these cardiovascular changes are for patients. A recent study by Silvani et al. examined middle-aged transgenic mice lacking hypocretin/orexin neurons with a narcolepsy with cataplexy phenotype and showed that they had similar changes in blood pressure as are known to occur in humans with narcolepsy. The study did not find any evidence of subclinical hypertensive organ damage in histological and ultrastructural analysis of the heart and kidneys of the mice [72]. A study by Maurice Ohayon comparing 320 narcoleptic patients with age-, sex-, and BMI-matched controls found five diseases more frequently observed in the narcoleptic patient than in the general population including hypercholesterolemia, diseases of the digestive system, heart diseases, respiratory tract diseases, and hypertension [73]. In addition narcoleptics may be more likely to be obese. Heier et al. examined body mass index in 49 patients with narcolepsy versus 43

controls and found the patients in the narcolepsy group to be significantly more likely to have a BMI over 30 (obesity) [74].

It is important to be aware of these relationships especially in the older patient population who is already at higher risk for many of these diseases due to age.

Another consideration when treating the older narcoleptic is sleep comorbidities. A cross-sectional study by Nevsimalova et al. found that the older the patient the higher the risk of sleep comorbidities including periodic leg movements, restless leg syndrome, and obstructive sleep apnea. This association was not found in RBD where around 1/3 of the younger and older patients had findings of REM tone disturbance on polysomnogram [29]. A treating physician must remember to look for these sleep disorders especially in the older patient who begins to have worsening EDS after previous good control.

The medications used for narcolepsy may pose certain challenges when used in an older population.

Modafinil is a relatively well-tolerated and safe wake-promoting agent that in the initial trials did not cause any significant blood pressure and heart rate changes [19]. Since then, however, there have been reports of hypertension and increased sympathetic activation [75]. A primary care-based study in England confirmed the potential for modafinil to rarely cause certain types of cardiac events including tachycardia, palpitations, chest pain, and hypertension, and the patients in which these events occurred were all over age 45 [76]. Older individuals have higher plasma levels of modafinil because of a combination of slowed metabolism and the higher likelihood of being on concomitant medications that may slow the metabolism of modafinil [77]. Systemic exposure after armodafinil dosing was 15 % greater in elderly patients compared with younger subjects. However, it was generally well tolerated in both groups [78]. Even though it is a relatively safe medication, modafinil (or armodafinil) should be administered with caution and if need be at reduced doses in older individuals.

Amphetamines and methylphenidate are traditional stimulants used in the treatment of EDS associated with narcolepsy, and although generally thought to be safe in the older population, they are associated with a risk of hypertension and increased heart rate because of their sympathomimetic activities [79–82]. Although the risk is modest in the healthy young adult, the situation is different when dealing with an older individual who already has a preexisting hypertension or cardiac disease. In addition, there have been rare reports of cardiomyopathy with both methylphenidate and amphetamines [81, 83].

Other agents include *selegiline*, *a monoamine-oxidase B (MAO-B) inhibitor*; *protriptyline*, an activating tricyclic antidepressant; and *codeine*. Selegiline has the potential of hypertensive crisis if a strict tyramine-free diet is not followed; therefore, its use in the treatment of a lifelong illness is limited [23]. Protriptyline at higher doses has the potential of cardiac arrhythmias, and in the older population can lead to significant anticholinergic effects including urinary retention [23]. Codeine can also cause significant constipation which potentially can be worse if there is preexisting age-related slowing of gastric motility [84].

Anti-cataplexy agents also have their set of adverse effects. The mainstay of treatment is *clomipramine* or similar tricyclic antidepressants. Here again, the problem when used in the older individual is the potential of urinary retention and other exaggerated anticholinergic effects. Also, these medications have the potential of exacerbating RLS/PLMD and RBD [23]. Other agents used are high doses of the *selective serotonin receptor inhibitors (SSRIs) and atypical antidepressants such as venlafaxine*. Here as well, the potential side effects in the older population are similar to those discussed above with clomipramine and related drugs.

Sodium oxybate is also used for the treatment of cataplexy, and although it is generally well tolerated, the amount of sodium per dose makes it a suboptimal choice for an individual with salt-sensitive hypertension or congestive heart failure. In addition, because of the profound sedation, it may be a fall hazard for an older person with nocturia [85, 86].

The treatment of other related sleep problems such as RBD, PLMD, and nighttime sleep disruptions has primarily been clonazepam, a benzodiazepine with a long half-life. In the elderly,

benzodiazepines, regardless of half-life, have been associated with more nighttime falls and hip fractures [87, 88]. Clonazepam can also cause morning hangover, worsening the already existing daytime sleepiness in a patient with narcolepsy. This effect can be worse in an older individual not able to metabolize and clear the drug as fast [89].

Lastly, the impact of medications prescribed for other conditions on the symptoms of narcolepsy should be considered. In addition to trying to avoid sedative medications in order to avoid worsening the EDS and tipping the fragile balance of wakefulness and drowsiness that narcoleptics live in, it is important to remember that the commonly prescribed alpha-1 agonists, for either hypertension or benign prostatic hypertrophy, e.g., prazosin, can frequently severely exacerbate cataplexy [90].

Conclusion

In our aging population, narcolepsy is no longer an illness exclusive to teenagers and young adults. A certain number of these patients start having symptoms late in life, others are not diagnosed until later because of lack of awareness about this syndrome in both the general population and the medical community, and a third category presents with other conditions that cause symptomatic narcolepsy. Overall the number of people presenting later in life with narcolepsy is small, but awareness of this condition in the older age group is important even if these patients present and get diagnosed early on. As they get older, their sleepiness should be reevaluated because of comorbid sleep disorders. In addition, there are therapeutic challenges that the medications used to treat the various symptoms of narcolepsy pose in the setting of age-related medical conditions.

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Hypnagogic Hallucinations and Sleep Paralysis

8

Armando D'Agostino and Ivan Limosani

I am quite desperate at times…things tend to get annoying in my relationship with others… the main problem is I tend to mix things that happen in my dreams with real elements of my everyday life. The things I see and hear especially when I fall asleep during the daytime are so realistic that afterwards I find myself struggling to remember whether I dreamt them or actually saw them, and if I saw them…was it because it actually happened or did I have a hallucination? The other day at work, I lay my head down on the desk because I was so drowsy…I had to take a nap…my boss and my colleagues know about my condition so it's okay for me to do so during my lunchtime or coffee break. Just as I lay my head down, I began to hear two of my colleagues arguing over something right beside my desk, and I could feel they were there but couldn't move my head to see them…and they began to be very aggressive, verbally aggressive, as they argued. Then I must have fallen asleep, and when I woke up I kept thinking they had had a row over something important, so when I saw one of them the following day, I asked him why he and M. were so upset the previous day. He looked at me as if I were crazy. He said he hadn't even been anywhere near my desk the previous day and that he hadn't spoken to M. for a week… and of course, he also specified he hadn't argued with anyone! I felt ashamed, as I always do…even if I'm used to it…people often think I'm strange, and though now I know it's related to my being narcoleptic, I still struggle to come to terms with all these things, because they seem so real.

C.C., 35-year-old female patient with a recent diagnosis of narcolepsy with cataplexy, tape-recorded oral account transcribed by the authors.

Introduction

Hypnagogic hallucinations and sleep paralysis are associated clinical features that commonly occur in subjects affected by narcolepsy. Data from different lines of research indicate the presence of these phenomena in 40–80 % of subjects who have a diagnosis of narcolepsy with cataplexy, while their incidence appears to be lower in narcolepsy without cataplexy. Hypnagogic hallucinations are abnormal perceptions that occur while falling asleep, whereas hallucinations that occur upon awakening are termed hypnopompic;

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sleep paralysis is a generalized inability to move or speak during the transition between wakefulness and sleep. The two phenomena often occur together but may also be independent, and it is relatively more common to find hallucinations without sleep paralysis than sleep paralysis without some form of hallucinatory experience. From a clinical perspective, neither sleep-related hallucinations nor sleep paralysis can be considered pathognomonic of this disorder, because occasional episodes may be precipitated by sleep deprivation, significant changes in sleep schedule or other factors disrupting normal sleep patterns in susceptible subjects without a diagnosis of narcolepsy. Indeed, according to recent classification manuals, this lack of specificity implies an absence of diagnostic value for either symptom. Despite being commonly used to guide clinical diagnoses in a tetrad of symptoms completed by cataplexy and excessive daytime sleepiness (EDS), hypnagogic hallucinations and sleep paralysis are not considered diagnostic criteria for narcolepsy in either the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1] or the International Classification of Sleep Disorders (ICSD-3) [2].

Because of the considerable departure from physiological sleep/wake transitions and of the intense emotional response provoked in terms of fear when first experienced, the understanding of these phenomena has posed a fascinating challenge over time, leading to various supernatural interpretations—from visitations of devils and spirits to possibly alien abduction—according to the cultural setting in which they were interpreted. The Latin word *incubus* (from *incubare*, to sit on) derives from a typical experience of sleep paralysis with frightening hallucinations, that has evolved to a belief universal to men across a variety of cultures: the incubus has been described with colourful variations as a malignant spirit responsible for terrifying dreams that sits on people's chest paralysing them and crushing their breath away. Over time, the meaning of the word has changed towards denoting frightening dreams and is now synonymous to nightmare. Etymological evidence can indeed be found in various languages correlating these sleep-related phenomena to the conceptualization of nightmares [3].

In narcolepsy, isolated hallucinatory phenomena were previously thought to occur predominantly in the transition from wakefulness to sleep, whereas sleep paralysis and associated hallucinatory experiences were thought to usually occur upon awakening. Current knowledge seems to indicate that both types of experiences can in truth occur in any transition between these two states of consciousness. In this chapter, the term hypnagogic will be used in relation to clinical and neurobiological aspects also shared by hypnopompic hallucinations. Distinct features of these sleep-related hallucinations and of sleep paralysis will be treated separately in various parts of the chapter to promote a clearer description of these symptoms, but it must be stressed that they often belong to the same articulate and transient brain/mind state.

Hypnagogic Hallucinations

Clinical Features

A broadly accepted definition of hallucinations is that of sensory perceptions in the absence of an objective stimulus; when they occur during transitions between sleep and wakefulness, they are specified as hypnagogic (occurring while falling asleep) or hypnopompic (occurring upon awakening). Alfred Maury first used the term hypnagogic by fusing the classical Greek words ὕπνος (*hypnos*, sleep) and ἀγωγεύς (*agōgeús*, conveyor) with reference to his own hallucinations just before falling asleep [4]. Such hallucinations can involve all senses but are more often visual: perceived objects range from simple forms that can be coloured or not to complex figures such as animals or humans. Auditory hallucinations are also common: patients can hear simple sounds, structured melodies or complete sentences that are often described as threatening or menacing [5]. The third type of hallucination often described is somesthetic,

ranging from simple tactile sensations including paraesthesia and formication to more complex cenesthopathic experiences, such as sudden changes in the perception of body parts' location or the sensation of movement of the entire body; these articulate forms of proprioceptive phenomena are commonly referred to as out-of-body experiences [6]. In general, hypnagogic hallucinations appear more often as complex and vivid dreamlike experiences rather than simple shapes or sounds [7]. Patients who experience these phenomena, especially when associated with sleep paralysis, often report an intense feeling of anxiety because of the terrifying nature of the hallucinations and the clear subjective awareness of being awake, without the possibility of escaping the frightening situation by running away or calling for help [8].

Compared to other cardinal manifestations of narcolepsy, hallucinatory phenomena usually appear later in the course of disorder, with daytime sleepiness often the first symptom and cataplexy usually occurring within the first year of onset. When hypnagogic hallucinations cause severe anxiety, they can seriously disrupt sleep; in some subjects, this condition evolves into sleep-onset insomnia.

Recent data suggest that hallucinations also occur during clear wakefulness in 40 % of narcoleptic patients [9].

Hypnagogic Hallucinations and Dreams

Hallucinatory phenomena on the edge of sleep are often described as dreamlike intrusions into waking cognition. The content of these hallucinations has never been investigated in detail, but the most common themes seem to be of attack and aggression, similarly to those found in REM sleep nightmares; in the untreated narcoleptic disorder, where subjects tend to fall asleep frequently and often enter the REM stage of sleep rapidly, hallucinations can be difficult to distinguish from nightmares and unpleasant dreams because of the fast transition between these conditions and the continuity found in terms of content. Though dreams occur across all stages of sleep, it seems appropriate to consider REM sleep as the neurophysiological framework for the most vivid, complex and bizarre dream mentation [10]. The extreme vividness of the two phenomena may also be an explanation for the difficulty in distinguishing the two experiences often reported [11]. Sometimes, detail and vividness of hypnagogic hallucinations seem to exceed anything experienced in real life, with the only condition in which hallucinations are as vivid being in course of intoxication with hallucinogenic drugs such as LSD [12]. Major differences between dreaming and hallucinations lie however in the engagement of the visual field and in the action: dreams fill the whole visual field with the dreamer actively participating, whereas visual hallucinations occupy the centre only, with the hallucinator as an observer [10].

Hypnagogic Hallucinations and Schizophrenia

The tendency to experience hypnagogic hallucinations frequently during the daytime may suggest the wrong diagnosis of psychosis in some cases of unrecognized narcolepsy [13]; though patients are usually retrospectively aware of the hallucinatory nature of these phenomena and the majority can easily distinguish them from dreams even in the presence of similar contents, a minority of narcoleptic subjects report constant difficulties in discerning reality from dreams and dreamlike hallucinations. The experience of mistaking dreams for reality has been termed "dream delusion" and could explain certain diagnostic failures. The attenuated phenomenon of dream-reality confusion is reported by 83 % of patients, compared to only 15 % of healthy subjects [14]. Various causes leading to limitations or decline in critical thinking may be hypothesized as a mechanism leading to secondary delusional elaborations of these phenomena, and some patients might occasionally be misdiagnosed

as schizophrenic [6, 15, 16]. Though "voices" remain by far the most common type of hallucination, visual hallucinations are now thought to be more frequent than traditionally reported in schizophrenia [17]. Indeed, narcolepsy-related hallucinations—confused with florid refractory schizophrenia—have been successfully treated by stimulants [18].

Overlapping aspects of narcoleptic hallucinations and hallucinations occurring in psychopathological conditions such as psychosis stand along the conceptual continuum linking threat sensations to frank persecutory delusions. The presence of threatening hallucinatory voices is commonly described by schizophrenic subjects, and similar contents can be found in descriptions of narcoleptic subjects' hypnagogic hallucinations. Interestingly, REM initiation of a threat-activated vigilance system and a threat-simulation function of REM mentation have been proposed in evolutionary theories of REM-related subjective experiences [19, 20].

Hypnagogic Hallucinations and Other Neurological Disorders

Complex visual hallucinations can be found in a number of clinical conditions which differ significantly from narcolepsy, such as Charles Bonnet's syndrome [21], peduncular hallucinosis [22, 23], treated Parkinson's disease (PD) [24], Lewy body dementia (LBD) [25], hallucinations associated with migraine [26] or focal epilepsy [27]. Narcolepsy with cataplexy appears to be the single pathological condition in which such hallucinatory phenomena occur more frequently, followed by LBD, PD with cognitive decline, schizophrenia and narcolepsy without cataplexy [28]. Drowsiness is often described as a predisposing factor for the emergence of hallucinations in all of these neurological conditions, indicating a common basis across different disorders that correlate with abnormalities in the sleep/wake cycle.

Hypnagogic hallucinations can also be reported by patients as an isolated symptom, typically with a low frequency of occurrence. The quality of sleep must be investigated in these patients along with the presence of insomnia related to psychopathological conditions; given that any condition causing sleep deprivation may induce these hallucinatory phenomena, behaviourally induced insufficient sleep syndrome must also be considered as a diagnosis [2]. Finally, it must be stressed that hypnagogic hallucinations, like all other clinical aspects of narcolepsy, can be found in the symptomatic form of the disorder, with the most important underlying conditions being cranial trauma, brain tumours and vascular disorders [29, 30].

Sleep Paralysis

Clinical Features

Sleep paralysis is the total or partial paralysis of the skeletal muscles in the transitions between wakefulness and sleep, during which the subject retains clear consciousness; it belongs to the classical tetrad of narcolepsy symptoms (hypersomnolence, cataplexy, sleep paralysis and hypnagogic hallucinations) and commonly occurs in narcoleptic patients with cataplexy. Occasional episodes may be experienced by subjects without a diagnosis of narcolepsy—especially after a dream or nightmare in the middle of the night—and can be distinguished from generalized fatigue and difficulties waking up because the subjects are unable to perform the slightest of movements, such as lifting a finger.

As a transient, generalized inability to move or speak when falling asleep or upon awakening, sleep paralysis can be very frightening, particularly when initially experienced. Control over gross movements is inhibited, and respiratory muscles are often paralysed, causing what has been described as an inability to breathe, oppressiveness or the more acutely distressing sensation of suffocation. The eyes can usually be opened, and the state is often accompanied by intense fear, especially in episodes that are accompanied by frightful hallucinatory phenomena. However, although the first events are often extremely frightening, subsequent episodes tend to be benign annoyances rather than terrifying experiences.

Sleep paralysis usually lasts a few minutes and ends spontaneously or after mild sensory stimulation but sometimes continues even after vigorous attempts at arousal. Sleep deprivation, a change in sleep schedule or other factors that disrupt normal sleep patterns can precipitate episodes in susceptible persons [31]. In narcoleptic patients, REM sleep-associated muscle atonia occurs at sleep onset/offset (sleep paralysis) and in full wakefulness (cataplexy).

Isolated Sleep Paralysis and Culturally Determined Interpretations

Sleep paralysis can be found as a symptom independent of narcolepsy ("isolated sleep paralysis") and has a high lifetime prevalence in the general population [20, 32]. Isolated sleep paralysis however differs in terms of severity from the paralysis found in narcoleptic subjects: the suppression of tonic muscle atonia appears to be weaker in isolated sleep paralysis, with subjects being able to terminate the experience voluntarily much more frequently than narcoleptic subjects, who often require external aid to terminate the episode [32]. The mentation connected to this motor paralysis is also often characterized by intrusions of frightening dreamlike hallucinations.

Frightening experiences of this nature are known to be similarly interpreted across different cultures, usually in relation to nightly visitations of spirits, demons or other grotesque creatures belonging to traditional folklore. In British and Anglophone North American popular culture, the term "Old Hag" refers to a nocturnal spirit essentially identical to the Anglo-Saxon *mæra*, a being with roots in ancient Germanic superstition. According to folklore, the Old Hag sat on a sleeper's chest inducing terrifying dreams (thus eventually called "nightmares") and causing successive inability to breathe or even move for a short period of time upon awakening. Similarly, subjects belonging to African American communities refer to the experience as "being ridden by the witch". Though the cause remains unclear and may be related to higher levels of psychosocial stressors, sleep paralysis appears to be more common in this population, especially in subjects with panic disorder [33]. The rich body of work on the subject by authors of Japanese origin has also made the term *Kanashibari* ("bound or fastened in metal") quite widespread in medical literature [34].

In late nineteenth-century medical literature, sleep paralysis was referred to in French as *crise de l'ètat de veille* ("crisis of the waking state") or *cataplexi du réveil* ("cataplexy of awakening"). The term sleep paralysis was first used by the British neurologist Samuel Wilson in 1928, in his description of an experience occurring in the transition between sleep and wakefulness during which the individual feels awake, yet incapable of voluntary motor movement [35]. In 1876, the phenomenon had been described as "night palsy", with other terms being "delayed psychomotor awakening, "cataplexy of awakening" or "waking fit [36, 37].

In his landmark study on dreaming and the unconscious, Sigmund Freud spoke of dreams in which the individual felt his movements impaired, referring to the sensation of inhibited motor movement as "conflicts of will" reflecting both a desire and the restraint of the same action [38]. Stephen Schoenberger addressed the "waking nightmare" more specifically in one patient, whom he interpreted to have felt a desire to replace his father upon witnessing parental coitus. According to the classical psychoanalytic theory, the nightmare attack represented a punishment for his sexual and aggressive fantasies, and the motor paralysis and breathing inhibition in particular were a defence against the incestuous wish: by pretending to be dead, the patient heard and saw nothing, thus avoiding sexual excitement [39]. Many authors who described the nightmare in these terms stressed the accompanying exhaustion, malaise and tendency to fall asleep of their patients, so it seems plausible to suspect that some of those subjects described essentially as susceptible to sleep paralysis attacks would today be diagnosed with some form of narcolepsy.

Neurobiology of Hypnagogic Hallucinations and Sleep Paralysis

General View

Although unanimous consent has not been reached over the neurobiological substrates of sleep paralysis and sleep-related hallucinations, these phenomena are usually referred to as dissociated manifestations of REM sleep [7, 10]. The first REM sleep period physiologically arises out of deep NREM sleep, while hallucinations may be a transitory manifestation of entrance into REM sleep from a relatively higher level of arousal. Indeed, narcoleptic subjects tend to enter this stage of sleep with a more direct continuity from waking, as shown by the frequency of sleep-onset REM periods (SOREMPs). SOREMPs may as such be considered a neurophysiological substrate for these phenomena, and early polysomnographic studies in narcoleptic subjects did show that sleep paralysis and hallucinatory phenomena only occurred in this particular stage [40, 41]. These data have been confirmed in non-narcoleptic subjects, when isolated sleep paralysis episodes with accompanying hallucinations were found to be associated with SOREMPs in sleep-deprived healthy subjects [32, 42]. At the other end of sleep, paralysis has been found to occur during offset REM, thus confirming the hypothesis of an underlying dissociation of the REM stage in the transition between wakefulness and sleep [43]. Moreover, these phenomena have been linked with various conditions that predispose to SOREM episodes, such as sleep deprivation, sleep fragmentation and withdrawal from REM-suppressant medication. Alcohol withdrawal—a well-recognized cause of visual hallucinations—determines a significant REM rebound, with analogous associations also found in barbiturate and benzodiazepine withdrawal syndromes [44, 45]. From a neurochemical point of view, the mutual interplay between cholinergic and aminergic systems involved in the control of wake/sleep transitions seems to play a significant role in the abnormal phenomena experienced by narcoleptic subjects on the edge of sleep: an imbalance in these systems is thought to underlie these unstable states of consciousness by shifting the brain towards cholinergically driven hallucinatory cognition and inhibition of motility [10]. Modern theories of brain function suggest that sleep and wakefulness are rough-grained conceptions in need of a finer resolution. For example, sleep-onset slow waves have been found to occur in hippocampal cortices several minutes before their onset in frontotemporal cortices, possibly justifying the inability to store memories in the minutes preceding sleep [46]. Likewise, the thalamic deactivation that occurs at sleep onset precedes that of the cortex, possibly promoting hallucinatory phenomena [47].

Neurobiology of Hallucinations

Neurological conditions in which complex visual hallucinations are often reported such as dementia, Parkinson's disease and delirium all share disturbances in sleep patterns and alertness—as of course is the case in narcolepsy—and virtually all non-pathological hallucinations occur between sleep and full wakefulness or in sleep-deprived patients [28].

Many authors have speculated that hallucinations may result from the intrusion of dream images into waking and semi-waking mentation [16, 48, 49, 50, 51]. Evidence from an early brain imaging study seems to support this view, with regional grey matter blood flow values being maximally increased in right parietal-occipital regions during both visual dreaming and hypnagogic hallucinations in narcoleptic subjects [52]. This common neurofunctional substrate points to a shared pattern of brain activation underlying these two cognitive processes; the activated area corresponds to the visual association cortex which is responsible for higher order integration of visual percepts and images, thus representing a neuroanatomical correlate of visual hallucinosis.

Though the available functional imaging studies have thus far failed to yield consistent results in terms of neuromodulatory abnormalities in narcolepsy [53], various data from other confining fields of research point to specific changes in aminergic/cholinergic balance as a

possible substrate for hallucinations. From a neurochemical point of view, serotonin and acetylcholine appear to be particularly relevant to the formation of visual hallucinations, with high concentrations of both found in visual thalamic nuclei and in the visual cortex [12]. Indeed, a linear correlation appears to exist between the serotonergic activity of hallucinogens and their hallucinogenic potential [54]. Furthermore, the association with the human leukocyte antigen (HLA) DR2/DQ6 (DQB1*0602) as well as the low level of hypocretin-1/orexin A in the CSF of narcoleptic patients are well-known biological markers in narcolepsy [55, 56]. Hypocretin/orexin neurones are involved in maintaining wakefulness, and their deficiency has been causally linked to EDS [57]; the major deficits in the hypocretin/orexin-driven stimulation of basal forebrain cholinergic neurones indicate that hallucinations may arise in this disorder as an indirect dysfunction of the cholinergic pathway [58, 59].

Though the general function of dopamine in sleep is less clear than that of acetylcholine and serotonin, the possibility of its involvement in the formation of oneiric and hallucinatory phenomena must also be stressed. Attentional binding has been suggested to play an important role in the formation of complex visual hallucinations, and many clinical data point strongly to the critical role of this neurotransmitter in attention [28]. Moreover, its relevance is well-known in schizophrenia, a disorder in which mainly auditory and also visual hallucinations are typically found along with a waking mentation similar to that of dreams [60]. The mesolimbic dopaminergic system has recently been proposed to have a functional role in the generation of dream imagery by activating motivational reward circuits [61]. Postmortem studies in narcolepsy have indeed shown an increase in striatal dopamine binding, but the failure to confirm this finding in functional imaging studies has lead to the hypothesis that increases in dopamine activity may be due to long-term effects of treatment rather than to pathophysiological modifications accounting for the symptoms of the disorder [53].

Neurobiology of Sleep Paralysis

Sleep paralysis is considered to be the persistence of typical REM muscle atonia into wakefulness, with the waking brain/mind seemingly trapped in a paralysed body. In these terms, sleep paralysis can be understood as a dissociation occurring along the physiological transition from REM sleep to waking [49].

REM atonia is thought to be controlled by a small centre in the pons, near the locus coeruleus, and by the magnocellular nucleus in the descending medullary reticular formation to which it is connected. Activation of cholinergic REM-on cells in the pontine reticular formation leads to modifications in this system that cause hyperpolarization of alpha spinal motoneurons and consequent inhibition of skeletal muscle activity [10]. Sleep paralysis may reflect the anomalous functioning of the system regulating REM sleep, possibly because of the hyperactivation of cholinergic REM-on neural populations or the hypoactivation of noradrenergic/serotonergic REM-off populations in the pons during REM onset and offset [43]. Clinical evidence of the efficacy of serotonin/noradrenaline reuptake inhibitors in reducing the incidence of this symptom in narcoleptic subjects seems to support this view. Two different types of state dissociation have been polysomnographically documented in sleep-deprived healthy subjects: the intrusion of an alpha EEG pattern (usually found in waking) into REM sleep and the persistence of muscular atonia into waking [32]. During sleep paralysis, the inability to control movement is in contrast with the subjective awareness of being awake. This type of dissociation, with waking awareness sustained by upward projections from the brainstem and motor ability blocked by inhibition of downward projections, appears to be the opposite of what happens during REM sleep behaviour disorder, where typical REM mentation is in contrast with a disinhibition of downward mechanisms that physiologically promote muscle atonia.

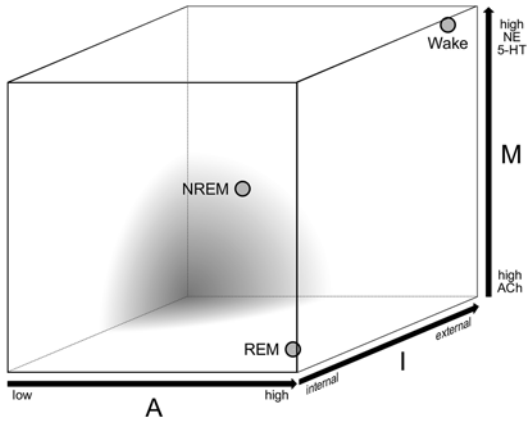

Fig. 8.1 AIM state space model, illustrating the physiological transitions across the three basic states of consciousness in the sleep/wake cycle; each unit of consciousness is represented by a grey circle. The figure was redrawn and adapted from Hobson, J.A. (2009) REM sleep and dreaming: towards a theory of protoconsciousness. Nat Rev Neurosci 10, 803–13. [62], with permission of Nature Publishing Group

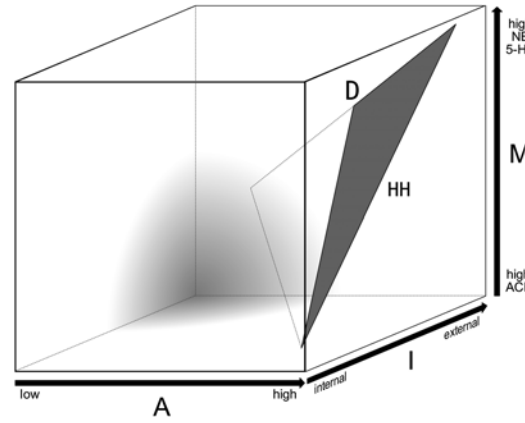

Fig. 8.2 Hypnagogic hallucinations (HH) are represented graphically as a dark triangle within the AIM state space. The three vertices are represented by wake, drowsiness (D) and REM. The broad extension indicates the transitory nature of this state along the input source (I) and modulation (M) parameters. HH could occur within a state of consciousness that may occupy any of the points on this broad area, with inputs oscillating from external to internal and modulation ranging from a predominant wake-like aminergic modulation to a REM-like cholinergic modulation of the brain/mind. After the hallucinatory experience, the subject may either return to full wakefulness or enter sleep, typically into the REM stage in narcoleptic subjects. The opposite transition can be hypothesized for hypnopompic hallucinations, with the unstable state being reached from REM sleep upon awakening, with subsequent return to sleep or progression to full wakefulness. The figure was redrawn and adapted from Hobson, J.A. (2009) REM sleep and dreaming: towards a theory of protoconsciousness. Nat Rev Neurosci 10, 803–13. [62], with permission of Nature Publishing Group

Theoretical Conceptualization of Dissociated REM Phenomena

Sleep-related hallucinatory phenomena and sleep paralysis can be interpreted within several different theoretical frameworks. According to Hobson's AIM state space model (Fig. 8.1), states of consciousness can be interpreted in terms of mutual interplay among three parameters [62].

Activation (A) is conceptually derived from data on the firing of reticular formation neuronal populations and EEG correlates of cortical activation; input (I) represents the source of information processed by the brain, along a continuum from purely internal to purely external inputs; modulation (M) expresses the ratio between the aminergic and cholinergic discharge systems that are considered to be competitors in the maintenance of a specific state.

Physiological variations in consciousness represented by REM sleep, NREM sleep and wakefulness all occupy different positions within the tridimensional model. Beyond these 3 coarsely defined states of consciousness, the AIM state space is useful to explain a variety of intermediate conditions in which both mentation and neurobiology are less clearly understood. The advantage of this model becomes evident when one considers that each point within the graphic cube can be filled by transient conditions, such as the dissociated REM phenomena we address here. Hallucinatory experiences at opposite ends of sleep reach the same position in the AIM state space from different starting points: hypnagogic hallucinations can be interpreted as a result of an activated REM-like increase of internal stimuli coupled with an activated, aminergically modulated waking brain (Fig. 8.2).

Studies of sensory deprivation and hallucinogenic drug administration suggest that the interplay of slow modulation (e.g., dopamine, acetylcholine, serotonin) and fast excitatory (e.g., glutamate) and inhibitory (e.g., **γ**-aminobutyric acid

(GABA) transmission mediates the brain's attempt to minimize prediction error [63]. Like visual sensory deprivation, serotonergic hallucinogens such as lysergic acid diethylamide (LSD) increase presynaptic glutamate release. According to this model, perceptual distortions generated in the absence of external stimuli are projected to the external space when prior expectation fails to match incoming information [64]. Although abnormalities of glutamatergic signalling in narcoleptic subjects are still to be elucidated, it has been suggested that phasic glutamatergic excitation from the amygdala could mediate muscle atonia by activating REM-on cells in the sublaterodorsal tegmental nucleus [65].

Intracerebral EEG recording for presurgical evaluation of drug-resistant epileptic patients also fostered relevant advances for the field of sleep research. Typically considered a global brain phenomenon, sleep is increasingly viewed as a complex interaction of different regional states. REM-like 1.5–3 Hz activity has been recorded from hippocampal/parahippocampal sites during cortically defined transitions from wakefulness to sleep [66]. Likewise, thalamic deactivation has been observed to precede cortical signs of sleep by several minutes [47]. In the light of this recent reconceptualization of sleep/wake states, vivid hypnagogic imagery could depend on decoupling of subcortical/cortical oscillations.

Treatment of Hypnagogic Hallucinations and Sleep Paralysis

According to the latest guidelines issued by the American Academy of Sleep Medicine, various pharmacological agents ranging from psychostimulant to antidepressant drugs may be useful in treating narcolepsy and its associated features, though the quality of published clinical evidence supporting them varies [67, 68]. Adequate explanation of the hypothesized mechanisms underlying the symptoms should however be considered the first step in the treatment of these patients, as the peculiar and often frightening nature of the subjective experience associated with sleep paralysis and hallucinatory phenomena can be very distressing.

Sodium Oxybate

Sodium oxybate (γ-hydroxybutyrate, GHB) is currently used to treat all core symptoms of narcolepsy: daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis. Its mechanism of action remains uncertain, but effects depend on GABAb receptors and specific GHB receptors especially in the hippocampus, neocortex and thalamus [69, 70]. Evidence of the efficacy of sodium oxybate for the treatment of hypnagogic hallucinations and sleep paralysis is considered uncertain. In one study in which narcoleptic patients received 4500–9000 mg per night doses, the efficacy of sodium oxybate was confirmed by significant self-reported decreases in the incidence of hypnagogic hallucinations and sleep paralysis episodes [71]. These data however were not confirmed in a large, randomized, placebo-controlled trial that nonetheless supported the efficacy of GHB in treating daytime sleepiness and disrupted sleep in these subjects [72]. Furthermore, one recent report suggests that GHB could exacerbate psychosis in narcoleptic patients [73].

Antidepressant Medications

Tricyclic antidepressants such as clomipramine, selective serotonin reuptake inhibitors (SSRIs) and venlafaxine may be useful in treating sleep paralysis and hypnagogic hallucinations, though no randomized trials have reported significant changes in the incidence of these symptoms after antidepressant treatment. Because of the rather disturbing side effects that can be associated with this type of medication, it should only be considered when both the physician and the patient believe that benefits of the treatment would outweigh the risks [67, 68].

Tricyclic drugs have been reported to be effective in controlling cataplexy and sleep paralysis but not in controlling daytime sleepiness, whereas amphetamines are considered mainstays for treatment of sleepiness but do not seem useful in controlling the auxiliary symptoms [74]. The reason for this appears to be that tricyclics suppress the REM state but do not inhibit sleep,

and the amphetamines inhibit sleep—or increase wakefulness—but have a weak REM-suppressant effect to which tolerance is quickly developed [75, 76]. That sleep paralysis may be alleviated by serotonin, and adrenergic reuptake inhibitors seem consistent with the hypothesis of a cholinergic/aminergic imbalance underlying this specific symptom.

Conclusive Remarks

Hypnagogic hallucinations and sleep paralysis in narcoleptic subjects can be considered dissociated manifestations of REM sleep, caused by the intrusion of REM-like mentation and REM sleep atonia into the waking state [31]. The hypocretins/orexins belong to a major excitatory system affecting the activity of monoaminergic and cholinergic systems, so that the hypocretin/orexin deficiency underlying narcolepsy may well induce a neurochemical imbalance, with effects on the regulation of vigilance and internal architecture of sleep [7]. The relative efficacy of antidepressant drugs which increase aminergic tone and inhibit cholinergic tone in contrasting REM abnormalities in narcoleptic subjects seems to support this view [77]. While cataplexy only occurs in narcoleptic subjects, sleep paralysis and hallucinatory phenomena can be found within the context of other neurological or psychopathological conditions, all of which include abnormalities of the physiological sleep/wake cycle. Although plausible neurobiological hypotheses seem to explain these phenomena, the full understanding of their complex nature will probably require the convergence of various fields of research. Bridging core elements of psychopathology, evolutionary psychology and cognitive neuroscience may prove successful in terms of elaborating satisfactory interpretations of the brain/mind's shift across varying states of consciousness. Detailed analyses of sleep paralysis episodes in the general population have suggested that the experience of a threatening presence during the episode may involve subcortical circuits responsible for a rough analysis of stimuli that is necessary to prepare emergency responses before addressing the perilous context in major detail through the sensory cortex. The impossibility of assessing the nature of the stimulus because of its objective absence may lead to a prolonged fear response and consequent misinterpretation of various sources of activation, ranging from benign external inputs to bizarre internal representations that will be perceived as dreamlike hallucinations [20]. Addressing this type of subjective experience in the context of its biological framework may prove useful in terms of developing future treatment strategies for dissociated REM phenomena in narcolepsy and other neurological and psychiatric disorders presenting overlapping clinical features.

Just a few minutes after I shut the lights out last night, I heard noises, and it seemed someone was trying to break into my apartment by forcing the lock to my door. Then these noises gradually grew louder, and a number of people tried to break into my bedroom by taking down the shutters. At this point, I was in panic and I heard steps in the kitchen, which is close by, and I thought "someone has got in". So I tried to get up to see whether someone had broken into the house, but I realized I could not move. I was breathing heavily at this point, and I thought that something terrible would happen to me. It was a very peculiar dream, as there were no images, only very loud sounds in complete darkness. When I woke up this morning, I wasn't actually sure it was a dream, because it did seem so real and vivid, especially my feeling of helplessness. And I had a distinct sensation of having been awake during the noises and of having fallen asleep afterwards.

A.R., 44-year-old male patient with narcolepsy with cataplexy, written report.

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9 Symptomatic Narcolepsy or Hypersomnolence with and Without Hypocretin (Orexin) Deficiency

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Introduction

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations (HH), and sleep paralysis (SP) (i.e., narcolepsy tetrad) [1, 2]. A major breakthrough in narcolepsy research was recently made through the identification of hypocretin deficiency in narcolepsy–cataplexy [2–9]. Hypocretins are hypothalamic neuropeptides involved in various fundamental hypothalamic functions including sleep/wake control, energy homeostasis, and autonomic and neuroendocrine functions [10–12]. Hypocretin-containing neurons are located exclusively in the lateral hypothalamic area (LHA). Since hypocretin deficiency in narcolepsy is also tightly associated with human leukocyte antigen (HLA) DR2/DQ6 (DQB1*0602) positivity, an acquired cell loss of hypocretin-containing neurons with autoimmune process is suggested in "idiopathic" cases of narcolepsy [2, 6]. "Idiopathic narcolepsy" is defined as narcolepsy cases unassociated with apparent radiographical or clinical evidence of brain pathology apart from sleep-related abnormalities. Hypocretin deficiency in the brain can be determined clinically via cerebrospinal fluid (CSF) hypocretin-1 measures with hypocretin-1 levels in healthy subjects above 200 pg/ml regardless of gender, age (from neonatal to 70s), and time of the CSF collections [1, 4, 6]. Due to the specificity and sensitivity of low CSF hypocretin-1 levels (less than 110 pg/ml or 30 % of the mean normal levels), narcolepsy–cataplexy is high among various sleep disorders [2, 13, 14], and CSF hypocretin measures were a diagnostic criteria for narcolepsy–cataplexy in the second edition of the International Classification of Sleep Disorders (ICSD-2) [15]. In the third edition of ISCD (ICSD III), narcolepsy was reclassified depending on hypocretin deficiency status (i.e., Type I and Type II narcolepsy) [16].

Impaired hypocretin systems may also be observed in some neurological disorders affecting the LHA (where hypocretin cell bodies locate)

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and/or hypocretin projection pathways. Indeed, Ripley et al. [13] had measured CSF hypocretin levels in 235 neurological patients and shown that a subset of subjects with acute or subacute neurological disorders [i.e., intracranial tumors, cerebrovascular events, craniocerebral trauma, central nervous system (CNS) infections, and Guillain–Barré syndrome (GBS)] had decreased CSF hypocretin-1 levels, although CSF hypocretin-1 levels in the majority of patients with chronic neurological conditions, such as Alzheimer's disease and Parkinson's disease, were not significantly reduced. Arii et al. [17] also studied CSF hypocretin-1 levels in 132 pediatric neurological conditions. The results were consistent with Ripley's study [13], and only a limited number of neurological conditions besides narcolepsy showed reduced CSF hypocretin-1 levels. These included intracranial tumors, craniocerebral trauma, autoimmune and postinfectious diseases (GBS and acute disseminated encephalomyelitis (ADEM)), and some inherited disorders, such as Niemann–Pick disease, type C (NPC), and Prader–Willi syndrome (PWS) [17].

These findings are particularly interesting since these neurological conditions are often associated with acutely disturbed consciousness, lethargy, sleepiness, and/or residual sleep disturbances.

In rare cases, symptoms of narcolepsy can be seen during the course of a neurological disease process (i.e., symptomatic narcolepsy). By 2005, we have counted 116 symptomatic cases of narcolepsy reported in the literature, and inherited disorders ($n=38$), tumors ($n=33$), and head trauma ($n=19$) are the three most frequent causes for symptomatic narcolepsy [18]. Involvements of the hypothalamic structures in symptomatic narcoleptic cases have been emphasized repeatedly for many decades [19, 20], and an impaired hypocretin system may also be involved in some symptomatic narcolepsy cases. Association with EDS/cataplexy in some inherited neurological diseases (such as NPC, PWS, or myotonic dystrophy) is also known [21–23]. An impaired hypocretin system may thus also be involved in these sleep-related symptoms of these neurological conditions.

In this chapter, we first overview cases of symptomatic narcolepsy reported in literature. Since EDS without other narcolepsy symptoms can also occur with a variety of neurological disorders and is not usually an indication of narcolepsy, we will also extend our discussion on the roles of hypocretin system in EDS associated with various neurological conditions.

Since data of CSF hypoocretin-1 measures are available for some recent symptomatic narcolepsy and/or EDS cases, we will focus on these cases and discuss the roles of hypocretin status in these disorders. For this purpose, we categorized the cases as follows: (I) symptomatic narcolepsy–cataplexy associated with focal/generalized CNS invasion, such as cerebral tumors, vascular diseases (section "Hypocretin Status in Symptomatic Narcolepsy–Cataplexy Associated with Distinct CNS Lesions"), and neurodegenerative disorders (section "Hypocretin Status in Symptomatic Narcolepsy–Cataplexy and/or EDS Associated with Inherited Disorders"), and (II) hypersomnia associated with (IIa) focal/generalized CNS invasion, such as cerebral tumors, brain infections, vascular diseases, neurodegenerative disorders (AD and PD), and head trauma (section "Focal/Generalized CNS Invasion"), and (IIb) with CNS diseases mediated with neuroimmune mechanisms, such as inflammatory and demyelinating diseases (section "CNS Diseases Mediated with Neuroimmune Mechanisms"). Non-narcoleptic hypersomnia categories include less defined EDS cases and likely consist of heterogeneous conditions. This is partially due to the fact that applying standardized polygraphic assessments [all-night polygraphic recordings followed by multiple sleep latency test (MSLT)] was often difficult in these neurological conditions. However, since the prevalence of these hypersomnia cases appeared to be much higher than that of symptomatic narcolepsy, we believe that the discussion on the roles of the hypocretin system in less well-defined EDS cases also has valuable clinical implications.

Definition of Symptomatic Narcolepsy and Its Overview

Symptoms of narcolepsy can sometimes be seen during the course of a neurological disease process. In such instances, the term "symptomatic

narcolepsy" is used, implying that the narcolepsy is a symptom of the underlying process rather than being idiopathic. For these cases, the signs and symptoms of narcolepsy must be temporally associated with the underlying neurological process. "Symptomatic narcolepsy" and "secondary narcolepsy" are used more or less indiscriminately, even though they have different meanings. We recommend the use of symptomatic narcolepsy/EDS, since "secondary EDS" has also been used to describe EDS associated with sleep apnea and restless leg syndrome.

In the ICSD-3 [16], "Narcolepsy Due to Medical Condition" is reclassified under "Narcolepsy Type 1 or Type 2 Due to a Medical Condition" depending on the hypocretin deficiency status, and the criteria for "Narcolepsy Type 1 Due to a Medical Condition" are reclassified under "The condition must fulfill criteria for narcolepsy Type 1 (i.e., hypocretin-deficient narcolepsy and be attributable to another medical disorder)." The criteria for "Hypersomnia Due to Medical Condition" have been changed to "Hypersomnia Due to a Medical Disorder." The following are the criteria:

Narcolepsy Type 1 **(Criteria A and B Must Be Met)**

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
B. The presence of one or both of the following:
   1. Cataplexy (as defined under Essential Features) *and* a mean sleep latency of ≤8 min and two or more sleep-onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
   2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/ml or <1/3 of mean values obtained in normal subjects with the same standardized assay.

"Narcolepsy Type 2 Due to a Medical Condition" is "[a] condition [that] fulfills criteria for narcolepsy Type 2 and is attributable to another medical disorder." The following are the criteria:

Narcolepsy Type 2 **(Criteria A–E Must Be Met)**

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
B. A mean sleep latency of ≤8 min and two or more sleep-onset REM periods (SOREMPs) are found on a MSLT performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
C. Cataplexy is absent.
D. *Either* CSF hypocretin-1 concentration has not been measured *or* CSF hypocretin-1 concentration measured by immunoreactivity is either >110 pg/ml *or* >1/3 of mean values obtained in normal subjects with the same standardized assay.
E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

"Hypersomnia Due to a Medical Disorder" fulfills the following criteria:

Hypersomnia due to a medical disorder **(Criteria A–D must be met)**

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
B. The daytime sleepiness occurs as a consequence of a significant underlying or neurological condition.
C. If an MSLT is performed, the mean sleep latency is ≤8 min, and fewer than two sleep-onset REM periods (SOREMPs) are observed.
D. The symptoms are not better explained by another untreated sleep disorder, a mental disorder, or the effects of medications or drugs.

Anatomical Substrate for the Symptoms of Narcolepsy

It is important to understand what mechanisms and which brain sites are involved in the occurrence of symptomatic narcolepsy, especially in relation to the hypocretin system. Although it is not simple to discuss mechanisms uniformly for symptomatic narcolepsy associated with various genetic disorders, analysis of symptomatic narcolepsy with tumor cases showed clearly that the lesions were most often (about 70 % of cases) involved in the hypothalamus and adjacent structures (the pituitary, suprasellar, or optic chiasm). Impairments in the hypothalamus are noted in most symptomatic cases of narcolepsy which also suggests a possible involvement of impaired hypocretin neurotransmission.

Lumber CSF hypocretin-1 measurements were carried out in neurological conditions possibly associated with symptomatic cases of narcolepsy/EDS using lumber CSF). The ventricular CSF data of PD in Drouot et al. [24] were not included. The following is a breakdown of the 345 cases measured in 2014, with incidence of low hypocretin-1 level out of total cases per neurological condition: narcolepsy/EDS associated with tumors (9 out of 14 had low levels of hypocretin), head trauma (3 out of 7), vascular disorders (1 out of 8), encephalopathies (4 out of 6), neurodegeneration (7 out of 209), immune-mediated demyelinating disorder (11 out of 19), immune-mediated polyneuropathy (1 out of 23), paraneoplastic autoimmune syndrome (2 out of 8), genetic/congenital disorders (7 out of 66), and others (2 out of 4) (Appendix Table 9.1). Among the 50 low hypocretin-1 cases, 22 (44 %) cases had hypothalamic lesions, and 28 (56 %) cases had no distinct lesions (Fig. 9.1).

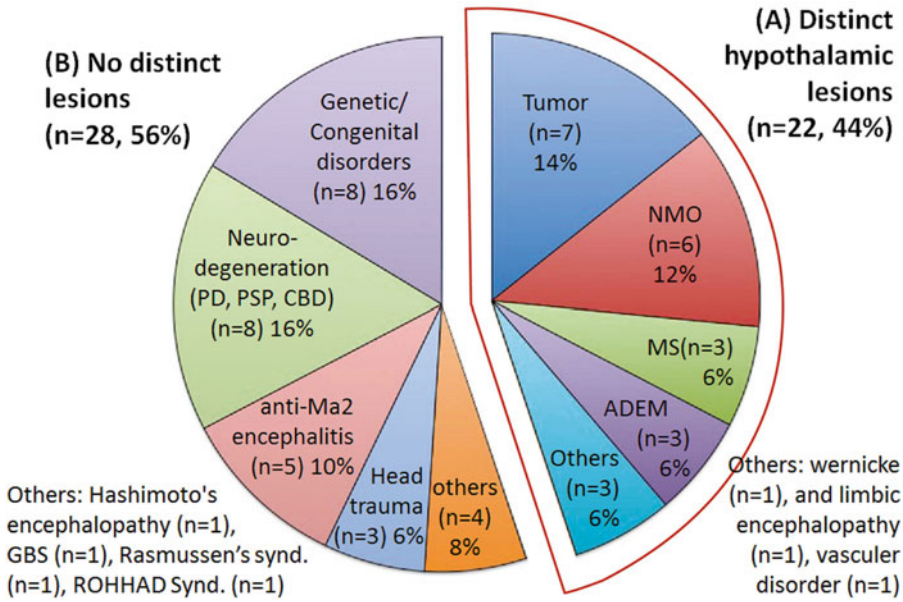

Fig. 9.1 Category of medical conditions associated with low hypocretin symptomatic narcolepsy. Fifty cases of narcolepsy due to medical conditions with low hypocretin are included. The percentage of each medical condition was displayed. (**a**) (I) Tumors ($n=7$, 14 %), (II) demyelinating disorders (NMO; $n=6$, 12 %), MS ($n=3$, 6 %), ADEM, ($n=3$, 6 %), (III) genetic/congenital disorders ($n=8$, 16 %) and (IV) neurodegeneration ($n=8$, 16 %), are the four most frequent causes. Several categories showed distinct hypothalamic lesions (**a**, $n=22$, 44 %), including tumors and demyelinating disorders, while genetic/congenital disorders, neurodegeneration, paraneoplastic autoimmune syndromes (anti-Ma associated encephalitis) and head trauma did not show distinct lesions (**b**, $n=28$, 56 %)

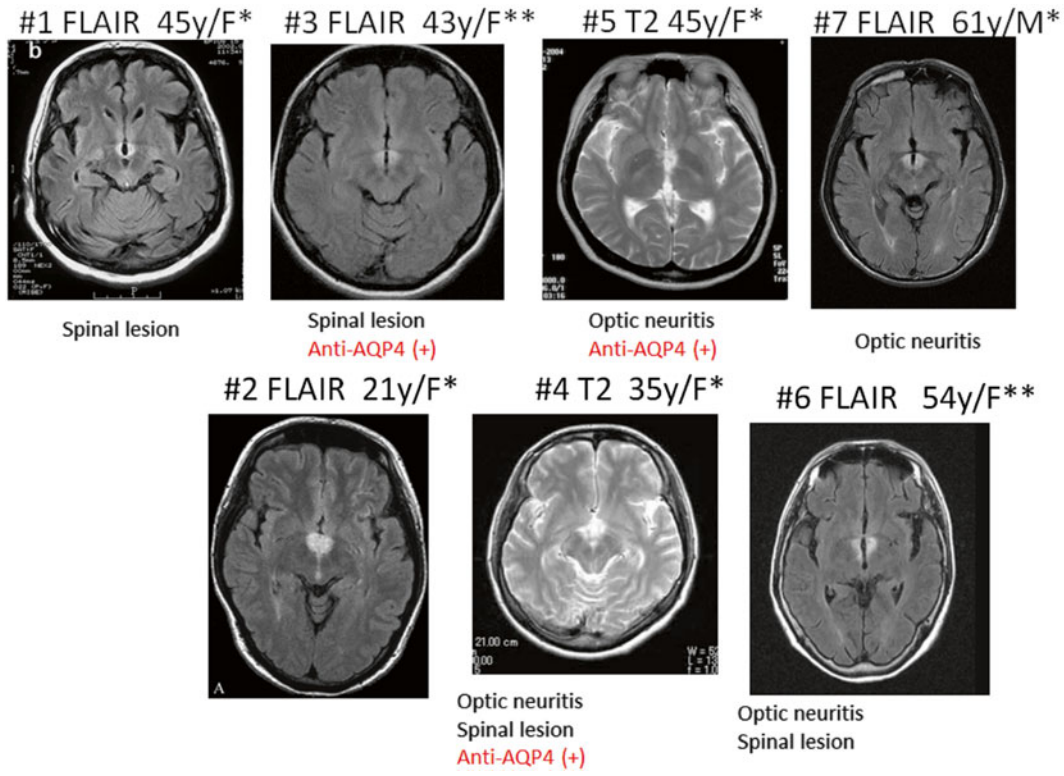

Fig. 9.2 MRI findings (FLAIR or T2) in multiple sclerosis (MS)/neuromyelitis optica (NMO) patients with hypocretin deficiency and excessive daytime sleepiness. A typical horizontal slice including the hypothalamic, periventricular area from each case is presented. All cases were female. *, met with ICSD-2 criteria for narcolepsy caused by a medical condition; **, met with ICSD-2 criteria for hypersomnia caused by a medical condition. All cases were initially diagnosed as MS. Cases 3–7 had optic neuritis and/or spinal cord lesions, and cases 4, 5, and 7 are seropositive for anti-AQP4 antibody and thus were diagnosed as NMO (Data from Kanbayashi, T, Shimohata T, Nakashima I, Yaguch H, Yabe I, Nishizawa M, Shimizu T, Nishino S (2009) Symptomatic Narcolepsy in Patients With Neuromyelitis Optica and Multiple Sclerosis: New Neurochemical and Immunological Implications. *Arch Neurol*. 66(12):1563–1566, with permission of the American Medical Association)

Recently, we have reported a new possible pathophysiology of symptomatic narcolepsy/EDS in patients with MS and its related disorders [25]. These cases often show unique bilateral symmetric hypothalamic lesions associated with significant hypocretin ligand deficiency. Interestingly, these patients often share clinical characteristics with neuromyelitis optica (NMO) patients, including optic neuritis or spinal cord lesions and the presence of NMO–IgG (anti-aquaporin-4 (AQP4) antibodies) (Fig. 9.2) [25]. AQP4 is highly expressed in the hypothalamic periventricular regions [26, 27], thus an immune attack to AQP4 may possibly be responsible for the bilateral and hypothalamic lesions and hypocretin deficiency in narcolepsy/EDS associated with these diseases. As AQP4 is found in nonneuronal structures such as astrocytes and ependymocytes, impairments of the hypocretin neurons are likely to be secondary to changes in their surrounding regions [25]. None of these cases exhibited cataplexy, but some exhibited REM sleep abnormalities, and thus some of these cases meet the ICSD narcolepsy criteria (Fig. 9.2). It should also be noted that many earlier narcolepsy–cataplexy cases were associated with MS (five out of six cases reported before 1970). Considering that most recent cases were treated with steroids (or other immunosuppressants) at the early stage of the disease and EDS and hypocretin deficiency

were often recovered, chronic impairments of the hypocretin system may be required for the occurrences of cataplexy (see [18]).

Although detailed mechanisms of hypocretin impairments in these NMO subjects need to be further explored, these new findings also confirm the importance of the hypothalamus, where the hypocretin neurons are located, as the brain structure involved in symptomatic narcolepsy.

Hypocretin Status in Various Neurological Conditions

Hypocretin Status in Symptomatic Narcolepsy–Cataplexy Associated with Distinct CNS Lesions

Soon after the discovery of the involvement of hypocretin impairments in idiopathic narcolepsy, Melberg et al. [28] reported a reduced CSF hypocretin-1 level (96 pg/ml) in a previously reported 51-year-old male case with autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCADN). In this Swedish pedigree (ADCADN; OMIM, Online Mendelian Inheritance in Man, accession number 604121), four out of five ADCA subjects are affected with narcolepsy–cataplexy [29], and CSF previously collected from one of these subjects (patients III-2) was available for hypocretin measures. The patient was negative for HLA-DR2. Since this case is a heredodegenerative disease with an enlargement of the third ventricle, moderate atrophy of the cerebellum and the cerebral hemispheres by MRI were observed, and we listed this case under narcolepsy associated with distinct CNS lesions.

Scammell et al. [30] subsequently reported a 23-year-old male who developed narcolepsy–cataplexy due to a large hypothalamic stroke after a craniopharyngioma resection. This lesion included 2/3 of the caudal hypothalamus except for the most lateral component on the right and extended into the mediodorsal thalamus bilaterally, the left amygdala, and parts of the basal forebrain and the rostral midbrain. Postoperative course was complicated by panhypopituitarism, staphylococcal meningitis, and hydrocephalus. He experienced HH. He became obese with a body mass index (BMI) of 31.7. Sleep latency was 0.5 min according to MSLT, and REM latency was 3.5 min. An overnight polysomnography (PSG) showed 1 min and 1.5 min of SL and REM latency, respectively, without significant sleep apnea. HLA was negative for DQB1*0602, and CSF hypocretin level was 167 pg/ml.

Nokura et al. [31] reported one case with narcolepsy and cataplexy-like phenomena in a 66-year-old female with hypersomnia due to a hypothalamic tumor. She showed EDS and cataplexy-like symptoms, such as abrupt falling without loss of consciousness. An MRI revealed lesions with high signal intensities in the hypothalamus, thalamus, and midbrain bilaterally. This case was accompanied with mild anterior hypopituitarism and a SOREMP in a daytime polysomnography. Hypocretin-1 level was 61 pg/ml. Symptoms improved with tumor reduction after radiotherapy and the intravenous administrations of nimustine hydrochloride and interferon beta.

The lesions in these cases had different etiologies: degeneration, infarction, and tumor. Although the number of cases is still limited, the hypothalamic lesions were noted in all cases. Moderate reduction of CSF hypocretin levels (low in two cases and intermediate in one) also confirmed the functional impairment of the hypothalamus. A massive impairment of hypocretin projections and projection sites is likely involved in the mentioned case with hypothalamic stroke after craniopharyngioma resection, implying that a more severe hypocretin neurotransmission impairment than that of the intermediate CSF hypocretin-1 level may exist. Although these results are consistent with the hypothesis of hypothalamic hypocretinergic involvement in symptomatic cases of narcolepsy, it is not certain if all cases with low hypocretin levels associated with hypothalamic damage develop narcoleptic symptoms.

Hypocretin Status in Symptomatic Narcolepsy–Cataplexy and/or EDS Associated with Inherited Disorders

There are clusters of cases of genetic or congenital disorders associated with primary central hypersomnolence and/or cataplexy, and CSF hypocretin-1 has also been assessed in several patients with Prader–Willi syndrome (PWS), Niemann–Pick type C disease (NPC), and myotonic dystrophy.

Prader–Willi Syndrome

EDS is a common symptom in PWS [32–34]. Sleep-disordered breathing (SDB) and narcoleptic traits such as SOREMPs and cataplexy have also been reported in these subjects [35, 36]. If SDB exists, primary hypersomnia should only be diagnosed if excessive daytime sleepiness does not improve after adequate treatment of sleep-disordered breathing. Mignot et al. [2] reported a 16-year-old male with the following: EDS, HLA-DQB1*0602 positive, 109 pg/ml hypocretin-1, obese (BMI = 48.1), documented 15q11-13 deletion, limited number of sleep-disordered breathing events [apnea hypoxia index (AHI) = 5.6], no cataplexy, SL = 3.0 min, and no SOREMPs by MSLT. Nevsimalova et al. [37] also measured CSF hypocretin-1 in another three PWS cases. One subject exhibited EDS (AHI = 3.1, age = 10) had low hypocretin-1 levels (130 pg/ml), and DQB1*0602, but the other two who did not exhibit EDS had intermediate (191 pg/ml) or normal (226 pg/ml) hypocretin-1 with (AHI = 46.8, age = 26) and (AHI = 0, age = 6), respectively. All three subjects were obese and did not exhibit cataplexy. Interestingly, AHIs in these PWS subjects were correlated with age and BMI, but not with CSF hypocretin-1 levels and EDS.

Additional reports suggested the possibility that EDS in PWS may also be attributed to the hypocretin system, not necessarily to sleep-disordered breathing caused by obesity. First, Arii et al. [17] reported a 2-week-old PWS male with severe hypotonia, poor feeding, documented 15q11-12 deletion, and intermediate hypocretin level (192 pg/ml). Then, Terashima et al. [38] reported an 11-year-old PWS female with the following: EDS, mild obesity (BMI = 19.9, %BMI = 108), no sleep-disordered breathing events, no cataplexy, SL = 3.0 min, SOREMPs confirmed by MSLT, and hypocretin 60 pg/ml. Dr. Nevsimalova also proposed that PWS cases may be a model for congenital dysfunction/developmental failure of the hypocretin system [37].

However, no decrease in the number of hypocretin-containing neurons was observed in postmortem human adult and infant brains [39], which suggests a lack of involvement of hypocretin in the pathogenesis of the disorder. In a larger context, this result underlies the need for larger studies to determine whether decreased CSF hypocretin-1 remains anecdotal in inherited neurological conditions.

Niemann–Pick Type C Disease (NPC)

NPC is an autosomal recessive and congenital neurological disorder characterized by the accumulation of cholesterol and glycosphingolipids in the peripheral tissues and of the glycosphingolipids in the brain. Classic NPC symptoms include hepatosplenomegaly, vertical supranuclear gaze palsy, ataxia, dystonia, and dementia. Subjects with NPC have been reported to frequently display narcolepsy-like symptoms, including cataplexy [21, 40–43]. This condition is remarkable as cataplexy is often triggered by typical emotions (laughing) and responsive to anticataplectic treatments.

Kanbayashi et al. [43] measured CSF hypocretin levels in two NPC cases with and without cataplexy. In the first case (male, age 5), cataplexy and an intermediate hypocretin level (142 pg/ml) were detected. Cataplexy was triggered by laughter since age 2. EDS was not claimed by the patient, and SL (16.5 min) was normal without SOREMPs [44]. No abnormalities in the hypothalamus were detected by MRI scans. He was negative for HLA DR2. In the second case (female, age 3), a normal hypocretin level (299 pg/ml) was detected. Neurological symptoms such as tremor, ataxia, and akathisia were present; neither cataplexy nor EDS was present.

Vankova et al. [41] reported five patients with juvenile NPC. Deterioration of intellectual func-

tion; the presence of pyramidal, dystonic, and cerebellar signs; and splenomegaly were observed in all cases as well as disrupted sleep in nocturnal polysomnography. Total sleep time, sleep efficiency, REM sleep, and delta sleep amounts were decreased when compared to age-matched controls. Cataplexy was reported in one patient. Shortened mean sleep latencies were observed in three patients during the MSLT, but SOREMPs were observed only in the case with cataplexy, and this case met with the criteria of symptomatic cases of narcolepsy. This patient was HLA-DQB1*0602 positive, while the other subjects were HLA-DQB1*0602 negative. CSF hypocretin-1 levels were reduced in patients (190 and 157 pg/ml in the subject with cataplexy), while in the two other patients, the CSF hypocretin-1 levels were at the lower end of normal (226, 245 pg/ml). The authors speculated that lysosomal storage abnormalities in NPC patients may also have an impact on the hypothalamus including the area where hypocretin-containing cells are located.

Oyama et al. [45] reported a Japanese patient with NPC caused by a homozygous c.2974 G>T mutation of the NPC1 gene, a well-known NPC1 gene mutation that causes a unique phenotype of NPC, which has been limited to a single Acadian ancestor in Nova Scotia, Canada. The patient characteristically started presenting with cataplexy at the age of 9 years, and the level of hypocretin-1 was moderately low, 174 pg/ml.

Eto et al. [46] reported a NPC case complicated by cataplexy (age 4, male) with hypocretin a level of 106 pg/ml. He had compound heterozygous *NPC1* mutations: a novel missense mutation (G9D) in exon 1 and a known missense mutation (R1186H) in exon 23.

Soda et al. [47] reported a NPC and narcolepsy–cataplexy case (age, 24) with hypocretin level of 88 pg/ml. Short sleep latency (1 min) and three SOREMPs in four naps were observed by MSLT. HLA typing was not typical for narcolepsy.

In these five reports, all of the NPC patients with cataplexy have an association with reduced hypocretin-1 levels, while CSF hypocretin-1 levels in the NPC cases without cataplexy are in the lower limit of normal, suggesting a degree of impairments of the hypocretin system which may contribute to the occurrence of cataplexy in this inherited diffuse CNS impairment condition.

Myotonic Dystrophy (MYD)

Myotonic dystrophy type 1 (MD1) is a multisystemdisorder with myotonia, muscle weakness, cataracts, endocrine dysfunction, and intellectual impairment [48–50]. This disorder is caused by a CTG triplet expansion in the 3′ untranslated region of the DMPK gene on 19q13. The expansion resides within ubiquitously expressed genes and when transcribed accumulates in the nuclei as RNA expansions. This induces the sequestration of muscleblind proteins (Mbnl 1,2,3—RNA-binding proteins selective for UG-rich domains) and upregulation of CUG-binding protein/Elav-like family (e.g., CELF) resulting in altered splicing of Mbnl-regulated transcripts and causing major aspects of DM [51–55]. MD1 is frequently associated with EDS and the presence of SOREMPs, which are sleep abnormalities similar to narcolepsy, during the MSLT [49, 50, 56–65]. The disease is also often associated with SDB, and thus this may also account for appearances of SOREMPs. However, adequate treatment of sleep-disordered breathing does not always eliminate EDS [59, 60]. Since many DM1 patients with no sign of sleep apnea or chronic alveolar hypoventilation also exhibit EDS, some authors believe that a central dysfunction is primarily involved in the EDS in DM1 [50, 61–63].

Martinez-Rodriguez [23] reported six patients with MYD1 complaining of EDS. The mean sleep latency on MSLTs was abnormal in all patients (<5 min in two, <8 min in four), and two SOREMPs were observed in two subjects, meeting the criteria for symptomatic narcolepsy. It should be noted that these two cases also had SDB. All patients were HLA-DQB1*0602 negative. Hypocretin-1 levels (181 pg/ml) were significantly lower in patients versus controls (340 pg/ml); the one case with two SOREMPs had hypocretin-1 levels in the low range (<110 pg/ml) generally observed in narcolepsy. Three

cases had intermediate levels (110–200 pg/ml). The authors suggested that a dysfunction of the hypothalamic hypocretin system may mediate sleepiness and abnormal MSLT results in patients with MD1.

In one case of late-onset congenital hypoventilation syndrome, a disorder with reported hypothalamic abnormalities [66], Martinez-Rodriguez found very low CSF hypocretin-1 levels in an individual with otherwise unexplained sleepiness and cataplexy-like episodes [23]. Excellent response to anticataplectic medication was observed in this case.

Iwata et al. [67] and Yasui et al. [68] each reported a case of MYD1 with narcolepsy due to medical condition. Both patients had no cataplexy and were HLA-DQB1*0602 negative. In the former case, hypocretin was markedly decreased to ≤40 pg/ml. The size of the CTG repeat was markedly increased in the 3′ untranslated region of the DMPK gene at 1800–2400 repeats, and PSG revealed severe sleep apnea (AHI = 59 h^{-1}, BMI = 27.7) and chronic alveolar hypoventilation indicating severe disease. Since her nocturnal sleeping time was extended to 18 h per day, MSLT revealed normal sleep latencies and no SOREMPs. In the latter case, the patient was using BiPAP due to nocturnal hypoxia (BMI = 27.3).

However, a larger study failed to confirm these results [69]. Hypocretin-1 concentrations did not correlate clinically with disease severity or duration or with subjective or objective reports of sleepiness. Because CSF hypocretin concentrations are often only slightly decreased in some patients, a functional abnormality that causes sleepiness and SOREMPs in myotonic dystrophy type 1 is unlikely to be a common occurrence.

It should also be pointed out that EDS in DM1 is distinctive (from such as that of narcolepsy), and a recent comprehensive sleep evaluations in 40 DM1 patients [64] demonstrated that unlike in narcolepsy, most patients did not show shortened sleep latency in MSLT [DM1 14. 2 min (2.8–20 min) versus control 14.2 min (8.2–20 min)], although most of them claimed moderate to severe subjective daytime sleepiness (79.5 vs. 17.1 %, $p < 0.002$) or fatigue (62.2 vs. 17.1 %, $p < 0.002$). The current International Criteria for Sleep Disorders sets the cutoff for the MSLT mean sleep latency as less than 8 min, and thus most of these sleepy DM1 patients do not even fit in the diagnostics category of hypersomnias [15]. Occurrence of cataplexy was also never reported in DM1 [49, 50, 56–64].

Thus, the pathophysiology of EDS in DM1 is truly mysterious.

Recent animal studies using the mouse model of DM demonstrated a selective and robust increase in REM sleep propensity [51]. Mbnl1 KO and Mbnl2 KO mice were recently generated and shown to develop muscle and other DM symptoms, and thus these KO mice are informative animal models of DM [53, 54]. As Mbnl2 plays a more important role as a splicing regulator during brain development compared to Mbnl1 [51, 70], the sleep phenotype of Mbnl2 KO mice has been evaluated [51]; Mbnl2 KO mice showed an increase of REM sleep amounts associated with increased EEG theta power. This change was most notable during the dark period when mice are normally awake. Interestingly, a larger portion of these dark period REM sleep episodes in Mbnl2 KOs exhibited a short latency from the proceeding wake episodes, but they did not exhibit cataplexy. A more profound REM sleep rebound after a 6-h sleep deprivation was also observed in KOs, compared to wild-type (WT) mice. These sleep changes were REM sleep specific, as no changes in wake and non-REM sleep were seen in these KO mice at the baseline and during sleep rebound, suggesting that Mbnl2 KO mice exhibit selective increases in REM sleep propensity. Based on these results and the fact that selective REM sleep deprivation in human induce a significant increase in REM sleep propensity and sleepiness during daytime [71], we hypothesize that abnormal REM sleep propensity may primarily cause EDS in DM1, and altered splicing of Mbnl-regulated transcripts can induce REM sleep abnormalities in DM1.

Hypocretin Status in Hypersomnia in Various Neurological Conditions

Focal/Generalized CNS Invasion

Symptomatic narcolepsy is relatively rare, but sleepiness without other narcoleptic symptoms can often occur with a variety of neurological disorders; they are more likely to be due to multifocal or global disturbances of the brainstem, diencephalon, and cerebral cortex. Recently, several clinical studies also suggested that the disruption of the hypothalamic hypocretin system in EDS is associated with various neurological conditions.

Cerebral Tumors

Cases with EDS seen along with various cerebral tumors have been reported. Six of these cases we reviewed presented low hypocretin-1 levels [72, 78].

Case 1: Hypersomnia seen after removal of a hypothalamic suprasellar Grade II pilocytic astrocytoma: MRI showed that the bilateral, medial, and lateral hypothalamic areas and right posterior hypothalamus were damaged. Hypocretin-1 levels were 104 pg/ml and HLA-DR2 negative. Symptoms included diabetes insipidus (DI), hypothyroidism, weight gain, and no cataplexy. MSLT: sleep latency is 1.7 min and no SOREMPs [72].

Case 2: EDS in a patient in a vegetative state following astrocytoma resection and CNS hemorrhage: MRI revealed a large suprasellar mass that extended into the sella inferiorly and was displaced posteriorly. Hypocretin-1 was undetectably low, and HLA-DR2 and DQB1*0602 were negative. Nocturnal EEG study showed fragmented sleep with 16 short REM cycles. The daytime EEG showed frequent REM periods. EDS improved with 200 mg modafinil and 5 mg methylphenidate [73, 74].

Case 3: Hypersomnolence in patient with extensive hypothalamic damage after removal of a craniopharyngioma: CSF hypocretin-1 level (93 pg/ml) was low with negative HLA-DQB1*0602 typing. Short sleep latency and SOREMPs during a MSLT suggested a diagnosis of symptomatic narcolepsy which indicated a destruction of hypocretin-producing neurons in the hypothalamus [75].

Case 4: Severe symptomatic narcolepsy in a patient with primary CNS B-cell lymphoma whose symptoms reversed after chemotherapy: MRI revealed an infiltrative hyperintensity in the left basal ganglia, thalamus, cerebral peduncle, splenium of the corpus callosum, and the right internal temporal lobe. CSF hypocretin-1 level was undetectable, and DQB1*0602 typing was negative. Patient had entered a permanent hypersomnia status, related to a coma-like state. After IV and intrathecal chemotherapy, hypersomnia resolved completely and without any abnormal REM sleep manifestation. Eight months later, a 24-h polysomnography was normal without daytime sleep episodes. Brain MRI and FDG PET scans as well as hypocretin-1 level (244 pg/ml) were normal after treatment [76].

Case 5: A 19-year-old woman suffered from severe EDS accompanied with long sleep episodes both in the daytime and nighttime and frequent episodes of cataplexy shortly after the removal of craniopharyngioma in the intrasellar space (Fig. 9.3). MSLT showed a typical finding of narcolepsy, and CSF hypocretin concentration (71 pg/ml) was below the narcolepsy cutoff value. MRI-tractography showed a clear lack of neuronal fiber connections from the hypothalamus to the frontal lobe [77].

Case 6: A 13-year-old girl suffered from severe hypersomnolence in the daytime and nighttime and several episodes of cataplexy after the removal of craniopharyngioma. She also had DI and hypothalamic-pituitary dysfunction. Her hypocretin level was <40 pg/ml [78].

We also reviewed three case reports in which hypocretin-1 levels were normal to high.

Case 7–11: EDS in a total of five patients who underwent relatively extensive surgeries involving the hypophysis and hypothalamus for craniopharyngioma ($n=3$), germ cell

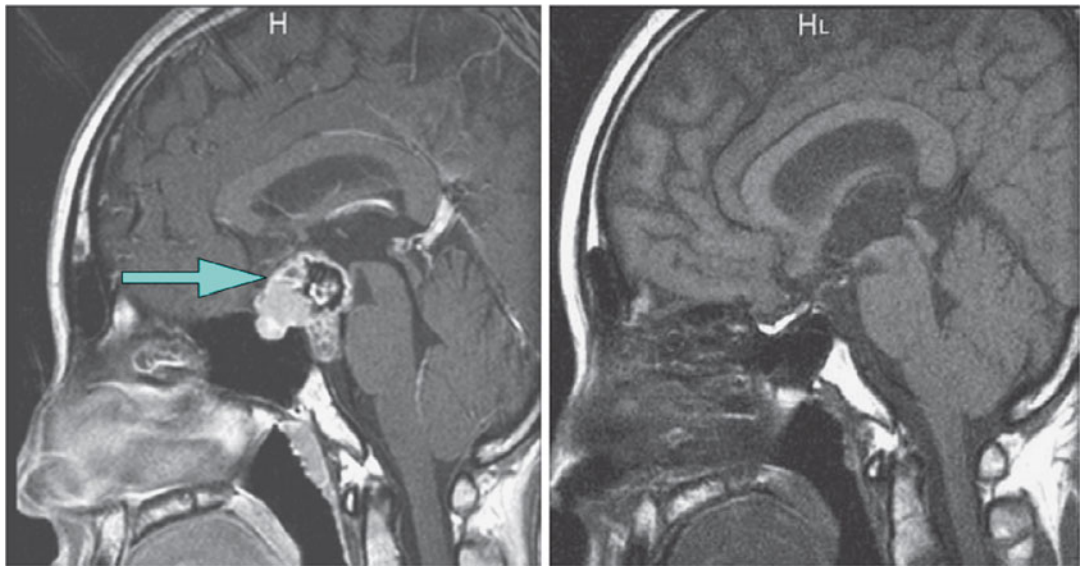

Fig. 9.3 Possible mechanism of secondary narcolepsy with a long sleep time following surgery for craniopharyngioma. *Left panel* (before surgery): a tumor (*arrow*) 30 mm in maximum dimension in the intrasellar, area. *Right panel* (after surgery): the expansion of the third ventricle and atrophy of the, pituitary gland, as well as a cavity forming in the hypothalamic area after surgery (Reproduced from Sakuta K, Nakamura M, Komada Y, Yamada S, Kawan F, Kanbayashi T, et al. (2012) Possible mechanism of secondary narcolepsy with a long sleep time following surgery for craniopharyngioma. Intern Med 51: 413–417, with permission of the Japanese Society of Internal Medicine)

tumor (1), and thalamic arachnoid cyst ($n = 1$): The craniopharyngiomas and germ cell tumor were located in the hypothalamus-hypophysis region, and the arachnoid cyst was in the thalamic region. All patients received hormone replacement therapies. Mean hypocretin-1 (133 pg/ml) was as same as their control range. The mean sleep latency by MSLT in the five patients was 10.3 min. Two patients were morbidly obese and had obstructive sleep apnea, and although treatment with continuous positive airway pressure resulted in complete resolution of their sleep-disordered breathing, daytime somnolence was unchanged [79].

Case 12: A patient who developed a narcoleptic-like sleep disorder immediately following pinealectomy for a choroid plexus carcinoma of the pineal gland: The patient also underwent chemotherapy and radiation treatment. Immediately after surgery, the patient developed EDS that she attributed to severe insomnia and an irregular sleep/wake rhythm. SP and HH were present but not cataplexy. An increased percentage of REM sleep was seen in nocturnal polysomnography, and three out of four SOREMPs were seen during the MSLT. CSF hypocretin level (518 pg/ml) was normal, and the patient was negative for HLA-DQB1*0602. The author proposed that her symptoms may be caused by an unknown mechanism unrelated to hypocretin depletion [80].

Case 13: Narcolepsy–cataplexy that developed in acromegaly patient, two weeks after completing radiotherapy for a pituitary adenoma: Hypocretin-1 was normal (275 pg/ml), and HLA was not typical for narcolepsy. Both HH and SP were present. Sleep latency by MSLT was 6.4 min, and REM latency was 9 min (three SOREMPs/five naps). He was obese (BMI: 35), and his AHI was 17 h^{-1}. The authors have speculated that the radiotherapy of the tumor was associated with a damage to a locus rich in hypocretin receptors [81].

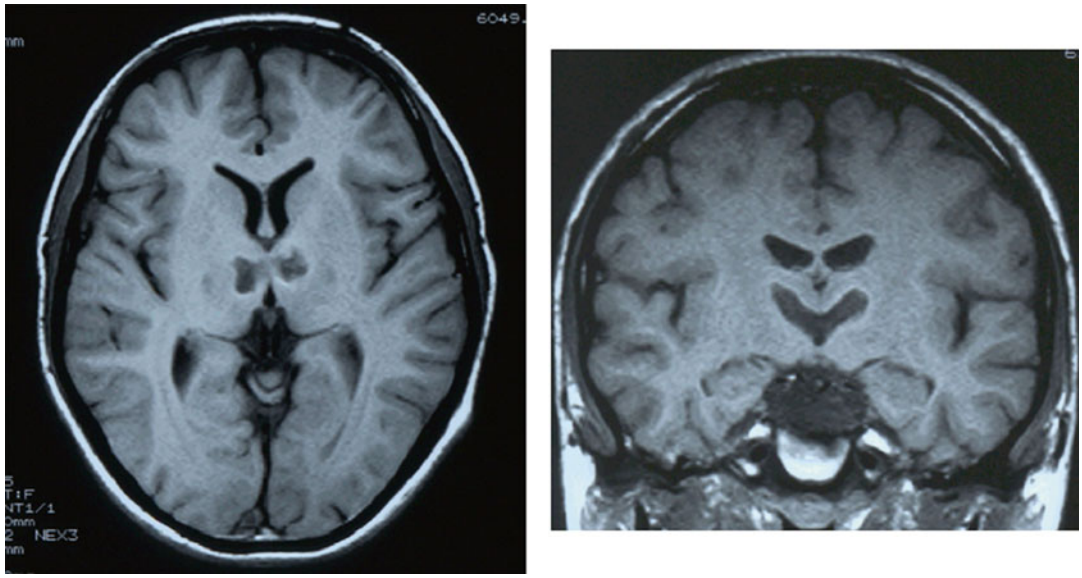

Fig. 9.4 (**a**, **b**) A case of a 15-year-old with paramedian thalamic infarctions and normal hypocretin level (274 pg/ml). Tohyama et al. (2004) [78] reported a case with paramedian thalamic infractions and normal hypocretin level (274 pg/ml). A 15-year-old male with EDS due to bilateral paramedian thalamic infarctions. Patients with bilateral paramedian thalamic lesions are known to often exhibit atypical hypersomnia (i.e., de-arousal or subwakefulness) (Guilleminault et al.) [79]. The lateral hypothalamus (where hypocretin cell bodies locate) was not affected, and CSF hypocretin level was in the normal range. It is not known whether the other hypocretin systems (projections or receptive sites) are still involved in EDS with paramedian thalamic infractions (Reproduced from Tohyama J, Kanazawa O, Akasaka N, Kamimura T (2004) A case of bilateral paramedian thalamic infarction in childhood with the sensory disturbance and the sensory loss of taste. No To Hattatsu 36(1):65–9, with permission of the Japanese Society of Child Neurology)

Overall, we reviewed seven symptomatic cases with EDS with low hypocretin-1 levels (one case in sect "Hypocretin Status in Symptomatic Narcolepsy–Cataplexy Associated with Distinct CNS Lesions") and seven cases in three case reports with normal to high hypocretin-1. All the cases with low CSF hypocretin-1 levels were either HLA-DR2 or HLA-DR2 and DQB1*0602 negative, thus EDS in these cases are likely secondary to the hypocretin deficiency caused by the tumors/tumor removal. Other mechanisms likely cause EDS in the seven cases with normal or high hypocretin-1 levels, although impairment in hypocretin projections, terminals, or postsynaptic receptors may also be caused by the tumors.

Infarctions

EDS has been reported in cerebra infarction cases. Bassetti et al. reported two cases with EDS and cerebral infarction. In a thalamic infarction case, mean sleep latency was 9 min, and hypocretin level was 265 pg/ml. In a pontomedullary infarction case, sleep latency was 1 min, and hypocretin level was 316 pg/ml [8].

Two hypersomnia cases with bilateral paramedian thalamic infarctions were also independently reported [31, 82]. The paramedian thalamus is believed to play an important role in the regulation of sleep, and disturbances of sleep regulation are known to occur in paramedian thalamic stroke [83, 84]. The first case suffered from bilateral paramedian thalamic infarctions and had EDS with SOREMPs (two times in four naps). His hypocretin-1 level was 312 pg/ml [31], and the symptoms met with the criteria for Narcolepsy Type 2 Due to a Medical Condition. The second case suffered from bilateral paramedian thalamic infarctions and hypersomnia. His hypocretin level was 274 pg/ml

[82] (Fig. 9.4). Since the lesions of infarctions did not include the hypocretin cell bodies, their hypocretin levels seemed to be normal. However, hypocretin projection could still be impaired. Guilluminault et al. has pointed out that patients with bilateral paramedian thalamic lesions do not present a typical hypersomnia but a de-arousal or subwakefulness with an inability to develop sleep outside the normal circadian boundary (pseudo-hypersomnia) [83]. Indeed these patients showed reduced latency to stage 1 during MSLT, but did not develop other normal non-REM sleep and REM sleep statuses during the daytime. It may also be possible that hypocretin deficiency is not involved in the so-called pseudo-hypersomnia associated with bilateral paramedian thalamic lesions, and other pathophysiological needs are to be considered for these unique sleep symptoms.

Encephalopathies

Wernicke's Encephalopathy

A 5-year-old female with Wernicke's encephalopathy (Fig. 9.5) was reported to have gradually developed sleepiness and an abnormal sleep/wake schedule [85]. She slept 15–20 h per day and fell asleep frequently even while eating. She developed ocular and neurological symptoms (such as involuntary movements, hemiparesis, depression of speech, and global confusional state). An MRI revealed lesions in the bilateral hypothalamus in addition to the dorsomedial nucleus of thalamus and mammillary bodies and periaqueductal gray and floor of the fourth ventricle. Vitamin B1 levels were low (38.7 ng/ml, normal range: 52–176 ng/ml), and the level of hypocretin of CSF was decreased (<40 pg/ml). Her sleepiness and MRI findings gradually improved with thiamine

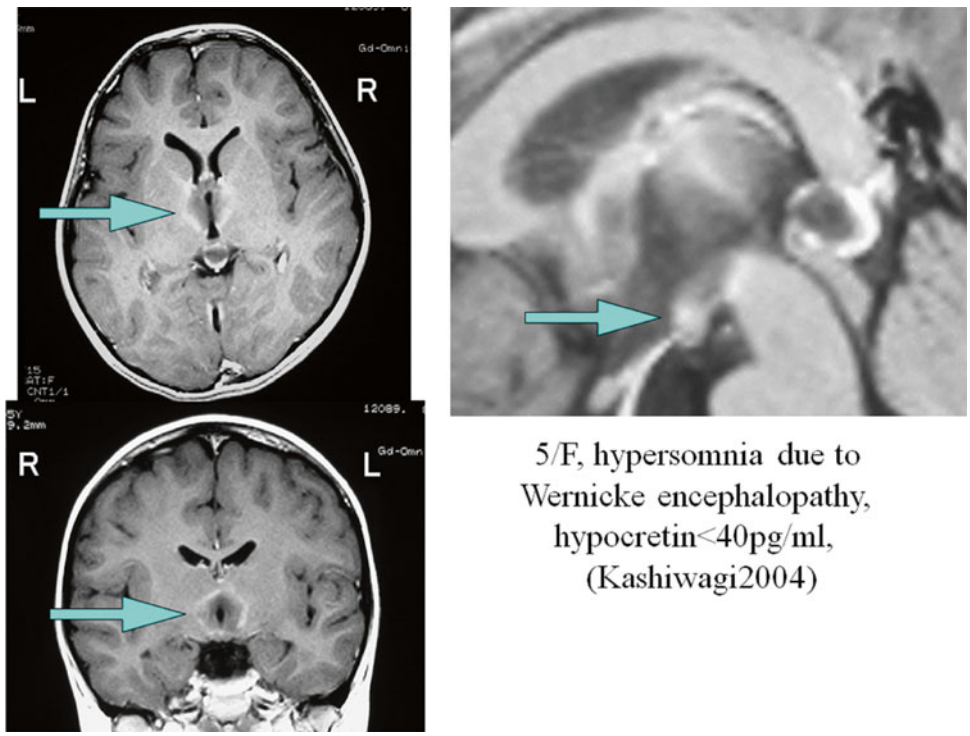

Fig. 9.5 Hypersomnia due to Wernicke's encephalopathy. A case of a 5-year-old with Wernicke's encephalopathy. Her sleep time was 15–20 h per day, and she fell asleep frequently even while eating. Gd-enhanced MRI revealed lesions in the bilateral hypothalamus in addition to dorsomedial nucleus of thalamus and mammillary bodies and periaqueductal *gray* and floor of 4th ventricle. The level of vitamin B1 was low. The level of hypocretin was decreased (<40 pg/ml). Her sleepiness and MRI findings gradually improved with replacement of vitamin B1 [81]

therapy. Six months after the onset of sleepiness, both MRI lesion and CSF hypocretin level (158 pg/ml) recovered to some degree. It is not clear whether Wernicke's encephalopathy affect the hypocretin system directly or indirectly. It is also not fully studied whether the change in the hypocretin neurotransmission is solely responsible for the occurrence of the EDS. The dysfunction of hypocretin neuron due to hypothalamic lesion would be caused by damages for AQP4 water channel [86].

Limbic Encephalopathy

Chronic progressive hypersomnia was seen in a patient with non-paraneoplastic immune-mediated limbic encephalitis. Hypocretin-1 concentration was low (87 pg/ml). An MRI of the brain showed bilateral signal abnormalities in the medial temporal lobes and the hypothalamus, but systemic examinations for malignant tumors were negative. Acyclovir treatment failed to amend his condition. Subsequent steroid treatment improved his hypersomnia and reduced the extent of abnormal signals on MRI. The CSF hypocretin concentration increased to 148 pg/ml 23 days after [87].

Rasmussen's Syndrome

Lagrange et al. reported a case of narcolepsy and Rasmussen's syndrome in a previously healthy 40-year-old man. Severe EDS, cataplexy, HH, and SP developed over the course of a few months. Brain MRI was normal, and polysomnography with MSLT confirmed a diagnosis of narcolepsy (SL: 1.6 min, three SOREMPs in four naps). His HLA haplotype is DQB1*0602, and CSF analysis showed no detectable hypocretin. Approximately 18 months later, he developed complex partial seizures. Further MRI showed a progressively enlarging lesion involving the left frontotemporal and insular areas. Pathology from a partial resection samples was consistent with Rasmussen's syndrome. Evaluation for tumor, infectious, and paraneoplastic etiologies was negative. There was no further progression of the residual lesion on serial MRI [88].

Although the pathophysiological bases of narcolepsy and Rasmussen's syndrome are unknown, the author speculated the possibility of a common underlying disease processes related to autoimmune mechanism. However, whether or not this case highlighted a temporal relationship between hypocretin deficiency and the onset of the disease is not known. It may also be possible for Rasmussen's syndrome to be the comorbidity with idiopathic narcolepsy, since the subject is HLA positive, and late-onset cases of idiopathic narcolepsy are also reported.

Brain Stem Encephalitis

Mathis et al. described a case of a previously healthy young man who concurrently developed a narcoleptic syndrome and a full-blown REM sleep-related behavior disorder (RBD) after an acute brainstem encephalitis with an isolated inflammatory lesion in the dorsomedial pontine tegmentum. Presenting with hypersomnia, sleep paralysis, hypnagogic hallucinations, and SOREMPs, the patient fulfilled the criteria of narcolepsy, although cataplexy was mild and rare. CSF hypocretin was normal (266 pg/ml), and HLA haplotypes were not typically associated with narcolepsy and RBD (DQB1*0602, DQB1*05) [89].

Hashimoto's Encephalopathies

Castillo [90] reported a 65-year-old male patient with steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) and hypersomnolence and then coma. He had undetectable levels of hypocretin-1 in the CSF during symptomatic period.

Neurodegenerative Disorders

Parkinson's Disease (PD)

Thirty percent of patients with Parkinson's disease (PD) have been reported to have EDS. Sleep problems are often related to the disease itself (e.g., difficulties in maintaining sleep because of motor disabilities), but they can also occur secondary to pharmacological treatments, especially with dopamine D2/D3 agonists. Ripley et al. initially reported that CSF hypocretin-1 lev-

els in 7 PD subjects were in the normal range, but sleep abnormalities of these subjects were not assessed [13]. In a separate study, CSF hypocretin levels were also normal in all three PD patients with EDS [91].

However, subsequent studies reported that patients with late-stage PD had low ventricular CSF hypocretin-1 levels ($n=16$, <50–97 pg/ml; $N=3$, 138–169 pg/ml) [24]. Hypocretin-1 levels decreased with increasing disease severity. The author described that CSF hypocretin-1 levels may reflect the size of the hypocretin neuron pool, and a decrease in hypocretin-1 level may indicate degeneration of hypocretin neurons in PD. The sleepiness of the patients was assessed by Epworth Sleepiness Scale (ESS). The mean ESS of these PD patients (11 ± 1) was significantly higher than that of controls (4 ± 1), but hypocretin-1 level was not correlated with ESS among PD subjects.

Two recent studies reported significant (50 %) hypocretin cell loss in postmortem hypothalami of patients with Parkinson's disease and the presence of Lewy bodies in some hypocretin-producing cells [92, 93]. In Parkinson's disease, hypocretin cell loss is 23–62 % and correlates with disease severity [93], as measured on the Hoehn and Yahr scale [94]. However, hypocretin cell loss was not specific, and nearby neurons containing melanin-concentrating hormone were similarly lost (12–74 %) in proportion to disease severity [93]. Furthermore, CSF hypocretin-1 levels were normal in Parkinson's disease [13, 91, 95–98], even if associated with severe sleepiness [91, 99], in most studies, excluding a few [24, 100–104]. Interestingly, however, significant reductions in the number of hypocretin cells in the hypothalamus [92, 93] and decrease in hypocretin-1 concentrations in the ventricles [24, 92] are evident, and thus moderate hypocretin deficiencies that are not detectable by lumbar CSF hypocretin-1 measures likely exist in a subset of PD subjects. Specificity of these finding and functional correlations, especially with EDS, are still unknown.

Dementia with Lewy Bodies (DLB)

Dementia with Lewy bodies (DLB) is the second major type of senile, degenerative dementia, after Alzheimer's disease (AD). DLB shares many features with PD. EDS, hallucinations, and REM sleep behavior disorder are symptoms reported in both DLB and narcolepsy. However, Baumann et al. [105] reported that patients with DLB had normal hypocretin-1 levels. No histological studies focusing on hypocretin neurons in DLB were available.

CSF hypocretin-1 concentrations have also been assessed in multiple system atrophy, DLB, and corticobasal degeneration [13, 95, 96, 105–108]. In almost all cases, CSF hypocretin-1 concentrations were normal.

Progressive Supranuclear Palsy (PSP)

EDS was reported in probable progressive supranuclear palsy (PSP) in a 74-year-old female. The EDS mimicked narcolepsy without cataplexy (MSLT showed short latencies of less than 2 min without SOREMPs), HLA was positive for DR2/DQB1, and CSF hypocretin-1 concentration was undetectable [109]. It is not clear if the co-occurrence of these disorders is due to a common process or comorbidity. The author speculated that the existence of neuropathological changes, such as neurofibrillary tangles in hypothalamus of the patient with PSP, might cause decreased hypocretin neurotransmission.

Narcolepsy with cataplexy has also been reported in probable PSP, in a 74-year-old male [110]. Patient medical history revealed cataplexy and EDS symptoms fluctuating since age 20, but by age 69, cataplexy and EDS had returned. PSP symptoms such as dysarthria, difficulty in writing, and gait disturbance appeared at age 70. At the time of detailed examinations, ESS was 14, and the patient showed sleep paralysis even during eating and the cataplexy induced by laughter. Other symptoms included the following: vertical gaze limitation, Myerson's sign, small voice, a masked face, wide gait, easily falling backwards, mild muscular rigidity in neck and wrists, bradykinesia in

the extremities, and no resting tremor; these symptoms were agreeable to diagnose as PSP. In the MRI, the third ventricular enlargement, midbrain tegmentum atrophy, and mild frontal lobe atrophy were detected. CSF hypocretin-1 was less than 40 pg/ml, and HLA DR2 and DQB1 were positive. In PSG, total sleep time was short with 274 min, and 43.1 % wake after sleep onset were present. The AHI was 14/h. Mean sleep latency was shortened to less than 2.9 min, and SOREMPs were present in all four naps. L-dopa and amantadine were slightly effective for gait, but never effective for other motor symptoms. Methylphenidate (20 mg/day) was effective for daytime sleepiness, and clomipramine was effective for cataplexy.

Yasui et al. also reported that hypocretin levels were significantly lower in the PSP group compared to PD ($p<0.001$) and that hypocretin levels were inversely correlated with duration of morbidity in PSP but not in the other conditions studied [96]. They speculated that loss of hypocretin neurons or impaired hypocretin neurotransmission might exist as a part of the neurodegeneration associated with advanced PSP with long duration of morbidity. Considering the aforementioned two case reports by Hattori et al. [109] and Sugiura et al. [110], PSP may be a susceptibility factor for EDS and/or symptomatic narcolepsy associated with hypocretin deficiency. However, more cases are needed to address this question.

Alzheimer's Disease (AD)

CSF hypocretin-1 levels in 24 patients with Alzheimer's disease (AD) were reported normal [13]. AD was known with established sleep abnormalities [111]. In AD subjects, dysfunction of other neurochemical systems, for example, cholinergic systems, may be more directly involved in sleep abnormalities.

Subsequently, several studies have explored hypocretin abnormalities in Alzheimer's disease. Studies in older rats have suggested a very slight hypocretin cell loss and significantly decreased CSF hypocretin-1 concentrations [112]. By contrast, lumber CSF hypocretin-1 concentrations have been shown to be normal in all studied patients with Alzheimer's disease [95, 106, 113], although wake fragmentation was correlated with lower CSF hypocretin-1 concentrations in one study [106]. No histological studies focusing on hypocretin neurons in Alzheimer's disease were available.

Huntington's Disease

In Huntington's disease, disrupted hypocretin transmission was first suggested through the study of R6/2 mice, a murine model of Huntington's disease with accelerated disease progression. Low CSF hypocretin-1 concentrations and decreased hypocretin cell counts were reported in these mice [114]. Huntington's disease is an autosomal dominant disorder with impaired motor coordination, caused by a CAG-triplet repeat extension in Huntington's disease gene (HTT). Huntington's disease is not associated with hypersomnia, cataplexy, or SOREMPs. Widespread cell loss occurs in Huntington's disease, including in the hypothalamus [115]. A slight (27 %) loss of hypocretin neurons was also reported in postmortem human brains [114]. More recent studies have shown that the cell loss is not associated with low CSF hypocretin-1 concentrations [116–119]. Functional roles of hypocretin cell loss in Huntington's disease are not known, but may not be strong. Indeed, studies in rats have shown that decreased CSF hypocretin occurs only when more than 50 % of cells are lost or affected [120, 121].

Head Trauma

The association of narcolepsy/EDS with head injury is controversial. Most people with hypersomnolence after closed head injury do not have narcolepsy [122], but some patients with narcolepsy report that their symptoms began after a head injury [123–128]. Lankford et al. [123] reported nine detailed cases with narcolepsy (five HLA positive, two HLA negative, and two undetermined), but hypocretin-1 levels were not measured. Later, low to undetectable CSF hypocretin-1 concentrations have been found in many patients with acute brain trauma or post-CNS hemorrhage [13, 129, 130]. Because adding blood to CSF in vitro does not alter CSF hypocretin-1 concentrations, the possibility of a functional connection has been raised.

Dauvilliers et al. [95] reported that a patient severely affected with posttraumatic hypersomnia with brain lesions (determined by MRI) had an intermediate CSF hypocretin-1 level (176 pg/ml, HLA negative), while another severely affected patient had a normal level (503 pg/ml, HLA positive). These two patients had no cataplexy but had shortened sleep latencies (4.5 min and 3.0 min, respectively) without SOREMPs by MSLT.

Arii et al. [131] reported a 15-year-old male affected with posttraumatic hypersomnia with an intermediate hypocretin-1 level. His Glasgow scale at 48 h after injury was 12 (E2V4M6). An MRI showed severe cerebral contusion of the bilateral basalis of the frontotemporal lobe and medial part of the right occipital lobe with CSF leakage. One year after injury, he needed more than 9 h nocturnal sleep and one or two 1–3-h naps daily. The hypocretin-1 level was 151 pg/ml. MRI showed atrophies in the basalis of the temporal lobe and medial part of the right occipital lobe. The hypothalamus showed moderate atrophy with dilatation of the third ventricle but no localized lesion.

Baumann et al. [129] reported abnormally low CSF hypocretin-1 concentrations immediately after traumatic brain injury in approximately 95 % of patients with severe-to-moderate brain injury. However, hypocretin-1 concentrations improved to normal in most patients 6 months after the traumatic brain injury, suggesting a functional alteration rather than neuronal loss [132]. Further studies are assessing the prevalence of residual hypersomnia and narcolepsy in correlation with CSF hypocretin-1 concentration and areas of focal damage. A temporary decrease in CSF hypocretin-1 could indicate a decrease in hypocretin tone (e.g., if CSF flow dynamics or dilution occurs) and/or contribute to changes in consciousness in patients with traumatic brain injury.

Baumann reported two male patients in whom MSLT revealed >2 SOREMPs and abnormally short mean sleep latencies (6.3 and 2.9 min, respectively) [132]. ESS scores were 13 and 9, respectively. In both patients, Ullanlinna and Swiss Narcolepsy Scales were normal. Neither of the patients had cataplexy-like episodes, hypnagogic hallucinations, or sleep paralysis. CSF hypocretin-1 levels in the acute phase were 63 and 83 pg/ml. Six months after TBI, levels were normal (468 pg/ml) and low (289 pg/ml), respectively. HLA typing was negative for both patients. In the younger patient, TBI was mild, but severe in the 26-year-old patient. Brain CT scans did not reveal hypothalamic lesions. These patients were asymptomatic before TBI. Based on the MSLT findings and according to the international classification of sleep disorders, these two patients can be diagnosed as narcolepsy without cataplexy (ICSD2) [15].

One male patient (22 years old) reported hypnagogic hallucinations and cataplexy-like episodes (subjective weakness in both knees with laughter), which did not fulfill the criteria of cataplexy [133]. ESS was 11, Ullanlinna Narcolepsy Scale 15, Swiss Narcolepsy Scale normal, and mean sleep latency 5.6 min, and there were no SOREMPs. This patient with a narcolepsy–cataplexy-like phenotype reported that he had not observed these symptoms prior to TBI. CSF hypocretin-1 was low 6 months after TBI (225 pg/ml). There were two other patients with a low CSF hypocretin-1 level 6 months after TBI (besides one patient with narcolepsy and one patient with a narcolepsy-like phenotype; see earlier). In a 58-year-old patient (211 pg/ml), PSG revealed a moderate sleep apnea syndrome (apnea–hypopnea index: 25 h^{-1}) and a short mean sleep latency on MSLT (2.5 min). In a 19-year-old patient (234 pg/ml), all findings were normal.

EDS appearing during the first year following a head injury may be considered as posttraumatic [134]. This typically presents itself as extended night sleep and episodes of daytime sleep. Sleepiness is usually associated with other characteristics such as headaches, difficulties in concentration, or memory disorder. Radioimaging studies may reveal several possibilities: lesions affecting the hypothalamic region or brainstem, midbrain, or pontine tegmentum or, more often than not, the absence of any significant lesions. Sleepiness should be objectively evaluated by a MSLT but often is not in clinical situation. Cases with hypersomnia after head or brain

trauma associated with sleep apnea syndrome were also reported [122].

Although two out of three patients with posttraumatic EDS had decreased CSF hypocretin-1 levels moderately, it is not known whether all posttraumatic subjects with declined CSF hypocretin-1 levels exhibit EDS. Similarly, it has not been studied whether more pronounced degree of hypocretin-1 impairments is evident for the posttraumatic symptomatic narcolepsy.

CNS Diseases Mediated with Neuroimmune Mechanisms

In this section, we will specifically discuss neuroimmunological disorders that meet the ICSD3 criteria of "Narcolepsy Due to Medical Conditions." There are three reasons for discussing this topic: (1) the etiology of idiopathic (hypocretin deficient) narcolepsy is not yet known, but an involvement of neuroimmune interaction is suggested, (2) functional significance of CSF hypocretin levels in symptomatic narcolepsy and symptomatic EDS has not been evaluated systematically, and (3) our recent study suggests an existence of a new clinical syndrome, symptomatic EDS associated with neuromyelitis optica (NMO), and with anti-aquaporin 4 (AQP4) antibody, with low CSF hypocretin-1 levels. Symptomatic narcolepsy cases with NMO and/or MS cases with anti-aquaporin 4 (AQP4) antibody cases are extremely interesting both in the clinical practice and research. Some of these cases were previously categorized as a multiple sclerosis (MS) subtype, and our findings may explain why some of MS cases show EDS and selective lesions in the paramedian hypothalamus and periventricular area.

We will include clinical data of "Narcolepsy Due to Medical Condition" from the following three subcategories: (1) acute disseminated encephalomyelitis (ADEM), (2) multiple sclerosis (MS), and (3) neuromyelitis optica (NMO) and anti-aquaporin 4 (AQP4) antibody.

Acute Disseminated Encephalomyelitis (ADEM)

Symptomatic narcolepsy was recently reported in four ADEM cases [101, 135–138]. All these cases associated with EDS had hypothalamic lesions and low CSF hypocretin-1 levels, suggesting an involvement of the hypothalamic hypocretin system in these conditions.

Improvement of sleepiness and increase in hypocretin-1 levels after treatment have also been reported in ADEM patients. A 38-year-old female had hypersomnia but with no REM-related symptoms such as cataplexy, hypnagogic hallucinations, or sleep paralysis. An MRI revealed lesions in the hypothalamus, walls of the third ventricle, corona radiata, floor of the aqueduct, and raphe nuclei. She was positive for DR2/DQB1*0602, and hypocretin-1 levels were 87 pg/ml. After treatment with high-dose steroids, MRI showed smaller and fewer lesions. Six months later, her subjective sleepiness was partially improved, and hypocretin-1 level was 148 pg/ml. One year after her initial examination, her sleepiness persisted, and the results of MSLT were almost unchanged [136].

In a 7-year-old girl with ADEM, visual symptoms, and hypersomnia, MRI revealed bilateral lesions in the white matter, basal ganglia, and hypothalamus. CSF hypocretin-1 level was intermediate (146 pg/ml) at admission, and with steroid plus treatment, the hypocretin level gradually recovered to the normal range (263 pg/ml) within 47 days, and excessive sleepiness was reduced. Decreased hypothalamic hypocretin neurotransmission may be involved in this symptomatic case of hypersomnia associated with a clinical course of ADEM, and interestingly, double vision was also noted in this case during the course of the disease [137].

Demyelinating Diseases

Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO)

Symptomatic narcolepsy in patients with MS has been reported for several decades. Because both MS and narcolepsy are associated with the HLA-DR2 positivity, an autoimmune target on the same brain structures has been proposed to be a common cause for both diseases [139]. However, the discovery of the selective loss of hypothalamic hypocretin neurons in narcolepsy indicates that narcolepsy coincidently occurs in patients with MS when MS plaques appear in the hypothalamic area and secondarily damage the hypocretin neurons. Supporting this interpretation, the hypocretin system is not impaired in patients with MS who do not exhibit narcolepsy [13]. Nevertheless, a subset of patients with MS predominantly shows EDS and REM sleep abnormalities, and it is likely that specific immune-mediated mechanisms may be involved in these cases.

Kanbayashi et al. recently reported seven cases of EDS occurring in patients initially diagnosed with MS with symmetric hypothalamic inflammatory lesions and hypocretin ligand deficiency that contrast with the typical MRIimage of MS (Fig. 9.2). CSF hypocretin measures revealed that marked (<110 pg/ml, $n=3$) or moderate (110–200 pg/ml, $n=4$) hypocretin deficiency was observed in all seven cases [25]. Four of these cases met with ICSD-2 criteria [15] for narcolepsy caused by a medical condition, and three cases met criteria for hypersomnia caused by a medical condition. HLA was negative for DQB1*0602 in the two cases evaluated for it. Hypocretin evaluation was repeated in six cases, and CSF hypocretin-1 levels became normal or significantly increased, along with marked improvements of EDS and hypothalamic lesions in all cases [25]. Because four cases had clinical characteristics of neuromyelitis optica (NMO) (either optic neuritis or spinal cord lesions, or both, were present), anti-AQP4 antibody was evaluated, and three cases came back positive; these were diagnosed as NMO-related disorder.

AQP4, a member of the AQP superfamily, is an integral membrane protein that forms pores in the membrane of biologic cells [26]. Aquaporins selectively conduct water molecules in and out of the cell while preventing the passage of ions and other solutes and are known as water channels. AQP4 is expressed throughout the central nervous system, especially in periaqueductal and periventricular regions [26, 140] and is found in nonneuronal structures such as astrocytes and ependymocytes but is absent from neurons. NMO-IgG, which can be detected in the serum of patients with NMO, has been shown to selectively bind to AQP4 [141]. Because AQP4 is enriched in the periventricular regions of the hypothalamus, where hypocretin-containing neurons are primarily located, symmetric hypothalamic lesions associated with reduced CSF hypocretin-1 levels in our 3 NMO cases with anti-AQP4 antibody might be caused by the immune attack to the AQP4 that secondarily affects the hypocretin neurons. However, as described earlier, Kanbayashi et al. also had 4 MS cases with EDS and hypocretin deficiency that tested negative for anti-AQP4 antibody, which leaves a possibility that other antibody-mediated mechanisms are additionally responsible for the bilateral symmetric hypothalamic damage causing EDS in the MS/NMO subjects. There is also a possibility that these 4 MS cases could be NMO, because anti-AQP4 antibody was tested only once for each subject during the course of the disease, and the assay was not standardized among the institutes [25].

It is thus essential to further determine the immunologic mechanisms that cause the bilateral hypothalamic lesions with hypocretin deficiency and EDS and their association with NMO and AQP4. This effort may lead to establishment of a new clinical entity, and the knowledge is essential to prevent and treat EDS associated with MS and its related disorders. None of these cases had cataplexy, contrary to the 9 out of 10 symptomatic narcoleptic MS cases reported in the past [18]. Early therapeutic intervention with steroids and other immunosuppressants may thus prevent

irreversible damage of hypocretin neurons and chronic sleep-related symptoms.

Guillain–Barré Syndrome (GBS)

Guillain–Barré syndrome (GBS) is an acute autoimmunepolyradiculoneuritis with sensory and motor impairment. Since GBS may also cause autonomic dysfunction, aspiration pneumonia, and respiratory failure, some patients undergo intensive care including invasive ventilation. Although GBS is generally restricted to the peripheral nervous system, clinically and pathologically, central dysfunctions have also been documented [142]. These include hyponatremia caused by abnormal antidiuretic hormone secretion [143], rapid eye movement sleep (REM sleep) motor behavior disorders [144], EDS [145], and abnormally low CSF hypocretin-1 levels [13, 146, 147]. A subset of Miller-Fisher syndrome subjects, but not chronic inflammatory demyelinating polyneuropathy (CIDP) subjects, also has significantly low CSF hypocretin-1 [147].

Undetectably low CSF hypocretin-1 levels were found in seven cases of GBS in the Japanese population [13, 146, 147]. Reduced CSF hypocretin-1 levels in GBS are not likely due to secondary effects of the treatment or associated health conditions, since two GBS patients showed undetectable levels at the time of admission to the hospital (before treatment), but only exhibited general fatigue and/or lower limb weakness, with no increase in CSF protein 1evels [147].

This finding was rather unexpected, since GBS is a presumed autoimmune disorder of peripheral polyradiculoneuropathy. However, additional CNS involvements (i.e., hypothalamus), such as occurrence of syndrome of inappropriate antidiuretic hormone (ADH) secretion and diabetes insipidus, have also been suggested in severe cases. Interestingly, all these GBS subjects with low hypocretin-1 were severe cases and developed tetraplegia, bulbar symptoms, and/or respiratory failure shortly after the disease onset. Since the clinical picture of these subjects is quite different from that of narcolepsy, any diagnostic confusion by measurement of CSF hypocretin-1 levels between the two is unlikely [147].

However, these findings were not confirmed in two studies of Caucasian patients [95, 142, 148]. In one study, CSF hypocretin-1 concentrations were lowered but within the normal range in GBS patients with hypnagogic-like hallucinations and severely disturbed sleep [142]. One possible explanation of this discrepancy is the difference in ethnic origin of the recruited patients (Japanese vs. Caucasian patients) and thus the possibility of different pathophysiological pathways [148]. Griffin et al. suggested that GBS in Northern China, which is acute motor axonal neuropathy (AMAN) associated with *Campylobacter* infection, is a different disease than GBS seen in Western countries [19, 92, 149, 150]. The seven Japanese GBS cases with undetectable CSF hypocretin-1 exhibited severe and rapid onsets with frequent respiratory involvement; this may suggest a link between AMAN and hypocretin deficiency, but low hypocretin levels were not associated with neither anti-ganglioside antibodies nor antecedent infection. Hypocretin deficiency in the brain, as observed in idiopathic hypocretin-deficient narcolepsy, has not yet been confirmed in GBS subjects with low CSF hypocretin-1 levels. For these reasons, future studies regarding the mechanism of low CSF hypocretin levels in a subset of GBS subjects are important.

Paraneoplastic Syndrome

A recent report described four anti-Ma2-associated encephalitis patients with EDS and undetectable CSF hypocretin-1 levels. Interestingly, hypocretin-1 levels of two other patients who did not exhibit EDS were in the normal range [151]. MRI showed abnormalities involving medial temporal lobes, hypothalamus, basal ganglia, or upper brainstem in the four patients with EDS. The author concluded that anti-Ma antibodies are an example of an immune-mediated cause that may result in EDS and low hypocretin-1 levels.

In contrast to MS and ADEM, distinct CNS lesions were not observed in GBS and neoplastic

syndromes. Nevertheless, hypocretin deficiency was observed in both conditions. This suggests that the hypocretin deficiency in these conditions may occur at the neuron or ligand levels. Considering that the autoimmune hypothesis is the most popular theory for hypocretin cell death in narcolepsy [152, 153], but no clear inflammation was observed in the hypothalamus [154], a subset of GBS and Ma2 antibody-positive paraneoplastic syndromes that is associated with hypocretin deficiency may be important models for studying possible autoimmune cell damage/ligand deficiency in narcolepsy.

Others

Behçet's Disease

Recently, a 31-year-old man with Behçet's disease was reported with acute diplopia, hypersomnia (>12 h sleep/day), and sleepiness (ESS: 14) [155]. Cranial MRI revealed diencephalic lesions with left-sided subthalamic gadolinium enhancement. CSF hypocretin-1 was decreased (215 pg/ml). Following treatment with prednisone and azathioprine for 1 month, diplopia, sleepiness, and hypersomnia disappeared within 2 months. Hyperintense lesions vanished on cranial MRI, and hypocretin-1 increased to a normal level (400 pg/ml).

A 19-year-old male with Behçet's disease, with EDS and intermediate hypocretin level (131 pg/ml), was also reported [156].

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome.

EDS has also been newly reported in ROHHAD syndrome. Firstly, a 7-year-old girl with ROHHAD syndrome displayed the classic features of narcolepsy with cataplexy [157]. ROHHAD is a rare and complex pediatric syndrome, essentially caused by dysfunction of three vital systems regulating endocrine, respiratory, and autonomic nervous system functions. Her nocturnal polysomnography revealed sleep fragmentation and a sleep-onset REM period characteristic for narcolepsy. The diagnosis was confirmed by undetectable CSF hypocretin-1.

In addition, an 11-year-old girl with ROHHAD syndrome was reported. She had EDS and an intermediate hypocretin level (151 pg/ml) [158].

Conclusion

Symptoms of narcolepsy can occur during the course of neurological conditions. Although it is difficult to rule out the comorbidity of idiopathic narcolepsy in some cases, literature review reveals numerous unquestionable cases of symptomatic narcolepsy. These include cases with HLA negative and/or late onset and cases in which narcoleptic symptoms occur in parallel with the rise and fall of the causative disease. Symptomatic narcolepsy cases are most often associated with brain tumors and inherited disease followed by head trauma. Cases associated with vascular diseases, degeneration, and autoimmune/immune-mediated diseases are also reported. Review of these cases, especially with brain tumors, illustrates a clear picture that the hypothalamus is most often involved. Several cases of symptomatic cataplexy (without EDS) are also reported. In contrast, symptomatic cataplexy appeared to be often associated with non-hypothalamic structures.

Recently, it was revealed that the pathophysiology of idiopathic narcolepsy was linked to hypocretin ligand deficiency. CSF hypocretin-1 measures were also carried out in some symptomatic cases of narcolepsy/EDS. Reduced CSF hypocretin-1 levels were seen in most symptomatic cases of narcolepsy/EDS with various etiologies, and EDS in these cases were sometimes reversible with an improvement of the causative neurological disorder and also the hypocretin status. It is also notable that some symptomatic EDS cases with Parkinson's diseases or thalamic infarction were not linked with hypocretin ligand deficiency, though nonspecific reduction of hypocretin neurons may occur in a subset of PD patients.

Since CSF hypocretin measures are still experimental, cases with sleep abnormalities/cataplexy are habitually selected for CSF hypocretin measures. Therefore, it is still not known whether all or a large majority of cases with low CSF hypocretin-1 levels with CNS intervention exhibit EDS/cataplexy.

Occurrences of cataplexy in idiopathic narcolepsy cases are tightly associated with hypocretin ligand deficiency. However, this link is less clear in symptomatic cases. Since none of the acute and subacute symptomatic cases (such as NMO, GBS, and ADEM) with undetectable CSF hypocretin-1 levels developed cataplexy, chronic hypocretin deficiency may be required to express cataplexy. Even when a very strict criterion for cataplexy is applied, approximately 10 % of narcolepsy–cataplexy patients have normal CSF hypocretin-1 [2, 4, 7]. Whether or not hypocretin neurotransmission is abnormal in these rare cases is unknown. Considering the fact that hypocretin production and hypocretin neurons appeared to be normal in hypocretin receptor 2-mutated narcoleptic Dobermans [159], it is possible that deficiencies in hypocretin receptors and a downstream pathway may exist in some of these patients. However, this cannot be tested currently. Similarly, it is not known whether narcoleptic subjects without cataplexy simply have milder neuropathology. Narcoleptic subjects without cataplexy may have sufficient hypocretin production to maintain normal CSF levels and stave off cataplexy, but the partial loss may still be great enough to produce sleepiness (see [160]).

A large number of HLA DR2/DQ6 (DQB1*0602)-negative symptomatic narcolepsy/EDS [53 % (31/59) in narcolepsy and 87 % (13/15) in EDS] were found (see section "Definition of Symptomatic Narcolepsy and Its Overview" and Ref. [18]). The brain system critical for these sleep abnormalities (i.e., the hypocretin system) could be damaged by certain neurological conditions such as tumors and vascular diseases. These cases are often associated with detectably low or intermediate CSF hypocretin levels, in contrast to the undetectable idiopathic narcoleptic cases.

Nevertheless, increased HLA DR2/DQ6 (DQB1*0602) positively [47 % (28/59)] was still observed in symptomatic narcoleptic cases. Although some HLA-positive hypocretin-deficient symptomatic cases may be due to simple comorbidities of idiopathic narcolepsy, HLA may also play a role(s) in other cases: brain insult may trigger/facilitate the HLA-mediated hypocretin cell damage in which the mechanism may also be shared with that in the hypocretin-deficient idiopathic cases of narcolepsy. Regarding hypocretin deficiency among immune-mediated neurological conditions, hypocretin deficiency with the hypothalamic lesions was noted in some NMO and ADEM cases. In contrast, no clear local lesions were noted in hypocretin deficiency in GBS and Ma2-positive paraneoplastic syndromes. Thus, it appears that hypocretin ligand deficiency in GBS and Ma2 may possibly be more selective at the cellular or ligand level, and the mechanism involved in these conditions should be further studied.

Finally, further studies of the involvement of the hypocretin system in symptomatic narcolepsy and EDS are helpful to understand the pathophysiological mechanisms for occurrence of EDS and cataplexy. Measuring CSF hypocretin-1 may be also useful to choose treatment options such as wake-promoting compounds, anticataplectic medications, and ultimately, for starting treatment with hypocretin agonists when they become available.

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Appendix

Table 9.1 Symptomatic narcolepsy, hypersomnolence or EDS with hypocretin measurements ($n=346$)

					Narcoleptic Symptoms									
Classification	Diagnosis	Location	Age	Gender	EDS	Sleep latency	SOREMP	CA	HLA	Hypocretin		Note	Referencess	Author
	Tumors (n = 14)	Lesion	Low hypocretin cases (7/14)		Narcolepsy due to medical condition (9/14)				DR2/ DQB1 *0602 (DQw1)					
Type 1, NM	Astrocytoma resection	Hypothalamus	16	F	+	1.7 m/MSLT	–	–	–	Low	104 pg/ml		[75]	Arii (2001)
Type 1, NM	Astrocytoma resection	Suprasellar	11	M	+	?	+	–	–	Low	<40 pg/ml		[76, 77]	Marcus (2002)
HM/SE ($n=5$)	Craniopharyngioma ($n=3$), germinoma ($n=1$), arachnoid cyst ($n=1$)	Hypothalamus, thalamus	Mean 15	M=2, F=3	+	Mean:10.3 m/ MSLT	?	–	?	Control level	Mean = 133 pg/ ml		[82]	Snow (2002)
Type 2, NM	Choroid plexus carcinoma resection	Pineal gland, thalamus	28	F	+	7.5 m/MSLT	+	–	–	Normal	518 pg/ml		[83]	Krahn (2002)
Type 1, NM	Adenoma	Pituitary, hypothalamus	60	M	+	6.4 m/MSLT	+	+	–	Normal	275 pg/ml	Acromegaly+	[84]	Dempsey (2003)
Type 1, NM	Tumor	Hypothalamus	65	F	+	5 m/1EEG	+	+	?	Low	61 pg/ml		[31]	Nokura (2004)
Type 1, NM	Craniopharyngioma	*Hypothalamus*	*11*	*F*	+	*1.4 m/MSLT*	+	–	–	*Low*	*93 pg/ml*		[78]	*Tachibana (2005)*
Type 1, NM	CNS lymphoma	Left basal ganglia, thalamus, cerebral pedunculus, splenium of the corpus callosum, right internal temporal lobe	46	M	+	?	?	–	–	Low	<40 pg/ml ->244 pg/ml		[79]	Dauvilliers (2007)
Type 1, NM	Craniopharyngioma	Expansion of the 3rd ventricle and a cavity forming in the whole hypothalamus	19	F	+	1 m/MSLT	+	+	–	Low	71 pg/ml		[80]	Sakuta (2012)
Type 1, NM	Craniopharyngioma	Bilateral thlamus, hypothamus	12	F	+	0.1 m/MSLT	+	+	–	Low	<40 pg/ml	DI, hypothalamic-pituitary dysfunction	[81]	Uchida (2014)
	Head trauma (n = 7)	Head injury location	Low hypocretin cases (3/7)		Narcolepsy due to medical condition (4/7)									
HM ($n=2$)	Head trauma ($n=2$)	Nonspecific	23, 21	M	+	4.5 m, 3 m/ MSLT	–	–	(–) = 1, (+) = 1	Intermediate, normal	176, 503 pg/ml		[98]	Dauvilliers (2003)
HM ($n=1$)	Head trauma	Base of skull	15	M	+	2 m/1EEG	–	–	?	Intermediate	151 pg/ml	GCS12	[17]	Arii (2004)
Type 1, NM (n = 3), type 2, NM (n = 1)	*Head trauma (n = 4)*	*Nonspecific*	*18, 26, 22, 58*	*M = 3, F = 1*	+	*2.5–6.3 m/ MSLT*	+	*(–) = 3, (+/–) = 1*	*(–) = 2, ? = 2*	*Low:n = 3, normal: n = 1, (33 % of controls)*	*211, 225, 289, 468 pg/ml*	*AHI: 25/h (n = 1)*	[132]	*Baumann (2007)*
	Vascular disorders (n = 8)		Low hypocretin cases (1/8)		Narcolepsy due to medical condition (3/8)									

(continued)

Table 9.1 (continued)

					Narcoleptic Symptoms									
Classification	Diagnosis	Location	Age	Gender	EDS	Sleep latency	SOREMP	CA	HLA	Hypocretin		Note	Referencess	Author
Type 1, NM	Infarction	Hypothalamus	23	M	+	0.5 m/MSLT	+	+	−	Intermediate	167 pg/ml		[30]	Scammell (2001)
HM ($n=1$), SE ($n=1$)	Infarction ($n=2$)	Thalamus, ponto-medullary	34, 40	M	+	9 m, 1 m/ MSLT	−	−	?	Normal	265, 316 pg/ml		[8]	Bassetti (2003)
Type 2, NM	Infarction	Thalamus	45	M	+	5 m/MSLT	+	−	?	Normal	312 pg/ml		[31]	Nokura (2004)
HM ($n=1$)	Infarction	Thalamus	15	M	+	?	−	−	?	Normal	274 pg/ml		[85]	Tohyama (2004)
HM ($n=2$)	Infarction ($n=2$)	Thalamus	61, 82	F	+	?	?	?	?	Normal	293, 184 pg/ml		[164]	Miyamoto (2004)
Type 1, NM	Infarction	Thalamus	83	F	+	?	?	?	?	Low	109, 323 pg/ml		[165]	Adachi (2013)
	Encephalopathies ($n=6$)		Low hypocretin cases (4/6)		Narcolepsy due to medical condition (5/6)									
Type 1, NM	Rasmussen's syndrome	Left frontotemporal and insular	40	M	+	1.6 m/MSLT	+	+	+	Low	<40 pg/ml		[91]	Lagrange (2003)
Type 1, NM	Wernicke encephalitis	Hypothalamus	5	F	+	?	−	−	?	Low	<40 pg/ml		[88]	Kashiwagi (2004)
Type 1, NM	Limbic encephalitis	Limbic, hypothalamus	65	M	+	?	−	−	?	Low	87 pg/ml		[90]	Yamato (2004)
Type 1, NM	*Brain stem encephalitis*	*Pontine tegmentum adjacent and rostral to both fourth nerve nuclei*	*30*	*M*	+	*<3 m/MSLT*	+	+	−	*Normal*	*266 pg/ml*	*RBD*	*[92]*	*Mathis (2007)*
HM	Meningo-encephalitis	Hypothalamus, 4th ventricle	36	M	+	?	?	−	−	Intermediate	122, 191 pg/ml	Mycoplasma pneumoniae	[166]	Sugeno (2012)
Type 1, NM	Hashimoto's encephalopathy	Nonspecific	65	M	+	?	−	−	?	Low	<40 pg/ml	Full recover by steroid	[93]	Castillo (2004)
	Neurodegeneration (lumber CSF; $n=190$, ventricular CSF; $n=19$)				Low hypocretin cases (8/190)		Narcolepsy due to medical condition (8/190)							
HM ($n=3$)	Parkinson's disease ($n=3$)	Nonspecific	52, 64, 69	M	+	4.4, 4.9, 6.1 m/MSLT	(−)=2, (+)=1	−	−	Normal	253, 307, 319 pg/ml		[94]	Overeem (2002)
Type 1, NM ($n=16$)	PD ($n=16$), ventricular CSF	Nonspecific	?	?	+/−	?	?	−	?	Low	<50–97 pg/ml	ventricular CSF	[24]	Drouot (2003)
HM ($n=3$)	PD ($n=3$), ventricular CSF	Nonspecific	?	?	+	?	?	−	?	Intermediate	138–169 pg/ml		[24]	Drouot (2003)
Type 1, NM	PD	Nonspecific	58	M	+	2 m/MSLT	+	+	+	Low	86 pg/ml		[103]	Maeda (2006), Takahashi (2011)
HM/REF ($n=62$)	PD ($n=62$)	Nonspecific	Mean=70	M: 23, F: 39	+/−	?	?	?	?	Intermediate: n=1, normal: $n=61$	Mean=302 pg/ml		[99]	Yasui (2006)
HM/REF ($n=25$)	PD ($n=25$)	Nonspecific	Mean=66	M: 14, F: 11	+/−	?	?	?	?	Normal	Mean=285 pg/ml		[100]	Asai (2009)

HM ($n=21$)	PD ($n=21$)	Nonspecific	Mean=69	M: 12, F:9	+	?	?	?	?	Normal	Mean=301 pg/ml		[101]	Compta (2009)
HM ($n=20$)	PD with dementia ($n=20$)	Cortical atrophy	Mean=73	M: 9, F:11	+	?	?	?	?	Normal	Mean=310 pg/ml		[101]	Compta (2009)
Type 1, NM ($n=2$), HM ($n=6$)	PD ($n=8$)	Nonspecific	48–69	M: 4, F:4	+	?	?	?	?	Low: $n=2$, intermediate: $n=2$, normal: $n=4$	39–50 pg/ml, 138–156 pg/m, 200–450 pg/mll		[106]	Drouot (2011)
Type 1, NM	PD	Nonspecific	57	M	+	5.4 m/MSLT	?	?	+	Low	<40 pg/ml		[105]	Wakai (2011)
Type 1, NM	PD	Nonspecific	83	F	+	?	–	–	–	Low	100 pg/ml		[107]	Teraoka (2013)
HM ($n=10$)	Dementia with Lewy bodies ($n=10$)	Cortical atrophy	69–82	M=7, F=3	+	?	–	–	?	Normal	382–667 pg/ml		[108]	Baumanna (2004)
HM/REF ($n=13$)	DLBD ($n=13$)	Cortical atrophy	Mean=76	M=7, F=6	+/–	?	?	?	?	Normal	Mean=297 pg/ml		[99]	Yasui (2006)
Type 1, NM	progressive supranuclear palsy	Enlargement of the 3rd V	74	F	+	2 m/MSLT	–	–	+	Low	<40 pg/ml		[112]	Hattori (2003)
Type 1, NM	*PSP*	*Enlargement of the 3rd V*	*74*	*M*	+	*2.9 m/MSLT*	+	+	+	*Low*	*<40 pg/ml*		[113]	*Sugiura (2007)*
HM/REF ($n=16$)	PSP ($n=16$)	Enlargement of the 3rd V	Mean=72	M=11, F=5	+/–	?	?	?	?	Intermediate: $n=2$, normal: $n=14$	Mean=258 pg/ml		[99]	Yasui (2006)
Type 1, NM ($n=1$), HM/REF ($n=6$),	Corticobasal degeneration ($n=7$)	Unilateral atrophy of the cerebral hemisphere	Mean=71	M=3, F=4	+/–	?	?	?	?	Normal: $n=6$, low: $n=1$	Mean=246 pg/ml		[99]	Yasui (2006)
	Immune-mediated Demyelinating disorders (n20)			Low hypocretin cases (12/20)		Narcolepsy due to medical condition (14/20)								
Type 1, NM	Multiple sclerosis (MS)	Hypothalamus	22	F	+	2.8 m/MSLT	+	–	–	Low	<40 pg/ml	AQP4-	[167, 168	Iseki (2002), Oka (2004)
Type 1, NM	MS	Hypothalamus	45	F	+	?	–	–	?	Low	<40 pg/ml	AQP4-	[169]	Kato (2003)
Type 1, NM	MS	No hypothalamic lesion	21	M	+	1.5 m/MSLT	+	+	DQB1*0602	Low	<40 pg/ml	AQP4-	[170]	Vrethem (2012)
HM	NMO spectrum disorders	Hypothalamus	43	F	+	?	–	–	?	Intermediate	191 pg/ml	AQP4+	[171]	Nozaki (2004)
Type 1, NM	NMO spectrum disorders	Hypothalamus	48	F	+	?	–	–	?	Low	106 pg/ml	AQP4+	[172]	Nakamura (2005)
Type 1, NM	Neuromyelitis optica	Hypothalamus	49	F	+	?	–	–	?	Low (33 % of control)	158 pg/ml	AQP4+	[173]	Carlander (2008)
Type 1, NM	Neuromyelitis optica	Hypothalamus	35	F	+	6 M/MSLT	+	–	–	Low	91 ->290 pg/ml	AQP4+	[174]	Baba (2009)
Type 2, NM	Neuromyelitis optica	Hypothalamus	41	F	+	4.8 m/MSLT	+	–	?	Intermediate	177 pg/ml	AQP4+, anhidrosis	[175]	Sekiguchi (2011)
HM	Neuromyelitis optica	Hypothalamus	31	F	+	?	?	–	?	Intermediate	187 ->230 pg/ml	AQP4+, SIADH	[176]	Nakano (2011)
HM	Neuromyelitis optica	Hypothalamus	36	F	+	?	–	–	?	Intermediate	118 ->195 pg/ml	AQP4+	[177]	Deguchi (2012)
Type 1, NM	Neuromyelitis optica	Hypothalamus	21	F	+	1 m/MSLT	+	–	–	Low	92 pg/ml	AQP4+, SIADH	[178]	Suzuki (2012)

(continued)

Table 9.1 (continued)

					Narcoleptic Symptoms									
Classification	Diagnosis	Location	Age	Gender	EDS	Sleep latency	SOREMP	CA	HLA	Hypocretin		Note	Referencess	Author
Type 2, NM	Neuromyelitis optica	Hypothalamus, basal ganglia, white matter	26	F	+	2.5 m/MSLT	+	–	–	Intermediate	166->185 pg/ml	AQP4+	[179]	Miyagawa (2013)
HM	Neuromyelitis optica	Bilateral cerebral cortex, and right posterior limb of internal capsule and the central part of pons	36	F	+	?	?	–	?	Intermediate	164 pg/ml	AQP4+, SIADH	[180]	Sakai (2014)
Type 1, NM	Neuromyelitis optica	Bilateral hypothalamus and the left caudate nucleus	46	F	+	?	?	–	–	Low	86->131 ->262 pg/ml	AQP4+, hypothalamic pituitary dysfunction	[181]	Kume (2014)
Type 1, NM	Neuromyelitis optica?	Bilateral lesions in the thalamus and basal ganglia	39	F	+	?	?	–	?	Low	<40 pg/ml	AQP4–	[182]	Saito (2014)
Type 1, NM	Acute disseminated encephalomyelitis	Hypothalamus	12	F	+	4.5 m/MSLT	–	–	–	Low	102 pg/ml		[138]	Kubota (2002)
Type 1, NM	ADEM	Hypothalamus, coronaradiata, aqueduct, raphe	38	F	+	4.4 m/MSLT	+	–	+	Low	87 pg/ml		[139]	Gledhill (2004)
HM	ADEM	Hypothalamus	7	F	+	?	–	–	–	Intermediate	146 pg/ml		[140]	Yoshikawa (2004)
Type 1, NM	ADEM	Hypothalamus	0.9	F	+	?	–	–	?	Low	<40 pg/ml		[141]	Yano (2004)
HM	ADEM	Hypothalamus	6	M	+	?	?	–	?	Intermediate	124 pg/ml		[104]	Mizuno (2011)
	Immune-mediated polyneuropathy (n = 23)		Low hypocretin cases (1/23)		Narcolepsy due to medical condition (1/23)									
Type 1, NM	Guillain-Barre syndrom	Nonspecific	28	M	+	0.7 m/TNST	–	–	?	Low	<40 pg/ml		[150]	Nishino (2003)
HM	Guillain – Barre syndrom	Nonspecific	19	M	+	0.8 m/TNST	–	–	?	Intermediate	151 pg/ml		[150]	Nishino (2003)
SE, REF (n = 20)	Guillain – Barre syndrom (n = 20)	Nonspecific	Mean = 48	M = 57 %	case by case,+/–	?	?	?	?	Normal	555 vs 664 pg/ml		[145]	Cochen (2005)
HM	Bickerstaff's brainstem encephalitis	Brainstem	33	F	+	?	–	–	?	Intermediate	128 pg/ml	GBS	[183]	Saji (2007)
	Paraneoplastic autoimmune syndromes (n = 6)		Low hypocretin cases (5/7)		Narcolepsy due to medical condition (5/7)									
Type 1, NM (*n* = 4)	Anti-Ma associated encephalitis (*n* = 4)	Multiple area in the brain including hypothalamus	45, 22, 67, 38	M = 3, F = 1	+	?	?	–	?	Low	<100 pg/ml	Tumor of the testis (*n* = 3), adenocartinoma of the lung (*n* = 1)	[154]	Overeem (2004)
REF (*n* = 2)	Anti-Ma associated encephalitis (*n* = 2)	Brainstem, periventricular region, basal ganglia, nonspecific	82, 53	F	–	?	?	–	?	Normal	237, 218 pg/ml	Lung cancer, Adenocarcinoma of ovary	[154]	Overeem (2004)
Type 1, NM	Anti-Ma associated encephalitis	Lesions surrounding the third ventricle in the thalamus, hypothalamus, and mammillary bodies	63	M	+	7.2	+	+	?	Low	<40 pg/ml	Ma-2 positive, no tumor detected	[184]	Dauvilliers (2013)

	Genetic/congenital disorders (n = 66)		Low hypocretin cases (7/66)		Narcolepsy due to medical condition (13/66)									
Type 1, NM	Prader – Willi syndrome	Nonspecific	16	M	+	3 m/MSLT	–	–	–	Low	109 pg/ml	BMI 48.1, AHI 5.6	[2]	Mignot (2002)
HM	PWS	Nonspecific	10	M	+	6 m/MSLT	–	–	?	Intermediate	130 pg/ml	BMI29.8, AHI 3.1	[37]	Nevsimalova (2004)
REF	PWS	Nonspecific	23	M	–	?	–	–	?	Intermediate	191 pg/ml	BMI49, AHI 46.8	[37]	Nevsimalova (2004)
REF	PWS	Nonspecific	6	M	–	?	–	–	?	Normal	226 pg/ml	BMI 25.8, AHI0	[37]	Nevsimalova (2004)
REF	PWS	Nonspecific	0.5 m	M	?	?	–	–	?	Intermediate	192 pg/ml		[17]	Arii (2004)
Type 1, NM	PWS	Nonspecific	11	F	+	3 m/MSLT	+	–	?	Low	60 pg/ml	BMI 19.9, (%BMI = 108)	[38]	Terashima (2012)
Symptomatic Cataplexy	Niemann–Pick type C	Nonspecific	5	M	–	16.5 m/ TNST	–	+	–	Intermediate	142 pg/ml		[43]	Kanbayashi (2003)
Type 1, NM	NPC	Nonspecific	14	F	+	5.1 m/MSLT	+	+	+	Intermediate	157 pg/ml		[41]	Vankova (2003)
HM ($n = 2$), SE ($n = 1$)	NPC ($n = 3$)	Nonspecific	24, 25, 31	M = 2, F = 1	+	3.2, 3.5, 10.7 m/MSLT	–	–	–	Intermediate:$n = 1$ normal:$n = 2$	190, 226, 245 pg/ml		[41]	Vankova (2003)
Symptomatic Cataplexy	*NPC*	*Nonspecific*	*10*	*F*	–	*?*	*?*	+	*?*	*Intermediate*	*174 pg/ml*		[45]	*Oyama (2006)*
Type 1, NM	NPC	Atophy in whole cerebrum	24	M	+	1 m/MSLT	+	+	–	Low	88 pg/ml		[47]	Soda (2011)
Type 1, NM	NPC	Atrophy in cerebrum, cerebellum and corpus callosum	4	M	?	?	?	+	?	Low	106 pg/ml		[46]	Eto (2014)
Type 1, NM	Myotonic dystrophy	Nonspecific	46	?	+	4.7 m/MSLT	+	–	–	Low	91 pg/ml		[23]	Martinez (2003)
Type 2, NM	MYD	Nonspecific	50	?	+	1.8 m/MSLT	+	–	–	Normal	206 pg/ml		[23]	Martinez (2003)
HM ($n = 4$)	MYD ($n = 4$)	Nonspecific	19, 25, 47, 68	?	+	5.7 m, 5.7 m, 7 m, 8 m/ MSLT	–	–	–	Intermediate:$n = 2$ normal:$n = 2$	167, 187, 200, 235 pg/ml		[23]	Martinez (2003)
Type 1, NM	MYD	Nonspecific	23	M	+	6.4 m/MSLT	+	–	–	Normal	401 pg/ml		[66]	Dauvilliers (2003)
Type 2, NM ($n = 3$), SE ($n = 14$), REF ($n = 21$)	MYD ($n = 38$)	Nonspecific	Mean 43, 24–72	M = 23, F = 15	+	9.1 m/MSLT	Five cases	–	3 cases: DQB10602(+)	Normal	mean = 277 pg/ml		[72]	Ciafaloni E et al. (2008)
Type 1, NM	MYD	Nonspecific	60	F	+	20 m/MSLT	–	–	–	Low	<40 pg/ml	BMI:27.7, AHI:59.2	[70]	Iwata T et al. (2009)
Type 1, NM	MYD	Nonspecific	49	M	+	?	?	?	–	Low	<40 pg/ml	BMI:27.3	[71]	Yasui.K et al. (2010)

(continued)

Table 9.1 (continued)

					Narcoleptic Symptoms									
Classification	Diagnosis	Location	Age	Gender	EDS	Sleep latency	SOREMP	CA	HLA	Hypocretin		Note	Referencess	Author
	Heredodegenerative disorders (n = 1)		Low hypocretin cases (1/1)		Narcolepsy due to medical condition (1/1)									
Type 1, NM	ADCA-DN	Enlargement of the 3rd V, brainstem atrophy	51	M	+	?	?	+	−	Low	96 pg/ml		[28]	Melberg (2001)
	Others (n = 5)		Low hypocretin cases (1/5)		Narcolepsy due to medical condition (1/5)									
REF	Whipple's disease	?	53	M	?	?	−	−	?	Intermediate	113 pg/ml		[185]	Voderholzer (2002)
Type 1, NM	ROHHAD syndrome	Nonspecific? Hypothalamic?	7.5	F	+	8 m/PSG	+	+	?	Low	<40 pg/ml	Intubated	[160]	Dhondt (2013)
SE	ROHHAD syndrome	Nonspecific? Hypothalamic?	11	F	+	11 m/PSG	−	−	?	Intermediate	152 pg/ml	AHI 4.5/h	[161]	Sato (2014)
HM	Behcet's disease	Thalamus	31	M	+	?	?	?	?	Intermediate (low: 33 % of control)	215 pg/ml		[158]	Baumann (2010)
HM	Behcet's disease	Thalamus, Hypothalamus	19	M	+	?	?	?	B51+, DQB1?	Intermediate	131 pg/ml		[159]	Ito (2007)
	Abbreviations used:	Type 1: narcolepsy, type 1	Type 2: narcolepsy, type 2		NM: narcolepsy due to a medical condition		HM: hypersomnia due to a medical disorder		SE: Symptomatic EDS					
		EDS: Excessive daytime sleepiness			+: Present									
		CA: Cataplexy			−: Absent									
		V: Ventricle			?: Not assessed									
		MSLT: multiple sleep latency test			ADCA-DN: autosomal dominant cerebellar ataxia, deafness and narcolepsy									
	O: Other	TNST: two-nap sleep test												
	REF: Reference cases (no EDS)	EEG: electroencephalogram												

Vascular; Miyamato [161], Adachi [162], Encephalitis; Sugeno [163], NMO; Iseki [164], Oka [165], Kato [166], Vrethem [167], Nozaki [168], Nakamura [169], Carlander [170], Baba [171], Sekiguchi [172], Nakano [173], Deguchi [174], Suzuki [175], Miyagawa [176], Sakai [177], Kume [178], Saito [179], GBS; Saji [180], Ma2; Dauviilliers [181], Whipple's; Voderholzer [182]

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Hypersomnias Other Than Narcolepsy: Differential Diagnosis

10

Michel Billiard

Introduction

Apart from narcolepsy, there are a number of other forms of hypersomnias. These include some of the sleep-related breathing disorders, mainly obstructive sleep apnea syndrome (OSAS) and, at a lesser degree, central sleep apnea syndrome (CSAS), and the central disorders of hypersomnolence including primary sleep disorders, idiopathic hypersomnia (IH) and Kleine–Levin syndrome (KLS) and various symptomatic hypersomnias, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, hypersomnia associated with a psychiatric disorder, and insufficient sleep syndrome.

In this chapter, we will first consider how to clinically suspect and confirm excessive somnolence, then suggest a decision tree to orient the differential diagnosis of excessive somnolence and decide on the laboratory investigations to be performed, and finally review the different causes of excessive somnolence apart from narcolepsy.

This review will be based on the recently released International Classification of Sleep Disorders, Third Edition [1].

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Definitions

Sleepiness, *somnolence*: the normal biological drive for sleep.

Excessive sleepiness, *hypersomnolence*: a biological drive for sleep whose intensity is such that there is an inability to stay awake and hence a high propensity to fall asleep, even in situations that are inappropriate, interfere with activities of daily living, and can be harmful to the individual. Most commonly excessive sleepiness occurs during the daytime [*excessive daytime sleepiness* (EDS)]. However excessive sleepiness may be present at night in a person whose major sleep episode occurs during the daytime, such as shift worker.

Excessive sleep: prolonged major sleep episode associated with prolonged daytime nap(s).

Hypersomnia: primarily a diagnostic term (e.g., idiopathic hypersomnia, hypersomnia due to medical condition).

Clinical Approach of Excessive Sleepiness

The circumstances of diagnosis are varied: some patients may consult for excessive daytime sleepiness (EDS), either on their own or through an

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Table 10.1 Decision tree

I. The complaint of EDS is directly related to insufficient sleep time	Insufficient sleep syndrome
↓ No	
Use of a medication or substance responsible for sedation, substance abuse, stimulant withdrawal	Hypersomnia due to a medication or substance
II. The complaint of EDS falls into the context of a medical or psychiatric condition EDS associated with a neurologic, infectious or parasitic, endocrine, multisystem, genetic disease	Hypersomnia due to a medical disorder
↓ No	
EDS associated with a psychiatric condition	Hypersomnia associated with a psychiatric condition
III. The complaint of EDS is independent of the above EDS of various degrees associated with some of the following symptoms: loud snoring, breathing pauses during sleep, nycturia, tiredness and/or headache on awakening, cognitive impairment, irritability, depression, reduced libido	Obstructive sleep apnea syndrome
↓ No	
Severe EDS, unwanted episodes of sleep and cataplexy ± hypnagogic hallucinations, sleep paralysis, disturbed nocturnal sleep	Narcolepsy type I
↓ No	
Severe EDS, unwanted episodes of sleep, not associated with cataplexy ± hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep	Narcolepsy type 2
↓ No	
EDS, more continuous and less irresistible than in narcolepsy, long and non-refreshing naps, abnormally long sleep time, difficulty awakening in the morning or at the end of a nap	Idiopathic hypersomnia
↓ No	
Recurrent episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks, associated with one of the following: cognitive dysfunction, altered perception, eating disorder, mostly hyperphagia, disinhibited behavior	Kleine–Levin syndrome

accompanying family member. Many complain of fatigue, which turns out to be EDS at the clinical interview. Other patients visit their family doctor for loud snoring, and the interview leads to the discovery of EDS and other symptoms of OSAS. Some others are referred by company doctors due to repeated traffic accidents or poor performance at work. Finally, some patients are found to be abnormally sleepy in the context of somatic or psychiatric disorders.

Once suspected, EDS must be confirmed by a subjective test, most commonly the Epworth Sleepiness Scale (ESS), a scale based on the chance of dozing in eight selected situations [2]. Patients are asked to rate their chance of dozing on a scale of 0–3. The highest possible score is 24 and the normal upper limit is generally considered to be 10.

Gaining a clinical impression should always precede the decision of performing laboratory investigations (Table 10.1). There are several reasons for that. First, the patient should benefit from some information prior to any test. Second, some of these tests are expensive and cannot be scheduled immediately. Thus, they must not be performed systematically. Last, but not least, results of laboratory investigations may be uninformative or even misleading in some cases, like a mean sleep latency of 10 min or more on the multiple sleep latency test (MSLT) in an ostensibly sleepy patient or the presence of sleep-onset REM periods (SOREMPs) in a subject with OSAS or in a subject discontinuing antidepressants before the test.

Laboratory Investigations

Measures of Sleepiness

Multiple Sleep Latency test

This test was developed on the basis of the following principle: the sleepier the subject, the faster he falls asleep. A standard methodology

has been specified by the American Academy of Sleep Medicine [3]. The test consists of five nap opportunities performed at 2-h intervals, starting about 2 h after morning awakening. The test should be conducted during the day following a polysomnographically documented night of adequate sleep, that is, at least 6 h of sleep. All psychotropic medications that can cause sleepiness or suppression of rapid eye movement (REM) sleep should be discontinued 2 weeks before the date of the test. A mean sleep latency of less than 5 min indicates pathological sleepiness, a mean sleep latency from 10 to 20 min is considered as normal, while latencies falling between the normal and the pathological values are considered a gray diagnostic area [4].

Maintenance of Wakefulness Test

The maintenance of wakefulness test (MWT) is a variant of the MSLT, designed to evaluate treatment efficiency in patients with excessive sleepiness. A standard methodology has also been specified by the American Academy of Sleep Medicine [3]. The test consists of four trials performed at 2-h intervals, with the first trial beginning about 2 h after morning awakening. The major difference with the MSLT is in the instruction given to the subject. The subject is asked to attempt to remain awake. He is seated in a comfortable position in bed, as opposed to lying down in the MSLT, with low light behind him (7.5 W, one meter). In contrast to MSLT, drug therapy should not be changed before the test. The recommendation is to use trials of 40 min [5]. Despite the use of the test for many years, there are extremely limited normative data for it. Mean and standard error of the sleep latency for the test show significant changes with age [5].

Measures of Total Sleep Time

Total sleep time can be documented on a 24- or 36-h polysomnography (PSG) or on a 7-day wrist actigraphy performed in a period of unrestricted sleep (e.g., holidays), in association with a sleep log [1].

Measures of Vigilance

These tests are not typically used in clinical practice. However, they may be of interest to test cognitive abilities in patients suffering from sleep-related breathing disorders or disorders of hypersomnolence.

Psychomotor Vigilance Task (PVT)

This test measures the patient's ability to sustain attention by using trials with a duration of about 10 min, in which a handheld, computerized display-and-response unit quantifies response latency to multiple light-emitting diode presentation of a stimulus, to measure deficits in attention and performance [6].

Oxford Sleep Resistance (OSLER) Test

This test consists of four 40-min-long trials during which there are multiple light emission diode presentations. The subject is instructed to respond to each signal with a simple button press. Trials are ended after 40 min or after a failure to respond, which is considered to constitute a failure to maintain wakefulness [7].

Sustained Attention to Response Task (SART)

This test measures the ability to sustain executive control for response inhibition over a given period of time. The SART requires fast responses to random single digits from 1 to 9 (go digit), except for the "3" stimulus (non-go digit) to which participants must not respond [8].

Brain Imaging

Computed tomography (CT) and/or magnetic resonance imaging (MRI) should be performed whenever there is clinical suspicion of an underlying brain lesion.

Psychometric/Psychiatric Evaluation

It should be made in all cases where there is some doubt on the role of the patient's personality in the development of excessive sleepiness.

Various Causes of Hypersomnia

Sleep-Related Breathing Disorders

Obstructive Sleep Apnea Syndrome

This syndrome was first described in 1976 [9]. It is most frequent in 50-year-old males. The prevalence of obstructive sleep apneas accompanied by EDS is 4 % in men and 2 % in women aged 30–60 years in North America [10], although the actual prevalence may be higher.

OSAS is characterized by repeated episodes of complete (apneas) or partial (hypopneas) upper airway obstructions occurring during sleep, associated with a nighttime and daytime symptoms. Nighttime symptoms include apnea/hypopnea episodes terminated by loud snoring, nycturia, fatigue, and sometimes headache on awakening. Daytime symptoms consist of EDS, which can vary from light to severe, irritability, negligence, impaired cognitive functions, depression, loss of libido, and impotence. Interestingly, the frequency of apneas/hypopneas during sleep correlates poorly with the daytime symptom severity.

A body mass index (weight in kg/height in m^2) greater than 30 and a neck circumference greater than 40 cm are frequent although not systematic. Systemic hypertension is frequent. The ear, nose, and throat examination usually reveals a narrow upper airway due to close-set posterior tonsillar pillars, an abnormally long and hypotonic soft palate, a hypertrophic uvula, and macroglossia.

The positive diagnosis rests on PSG or on out of center testing (OCFS) when there is a high pretest probability of moderate-to-severe OSAS. The procedure shows obstructive sleep apneas (cessation of airflow but ongoing respiratory efforts) and/or hypopneas (reduction rather than cessation of airflow with ongoing respiratory effort) and enables quantification of the number of apneas/hypopneas per hour of sleep (apnea or respiratory disorder index). Oxygen saturation typically declines for a variable period of time following the onset of apnea or hypopnea. Obstructive sleep apneas or hypopneas may be accompanied by bradyarrhythmia or tachyarrhythmia.

Of note, some patients do not have apneas or hypopneas but have increasing respiratory efforts resulting in respiratory effort-related arousals (RERAs). This condition is presumed to have the same underlying pathophysiology as obstructive apneas and hypopneas. It is most accurately identified with a quantitative measurement of airflow and esophageal manometry, although it can be inferred when there is obvious inspiratory airflow limitation on a nasal pressure recording. It is considered to be as much as a risk factor for symptoms of unrefreshing sleep and daytime symptoms of OSAS.

The issue of EDS and OSAS is not clear-cut. Although EDS is one of the major complaints in patients with OSAS, not all patients with OSAS complain of EDS. In a large cohort of sleep apnea patients ($n = 2882$), EDS as defined by an ESS > 10 was present only in 57 % of patients [11]. However, there is a frequent tendency in sleep apnea patients to minor the symptom of EDS. This is reflected in the moderate correlation [12, 13] or even the lack of correlation [14] between scores on the ESS and results of the MSLT.

The mechanisms underlying EDS are complex. Arousal responses ranging from autonomic changes to intrusion of alpha activity into sleep may theoretically play a role in EDS. However, there is not much evidence in favor [15]. A poor nocturnal sleep quality has also been advocated. According to Heinzer et al., daytime sleepiness in OSAS patients may be the result of a lack of SWA during the first part of the night [16]. However, greater sleep efficiency has been found in OSA patients with EDS than in those without [11, 17]. Nocturnal hypoxemia is a major determinant of EDS in sleep apnea patients [17], at least in those with severe OSAS [18].

Central Sleep Apnea Syndrome

CSAS is characterized by recurrent cessation of respiration during sleep with the apneas having no associated ventilatory effort. Ventilation and ventilatory effort cease simultaneously, in a repetitive pattern over the course of the night. Prevalence is unknown but probably low. Patients present with symptoms of EDS or frequent nocturnal awakenings or both.

Diagnosis of primary CSAS rests on PSG demonstrating recurrent cessations in ventilatory effort and ventilation during sleep.

CSAS is caused by the instability of the respiratory control system in the transition from wakefulness to sleep and less commonly during stable non-rapid eye movement (NREM) sleep. Central sleep apneas tend to occur in individuals with a high or increased ventilatory responsiveness to CO_2 [19].

Central Disorders of Hypersomnolence

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) was progressively identified, beginning with the description of sleep drunkenness in 1956 [20] and ending with the publication by Roth in 1976 of a series of 642 personally observed patients including 368 with narcolepsy and 274 with hypersomnia, 191 of whom had hypersomnia with a short cycle (sleep attacks lasting from one to several hours and intervals between the attacks being maximally 1 day), and 22 had hypersomnia with a long cycle (attacks lasting from 1 day to several weeks and intervals between the attacks being from 1 month to several years apart). Within these 191 patients having hypersomnia with a short cycle, Roth distinguished 171 patients with "IH polysymptomatic form," 71 with "IH monosymptomatic form," 5 with neurotic hypersomnia, and 12 with disorders of breathing during sleep [21]. IH polysymptomatic form was characterized by excessive diurnal sleep, prolonged night sleep of a duration of 12–18 h, and great difficulty waking up in the morning, while IH monosymptomatic form was characterized by the most prominent symptom of diurnal sleep of a duration of one to several hours, not as irresistible as in narcolepsy. In 1979, not maintaining the division of idiopathic hypersomnia into two forms, the Diagnostic Classification of Sleep and Arousal Disorders referred to idiopathic CNS hypersomnolence as one of the disorders of excessive somnolence [22], and, in 1990, the first edition of the International Classification of Sleep Disorders (ICSD) referred to IH as one of the intrinsic sleep disorders [23]. In 2005, the second edition of the International Classification of Sleep Disorders (ICSD-2) came back to a division into two forms, namely, IH with and without long sleep time, in which the first form was similar to Roth's polysymptomatic form, while the latter differed by the presence of short refreshing naps [24]. Finally, in March 2014, the third edition of the International Classification of Sleep Disorders was released, and in the absence of specific symptoms in IH with and without long sleep time, the division into two forms was abandoned, waiting for consistent biologic markers [1].

Due to uncertainty on the nosological limits of IH, no prevalence study has ever been conducted. However, ratios of IH to narcolepsy in cohorts of patients published by different sleep disorders centers are available. These ratios range from 9.2 % [25] to 47.2 % [21], corresponding to estimated prevalences of 0.0048–0.095 %, if one accepts a prevalence of around 0.045 % for narcolepsy [26]. The onset of the condition is most often during adolescence or young adulthood. According to some cohorts, there is a higher prevalence of IH in women than in men.

A familial background has been found in up to 40 % of IH patients in a former study [27], but more rigorous studies are warranted.

EDS is the key manifestation of IH and is generally considered more continuous and less irresistible than in narcolepsy. Naps are few, long, and non-refreshing in half to three quarters of patients [1]. Night sleep is abnormally long in at least a third of patients [1]. Awakening in the morning or at the end of naps may be difficult or present as "sleep drunkenness": severe morning inertia consisting of difficulty in coming to complete wakefulness, accompanied by confusion, disorientation, poor motor coordination, slowness, and repeated returns to sleep [28]. Headache, orthostatic hypotension, and cold hands and feet are sometimes present. In addition, subjective symptoms such as being more alert in the evening than in the morning, difficulty focusing more than 1 hour, complaint of attention and memory deficits, mental fatigability, and hyperactivity helping to resist sleepiness have been reported [29]. Altogether, the phenotype of

idiopathic hypersomnia is not unitary, hence the successive suggestions of nosological separation of the condition into two or three forms.

In addition to the above clinical features, the diagnosis of IH requires laboratory investigations. PSG followed by MSLT is mandatory [1]. PSG generally demonstrates a normal architecture of sleep. Episodes of obstructive sleep apneas should theoretically be fewer than 5 h^{-1} and respiratory RERAs fewer than 10. If not, a short-term continuous positive airway pressure (CPAP) trial should be performed, and if there is no change in sleepiness, the diagnosis of IH is confirmed.

A MSLT performed according to standard techniques shows fewer than two SOREMPs or no SOREMP if the REM latency on the preceding PSG is less or equal to 15 min. Finally, one of the following should be present: either a mean sleep latency of <8 min on the MSLT or a total 24-h sleep time >660 min documented on a 24-h PSG or on a 7-day wrist actigraphy performed in a period of unrestricted sleep (e.g., holidays) in association with a sleep log, to account for the fact that mean sleep latency is frequently normal in idiopathic hypersomnia [30, 31].

In addition, psychiatric evaluation should be performed in subjects suspected of having a psychiatric disorder and neuroimaging in case of neurological signs.

Once established, IH is usually stable and long lasting, although cases of spontaneous disappearance have been reported [30, 32, 33]. At first sight, the complications of IH appear similar to those of narcolepsy, including poor performance at school or at work, sleeping during recreational activities, and car or machine accidents. However, in the case of patients complaining of long sleep time and difficulty on awakening, complications have some peculiarities such as arriving late at work, lengthy time in bed hardly tolerated by family members, and not benefiting from night sleep or from naps.

Several non-mutually exclusive hypotheses have been proposed to explain the pathophysiology of IH, but the outcome is still limited. Reduced cerebrospinal fluid (CSF) histamine levels have been observed in hypocretin-deficient narcolepsy with cataplexy, in hypocretin non-deficient narcolepsy and in IH patients but not in OSAS patients [34]. This finding has led to the suggestion that CSF histamine is a biomarker reflecting the degree of hypersomnia of central origin. However, using a new validated method of CSF histamine and tele-methylhistamine (t-MHA) measurement [35], Dauvilliers et al. did not find any CSF histamine and t-MHA level differences between the various etiologies of central hypersomnia (narcolepsy with and without cataplexy, idiopathic hypersomnia, unspecified EDS. and neurological controls) [36].

Another perspective comes from a recent experiment showing that CSF from hypersomnolent subjects (excluding known causes of excessive sleepiness) contains a small (500–3000 daltons) not yet identified trypsin-sensitive substance that stimulates the in vitro function of selected γ-aminobutyric acid receptors, only in the presence of GABA, relative to the stimulation obtained with CSF from control subjects [37]. Furthermore, flumazenil, a drug that is generally believed to antagonize the sedative-hypnotic action of benzodiazepines, improved psychomotor vigilance and subjective alertness in seven hypersomnolent patients [37].

Before the eventual identification of IH in 1976, a series of 23 probands with hypersomnia with data from 190 families was published by Czech authors [27]. Nine of these probands (39.1 %), of whom seven had hypersomnia of the sleep drunkenness type, had a positive family history of the disease, and an autosomal dominant mode of inheritance was suggested. In 2001, in a series of 35 IH patients, 25 with the polysymptomatic form and 10 with the monosymptomatic form, a familial history was found in 10 patients with the polysymptomatic form (40 %), including three with several relatives, and in three subjects with the monosymptomatic form (30 %), including one with several relatives [25]. Recently a report of three adolescent-onset cases of IH, assessed clinically and by use of ad libitum PSG, was published, arguing for a genetic origin in this family [38]. The pedigree was compatible with an autosomal dominant inheritance. By analogy with narcolepsy, there has been an early interest

in potential HLA markers in IH, but no consistent findings have emerged so far.

Another pathophysiological hypothesis lies in an alteration of the homeostatic or circadian regulation. In a study comparing the level of slow-wave activity (SWA) in the first two NREM–REM sleep cycles, this level was significantly lower in IH patients than in controls [39]. Thus, patients with IH may need a prolonged sleep time due to lower intensity of NREM sleep. Two other studies compared the sleep spindle index in idiopathic hypersomnia and controls [40] and in IH and narcolepsy [41]. They documented an increased spindle index predominating by the end of night sleep in IH, which may explain the symptoms of difficulty waking up and "sleep drunkenness." In addition, a disturbed circadian rhythm has been hypothesized on the basis of a phase delay in the rhythm of melatonin and cortisol secretion in 15 patients with IH with long sleep time [42]. In a more recent study, Horne and Östberg scores were lower in IH patients than in controls, consistent with a delayed sleep phase in IH [31]. Moreover, investigation into the diurnal dynamics of circadian clock gene expression in dermal fibroblasts of IH patients in comparison with those of healthy controls has shown that the amplitude of the rhythmically expressed BMAL1, PER1, and PER2 was significantly dampened in dermal fibroblasts of IH patients compared with healthy controls, suggesting an aberrant dynamics in the circadian clock of IH patients [43].

Given its phenotypic variety, IH is certainly a heterogeneous condition. Based primarily on clinical symptoms, different divisions of the condition have been proposed: polysymptomatic and monosymptomatic [21], classic, narcolepsy-like and mixed [32], complete and incomplete [44], and with and without long sleep time [24]. However, several studies published after the introduction of the ICSD-2 have suggested that a division of IH based on clinical symptoms lacks validity and that future separation of the disorder into distinct conditions must await progress in understanding the underlying biology [30, 31].

Another issue is the relationship between narcolepsy type 2 and IH. The ICSD-3 clinical criteria, A and C in the case of narcolepsy type 2 and A and B in the case of IH, are similar [1]. As for MSLT criteria, mean sleep latency greater than or equal 8 min is the same in both conditions, and the distinction between two SOREMPs or more for narcolepsy type 2 and fewer than two SOREMPs or none for IH seems rather arbitrary, as the number of SOREMPs may vary from one MSLT to another in a same individual in narcolepsy without cataplexy and in IH [45]. Thus, distinction between the two conditions might be provisional, dependent upon further pathophysiological insights. A further difficulty remains in the recent description of narcolepsy with long sleep time, a condition combining features of both narcolepsy with cataplexy and IH with long sleep time [46]. Indeed narcolepsy with long sleep time resembles IH with long sleep time but manifests numerous REM sleep abnormalities, further complicating the spectrum of IH.

Kleine–Levin Syndrome

The name Kleine-Levin syndrome (KLS) was coined in 1942 [47]. However "a syndrome of periodic somnolence and morbid hunger" had been described as early as 1936 [48], and reports of patients with episodes of hypersomnia, gluttony, odd behaviors, and cognitive symptoms had been published in the 1920s [49–51]. In 1962, Critchley wrote a masterpiece article "Periodic hypersomnia and megaphagia in adolescent males" in which he collected 15 "genuine" instances from the literature and 11 cases of his own which he described in depth [52]. He gave the definition of "a syndrome composed of recurring episodes of undue sleepiness lasting some days associated with an inordinate intake of food, and often with abnormal behavior." In addition, he emphasized four hallmarks: (1) sex incidence whereby males are preponderantly if not wholly affected, (2) onset in adolescence, (3) spontaneous eventual disappearance of the syndrome, and (4) the possibility that the megaphagia is in the nature of compulsive eating rather than bulimia. From this time on, several reviews have been published with the emphasis put on clinical features. In 2005, the second edition of the ICSD published diagnostic criteria of recurring hypersomnia and gave a definition of KLS

modifying Levin's and Critchley's views that hyperphagia was no more necessary for the diagnosis but only one of the possible symptoms of the syndrome: "A diagnosis of KLS should be reserved for cases in which recurrent episodes of hypersomnia are clearly associated with behavioral abnormalities. These may include binge eating, hypersexuality, abnormal behavior such as irritability, aggression, odd behavior; and cognitive abnormalities such as feeling of unreality, confusion and hallucination [24]." Following this publication, several large reviews came out, allowing quantitative evaluations of predisposing factors, circumstances at onset, symptoms, physical signs, and comparisons of symptoms in men and women [53–55].

Finally, the third edition of the International Classification of Sleep Disorders recently came out and changed the name recurrent hypersomnia (including KLS and menstrual-related hypersomnia) to the name KLS [1].

KLS is a rare disorder. There is no prevalence study available. Today, over 400 cases have been published in the world literature. Age of onset is predominantly adolescence and young adulthood. Familial cases are not exceptional: 5 of 194 patients (4.8 %) in one series [53] and 9 of 297 patients (3 %) in a larger series [55]. Prevalence is high in Israel [56] and among American Jews [53] suggesting a founder effect in the Jewish population.

Factors precipitating the first episode are mentioned in all series, consisting most frequently of an upper airway infection or a flulike illness and less frequently of an emotional stress, an alcohol intake, a head trauma, an anesthesia, a vaccination, or an exhaustion.

The episodes begin within a few hours or gradually over a period of 1–3 days, with patients becoming extremely tired or complaining of headache. Hypersomnia is the major symptom present in each episode. Patients lie in bed, sometimes with restlessness and untidiness. Vivid dreams may occur. Usual sleep duration ranges from 12 to 18 h, especially during the first days. Patients wake up spontaneously to void and eat. They may be irritable or even aggressive when awakened or prevented from sleeping. Behavioral symptoms include compulsive eating, disinhibited sexuality, and odd behaviors. Patients do not necessarily look for food, but cannot refrain from eating food within reach, in a compulsive manner. A preference for sweets is common. Increased drinking is sometimes associated. In some cases or in some episodes, compulsive eating may be replaced by anorexia. Sexual disinhibition can take the form of overt masturbation, sexual advances, and shamelessly expressed sexual fantasy. It is apparently less frequent in females than in males. Odd behaviors, also designated as compulsive behaviors, are very special to KLS. They include stereotyped behaviors (repetitive and excessive), disinhibited social behavior, childish behavior, aggression, loss of decency, bizarre postures, or imaginative actions.

Cognitive symptoms may be severe such as altered perception (with people and objects appearing as distorted, distant, unreal), confusion, delusions, or hallucinations or less spectacular such as abnormal speech, impaired concentration, impaired memory, and apathy.

Mental symptoms include depression during the episodes, less frequently in men than in women. Anxiety is less frequent and equally reported by men and women.

KLS is remarkable for the absence of any neurological sign. On the other hand, dysautonomic symptoms such as profuse sweating; reddish, congestive, or puffy face; low or high blood pressure; bradycardia or tachycardia; and intense body odor or nauseating urines are found in about 20 % of men and women. In addition, weight gain of a few kilograms may be observed during the attack and is significantly more frequent in women than in men [55].

The episodes of hypersomnia may end abruptly or insidiously over a few days. In up to a third of cases, the episode is followed for 1 or 2 days by amnesia of the past events, elation with insomnia as if the subject was trying to catch up for lost time.

The diagnosis of KLS is purely clinical. Routine blood tests including blood count, plasma electrolytes, urea, creatinine, and hepatic function are normal. Static and dynamic function hormonal tests (growth hormone, prolactin,

thyroid-stimulating hormone, testosterone, and cortisol) are normal. Agents responsible for upper airway infection, flulike illness, or other infections are rarely identified. CSF, white blood cell count, and protein levels are normal in all patients, ruling out infectious meningitis. Immunoelectrophoresis is also normal. Electroencephalography is often remarkable for a general slowing of the background activity. Bursts of bisynchronous, generalized, moderate to high voltage, 5–7 Hz waves 0.5–2 s in duration, mainly in the bilateral temporal or temporofrontal areas, are frequent and often cause of misdiagnosis with epilepsy. PSG is not easy to organize within 24 or 48 h and difficult to interpret due to the frequent rapid evolution of sleep patterns throughout an attack. The duration of recorded sleep is often shorter or much shorter than the behavioral sleep as observed by parents or nurses. Sleep efficiency is poor, while SOREMPs are frequent. MSLT is of questionable interest in view of the frequent limited cooperation of patients. Structural brain imaging, computerized tomography or MRI, is normal in primary forms of KLS. Psychological interview and testing should be performed during and after the episode.

KLS is characterized by episodes lasting a median of 7–9 days (range: 1–180 days) and a cycle length (time elapsed from the onset of one episode to the onset of the next episode) of 60–100 days [55]. KLS vanishes spontaneously within months or years. However, the overall duration of the condition is variable and, in some patients, may exceptionally last up to 20–30 years. It is commonly assumed that the episodes of KLS decrease in frequency, severity, and duration with time before fading out. Yet, this was clearly evidenced in a limited number of cases only in one series [55].

Menstrual KLS is a very rare disease characterized by episodes of hypersomnia, plus or minus other symptoms and physical signs, which occur in association with the menstrual cycle and sometimes with puerperium [55]. The condition occurs for the first time within the first months after menarche or later. Episodes generally last about 1 week, with resolution at the time of menses.

Neuropathological examinations have been performed in three cases of typical KLS [57–59] and in one case of KLS secondary to a presumptive brain tumor [60]. They have shown various abnormalities in different locations of the brain, which however did not lead to consistent conclusions.

As indicated before, familial cases of KLS have been reported. In one series [55], nine cases were familial and three of these families had more than two affected relatives [61–63] in favor of an autosomal Mendelian inheritance. Moreover, two cases of monozygotic twins have been reported, suggesting a strongly genetic basis for the condition [64, 65].

Single-photon emission computed tomography (SPECT) performed during symptomatic periods and asymptomatic intervals has documented widespread decreased tracer perfusion during symptomatic periods. Of 30 KLS patients, 18 (66.7 %) showed unilateral hypoperfusion in the left thalamus, 3 (11.1 %) in the right thalamus, 3 (11.1 %) in the left basal ganglia, 6 (22.2 %) in the right basal ganglia, and 2 (7.4 %) in the right cerebellum, during the symptomatic periods [66]. In 41 KLS patients, persistent hypoperfusion was documented in the hypothalamus, the thalamus (mainly the right posterior part), the caudate nucleus, and cortical associative areas, e.g., the anterior cingulate, the orbitofrontal, and the right superior temporal cortices extending to the insula, also during the symptomatic periods [67]. It has been suggested that decreased thalamic activity may mediate increased sleep, decreased diencephalic/hypothalamic activity may mediate deregulated instinctual behaviors, and widespread and variable cortical changes may mediate abnormal perception and cognition.

Based on the generally young age at onset, the recurrence of symptoms, the frequent infectious trigger, and a significant increased frequency of the HLA-DQB1* allele in a multicenter group of 30 unrelated patients with KLS, an autoimmune origin had been suggested [68]. However, the increased frequency of the HLA-DQB1* allele was not supported by a later large American study [53].

Due to the role of hypocretin neuropeptides in both sleep–wake regulation and feeding,

hypocretins seem good candidates to be involved in KLS. Although it is generally considered that CSF concentrations of hypocretin-1 are most frequently in the normal range, a recent study, in a large population of 42 Chinese KLS patients, has shown that CSF hypocretin-1 levels were lower in KLS patients during episodes, as compared with controls, and in KLS patients during episodes as compared with KLS patients during remissions [69].

Hypersomnia Due to Medical Disorders

The direct cause of EDS is a coexisting medical disorder. In most cases, EDS only stands as an associated symptom, to the extent that it is often neglected in comparison with the main manifestations and signs of the medical disorder.

Neurologic Disorders

Brain Tumors

Clinically, EDS tends to be continuous, interspersed with brief arousals either spontaneous or provoked. EDS may occur in any intracranial hypertension syndrome or more rarely result from tumors of the diencephalon or peduncular region, with no associated intracranial hypertension. These tumors include glioma or hamartoma affecting the posterior hypothalamus, posterior and superior suprasellar craniopharyngioma compressing the floor of the third ventricle, and pinealoma or teratoma affecting the posterior part of the third ventricle. A number of cases of narcolepsy symptomatic of brain tumors affecting the hypothalamus or midbrain regions have been reported [70].

Stroke

EDS is often a transient state between confusion, agitation, or even coma marking the initial period of the stroke. Among the most frequent causes of sleepiness of vascular origin are paramedian uni or bithalamic infarcts characterized by vertical ocular paresis, "skew deviation," paresis of the third cranial pair, dysarthria and instability in walking; paramedian peduncle-thalamic infarcts characterized by altered ocular motility due to paresis of the third or of the sixth cranial pair; and tegmental infarcts affecting the pontine tegmentum and the reticular formation of this region [71].

Neurodegenerative Disorders

EDS affects 16–50 % of Parkinson's disease patients [72]. It may precede Parkinson's disease by several years and often worsens after the introduction of dopaminergic treatment. A degeneration of hypocretinergic neurons and monoaminergic neurons is most probably involved. Of concern, the occurrence of sudden irresistible sleep episodes is facilitated by the intake of dopaminergic agonists [73].

Multiple system atrophy gives rise to EDS in 25–30 % of patients [74]. However, the mechanism is not the same as in Parkinson's disease. It often depends on OSAS present in 15–37 % of patients [75].

EDS is common in Alzheimer-type dementia. This symptom may be the expression of three different conditions: a sundowning syndrome which affects a quarter of subjects with dementia, the intake of psychotropic medications, or the presence of OSAS [76].

Neuromuscular Diseases

Any neuromuscular disease, motoneurone disease, motor neuropathy, neuromuscular junction disorder, or muscular disease is likely to be accompanied by sleep-related breathing impairment resulting in EDS. A typical example is myotonic dystrophy characterized by weakness of limb, facial and respiratory muscles, myotonia, cardiomyopathy, endocrinopathy, frontal baldness, neuropsychological deficits, and cataract. Myotonic dystrophy type 1 (DM1), or Steinert's disease, is the most common adult-onset form of muscular dystrophy. It also constitutes the neuromuscular condition with the most significant sleep disorders including EDS, central and obstructive apneas, restless legs syndrome, and periodic leg movements. EDS is present in about 70–80 % of patients [77]. In a study comparing six patients with DM1 and 13 healthy controls, the mean sleep latency on the MSLT was abnormally short in all patients, and hypocretin-1 levels were significantly lower in patients versus controls ($p<0.001$) [78]. Thus a dysfunction of the hypothalamic

hypocretin system may mediate EDS. Sleep disturbances are not as well characterized in myotonic dystrophy type 2 (DM2). However, a recent survey performed in 30 patients and 43 controls showed EDS and fatigue independently associated with DM2 diagnosis [79].

Posttraumatic Sleepiness

In addition to residual symptoms such as focal neurological deficit, posttraumatic epilepsy, movement disorder, hormonal disturbance, cognitive deficit, and psychotic disorder, subjects with traumatic brain injury (TBI) may develop sleep–wake disturbances including posttraumatic sleepiness. Subjective posttraumatic sleepiness (as assessed by the ESS) was found in 28 % of 65 consecutive patients, 6 months after TBI and objective posttraumatic sleepiness (as assessed by the MSLT) in 25 % [80]. Another prospective study conducted in 87 subjects, at least 3 months after TBI, found posttraumatic sleepiness in 25 % of subjects [81]. The etiology of posttraumatic sleepiness has not yet been elucidated, and multiple factors, both physical and psychological, may be involved.

Epilepsy

Although epilepsy can be the cause of sleepiness, the association of epilepsy and sleepiness is not clear-cut. Some studies demonstrated EDS in 17–28 % of patients with epilepsy [82, 83], while others did not find a difference in ESS scores in patients with epilepsy and in controls [84, 85]. The location of the ictal focus likely influences the expression of sleepiness; patients with frontal lobe epilepsy have increased sleep fragmentation and EDS [86]. Moreover, many antiepileptic drugs are known to induce EDS.

Multiple Sclerosis

There is conflicting evidence regarding EDS in multiple sclerosis (MS), with one study reporting sleep disturbances and EDS in MS patients compared to non-MS groups [87] and others revealing ESS scores at the high end of normal [88, 89]. When present, sleepiness in MS is likely due to hypothalamic lesions and low CSF hypocretin levels [90]. Cases of narcolepsy with EDS and several SOREMPs, with or without cataplexy, secondary to bilateral hypothalamic lesions and hypocretin levels <40 pg/ml have been reported [91].

Infectious and Parasitic Diseases

Infectious Mononucleosis

In the aftermath of infectious mononucleosis, the subject may feel intense asthenia and lengthening of his total sleep time, difficulty awakening, and EDS evoking idiopathic hypersomnia [92]. This type of hypersomnia also develops following viral pneumopathy, hepatitis B viral infection, and the Guillain–Barré syndrome, probably through the same mechanism.

Viral Encephalitides

Disorders of wakefulness and/or consciousness are found in virtually all patients affected by viral encephalitis. However, in the absence of PSG studies, it is very difficult to define the border between wakefulness disorders and disorders affecting consciousness. Two nosological entities are worthy of mention: arbovirus diseases and epidemic encephalitis. The arboviruses represent a heterogeneous group of viruses whose common characteristic is that they are transmitted by arthropod vectors. The various arbovirus diseases share the same first symptoms evoking a fairly severe state of flu with high fever, headache, and myalgias. Encephalitic signs then develop, which vary according to the agent responsible. Sleepiness is a fairly characteristic feature of the European tick-borne encephalitis [93].

First appearing in Europe in 1917, epidemic encephalitis affected tens of thousands of subjects in the 10 years which followed. Its cause has never been fully identified, even if the pathological lesions and inflammatory sites located mainly in the gray matter of the diencephalon and basal ganglia strongly suggest a viral infection. The most common form, referred to as the lethargic form, consisted of a febrile flulike condition, rapidly complicated by sleepiness culminating in a permanent state of sleep, stupor, and coma, associated with frequent oculogyric crises with nystagmus. This clinical picture corresponded to lesions in the posterior hypothalamus and midbrain tegmentum [94]. Sporadic cases are still exceptionally reported.

Acquired Immunodeficiency Syndrome (AIDS)
Subjects infected by HIV sometimes complain of EDS. HIV-infected patients are significantly more likely to sleep more, nap more, and have diminished midmorning alertness in comparison with nonaffected subjects [95]. More recently, poor nighttime sleep was significantly correlated with fatigue intensity ($p<0.05$) and EDS ($p<0.05$) in a sample of 128 individuals on a longitudinal study [96].

African Trypanosomiasis (Sleeping Sickness)
African trypanosomiasis is a subacute or chronic parasitic disease caused by the inoculation of a protozoon, *Trypanosoma brucei*, transmitted by the tsetse fly. It is endemic to certain regions of tropical Africa. The form found in West and Central Africa is due to *Trypanosoma gambiense*. It causes over 98 % of reported cases. The form found in East Africa is caused by *Trypanosoma rhodesiense*. The first form is divided in three successive stages. Several hours after the sting, a hot, edematous, and erythematous tender nodule, referred to as the chancre, appears around the inoculation point. After a phase of inoculation varying from several days to several months, the invasion of the blood and lymphatic organs by multiple trypanosomiasis constitutes the hemolymphatic stage 1. This stage lasts until the appearance of the parasite in the CSF, referred to as meningoencephalitic stage 2. It is characterized by exacerbated headache and fatigue, mental disturbances, and a wealth of neurological signs including disorders of tone and mobility. Sleep and wake alterations consist of sleep episodes randomly spread over 24 h, causing a loss of circadian alternation of sleep and wakefulness and the occurrence of SOREMPs in several sleep episodes [97]. Demyelinating encephalitis ends the time course of the disease along with apathy, dementia, epileptic seizures, incontinence, and death in a state of cachexia.

Multisystem Diseases

Sarcoidosis, a chronic, multisystem disease, most frequently affects the lung. However, CNS involvement is thought to occur in about 10 % of cases. Neurosarcoidosis can affect any part of the CNS, specially the hypothalamus and pituitary gland and in that case includes symptoms of EDS, hyperphagia, polydipsia, and variations in body temperature.

Systemic lupus erythematosus is also a chronic, multisystem disorder which may be associated with EDS.

Endocrine Disorders

EDS has been associated with several endocrine disorders, in part due to the co-occurrence of OSAS.

Several studies have demonstrated that OSA is more prevalent among patients with hypothyroidism than among control subjects [98]. However, a primary effect of hypothyroidism on sleep is also possible [99].

Sleep-disordered breathing is common in acromegaly in relation with the insidious onset of facial features, bony proliferation, and soft tissue swelling. In a study involving 17 patients (11 women and 6 men) diagnosed with acromegaly, 10 patients (58.8 %) had an apnea/hypopnea index greater than 10, 9 had OSAS, and one had central sleep apneas [100]. Seven patients, 5 with an AHI >10 and 2 with an AHI <10, reported EDS with an ESS score greater than 10.

Diabetes and OSAS share a high prevalence in industrial nations. The presence of OSAS seems to promote the development of diabetes mellitus and vice versa. There are limited data regarding EDS in type 2 diabetes patients. In one study involving 614 type 2 diabetes patients, EDS, as measured by the ESS, occurred in 8.5 % of the patients [101]. However, apneas were assessed by the Sleep Disorders Questionnaires using sleep apnea subscales only, and the relationship between apneas and EDS was not specifically assessed. In another study involving 110 patients with type 2 diabetes, EDS was found in 55.5 % of patients, in association with depressive symptoms in 44.5 % of them [102].

Genetic Disorders

EDS is highly prevalent in patients suffering from various genetic syndromes. It is often the consequence of nocturnal breathing disorder, most often OSAS, but it may also be due to a primary wakefulness dysfunction. An excellent review of these syndromes was recently pub-

lished [103], and the present subchapter will only review the most common genetic disorders accompanied by EDS.

Chromosomal Abnormalities

Three chromosomal abnormalities, trisomy 21, translocation of the long arm of an extra chromosome 21 to chromosome 14 or 22, and mosaicism of trisomy 21, may be involved in Down syndrome. EDS is frequent, in relation with OSAS, the prevalence of which is higher than 50 %, or in relation with sleep fragmentation, independent of respiratory events and periodic limb movements.

Prader–Willi syndrome (PWS) is due to a lack of expression of the paternally active genes in the q 11–13 region of chromosome 15. EDS is a common symptom in PWS. Camfferman et al. identified 13 studies that have undertaken MST [104]. Eighty-nine patients underwent MSLT. Thirty-seven (41.6 %) showed a mean sleep latency of less than 5 min, and 27 (32.7 %) showed at least one SOREM. Given the risk factors for OSA, obesity, narrowing of the upper airway, facial dysmorphism, scoliosis, and hypotonia, one of the proposed causes of EDS in PWS is a combination of obesity and OSA. However, no convincing correlation has been established between OSA severity and EDS intensity. Therefore, additional mechanisms of EDS including hypothalamic dysfunction supported by decreased CSF hypocretin-1 level may be involved [105].

Smith–Magenis syndrome is associated with a deletion of 17p 11.2. Most patients exhibit sleep attacks occurring at the end of the day, suggesting an advanced sleep phase syndrome.

Norrie disease is a rare genetic form of blindness and variable mental retardation due to a Xp11.3–p11.4 microdeletion. Features of narcolepsy including irresistible episodes of sleep and attacks resembling cataplexy have been described in three related boys in North America [106].

Inherited Metabolic and Neurodegenerative Diseases of the Nervous System

These diseases result from a single mutant gene coding for an enzymatic protein mostly involved in the catabolic pathways. Most striking sleep disorders are found in lysosomal storage disorders including glycogenoses, mucopolysaccharidoses, and sphingolipidoses. Pompe's disease results from an acid α-glucosidase deficiency. Diaphragm weakness responsible for respiratory insufficiency or sleep apnea may appear at any stage of the disease and be associated with EDS.

Mucopolysaccharidoses are heterogeneous syndromes consisting of mental and physical retardation. OSAS associated with EDS is almost systematic. Niemann–Pick disease type C (NPC) is a lysosomal storage sphingolipidosis with four main forms: early infantile, late infantile, juvenile, and adult. Five patients with juvenile NPC have been reported [107]. Cataplexy was present in one patient. Nocturnal PSG revealed shortened mean sleep latencies on the MSLT in three patients and SOREMPs in the case with cataplexy. CSF hypocretin-1 levels were reduced in two patients (one with cataplexy), while in the two other patients, the levels were at the lower range of the normal values.

Hypersomnia Due to a Medication or Substance

Patients with this type of disorder have excessive nocturnal sleep, daytime sleepiness, or excessive napping attributable, either to sedating medications or to alcohol, to drugs of abuse, or to withdrawal from amphetamine and other drugs. The sleep disorder has become a public health concern, due to the consequences of somnolence, not only on driving but also on occupational activities and thus on productivity.

Sedating medications lead to "a state of calm or reduced nervous activity" (Collins's dictionary) which may eventually result into EDS. They cause sedation via effects on the neural systems involved in the sleep–wake regulation, primarily by increasing GABA or inhibiting histamine, norepinephrine, or serotonin. Important factors affecting the degree of sedation include receptor binding profile, dose, half-life, and time of administration as well as age and association with multiple medication ingestion. These medications include benzodiazepine and nonbenzodiazepine hypnotics, antianxiety drugs, some antidepressants, first-generation antihistamines, antipsychotic drugs, antiepileptic drugs, opiates,

anticholinergic drugs, and skeletal muscle relaxants. A frequent source of excessive somnolence is also the use of some dopamine agonists such as pramipexole and ropinirole. Excessive somnolence may less frequently be caused by various medications including antihypertensive drugs, mostly α2 agonists (e.g., clonidine and methyldopa) and less frequently nonselective beta-antagonists (e.g., propranolol) and α1 antagonists (e.g., prazosin), nonsteroidal anti-inflammatory drugs, and antispasmodic drugs. Of note, EDS occurs only in a fraction of patients using these drugs, and its severity can vary considerably rending the diagnosis uneasy. In some cases, failure to provide treatment by the incriminated drug may be more disruptive than EDS.

Alcohol intoxication causes sedation for 3–4 h and then insomnia, whereas intake of caffeine or cocaine causes insomnia and their withdrawal sedation. Sedation is a common adverse effect of opioid medications. The degree of sedation may depend on the specific drug, dosage and duration of use, as well as on the severity of the underlying disease. Cannabis use may be associated with EDS, sluggishness, giddiness, and inability to concentrate. In chronically heavy amphetamine users, EDS peaks during the first week of withdrawal and can persist for up to several weeks. In people consuming caffeine daily, discontinuation can produce EDS and fatigue for several days.

Hypersomnia Associated with a Psychiatric Disorder

Significant evidence links EDS to depression. In a study conducted with a large-scale American population sample of 16.583 men and women, 8.7 % had EDS, which was strikingly associated with depressive symptoms [108].

EDS can be a symptom of various psychiatric disorders involving depression (Table 10.2).

However, EDS is not systematically present in these disorders. First, the accompanying sleep symptom is either insomnia or EDS; second, the sleep symptom is only part of a list of symptoms, a certain number of which have to be present during the same 2-week period and represent a change from previous functioning; third, subjective sleepiness, as assessed by the ESS or other subjective tests, has been evidenced in most of these psychiatric disorders, but rarely objective sleepiness as measured by MSLT, actigraphy, or continuous PSG [109].

Table 10.2 Psychiatric disorders potentially associated with hypersomnolence (DSM-5)

Psychiatric disorders	Subtypes	Specifiers
Bipolar and related disorder	Bipolar I disorder	With atypical features
	Bipolar II disorder	With seasonal patterns
Depressive disorders	Major depressive disorder	With atypical features
	Persistent depressive disorder	With seasonal patterns
	Premenstrual dysphoric disorder	
	Other specified depression disorder	
Schizophrenia spectrum and other psychiatric disorder)	Schizoaffective disorder	

Despite the significant evidence linking EDS to depression, the pathophysiological mechanisms underlying this relationship remain uncertain. Among the current hypotheses are a cholinergic–aminergic imbalance [110] and disturbances in the circadian system [111].

Insufficient Sleep Syndrome

"Insufficient sleep syndrome occurs when an individual persistently fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness" [1]. As a consequence, the subject is abnormally sleepy with daily periods of irrepressible need to sleep or daytime lapses into sleep. The patient's sleep time, established by personal or collateral history, sleep diary, or actigraphy, is usually shorter than expected for age. Sleep time is markedly extended on weekend nights or during holidays compared to weekday nights. Depending upon extent of sleep loss, individuals are at risk for a range of neurobehavioral deficits,

including lapses of attention, slowed working memory, reduced cognitive function, depressed mood, and fatigue.

This syndrome has been systematically investigated for the first time in 1983, in a population of 59 adults, 37 men and 22 women, mean age 40.8 ± 12.2 [112]. Since then, studies have been mainly carried out in adolescents [113, 114], except for a Japanese study based on the interview of 1243 patients referred to a sleep disorder outpatient clinic for complaint of EDS: the combination of insufficient sleep and EDS was about 7.1 % of the sample [115]. However, no differential diagnosis was applied.

Positive diagnosis is primarily based on interview and actigraphy associated with sleep log for a minimum of 1 week. PSG and MSLT are not required to establish a diagnosis of insufficient sleep syndrome. Rather, sleep time is extended first, and the patient is clinically reevaluated; if the symptoms disappear, insufficient sleep syndrome is confirmed. If unchecked, insufficient sleep syndrome may predispose to depression and other psychological difficulties as well as poor work performances or traffic accidents.

Conclusion

In addition to OSAS and narcolepsy, etiologies of EDS are numerous. Some of them idiopathic hypersomnia, KLS, and insufficient sleep syndrome are well known to sleep physicians, while others, mainly symptomatic causes, are familiar to some of them only. It is of utmost importance that sleep physicians are aware of the possibility of EDS in a large variety of somatic and psychiatric conditions and that specialists, neurologists, psychiatrists, cardiologists, chest physicians, endocrinologists, and specialists of infectious diseases and internal medicine learn to recognize EDS as an important symptom, both in terms of diagnosis and treatment.

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Narcolepsy and Other Comorbid Medical Illnesses

11

Lori A. Panossian and Alon Y. Avidan

Introduction

Narcolepsy is a chronic neurological disorder of sleep that typically presents between 10 and 25 years of age in most cases, but may occur at any age [1]. The condition is associated with pathological unremitting excessive daytime sleepiness (EDS) and abnormal intrusion of rapid eye movement (REM) sleep phenomenon such as cataplexy, sleep paralysis, and hypnagogic hallucinations into wakefulness. The pathophysiology of narcolepsy is thought to be related to a deficiency in the neuropeptide hypocretin (orexin) [2] and has a genetic association with certain human leukocyte antigen (HLA) alleles such as HLA-DR2 and HLA-DQB1*0602 [3]. It is postulated that environmental factors such as viral antigens may trigger an autoimmune reaction through the process of molecular mimicry, resulting in destruction of the hypothalamic cells responsible for hypocretin production [4].

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Narcolepsy is associated with a number of other comorbid medical problems. Potential comorbidities include eating disorders, obesity, hypercholesterolemia, gastrointestinal disorders, diabetes, psychiatric conditions including schizophrenia and depression, fibromyalgia, neurological symptoms including migraine headaches and cognitive dysfunction, other autoimmune disorders, and impairment of psychosocial function (Fig. 11.1).

Comorbid Eating Disorders and Obesity

There has been a long-standing correlation between narcolepsy and increased body mass index (BMI, expressed as kg/m^2) as well as a possible association with comorbid eating disorders. Growing evidence suggests that both adults and children with narcolepsy are more likely to be overweight or obese [5–10]. Rates of obesity nearing 60 % have been reported among children with narcolepsy [11]. Adults with narcolepsy with cataplexy [type 1 narcolepsy (NT1)], but not those with idiopathic hypersomnia, are more likely to be obese or overweight; however, BMI does not appear to correlate with cerebrospinal fluid (CSF) hypocretin levels [5]. Similar rates of BMI elevation are seen among men and women, and also among those with and without a history of narcolepsy medication use, which suggests that the narcolepsy medications are not

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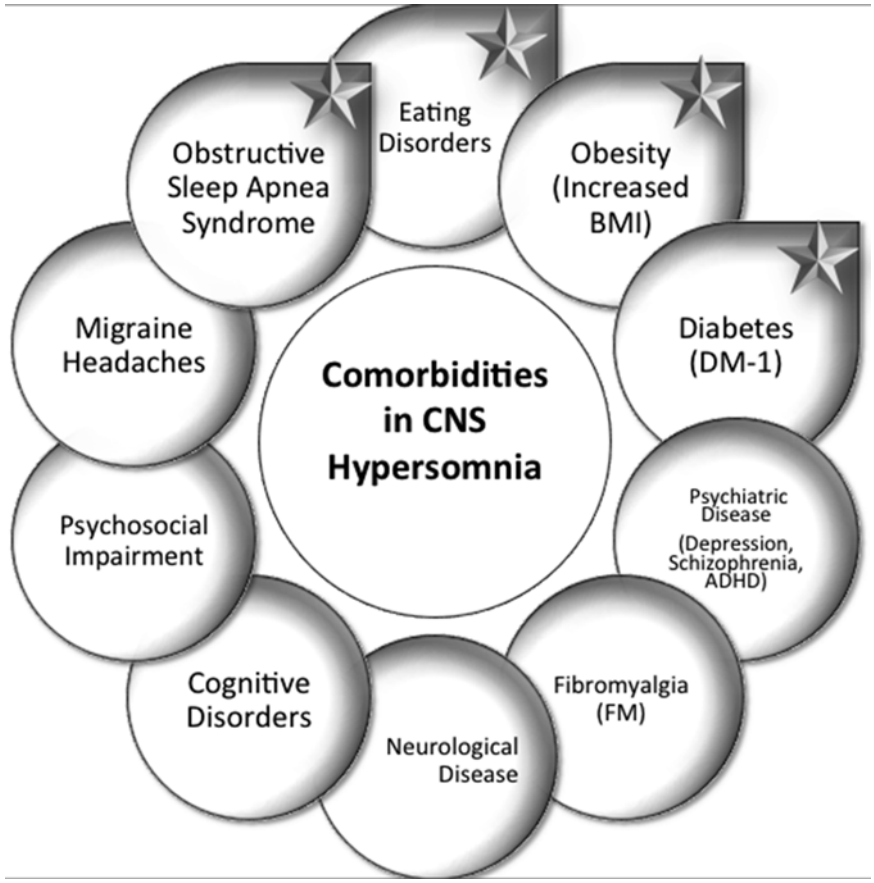

Fig. 11.1 Comorbid conditions associated with narcolepsy. Patients affected by narcolepsy are at risk for a variety of conditions including obesity, diabetes (diabetes type 1, DM-1), psychiatric conditions including schizophrenia, attention deficit/hyperactivity disorder (ADHD) and depression, fibromyalgia, neurological symptoms including migraine headaches and cognitive dysfunction, as well as psychosocial impairment. The risk for metabolic syndrome conferred through obesity, sleep apnea, eating disorder, and diabetes uniquely characterizes the hypocretin deficiency phenotype

significantly contributing to weight increases [8, 11]. In addition to increased obesity and when compared to those with idiopathic hypersomnia, patients with narcolepsy have BMI-independent higher waist circumference, increased waist-to-hip ratio, elevation of diastolic blood pressure, and high cholesterol and triglyceride values [12, 13].

The reason for weight gain in narcolepsy remains unclear. It does not appear to be due to increased sleepiness alone, given the lack of significant BMI elevation in idiopathic hypersomnia patients [5]. An individual's genetic background may play a role; in mouse models of narcolepsy, the development of obesity despite eating less depends on both environmental factors and the genetic background of the transgenic mouse [14]. In humans, first-degree relatives of narcoleptics have significantly higher BMIs than the general population (but lower than the patients themselves) [15]. However, while there are known differences in NT-1 susceptibility genes among different racial groups [16, 17], the few systematic studies in this cohort have not found significant associations between racial/ethnic background and obesity risk [10]. One study looking at the human leukocyte antigen

HLA-DR2 haplotype, commonly associated with narcolepsy, did not find any increased rates of obesity among healthy non-narcoleptic individuals who are HLA-DR2 positive [7]. Thus, there does not appear to be a genetic linkage between the HLA-DR2 allele and obesity in and of itself.

Weight gain may be related to underlying hypothalamic dysfunction in narcolepsy, potentially affecting behaviors related to eating, physical activity, and energy expenditure. In support of hypothalamic derangement extending beyond the sleep–wake disruption, children and adolescents with narcolepsy have a greater incidence precocious puberty compared to obese controls [18]. It has been postulated that the hypothalamic dysfunction due to loss of hypothalamic hypocretin neurons in NT-1 may result in neuroendocrine changes, autonomic dysregulation, and altered energy homeostasis [2, 8]. Hypocretin interacts with peripheral metabolic signals including leptin, ghrelin, and glucose to regulate energy expenditure and physical activity and stimulate eating behavior [19, 20]. It might then be inferred that deficient hypocretin would cause less food intake and reduced BMI; however, this is not the case in narcolepsy. Narcolepsy patients do in fact have relative hypophagia (under eating) with reduced daily caloric intake but are nonetheless more likely to be obese [12, 21]. A possible explanation may be that hypocretin deficiency reduces energy expenditure to a greater degree than it reduces food intake, resulting in net weight gain [22].

A number of studies recently examined the association between narcolepsy and the adipose tissue-derived hormone leptin, involved in signaling the size of adipose cells to the central nervous system [23]. A deficiency in leptin may be predicted to reduce feedback to the central nervous system and result in obesity. Leptin and hypocretin appear to work synergistically to inhibit REM sleep [24, 25], and thus their loss may play a role in the increased sleep-onset REM periods that are observed in patients with narcolepsy. While an earlier study measuring serum and CSF levels of leptin found a significant reduction in serum but not in CSF leptin in narcolepsy [23, 26], subsequent larger, controlled studies found no alterations in leptin levels. Leptin concentrations were similar to healthy controls in serum, CSF, and the CSF-to-serum ratio (an indicator of leptin transport across the blood–brain barrier) [22, 27].

Levels of ghrelin and growth hormone, both involved in hunger/satiety signaling, were also found to be unchanged in NT-1 [28–30]. Obestatin is another peripheral hormone that increases adipogenesis by regulating adipocyte metabolism [31]. A recent small study showed increased plasma levels of obestatin in NT-1 [29]; further studies are required to confirm this association and its role in obesity.

There is growing recognition of increased eating disorders in narcolepsy, especially in patients with NT-1 who have scored significantly higher on almost all measures in a clinical eating disorders assessment tool [6, 13]. Even after controlling for BMI, patients with NT-1 demonstrate a high propensity of overeating, binge eating, and cravings for food [6]. Although many patients with NT-1 exhibited symptoms and approximately one quarter of patients met formal criteria for an eating disorder, there was no predilection for a specific type of eating disorder. The eating disorders present in the narcoleptic group included anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified [6]. Other studies have confirmed increased features of bulimia nervosa that did not meet formal diagnostic criteria but were instead classified as eating disorder not otherwise specified [32].

Eating disorders may be related to increased impulsivity in NT-1, given the association between hypocretin signaling and reward/addiction behavior [33]. Impulsive eating in NT-1 is evidenced by higher rates of moderate-to-severe binge eating and sleep-related eating disorder (SRED) [34, 35]. However, there are conflicting findings across studies, as other groups have found no association between narcolepsy and eating disorders using DSM-IV criteria, including no increase in hyperphagic behavior among patients with narcolepsy [36]. These differences may be due to the more stringent diagnostic criteria used in the latter study or possibly the disease

course timing during which the eating disorder symptoms are assessed, given that the weight gain seen in narcolepsy may occur early on at the time of diagnosis [36, 37].

Metabolic rate has been measured in narcolepsy as a possible contributor to weight gain. Because of the lack of unequivocal data implicating increased caloric intake or abnormal eating behavior as the cause of weight gain in narcolepsy, it has been hypothesized that decreased basal metabolic rate may be a cause. This is in fact seen in orexin-deficient transgenic mice, which have higher rates of obesity and decreased basal metabolic rates compared to controls [14]. However, in a trial comparing hypocretin-deficient narcoleptic men with healthy controls, there was no difference in resting metabolic rate [38]. Another study found a strong inverse correlation between resting energy expenditure and BMI in narcolepsy, but there was also a nonsignificant trend toward the same in control subjects [32]. Confirming the effect of BMI on metabolic rate, a third trial demonstrated differences only among nonobese narcoleptics in resting metabolic rate and energy expenditure when compared to age- and BMI-matched controls [39]. Together these data suggest that while obesity and decreased muscle mass likely cause slowed metabolic rates, this effect may be more pronounced in narcolepsy.

In summary, narcolepsy in both children and adults is associated with increased rates of obesity and overweight with associated behavioral differences related to eating (decreased daily caloric intake, increased risk of eating disorder symptoms). No clear etiology has been elucidated for this. There is no unambiguous association between weight gain and HLA haplotype [7], caloric intake [21], peripheral metabolic hormones, or resting metabolic rate [38]. There is conflicting data on the role of eating disorders and behavioral factors on weight gain in narcolepsy [6, 36]. It may be that weight gain in NT-1 involves a complex interaction between behavioral factors, genetic/familial predisposition [15], neuroendocrine pathways such as obestatin or other hormones [29], and deficiency of hypocretin neuronal signaling.

Diabetes Mellitus

Diabetes mellitus has previously been associated with narcolepsy; however, this has not been borne out in more recent studies and may be conferred to the underlying obesity and metabolic syndrome rather than a function of narcolepsy itself. An initial study of 48 adult narcolepsy patients found an elevated 12.5 % rate of diabetes based on abnormal glucose tolerance testing (GTT), as compared to the 1.75–5.5 % historical prevalence of diabetes in the general Japanese population [40]. There was no significant association with obesity in this sample [40].

By contrast, a number of more recent studies have shown no increase in diabetes rates. Two small studies using GTT in patients with NT-1 and age- and BMI-matched controls found no significant difference in insulin resistance rates [41, 42]. Other methods of testing for insulin resistance included measurements of glucose, insulin, and proinsulin levels in 43 patients and 47 BMI- and age-matched controls, showing no difference between groups [43]. In addition, glycosylated hemoglobin (HgbA1C) levels were similar in NC, idiopathic hypersomnia, and healthy controls [5]. These negative findings were confirmed in a hyperinsulinemic-euglycemic clamp experiment, which is considered the most accurate way to diagnose insulin-sensitivity; in fact, narcolepsy patients were found to be *more* insulin-sensitive than matched controls [44].

Recent epidemiological studies have also examined diabetes prevalence in narcolepsy. An interview sample of 320 patients and 1464 age-, sex-, and BMI-matched population controls found an equal diabetes prevalence of 3.8 % in both groups [13]. Another database review did find increased diabetes rates in 757 narcolepsy patients compared to 3013 controls that were matched for age, sex, and socioeconomic status [9]. However, in this study, the narcolepsy group also had significantly higher rates of obesity that may have confounded the diabetes association, as BMI was not controlled for.

Both diabetes mellitus type 1 (insulin-dependent diabetes) and narcolepsy are thought and believed to be mediated through an underlying

autoimmune pathophysiology. Both are associated with specific HLA haplotypes, and both involve the selective, likely autoimmune-mediated, destruction of specific cell types (pancreatic islet cells in type 1 diabetes and hypocretin-producing hypothalamic neurons in narcolepsy) [45]. To explore a potential genetic association between narcolepsy and diabetes mellitus type 1, studies have examined the role of HLA subtypes. Results have demonstrated that the HLA-DQB1*0602 haplotype, which is known to confer susceptibility to NT-1, is however strongly protective against type 1 diabetes [46, 47]. This implies that patients with NT-1 who are positive for the HLA-DQB1*0602 allele are expected to have much lower rates of type 1 diabetes than the general population. Studies to determine the incidence of type 1 versus type 2 (non-insulin-dependent) diabetes mellitus in narcolepsy have not yet been carried out.

Psychiatric Disorders

There is an association between narcolepsy and increased rates of comorbid psychiatric disorders, including depression and schizophrenia [1]. In a large cohort of narcolepsy patients, there were significantly increased rates of major depression that often preceded the narcolepsy diagnosis. In this study, women with narcolepsy had higher rates of panic disorder and posttraumatic stress compared to age-, sex-, and BMI-matched controls [13]. Men with narcolepsy were more likely to have had attention deficit/hyperactivity disorder (ADHD) as children [13]. Other mental disorders significantly increased in narcolepsy-included bipolar disorder, agoraphobia, a variety of anxiety disorder subtypes, and obsessive-compulsive disorder [13].

This association was also found in children. Interview-based studies of children and adolescents with narcolepsy found that 43 % have met criteria for comorbid psychiatric disorders, 29 % had ADHD, 25 % had depressive symptoms and 20 % had major depression, 10 % had general anxiety disorder, 7 % had oppositional defiant disorder, 3 % had a pervasive developmental disorder such as atypical autism, and 3 % had an anorectic-type eating disorder [48, 49]. In addition, more than 70 % of patients were diagnosed with temper tantrums [48].

Symptoms of NT-1 can often overlap with mood disorder symptoms, making it difficult to determine the relative contribution of each. Sleep disturbances, particularly insomnia and hypersomnia, are known comorbidities of depression [50, 51]. In addition, the diagnosis of narcolepsy, particularly NT-1, may be confounded with the diagnosis of major depressive disorder due to similar presenting symptoms. For instance, approximately 10–20 % of patients with major depression have been reported to exhibit EDS [51]. A large study investigated the presence of narcolepsy symptoms among non-narcoleptic patients with depression [50]. They found a strong correlation between severe depression and sleep paralysis, hypnagogic or hypnopompic hallucinations, and automatic behaviors even after controlling for use of antidepressant medications, age, sex, and BMI as shown in Fig. 11.2. In addition, both severe and milder forms of depression were strongly correlated with cataplexy [50]. Cataplexy has been proposed to have a similar pathophysiology to depression, and both conditions respond to antidepressant medications [52].

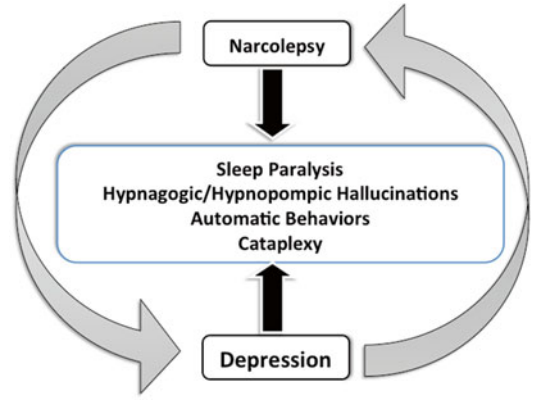

Fig. 11.2 Interrelationship between narcolepsy and depression symptoms. Overlap between the presenting symptoms of narcolepsy and of severe depression can present as a diagnostic challenge. A significant subgroup of patients may have comorbid depression and narcolepsy. Depression can cause hypersomnia, and narcolepsy can also cause depressed mood

Sleep paralysis can also occur in otherwise healthy people suffering from disturbed sleep or insomnia, and it may be that the sleeping problems and insomnia in depression exacerbate symptoms of sleep paralysis [50]. However, despite the potential confounding effects of sleep deprivation, sleep paralysis does appear to occur more frequently among patients with comorbid mental disorders and users of anxiolytic medication as compared to the healthy population, even after controlling for the effects of sleep problems [53]. In addition to depression, sleep paralysis also has an association with trauma and posttraumatic panic symptoms, with particularly high prevalence among African–Americans [54]. However, this effect again may be due to posttraumatic disturbed sleep and insomnia that then precipitates sleep paralysis rather than a clear association between sleep paralysis and a psychiatric diagnosis [54].

Psychosis can occur comorbid with narcolepsy or can overlap with the symptoms of narcolepsy. Hypnagogic and hypnopompic hallucinations in narcolepsy can present similar to psychosis, with visual and tactile perceptual phenomena. In general the hallucinations associated with schizophrenia tend to be primarily auditory rather than visual or tactile; however, some hypnagogic hallucinations can be complex and multimodal with an auditory component also present [55].

A small number of narcolepsy patients may also experience hallucinations while fully awake [55]. The presence of hallucinations can make it difficult at times to differentiate between narcolepsy and schizophrenia, and there have been several reports of narcolepsy patients being misdiagnosed as having refractory schizophrenia [55–58]. This may represent a psychotic subtype of narcolepsy, in which patients have hallucinations while awake in addition to nocturnal hypnagogic and hypnopompic hallucinations. Typically these patients have good insight into their illness, with appropriate affect and interpersonal interactions and no loose associations. The psychotic form of narcolepsy does not typically respond to antipsychotic medications, but does improve with central nervous system stimulants such as methylphenidate or modafinil [57].

Schizophrenia and narcolepsy can coexist in the same individual, although this is rare [57, 59]. Some studies have shown a higher incidence of comorbid schizophrenia among children and adults with narcolepsy compared to the general population; documented rates of schizophrenia among narcoleptics vary, with reports citing a prevalence ranging from 0 to 14 % [9, 55, 60]. The diagnosis of comorbid schizophrenia can be somewhat controversial, as amphetamines and sodium oxybate used in narcolepsy treatment can also cause psychotic symptoms that resolve with dose changes [55, 61]. Nevertheless, there are published reports of patients with NT-1 with comorbid schizoaffective disorder or schizophrenia who had psychotic symptoms and paranoid delusions that began prior to initiating any stimulant treatment for narcolepsy [56, 60]. Often treatment response to antipsychotic medications can be poor [60]. A recent case series attempted to characterize symptoms experienced by patients with dual diagnoses of narcolepsy and schizophrenia, schizoaffective disorder, schizophreniform, or delusional disorder [62]. Ten patients were identified who all had childhood-onset narcolepsy preceding their psychotic symptoms of auditory hallucinations and variable responses to antipsychotic medications. Their psychotic symptoms did not remit with narcolepsy medication changes.

Highlighting the possible relationship with autoimmunity, cases of autoimmune NMDA-receptor encephalitis have been described that cause new-onset narcolepsy with comorbid severe psychosis [63]. Further research may yield insights into the molecular mechanisms of hypothalamic autoimmune injury and neuropsychiatric symptoms.

Fibromyalgia

Case reports have documented patients with long-standing narcolepsy that went on to develop classic symptoms of fibromyalgia (FM) [64, 65] as well as patients with FM who were found to have concurrent NT-1 [66]. FM is a chronic pain disorder with symptoms of diffuse musculoskeletal soreness as well as widespread points of muscle

tenderness to palpation on the body [67]. Approximately 2 % of the population suffers from FM syndrome, with a higher prevalence in women [67, 68]. FM is also frequently associated with fatigue and non-restorative sleep [67].

While reports of narcolepsy with comorbid fibromyalgia are exceedingly rare, the pathophysiology of the two disorders may share a common mechanism. As also evidenced by narcolepsy's association with headaches, it is possible that the underlying pathophysiology of narcolepsy plays a role in pain sensation [69]. Hypocretin has been shown to interact with pain modulation and sensory input pathways [70] and may thus play a role in the development of pain syndromes such as FM. CSF hypocretin levels are normal in FM [67], but signaling pathways may be altered. Genetic studies in FM found an association with the HLA-DR4 allele, but not with the HLA subtypes most commonly associated with narcolepsy (HLA-DR2 and HLA-DQB1*0602) [71]. Therefore, at this time, there is no clear evidence of a pathophysiological association between fibromyalgia and narcolepsy and only rare reports of narcolepsy being associated with comorbid fibromyalgia.

Large studies have found an increased incidence of nonspecific musculoskeletal pain and debilitating pain symptoms in narcolepsy as compared to matched controls [9, 72]. However, this has not been confirmed by another trial using a BMI-matched control group and may therefore reflect an obesity-pain association rather than a specific narcolepsy comorbidity [13].

Migraines and Other Headaches

Studies have shown that the prevalence of migraine headaches (either with or without aura) is increased by two- to fourfold among patients with narcolepsy as compared to the general population [73, 74]. The presence of migraines in patients with narcolepsy has not been significantly linked to the severity of their narcolepsy symptoms, daytime sleepiness, BMI, or HLA-DR2 phenotype [74]. However, those patients who develop migraines tend to have narcolepsy onset at a younger age and typically have their first migraine headache approximately 12 years after experiencing their first symptoms of narcolepsy [74]. In addition, migraine prevalence among narcoleptics remains high even when controlling for use of stimulant and antidepressant medications. This suggests that migraines may be a comorbid medical problem associated with narcolepsy itself rather than an adverse effect of pharmacological treatments for narcolepsy [74]. It has been postulated that both narcolepsy and migraines arise from pathology in similar neuroanatomical areas in the brainstem, including the dorsal raphe nuclei and the locus coeruleus [74]. These brain areas exhibit increased blood flow during migraine headaches and are also involved in control mechanisms for REM sleep [74].

Alternatively, migraines may be more prevalent among patients with narcolepsy due to the underlying sleep disturbances associated with narcolepsy, poor quality sleep, and frequent nocturnal awakenings [75]. Migraines may be triggered or exacerbated by changes in sleep, either due to excessive sleep or sleep deprivation [76].

Data regarding the prevalence of migraine headaches in narcolepsy has been somewhat conflicting; a multicenter case–control study found no significant association between migraines and narcolepsy [77]. However, this trial did find that narcoleptics had a much higher rate of non-migrainous headaches, particularly tension-type headaches, when compared to healthy controls [77]. These nonspecific headaches may be secondary to sleep disturbance associated with narcolepsy or may be secondary to medications used to treat narcolepsy, which were not controlled for in this study [77].

There is also a case report of one patient who had cluster headaches that preceded the onset of his narcolepsy symptoms [78]. Cluster headaches consist of episodic bouts of severe unilateral pain centered around the periorbital area, often with associated rhinorrhoea and lacrimation. The onset of narcolepsy with symptoms of hypersomnia and disturbed nocturnal sleep did not have any significant effect on this patient's cluster headache frequency or severity [78]. This suggests that there is no pathophysiological

association between cluster headaches and narcolepsy [78]. The demographics and genetic associations also differ between the two disorders; narcolepsy has no clear gender predilection, while cluster headaches are much more common in men. In addition, cluster headaches have an association with the HLA-DR5 haplotype rather than HLA-DR2 which is commonly found in narcolepsy [78]. Thus cluster headaches do not appear to be a significant comorbid disorder in narcolepsy.

To address the question of whether migraines and narcolepsy may have a direct association, the frequency of the HLA-DQB1*0602 allele was measured in patients with migraine but not sleep disorder [69]. This HLA subtype is present in the majority of patients with NC [3], but was not found at increased frequency among migraine patients with aura or without aura, compared to healthy controls [69]. While this does not rule out the possibility that migraines and narcolepsy may have a direct association through another mechanism, further research needs to be done to elucidate the association between the two disorders.

Cognitive Dysfunction

Narcolepsy has been associated with specific impairments in several cognitive domains. This effect is apparent among both older and younger age groups [79]. A cohort of narcolepsy patients younger than age 45 had significant impairments in attention and concentration, delayed recall, and difficulty with orientation to persons (recalling names or recognizing acquaintances), among as compared to healthy controls [79]. Narcolepsy patients older than age 45 exhibited cognitive difficulties that were significantly worse than age-matched healthy controls across multiple areas, including attention and concentration, praxis, delayed recall, orientation to persons, temporal orientation, and prospective memory [79]. In a pediatric sample of children and adolescents with narcolepsy, cognitive assessments revealed normal intelligent quotient (IQ) and perceptual speed but lower verbal comprehension and working memory [48]. An adult cohort similarly demonstrated impaired working memory as well as visual attention deficits compared to controls [80]. Comorbid psychiatric diagnoses were associated with significantly lower IQ in narcolepsy [48], and correspondingly, higher IQ was associated with better cognitive function and mood [80].

Sleepiness alone may cause cognitive impairment; but even when controlling for Epworth Sleepiness Scale scores, narcolepsy was still associated with increased risk of attention and concentration deficits and difficulty with prospective memory [79]. Thus, while EDS certainly plays a role, evidence suggests that the underlying disease pathophysiology also results in cognitive dysfunction in narcolepsy.

However, results have been conflicting across studies, and other groups have found no evidence for specific cognitive deficits, despite subjective cognitive complaints by the majority of patients in these studies. Negative trials include a small sample of 10 medication-untreated narcolepsy patients with no significant difference compared to controls on tests of verbal and nonverbal learning, digit span, naming, and fluency [81]. Other studies also failed to show any significant difference, or only mild impairment, between narcoleptics and age- and education-matched healthy controls on an extensive battery of neuropsychological tests, except that narcolepsy patients did exhibit more lapses in attention and some difficulty with executive function as compared to controls [82, 83]. These attention problems did not impair their performance on cognitive tests in a laboratory setting compared to controls [82]. Medication use also had no significant effect on memory tasks among subgroups of narcolepsy patients [83]. These results suggest that rather than a problem in a specific cognitive area, narcolepsy patients appear to exhibit a limitation or reduction in cognitive processing resources [83].

Psychosocial Comorbidities

Narcolepsy, along with other disorders of EDS, may result in significant difficulty with social functioning and quality of life among both children

and adults. Children and adolescents may be particularly vulnerable early in the disease course, as quality of life measures tend to improve with the passage of time after the initial narcolepsy diagnosis [84]. However, from a socioeconomic standpoint, a younger age at diagnosis (before age 30) has been associated with higher rates of employment and general health perception [85].

In adults, narcolepsy has been shown to have a negative effect on health-related quality of life (HRQL) assessments, particularly in the domains of bodily pain, social function, and general health, as compared to data from the general population [86, 87]. In children and even more so in adolescents, HRQL measures are low including poor vitality, physical well-being, and social and leisure activities; comorbid depression significantly worsened HRQL in this group [88]. A study of children ages 4–18 also showed significant problems in behavior, emotional state, quality of life, educational progress, and family impact among children with narcolepsy when compared to healthy age and gender-matched controls [89].

The rate of such problems was also increased among children with EDS not due to narcolepsy. Problem areas included difficulties with peer interactions, behavioral conduct, and emotional symptoms. Children with narcolepsy as well as those with isolated EDS had significantly higher scores on the Child Depression Inventory as compared to controls. These data suggests that the symptom of excessive sleepiness, which is present in children with narcolepsy as well as in children with idiopathic hypersomnia, may be responsible for many of the apparent psychosocial and quality of life issues that arise [89]. Patients with narcolepsy unfortunately exhibit comparable and at times poorer quality of life when compared to other neurologic disorders including lower vitality and reduced social functioning [90].

Obstructive Sleep Apnea

Patients with narcolepsy demonstrate high incidence of sleep, co-occurring in approximately 24–28.5 % of narcolepsy patients [9, 91–93]. The presence of sleep apnea may sometimes delay the diagnosis of and proper management for patients with narcolepsy when daytime sleepiness is attributed exclusively to the former. It is recommended that providers entertain the possibility of comorbid narcolepsy should therefore it be considered in patients where EDS is out of proportion to the severity of sleep-disordered breathing or does not improve with positive airway pressure treatment [91]. Comorbid OSA may be secondary to high obesity rates in this population. An alternative explanation is selection bias, given that patients suspected of narcolepsy are more likely to have had polysomnography or other sleep testing and therefore sleep apnea is more frequently detected [9].

It is also possible that the underlying pathophysiology of disrupted hypocretin in narcolepsy can induce or exacerbate sleep-disordered breathing [94] (see Fig. 11.3). Hypocretin neurons normally have axonal projections to brainstem medullary respiratory control centers responsible for breathing signals. Hypocretin neurons express acid-sensing ion channels that increase neuronal firing under hypercapnia conditions and stimulate increased respiratory drive, as demonstrated in animal studies [95]. In transgenic mice that are deficient in the orexin gene, hypercapnic respiratory drive is diminished and spontaneous apneas in sleep are increased [96]. Conversely in animals with mechanical upper airway obstruction, increased orexin is critical for maintaining respiratory homeostasis and preventing apneas [97]. The animal data strongly suggest that hypocretin deficiency can lead to sleep apneas in the setting of narrow upper airway anatomy and hypercapnia. Additional research is needed into this potential biochemical etiology of increased sleep apnea rates in humans with NT-1.

Other: Cardiovascular, Gastrointestinal, and Pulmonary Diseases

NT-1 has been linked to higher rates of heart disease and hypertension [13]. This may be secondary to obesity and metabolic syndrome (as shown

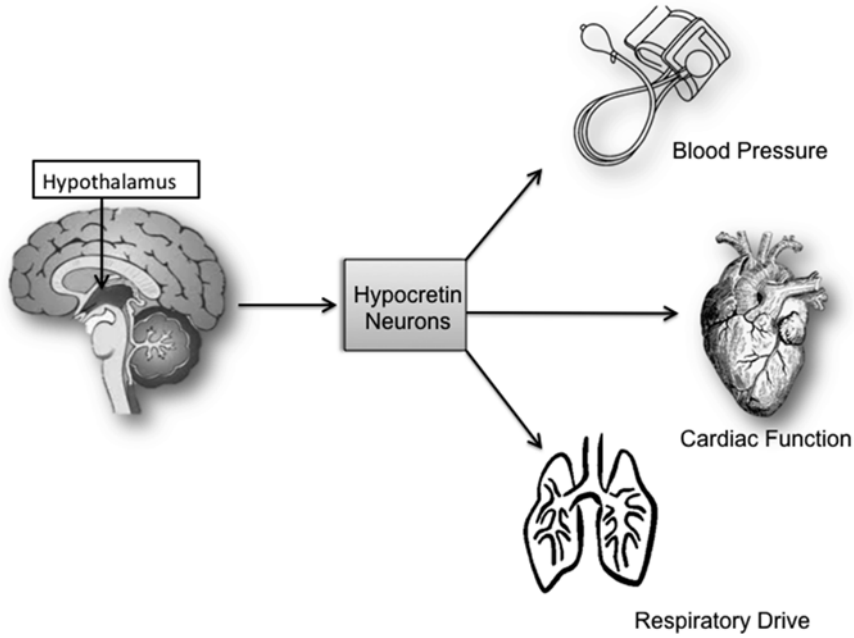

Fig. 11.3 Hypocretin/orexin influences on cardiovascular and respiratory parameters. Hypocretin neuronal projections affect hypercapnic respiratory drive, blood pressure, and heart rate through axonal projections to respiratory and autonomic nervous system control centers in the brainstem and spinal cord. Hypocretin deficiency may therefore influence the development of hypertension, heart disease, and sleep apnea

in Fig. 11.1 by the stars) and chronic use of stimulant medications or may be related directly to narcolepsy mechanisms and hypocretin deficiency as depicted in Fig. 11.3. Hypocretin neurons in the hypothalamus project to sympathetic autonomic centers in the brainstem and spinal cord. Research studies have shown hypocretin involvement in autonomic stress response including blood pressure and heart rate [98, 99]. Chronic hypocretin deficiency and associated compensatory autonomic changes may increase cardiovascular disease risk in ways that are not yet fully understood.

Other comorbidities include digestive tract and pulmonary disorders [9, 13]. Medications for narcolepsy can affect gastric motility, and stimulants may cause diarrhea and nausea as side effects. Higher rates of autoimmune gastrointestinal disorders have also been linked to NT-1, including Crohn's disease, celiac disease, and ulcerative colitis [13]. Pulmonary conditions associated with NT-1 include asthma, upper respiratory tract allergies, and chronic obstructive pulmonary disease [9, 13]. The autoimmune nature of these conditions may reflect a common immune susceptibility present in patients with narcolepsy, perhaps related to HLA alleles or other as yet unknown immune alterations. Future studies examining the mechanism of gastrointestinal and respiratory comorbidities in narcolepsy may help elucidate the nature of the immune disruption.

Mortality

Recent reports describe increased mortality rates in narcolepsy. A large retrospective study found a nonsignificant trend toward increased all-cause 12-year mortality in narcolepsy [9]. A subsequent study that was specifically designed to evaluate mortality in narcolepsy confirmed a statistically significant 1.5-fold increase in all-cause mortality for each of the three consecutive study years [100]. Because the latter was a retrospective database evaluation, it remains unknown

whether the increased mortality rates are due to narcolepsy itself or due to other comorbid medical illnesses [100].

Conclusion

Narcolepsy can be associated with a wide range of medical and psychiatric comorbidities. Some comorbidities, such as the increased rates of sleep apnea and obesity, have been well established in the literature. Other associations, such as between narcolepsy and schizophrenia or between narcolepsy and migraine headaches, have been inconsistent and have occasionally demonstrated contradictory findings. Behavioral and psychosocial factors play an important role in the development of many comorbid conditions such as obesity and metabolic syndrome. However, there is growing animal and human research that suggests a direct pathophysiological link with hypocretin deficiency that warrants further investigation. While the true incidence and etiology of many of these disorders in narcolepsy is unknown or disputed, it is important to be aware of possible medical comorbidities when caring for patients with narcolepsy. Clinician vigilance in screening for these conditions can prevent delays in diagnosis and treatment of many comorbid medical illnesses.

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Sleep Disorder Comorbidities in Narcolepsy

12

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Introduction

Narcolepsy with cataplexy (NC) is a chronic sleep disorder caused by a deficiency in hypothalamic hypocretin neurotransmission, through a selective loss of hypocretin-producing neurons [1–3]. This very specific mechanism of neural destruction potentially indicates an autoimmune process. Based on its tight association with the human leukocyte antigen (HLA) system, it has been postulated that narcolepsy may be autoimmune in nature, although no evidence is available. Furthermore, it remains unclear how some specific HLA alleles predispose to autoimmune diseases. Most patients suffer from the non-familial (or sporadic) form of narcolepsy, but genetic factors still play an important role in those cases. In rare cases with a familial pattern, the mode of inheritance is typically autosomal dominant [4]. Genuine multiplex families (with several generations affected) are very rare [5]. Some neurological diseases such as multiple sclerosis (MS) and acute disseminated encephalomyelitis [6, 7] can cause focal lesions in the hypothalamus and, thus, symptomatic narcolepsy demonstrating that an autoimmune mechanism can damage the hypocretin system.

Currently the diagnosis of narcolepsy is based on the criteria of the International Classification of Sleep Disorders, third edition (ICSD-3), which distinguishes narcolepsy type 1 and narcolepsy type 2 [8]. Narcolepsy type 1 is characterized by disabling daytime sleepiness and/or a transient loss of muscle tone triggered by emotions (cataplexy), optional symptoms such as disturbed night sleep, hallucinations and sleep paralysis, and hypocretin-1 deficiency. Narcolepsy type 1 could be diagnosed without cataplexy being present. Narcolepsy type 2 is characterized by excessive daytime sleepiness (EDS) confirmed by the multiple sleep latency test (MSLT). Despite this new definition, narcolepsy is mainly a clinical diagnosis with two leading symptoms: EDS and cataplexy and ancillary symptoms like sleep paralysis, hypnagogic hallucinations and sleep fragmentation. EDS is diagnosed with the MSLT requiring a mean sleep latency <8 min and >2 sleep-onset REM periods (SOREMPs). In the absence of cataplexy the diagnosis depends on the assessment of the neuropeptide hypocretin-1 (hcrt-1) in the cerebrospinal fluid (<110 pg/ml).

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Ninety percent of clear cases fulfill this requirement, but in narcolepsy without cataplexy (N) only 80 %. In patients presenting intermediate hcrt-1 CSF levels (110–200 pg/ml), many other neurological diseases have to be ruled out [9].

The pathogenesis of narcolepsy is less clear. According with Nevšímalová et al. (2013) [10], 148 patients underwent clinical face-to-face interviews, polysomnography, multiple sleep latency testing, and HLA-DQB1*06:02 typing. The cohort was divided into four age groups: children and adolescents under 19 years ($n=31$), adults aged 20–39 years ($n=51$), 40–59 years ($n=28$), and over 60 years ($n=38$). NC was found in 93 adults (79.5 %) compared with 16 pediatric patients (51.6 %) ($p<0.01$), suggesting that at least some of the children were candidates for developing cataplexy in the future. Statistical evaluation showed an increasing age-related proportion of associated sleep disorders-obstructive sleep apnea, periodic leg movements, and restless leg syndrome ($p<0.001$). Narcolepsy without cataplexy patients showed sleep comorbidities less frequently than NC group. A close connection with NC was found particularly in REM behavior disorder (RBD) ($p<0.05$). RBD affected a third of the patients in the youngest as well as in the oldest groups. However, the association with other sleep disorders had no significant effect on nocturnal sleep (with the exception of obstructive sleep apnea), and the sleep comorbidities under study had no noticeable effect on daytime sleepiness.

In this chapter, we will review the literature to give an overview about the sleep disorders associated with NC in children and adults and the management of these comorbidities whenever possible. A chronological list of the principal articles related with sleep comorbidities in narcolepsy is summarized in Table 12.1.

Table 12.1 Chronological list of articles related with sleep comorbidities in narcolepsy

Sleep comorbidities in general	Nevšímalová S et al. (2013) Frauscher B et al. (2013) Jennum P et al. (2013)
Sleep comorbidities in pediatric narcolepsy	Guilleminault C and Pelayo R (2000) Lecendreux M et al. (2008) Nevšímalová S (2009) Peraita-Adrados R et al. (2011)
Sleep-related breathing disorders (SRBD)	Chokroverty S (1986) Inoue Y et al. (2002) Sansa G et al. (2010)
Nightmares	Schredl M (1998) Sturzenegger C et al. (2004) Cipolli C et al. (2008) Li SX et al. (2010) Pisko J et al. (2014)
Sleepwalking (SW)	Mayer G et al. (2002) Sturzenegger C et al. (2004)
REM sleep behavior disorder (RBD)	Wittig R et al. (1983) Geisler P et al. (1987) Schenck CH et al. (1992) Nightingale S et al. (2005) Dauvilliers Y et al. (2007) Ferri R et al. (2008) Buskova J et al. (2009) Knudsen S et al. (2010) Cipolli C et al. (2011)
Restless legs syndrome and periodic leg movements (RLS–PLMS)	Montplaisir J et al. (2000) Bahammam A (2007) Dauvilliers Y et al. (2007) Plazzi G et al. (2010) Jambhekar SK et al. (2011) Plazzi G et al. (2012)
Hallucinations and psychotic comorbidity	Fortuyn HA et al. (2009) Canellas F et al. (2014)

Sleep Comorbidities in Pediatric Narcolepsy

Pediatric narcolepsy is frequently undetected and misdiagnosed [11]. Failure to recognize the condition may lead to a child being mislabeled as lazy, depressed [12], or even as suffering from atonic epileptic seizures [13]. The spectrum of this disorder is quite broad in childhood; therefore, the absence of cataplexy is associated with a diagnostic delay in patients with suspected narcolepsy. In addition, the characteristic "cataplectic facies" described by Serra et al. (2008) [14] includes drooping of facial muscles, mouth falling open, and tongue lolling. Partial cataplexy is also common with dysarthria, facial flickering, jaw tremor, head/jaw dropping, or just a feeling of knee buckling. More recently, it has also been suggested that pediatric narcolepsy with cataplexy often co-occurs with a complex movement

disorder in addition to "negative" (hypotonic) motor features: the "active" movement abnormalities, including eyebrow raising, perioral and tongue movements, facial grimacing, body swaying, dystonic movements of the arms and of the tongue, and stereotype motor behaviors [15].

In children, cataplexy and other abnormal rapid eye movement (REM) sleep phenomena such as hypnagogic hallucinations and sleep paralysis can develop later, and EDS may be the only clinical symptom leading to the diagnosis of narcolepsy without cataplexy. However, prepubertal children have been reported to experience irresistible sleep episodes that are longer than in adults, and cataplexy appears before; the MSLT shows sleep-onset REM sleep periods (SOREMPs) several months after the onset of hypersomnia [16]. Occurrence of early and frequent cataplectic attacks should lead to detailed clinical, neuroimaging, and immunogenic examinations to rule out "symptomatic" narcolepsy [11]. An association between pediatric narcolepsy–cataplexy, obesity, and precocious puberty has been described [17]. Peraita-Adrados et al. (2011) [18] in a series of nine children found that NC was sporadic in all children—DQB1*06:02 positive—and associated with precocious puberty and polycystic ovary syndrome (PCOS), hyperandrogenism, and insulin resistance in one case. EDS, cataplexy, disturbed nocturnal sleep, nocturnal eating, poor school performance, and emotional disorders were the principal complaints.

Nevšímalová et al. (2013) [10] suggest that children with N may later on develop cataplexy. In addition, that NC has more sleep comorbidities such as sleep apnea, PLMS, and RBD. As distinct from the general population, RBD in NC is present already from childhood. At the 22nd Congress of the European Sleep Research Society, Kovalska et al. (2014) [19] were able to show that hypnagogic hallucinations and sleep paralysis may occur from the onset of the disease to the rest of the patient's life with the symptoms disappearing in only some of the patients. They are exploring this condition and its comorbidities in their patients because the research interest in the disease is not only the onset but, indeed, also the lifetime development of the patient's state of health and social situation. They conclude that the clinical severity of narcolepsy does not depend on the age at onset or with the duration of the disease.

The prevalence of PLMS in children with narcolepsy has also been assessed [20]. A controlled study of 44 narcoleptic children with a mean age of 13 years showed that—using the common criterion of PLMS index ≥5/h—they did not have a higher prevalence of PLMS as compared to most of the previously reported prevalence rates in control population or children with other comorbid conditions. These results suggest that the use of adult criteria for diagnosis of "significant" PLMS in children may not be sufficiently sensitive. In contrast, children with any PLMS had more disturbed sleep and increased arousal index compared with children without PLMS. These findings may suggest that PLMS in children with narcolepsy lead to worsening of sleep quality and daytime sleepiness and may suggest, as for adults, that PLMS are a feature of a more severe form of narcolepsy.

School and social life are affected, and the permanence of the disorder means that familial education, psychological and academic support, and long-term pharmacological treatment are crucial for management of symptoms [21]. Treatment of the condition at onset could ameliorate the long-term effects and improve quality of life, even if treatment of narcolepsy remains limited and understudied in the pediatric population.

Sleep-Related Breathing Disorders

It has been generally accepted that sleep-related breathing disorders (SRBD) are more frequent in narcolepsy [22]. Although the relationship between the mechanisms of both disorders has not been clearly identified, recent evidences suggest that the pathogenesis of obstructive sleep apnea–hypopnea syndrome (OSAHS) in narcolepsy is similar to that of typical OSAHS. To clarify the upper way mechanism of OSAHS, 10 patients with untreated narcolepsy–cataplexy

and apnea–hypopnea index (AHI) value of more than 5/h underwent upper airway magnetic resonance imaging (MRI) and esophageal pressure recording during daytime napping [23]. On MRI, the obstructive site of the upper way was located in the velopharyngeal area. Both maximal esophageal negative pressure values recorded during the naps and body mass index (BMI) correlated significantly with the AHI ($p<0.05$ and $p<0.01$, respectively). These features are similar to the typical features found in patients with OSAHS.

In OSAHS, an increased BMI is a frequent finding that leads to upper way obstruction. Narcolepsy is also associated with increased BMI. Besides, both disorders may be confounded as they are associated with EDS as well, and patients with OSAHS may show SOREMPs on the MSLT. Most patients with EDS presenting to sleep centers are evaluated with nocturnal sleep studies to discard the presence of SRBD. Thus, it is possible that narcoleptics with comorbid OSAHS may be initially diagnosed with OSAHS alone. A study with nocturnal polysomnography on 133 narcoleptic patients (88 male and 34 female), with a mean BMI of 23.9 ± 4.7, showed an AHI ≥ 10 in 33 of them (24.8 %), and the mean AHI was 28.5 ± 15.7 [24]. Like in the general population, OSAHS was associated with a higher BMI, male gender and older age. Among the 33 patients, 20 were initially treated only with CPAP: 15 patients reported no change in EDS, three reported a mild improvement, and two a better nocturnal sleep quality, suggesting that OSAHS does not play an important role in the pathophysiology and severity of EDS in narcolepsy.

A retro- and prospective national study in Denmark on the comorbidity and mortality of narcolepsy [25] from a National Patient Registry with health information at least 3 years prior to and after the diagnose of narcolepsy was performed in 757 patients who were diagnosed with narcolepsy between 1997 and 2009. The most common significant diagnosis before the diagnosis of narcolepsy was sleep apnea (44.5 %, $p<0.001$). After diagnosis, the most common diagnoses were sleep apnea (19.2 %, $p<0.001$), obesity (13.4 %, $p<0.001$), and other sleep disorders (78.5 %, $p<0.001$). They concluded that patients with narcolepsy present higher morbidity several years prior to diagnosis and even higher thereafter, and the mortality rate due to narcolepsy was slightly but not significantly higher.

Obesity is consistently reported in narcolepsy [26], and some studies have stated the prevalence of obesity (BMI ≥ 30 Kg/m^2) and overweight (BMI ≥ 25–30 Kg/m^2) in 33 % of narcoleptics [27]. Moreover, these patients have an increased waist circumference, indicating excess fat storage in abdominal depots. This fact has been partly linked to hypocretin deficiency, but was not confirmed in other studies [28], suggesting that overweight in narcolepsy may be caused by other mechanisms. A clinical and polysomnographic analysis of the Innsbruck narcolepsy cohort was performed on 100 patients (56 men, 44 women) who met diagnostic criteria for narcolepsy [29]. The median BMI of the total group was 26.2 kg/m^2 (18.2–43.0 kg/m^2), and 23 % of patients (12 men, 11 women) had a BMI > 30 kg/m^2. SRBD were highly prevalent (24 %): 14 had mild sleep apnea syndrome (AHI = 5–15/h), eight moderate sleep apnea syndrome (AHI = 15–30/h), and two had severe sleep apnea syndrome with an AHI > 30/h.

The causal effect of obesity and metabolic diseases (type 2 diabetes mellitus) in narcolepsy has not been identified, and a relation to glucose response has been suggested. Some studies [30] also indicate that hypocretin/orexin neurons can alter their intrinsic electrical activity according to ambient fluctuations in the levels of nutrients and appetite-regulating hormones. These electrical responses are the strongest candidates to date for the neural correlates of after-meal sleepiness and hunger-induced wakefulness. A recent study [31] found increased peripheral insulin sensitivity in narcolepsy patients, whereas hepatic insulin sensitivity and β-cell function were not different from matched healthy controls. The higher insulin sensitivity was reflected by a higher rate of insulin-mediated glucose uptake in peripheral tissues, of which skeletal muscle is the most important. Lipolysis tended to be lower in narcolepsy

patients, which could be due to insulin sensitivity of adipose tissue. This finding may partly explain comorbid overweight in narcolepsy, and the higher insulin sensitivity itself might contribute. Moreover, sodium oxybate (SXB) stimulated lipolysis, which might be one of the reasons why patients lose weight while on this drug. The mechanisms through which hypocretin deficiency affects glucose and fat metabolism might involve a modulation of autonomic nervous system activity, which recently has been demonstrated to be critically implicated in the regulation of energy homeostasis. Sleep apnea may occur more often among narcoleptic patients due to overweight/obesity, although this increased occurrence is explained in part by a bias arising from the greater number of PSG recordings performed before and after the diagnosis of narcolepsy.

Standard treatments for narcolepsy do not significantly affect the severity of SRBD. Moreover, studies to date indicate that SXB does not increase AHI or decrease mean SaO_2 in patients with OSAHS [32, 33]. However, a case study reported an increased AHI following SXB treatment in a patient with narcolepsy and comorbid heart disease [34]. In a recent study, the administration of 9 GR per night of SXB did not increase the severity of SRBD [and moreover decreased, as SXB increases slow-wave sleep (SWS) and decreases REM sleep], and no significant effect on mean AHI and SaO_2 indexes was seen [35].

Circadian Rhythm Disorders and Narcolepsy in Shift Workers

Employment, which requires frequent shift rotation, may lead to the development of specific sleep disorders [36]. Delayed sleep phase (DSP) insomnia can greatly impair an individual's circadian rhythm-dependent functions; it can occur when shift work disrupts normal sleep–waking schedules. Disorders of EDS, such as narcolepsy, occur in some subjects after they have been involved to frequently rotating shifts. Understanding the problems associated with circadian rhythm disturbances and their interaction with sleep disorders is particularly important in industrial medicine; any clinician whose patients are subjected to frequent shift rotations should consider the effects of disrupted sleep–waking schedules. The diagnostic value of MSLT is strongly altered by shift work and, to a lesser extent, by chronic sleep deprivation. The prevalence of narcolepsy without cataplexy may be threefold higher than that of narcolepsy–cataplexy.

The International Labor Organization and the European Union recognize a periodic medical evaluation of the shift workers. The aim of this evaluation is the diagnosis of disorders that can be aggravated by shift work schedules and some unrecognized factors (sleep disorders including narcolepsy) that could be determinants in the adaptation to shift work.

Parasomnias

Nightmares

Narcolepsy is associated with abnormal characteristics of REM sleep, such as SOREMPs and a greater REM sleep density, attributable to a primary NREM–REM sleep deregulation. Since REM sleep is associated with the most vivid dreams and the best dream recall, oneiric activity has been explored in several studies, with different results. Even for the general population, there are few epidemiological studies on nightmares, having stated a prevalence of around 5 % [37]. A high prevalence of aggressive dreams was initially found in narcoleptic patients [38], including dreams with sexual themes. Other studies have found a negative tone of narcoleptic dreams more often than in healthy controls [39], high emotiveness including positive emotions [40], or even interesting cases of narcoleptic patients with positive dreams of flying experience [41]. However, most of these studies included quite limited numbers of patients. More recently, a clinical reappraisal to evaluate the spectrum of narcolepsy with cataplexy in a cohort of 41 NC patients observed nightmares in 54 % of them and 5 % controls ($p<0.001$) [42].

Previous laboratory studies have shown that dreams including frightening and visually vivid contents are more frequent during the first period of REM sleep in NC patients than in healthy subjects. During an experimental night, two awakenings were provoked after 8 min of REM sleep in the first and third sleep cycle [43]. While dream recall was comparable in NC patients and controls (about 85 %), first-REM dream reports were longer and had a more complex organization in NC patients. Another study of the same authors [44] confirmed that the cognitive processes underlying dream generation reach their optimal functioning earlier in the night in NC patients than in normal subjects.

As nightmares, lucid dreaming, the phenomenon of becoming aware of the dreaming state during dreaming, has also been reported to be frequent in narcolepsy patients. A study, performed by a telephone interview, evaluated the frequency of recalled dreams, nightmares, and lucid dreams in 35 narcolepsy patients and observed a higher frequency of lucid dreaming compared to healthy controls [45]. Recently, the analysis of a cohort of 53 narcolepsy patients and 53 healthy controls has observed a frequency of lucid dreaming in 77.4 % of narcoleptic patients and 49.1 % of controls ($p < 0.05$). The duration of REM sleep was also longer, the REM sleep-onset latency tended to be shorter, and the percentage of atonia tended to be higher in lucid vs. non-lucid REM sleep [46].

The oneiric activity in both narcolepsy with (NC) and without (N) cataplexy has also been recently assessed [47], to compare the occurrence of nightmares in both types of the disease and to search for factors that might be related to vivid dreams and nightmares in particular. The medical history of 118 narcoleptics (64 men, 54 women, 86 NC) was retrospectively analyzed. Mundane dreams were reported in 42 patients (36 %); vivid, but not unpleasant dreams, in 31 patients (26 %); and nightmares in 39 patients (33 %). Whereas nightmares were reported with the same frequency in N and NC, vivid dreams appeared more frequently in NC patients. Patients with nightmares had a lower prevalence of OSAHS (37 vs. 26 %), whereas no changes in oneiric activity were found in patients with PLMS. Patients with RLS had increased occurrence of vivid dreams (32 vs. 23 %), but the most significant changes were found in patients with narcolepsy and RBD (both NC and N), with increased rates of vivid dreams (33 vs. 26 %) and nightmares (52 vs. 20 %). Compared with the general population, nightmares seem to be significantly more prevalent in both NC and N (≥ sixfold higher), and they are not sufficiently investigated and treated.

The neurobiological basis of narcolepsy and patients' dreaming activities appears to be closely related. Neurobiological imaging studies indicate amygdala-hypothalamus dysfunction in narcolepsy [48]. Since the amygdala is involved in processing emotional memory and fear, this could be associated with frightening dreams. A new model known as the "arousal-retrieval hypothesis" has been described [49]. This model points to the possibility that the occurrence of vivid dreams, and dream recall, may be increased by more frequent awakenings during sleep, which are typically present in narcolepsy. The effect of pharmacological treatments for narcolepsy has been scarcely evaluated, although some authors have reported an increase in nightmares after SXB treatment in pediatric population [50].

Sleepwalking

Sleepwalking (SW), a common NREM sleep parasomnia characterized by behaviors usually initiated during arousals from SWS. Clinical presentation ranges from a benign disease with simple and infrequent episodes to a severe disease with complex behaviors, resulting in walking during sleep with partial to complete amnesia the next day. Some authors have proposed a continuum with other NREM parasomnias such as sleep terrors or confusional awakenings. SW can occur at any age, with an estimated prevalence in adults of 2–4 % that decreases with age and up to 20 % in children. SW can seriously affect the life of a subject by its frequency (one or several episodes per night) or severity (risk of severe injury) [51]. Genetics

seem to play a role in the pathogenesis of this parasomnia. HLA-DQB antigens are known to be associated with disorders of REM sleep like narcolepsy (DQB1*06:02) and RBD (DQw1). Lecendreux et al. (2003) [52] described an association with DQB1*05:01 in SW, which suggests that DQB1 genes could be implicated in disorders of motor control during sleep.

Only a few studies have evaluated the prevalence of SW in narcolepsy. The previously cited clinical reappraisal in a cohort of 41 NC patients observed sleepwalking in 8 % of them and 0 % controls [41]. Another study in 106 narcolepsy patients stated a frequency six times higher than in the general population [53]. In the Innsbruck narcolepsy cohort, NREM parasomnias affected 10 % of patients [29]. All of them consistently report a high prevalence of SW in narcolepsy.

Parasomnia episodes occur during complete or partial arousals while transitioning from SWS sleep to a lighter stage of NREM sleep and can be facilitated by medications. Somnambulism has been reported to occur in 0.4–5.7 % of patients treated with SXB in a dose-dependent manner [54], but there is limited information in the literature concerning complex motor behaviors associated with SXB. A recent publication on SXB reported the second known case of sleep-driving and sleep-related eating disorder (SRED), 2 weeks after reaching the dose of 8 g/night [55]. Complex interactions are important in these cases for the predisposition and precipitation of NREM parasomnias, like mental illness (i.e., depressive disorders), other comorbid sleep disorders, stress, or medications, and further research is necessary to elucidate the mechanism of SXB-induced motor behaviors.

REM Sleep Behavior Disorder

Different abnormalities in REM sleep motor regulation have been described in narcolepsy, including persistence of muscle tone (REM sleep without atonia, or RWA), excessive twitching, and periodic leg movements during sleep (PLMS) [56]. The frequency of RBD observed in narcolepsy ranges between 7 and 36 %. The discrepancies between these results may be due to the small number of patients studied, some differences in the diagnostic criteria of RBD, and the inclusion of patients treated with antidepressants known to facilitate manifestations of RBD. To evaluate the proportion of RWA in narcolepsy, 34 patients with narcolepsy–cataplexy were evaluated in a retrospective study [57]. The analysis showed a significant increase in the proportion of RWA during successive nocturnal REM periods in narcoleptic patients ($p<0.01$), and no correlation was found between the percentage of RBD and the severity and duration of the disease. The study demonstrated for the first time an increasing amount of RBD during the night suggesting enhanced nocturnal REM sleep motor disturbance. The Innsbruck narcolepsy cohort [29] showed the same tendency: RWA was present in most patients (100 %) and RBD in 24 % of patients.

Patients with narcolepsy and with RBD share several polygraphic features of REM sleep deregulation. Both disorders have increased PLMS at night with a specific increase of PLMS in REM sleep [58, 59], and both have dissociated manifestations of REM sleep, with a loss of REM sleep muscle atonia in RBD and an inappropriate occurrence of atonia during wakefulness in narcolepsy. The loss of hypocretin neurons causes narcolepsy in humans, and recent results based on detailed anatomy and lesion experiments in rats have identified independent pathways in brainstem that mediate the atonia and EEG phenomena of REM sleep [60]. As hypocretin neurons are excitatory and have strong projections to the brainstem structures implicated in REM sleep motor regulation, a decreased hypocretinergic tone may cause REM sleep without atonia and RBD in humans.

Several groups have demonstrated a strong association between RBD and neurodegenerative diseases in the group of α-synucleinopathy in middle-aged and older adults; RBD appears to be the preclinical stage of a neurodegenerative disease [61, 62]. Early-onset RBD, defined as RBD beginning prior to 50 years of age, has been distinguished from late-onset or "typical" RBD. Narcolepsy is the most common cause of secondary

RBD in early-onset RBD. The first systematic study of narcolepsy-associated RBD [63] examined 17 patients with narcolepsy and RWA, 10 of them with clinical criteria for RBD. This group of narcolepsy-RBD patients was very young compared to prior studies, with a mean age at onset of RBD symptoms of 28.4 years (14 cases were early-onset). Those with RWA, but without clinical features of RBD, were also young (mean 33.8 years), and all but one were under 50 years of age. Based on the age difference compared to prior reports of RBD, and the coincidence in the onset of RBD and other narcolepsy symptoms, the authors proposed that RBD is another manifestation of REM sleep decontrol in narcolepsy. A large survey of narcoleptic patients revealed a high rate of RBD, 36 and 68 % of patients who regularly experienced cataplexy [64]. Again, individuals with RBD and narcolepsy were younger than the typical RBD population, with mean age of 41 years. Another study with 34 NC patients found that 17 (50 %) had RBD, 13 of them under the age of 50. All patients, regardless of nocturnal behaviors of RBD, had increased tone during REM sleep [65].

A study was performed in 16 patients with narcolepsy with cataplexy (11 men and 5 women), 16 gender-matched patients with idiopathic RBD, and 16 controls [66]. All patients with RBD reported frequent episodes of dream mentation during sleep and showed behavioral manifestations such as jerking, kicking, or gesturing during REM sleep. In contrast, none of the 16 patients with narcolepsy and none of the 16 normal controls reported nocturnal behavioral manifestations associated with dreaming. This study demonstrated that patients with narcolepsy, like patients with RBD, present a higher percentage of REM sleep without atonia and an increased density of phasic chin EMG activity during REM sleep (68.8 % of narcoleptics and 81.3 % of RBD patients) than in normal controls. The study also showed that narcoleptic patients have higher PLMS and PLMW indexes than controls, and a similar trend was found for RBD patients compared to controls. The authors hypothesize that inhibitory systems of motor regulation are globally damaged in narcolepsy and suggest that some basic mechanism is involved in both narcolepsy and RBD resulting in REM without atonia. Besides, the nocturnal behaviors in RBD associated with narcolepsy may be different. In a study of 37 participants with narcolepsy and RBD (62 % were early-onset RBD), abnormal behaviors occurred in the first and second half of the night [67], in contrast to typical RBD, in which behaviors tend to occur in the second half of the night, when the percentage of REM sleep is greater.

The pathophysiological basis by which narcolepsy is closely linked to RBD has not been conclusively demonstrated although part of this association is likely due to treatment of cataplexy with antidepressants. There are no known structural lesions in narcolepsy affecting pontine regions that maintain REM sleep atonia. Further analysis shows that the association can be explained by hypocretin deficiency, suggesting that RBD occurs because of a functional defect in pontine neurons innervated by hypocretinergic projections [68]. This implies that RBD in narcolepsy could have a different pathogenesis than idiopathic RBD, supported by findings that RBD in narcolepsy is not associated with the changes in dream content reported in idiopathic RBD, and a less severe tendency for movements. Unlike idiopathic RBD, narcolepsy is associated with a sleep state instability of all sleep stages, and it remains unclear whether REM atonia loss in narcolepsy may sometimes be due to microintrusions of other sleep stages, or even microarousals, into REM sleep.

Although the pathogenesis of narcolepsy has not yet been established, evidence suggests an autoimmune basis, and there are indications that other autoimmune diseases may also be associated with narcolepsy [69] and with RBD. There have been cases of encephalitis secondary to voltage-gated potassium channel antibody and anti-Ma antibody associated with RBD [70]. No evident brainstem lesions were present in these cases and a potential role of hypocretin deficiency or limbic lesions could have contributed to dream enactment in them. Transient RBD has also been associated with Guillain–Barre syndrome, mainly in patients experiencing

autonomic dysfunction and hallucinations [71]. These authors also found a high prevalence of associated autoimmune diseases, particularly in female patients with young-onset RBD. More recently, a case of RBD, narcolepsy–cataplexy, Parkinsonism, and rheumatoid arthritis has been described [72]. In this patient, the dream enactment episodes preceded the onset of excessive daytime somnolence and cataplexy and started to develop RBD at an older age (60 years). On the other hand, the age at onset of narcolepsy was not typical and the symptoms were incomplete. In addition, the patient developed rheumatoid arthritis and Parkinsonism. The authors hypothesize that patients predisposed to RBD and later Parkinsonism might be susceptible to several triggers that, in this patient, might have been represented by a latent autoimmune process leading to the development of narcolepsy and rheumatoid arthritis.

Restless Legs Syndrome and Periodic Leg Movements

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an irresistible urge to move the legs accompanied by uncomfortable and unpleasant sensations in the legs and during periods of rest or inactivity that are partially or totally relieved with movement [8]. RLS is typically associated to periodic leg movements, which can occur in sleep (PLMS) or wakefulness (PLMW). While PLMS are seen in 80–90 % of patients with RLS, they are not necessary or sufficient for the diagnosis. PLMS are defined as rhythmical extension of the big toe and dorsiflexion of the ankle with occasional flexion of the knee and hip [73]. PLMS are frequently associated with arousals and awakenings and they occur in a wide range of other sleep disorders, including RBD, OSAHS, and insomnia.

The presence of PLMS in patients with narcolepsy was initially reported in a few uncontrolled studies [74, 75]. The first controlled study to determine the prevalence of periodic leg movements during NREM and REM sleep (PLMS) and while awake (PLMW), and to assess the impact of PLMS on nocturnal sleep and daytime functioning in patients with narcolepsy, was performed in 2007 [76]. One hundred and sixty-nine patients with narcolepsy and 116 normal controls, matched for age and gender, were included. The impact of PLMS on sleep and MSLT variables was assessed in narcoleptics with high and low PLMS indices. The study demonstrated that more narcoleptics than controls had a PLMS index greater than 5/h of sleep (67 vs. 37 %, $p<0.0001$) and an index greater than 10 (53 vs. 21 %, $p<0.0001$). PLMS associated with microarousals were more frequent in the narcoleptic group, PLMS indices were higher in both NREM and REM sleep in narcoleptic patients, and a significant increase of PLMS index was found with aging in narcoleptics and controls. The study demonstrated a high frequency of PLMS and PLMW in narcolepsy and an association between the presence of PLMS and daytime functioning disruption. Another controlled study, with age, gender, and BMI-matched normal controls, reported similar findings in 47 newly diagnosed narcolepsy patients [77]. The same tendency with aging was found by Nevsimalova et al. (2013) [10] in their cohort of 148 narcoleptic patients: severe PLMS form (PLMS index ≥ 30) was diagnosed in 2.4 % of those aged 20–39, in 33.3 % of those aged 40–59, and in 39.1 % of those aged 60 years and older.

The possible occurrence of RLS in NC was investigated in a case–control study with 184 NC patients that was conducted in three European sleep disorder centers, two in Italy and one in France [78]. The study showed that RLS was significantly more prevalent among NC patients (14.7 %) than in controls (3.0 %). The mean age at onset of RLS in NC patients fits with the age at onset in idiopathic RLS, and RLS appeared more than 10 years after NC onset. Unlike idiopathic RLS (iRLS), RLS in NC subjects was not more prevalent in women and was less familial (15.4 % of cases). NC patients with RLS also showed a moderate disease severity and an almost daily occurrence of symptoms. Supporting these results, in the Innsbruck narcolepsy cohort [29], 24 % of the 100 narcoleptic patients had RLS.

The occurrence of PLMS in a group of 100 NC patients was compared with patients having iRLS and normal controls [79]: PLMS were highest in iRLS and lowest in controls; the periodicity indexes showed the highest value in iRLS followed by NC with or without RLS and, finally, by controls. However, while patients with iRLS presented the highest PLMS values in NREM sleep, in NC plus RLS periodic leg movements tended to be equally distributed in REM and NREM sleep. Moreover, while patients with iRLS showed a typical gradual decline of the PLMS number over time, NC subjects presented an irregular overnight PLMS representation. The results indicate that the time structure of PLMS in NC associated with RLS is similar, but not identical, to iRLS. This difference probably indicates that different motor dyscontrol modulations are implicated in iRLS and NC.

The underlying pathophysiologic mechanisms of both narcolepsy and RLS remain unclear, although dopaminergic abnormalities may be responsible. The dopaminergic hypothesis of PLMS is supported by evidence that the treatment of RLS–PLMS patients with levodopa or with dopaminergic agonists not only alleviates symptoms of RLS in the waking state but also strongly suppresses PLMS. Similar results were obtained in a study of narcoleptic patients where levodopa decreased the mean PLMS index from 21.3 to 9.9 [80]. The dopaminergic system has been strongly implicated in RLS, and modifications in dopaminergic pathways were also reported in human narcolepsy–cataplexy with lowered metabolism of dopamine [81] and altered striatal postsynaptic D2 receptor findings in SPECT [82]. Dopaminergic abnormalities are critical downstream mediators of the hypocretin deficiency, and a dysfunction in the hypocretin/dopaminergic system is probably the most important mechanism involved in the pathophysiology of narcolepsy, with alterations in arousal systems but also in sleep-related motor activation with a large amount of PLMS.

PLMS also associate some physiologic activation and represent a model to study the responses of the autonomic nervous system. Studies conducted in patients with RLS and in healthy control subjects without RLS have reported that heart rate (HR) changes occurring with PLMS, consisting of a tachycardia followed by a bradycardia, are sensitive markers of autonomic responses [83]. A recent study found a significant reduction in the amplitude of PLMS-related HR responses in both tachycardia and bradycardia in patients with NC [84]. These findings support the physiologic relevance of the action of hypocretin on autonomic function that could be clinically significant, like increasing the risk of vascular diseases.

Another important matter to examine is the influence that standard pharmacological treatments for narcolepsy could have on PLMS/RLS. A randomized, double-blind, placebo-controlled crossover trial of modafinil showed no effect on PLMS [85]. On the contrary, the administration of SXB has shown some contradictory results. An early study associated SXB with the appearance of pathological levels of PLMS in patients who were unaffected before treatment [86] (Fig. 12.1), and there is a report describing a case of severe RLS in a NC patient who used SXB [87]. However, a recent study showed a general moderate decrease in total sleep legs movement activity, which was significant during NREM sleep, and the number and index of PLMS was significantly decreased after SXB [88]. In addition, RLS has been reported in up to 10 % of depressed subjects treated with antidepressants [89], also used to manage cataplexy in narcolepsy.

Narcolepsy with Cataplexy, Hallucinations, and Psychotic Comorbidity

The co-occurrence of narcolepsy with psychotic symptoms raises clinical and pathophysiological questions according to Fortuyn et al. (2009) [90]. At the clinical level, narcolepsy can be misdiagnosed as a psychiatric condition, especially if cataplexy is not reported or is unrecognized. In adolescents, misdiagnosis often results from overlapping age of onset and symptoms (notably

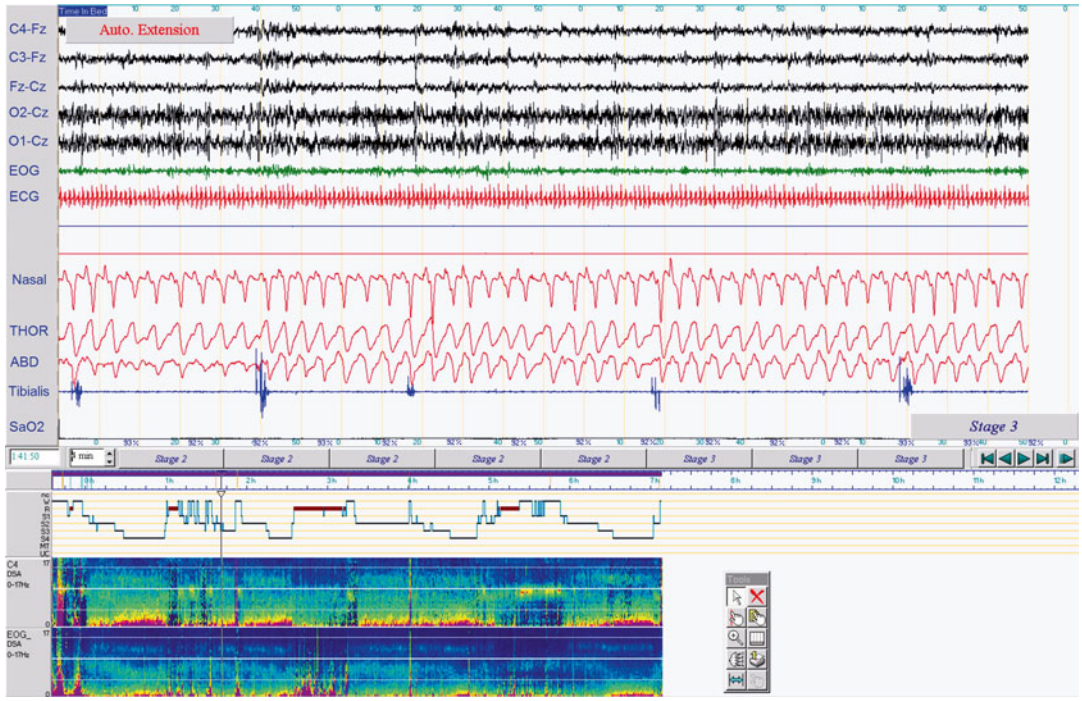

Fig. 12.1 Polysomnography, hypnogram, and power spectrum analysis of a 43-year-old patient who developed PLMS after treatment with 4.5 GR/D of SXB. PLMS can be observed in tibialis anterior (in *blue*), as well as a SOREMP in the hypnogram (4-min epoch)

hallucinations and behavioral problems) between narcolepsy and schizophrenia. Psychotic symptoms (schizophrenia and bipolar disorders) could appear after the start of narcolepsy treatment as a side effect of treatment.

A large number of HLA association studies in small schizophrenia samples have produced controversial results. Due to the high level of linkage disequilibrium in the region, the signal has been difficult to map, but it is interesting to note that HLA-DRB1*03:01 and DRB1*13:03 appeared to confer protection while DQB1*06:02 frequency was slightly increased in schizophrenic patients.

In Canellas et al.'s (2014) case series [91], narcolepsy symptoms began during childhood or adolescent years but were often not diagnosed for years and, in some cases, were not identified after psychotic symptoms had manifested. Prepubertal children raise difficult diagnostic issues. When cataplexy attacks are preeminent, a misdiagnosis of pediatric autoimmune neurological disease associated with streptococcus (PANDAS), atonic seizures, or paraneoplastic syndrome could be made.

The characteristics of cataplexy in children are quite different from those of the adult cataplexy, complicating diagnosis. Irritability, anger, and odd and violent behaviors secondary to sleepiness may emerge in a child who has been previously good tempered and has gained weight unexpectedly. When hypnagogic hallucinations are preeminent, young children, depending on their maturational stage, may not be able to understand that these are unreal experiences, especially just after waking up. In most cases, however, children accept that these are similar to dreams once explained carefully by the clinician, a critical difference compared to schizophrenia or true psychotic disorder.

Management of Sleep Comorbidities in Narcolepsy

Research in all of these areas goes on, but our attention must also be focused on the daily problems of our current patients. EDS affects nearly 20 % of the general population and is associated with many medical conditions, including shift work disorder (SWD), OSAHS, and narcolepsy. Excessive sleepiness imposes a significant clinical, quality-of-life, safety, and economic burden on society.

Carlton et al. (2014) [92] compared healthcare costs for patients receiving initial therapy with armodafinil or with modafinil for the treatment of excessive sleepiness associated with OSAHS, SWD, or narcolepsy. A retrospective cohort analysis of medical and pharmacy claims was conducted using the IMS LifeLink Health Plan Claims Database. A total of 5.693 patients receiving armodafinil and 9.212 patients receiving modafinil were included in this study. A lower daily average consumption (DACON) was observed for armodafinil (1.04) compared with modafinil (1.47). As shown in this analysis, armodafinil may have real-world DACON advantages and may be associated with lower overall healthcare costs compared with modafinil.

Narcolepsy and psychoses can coexist; when in doubt and unless proven otherwise, it is always better to treat narcolepsy first, hoping all psychotic symptoms are narcolepsy related rather than the converse, especially if the premorbid personality was entirely normal.

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Neuroimaging of Narcolepsy

13

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Introduction

Narcolepsy is a life-long, debilitating sleep disorder characterized by excessive daytime sleepiness. Most often, it is also accompanied by cataplectic attacks, which are sudden, transient decreases in muscle tone that can be triggered by strong, usually positive emotions (such as laughter or pleasant surprise). Another core feature of narcolepsy is early entry into rapid eye movement (REM) sleep after sleep onset, known as sleep-onset REM periods (SOREMPs). REM sleep-like phenomena may also intrude in the narcoleptic waking state, such as hypnagogic hallucination and sleep paralysis [1]. Nocturnal sleep patterns are typically fragmented in narcolepsy, such that individuals with narcolepsy are chronically sleep-deprived and take frequent naps throughout the day, which are refreshing only for a few hours. When these naps occur uncontrollably, they are known as sleep attacks. Their daily occurrence in narcolepsy impedes quality of life and increases the risk of accidents [2].

The diagnosis of narcolepsy is usually based on clinical interview and polysomnography (PSG) coupled with the multiple sleep latency test (MLST), during which the patient is invited to take 5 daytime naps in succession [3]. Rapid sleep onset and two or more SOREMPs during naps, as measured by PSG/MSLT, are suggestive of narcolepsy. The prevalence of narcolepsy follows a bimodal age distribution at 15 and 35 years old and affects males and females equally [4]. When first detected, symptoms can be mistaken for epilepsy or depression [1]. Treatment options mostly consist of central nervous system stimulants (such as methylphenidate and modafinil), but antidepressants and sodium oxybate are sometimes administered, especially in cases with frequent cataplexy [5]. These medications are purely symptomatic and do not provide a cure for the disease.

Early research into the pathophysiology of narcolepsy identified a genetic autoimmune factor; blood typing revealed that 90 % of narcoleptic patients with cataplexy possessed the DQB1*0602 subtype of the human leukocyte antigen (HLA) [6]. More recently, narcolepsy has been linked to a central deficiency in hypocretin (otherwise known as orexin) [7–10], as evidenced by low levels of

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the neuropeptide (specifically, hypocretin-1) in the cerebrospinal fluid (CSF) [11]. Since hypocretin-1 neurons are implicated in the arousal system [12, 13] and control motor function (e.g. muscle tone) [14], their deficiency might explain the abnormal sleep–wake patterns and sleep attacks that are characteristic of narcolepsy. One major hypothesis today is thus that narcolepsy with cataplexy is an autoimmune disease, associated with the HLA-DQB1*0602 genotype, specifically targeting hypocretin-secreting cells situated mainly in the lateral hypothalamus [1].

A growing body of literature is now using neuroimaging techniques to reveal the neural correlates of narcolepsy and further inform its neurological causes and consequences. Structural neuroimaging using magnetic resonance imaging (MRI), in concert with analytical techniques such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI), has identified alterations in brain anatomy that are associated with the disorder (see Table 13.1). Large-scale metabolic changes have been probed by magnetic resonance spectroscopy (MRS) (Table 13.1). Functional neuroimaging studies have examined changes in brain activity during wakefulness and cataplexy in narcoleptic patients, using positron emission tomography (PET), single-photon emission computed tomography (SPECT) and functional MRI (fMRI) (see Table 13.2). The present review will synthesize the findings of these neuroimaging studies of narcolepsy. Neuroimaging has also been used to assess the effect of therapeutic drugs on the narcoleptic brain; these studies exceed the scope of this chapter and are reviewed elsewhere [15].

Structural Imaging in Narcolepsy

Grey Matter Alterations

Early etiological theories of narcolepsy proposed that an impairment of the pontine tegmentum, which is involved in the modulation of vigilance states, is at the root of narcoleptic pathophysiology. Anatomical alterations of the pontine tegmentum were reported in a first MRI study of three narcoleptic patients by Plazzi and colleagues [16], but subsequent MRI studies did not reproduce these results [17, 18]. In one of these latter studies [18], pontine lesions were detected in 2 of 12 narcoleptic patients, but these patients suffered from long-standing hypertension, and the lesions were indistinguishable from ischemic damage. Similar age-related pontine lesions have been reported by Pullicino and colleagues [19], and so it may be that the results of Plazzi's study were also due to age-related cardiovascular conditions.

Whereas early studies visually assessed anatomical changes in MRIs of narcoleptic patients, more recent studies have used VBM to systematically quantify small-scale structural alterations in grey matter density (Fig. 13.1). Among these, several reported grey matter volume decreases in the hypothalamus [20–23], in line with the hypocretinergic dysfunction theory of narcoleptic pathophysiology. In contrast, an equal number of VBM studies found no hypothalamic differences between narcoleptic patients and healthy controls [24–27]. Hypothalamic grey matter reductions in narcoleptic patients were also correlated with scores on a subjective scale of disease severity, the Ullanlinna Narcolepsy Scale [23]. Other notable brain areas showing decreased volume in narcolepsy were the nucleus accumbens [21, 22], a major projection site of hypocretinergic neurons, and the thalamus [22, 23], which is an important modulator of sleep oscillations. Fronto-temporal cortices have also shown consistent decreases in several VBM studies [21–23, 25–27]. This result has been interpreted as mirroring attentional deficits reported by narcoleptic patients, but this remains speculative. Widespread volumetric decreases in the narcoleptic brain may together reflect secondary neuronal loss from the destruction of afferent hypocretinergic neurons in the hypothalamus. However, global grey matter reduction was not correlated with disease duration [25]. A single VBM study reported no significant structural difference between narcoleptic patients and controls [24]. Divergent findings among VBM studies may be due to differences in data preprocessing among studies, as well as patient sample heterogeneities (e.g. age, disease severity).

Table 13.1 Structural neuroimaging studies of narcolepsy

Study	Technique	Number of participants		Mean age (years ± SD)		Cataplexy	Treatment	Results
		Pat(f)	Ctrl(f)	Pat	Ctrl			
Kaufmann et al. [25]	MRI 1.5 T/ VBM	12(6)	32(16)	36.9 ± 15.8	36.2 ± 14.7	All	6	Decrease in fronto-temporal areas
Draganski et al. [21]	MRI 1.5 T/ VBM	29(17)	29(17)	39.7 ± 11.3	38.6 ± 9.3	nr	nr	Decrease in hypothalamus, nucleus accumbens
Overeem et al. [24]	MRI 1.5 T/ VBM	15(8)	15(8)	44.7 ± 14.3	44.5 ± 14.2	All	13	No change
Brenneis et al. [26]	MRI 1.5 T/ VBM	12(4)	12(2)	35.8 ± 13.2	35.0 ± 8.4	11	10	Decrease in prefrontal cortex
Buskova et al. [20]	MRI 1.5 T/ VBM	19(9)	16(7)	43.4 ± 13.8	40.3 ± 10.9	All	9	Decrease in hypothalamus
Joo et al. [22]	MRI 1.5 T/ VBM	29(14)	29(14)	31.2	31.2	All	0	Decrease in hypothalamus, nucleus accumbens, thalamus, and fronto-temporal areas
Kim et al. [23]	MRI 3.0 T/ VBM	17(4)	17(4)	24.6 ± 4.9	26.6 ± 5.2	All	11	Decrease in hypothalamus (correl. with subjective severity), thalamus, brainstem, putamen, cingulate, fronto-temporal & occipital areas
Brabec et al. [31]	MRI 1.5 T/ MVol	11(6)	11(6)	41.7 ± 17.7	a-m	All	9	Decrease in amygdala
Joo et al. [28]	MRI 1.5 T/ CoTh	28(18)	33(18)	26.9 ± 7.9	30.1 ± 11.1	All	0	Decrease in cingulate, fronto-temporal, and inf. parietal (correl. with subjective severity) areas
Schaer et al. [29]	MRI 3.0 T/ CoVo & CoTh	12(7)	12(7)	28.8 ± 6.8	31.5 ± 6.2	All	0	Increase in lateral prefrontal cortex, decrease in paracentral lobule, thinner orbitofrontal cortex correl. with subjective severity
Joo et al. [30]	MRI 1.5 T/ MVol	36(11)	36(11)	29	29	All	0	Decrease in hippocampus (correl. with objective severity)

(continued)

Table 13.1 (continued)

Study	Technique	Number of participants		Mean age (years ± SD)		Cataplexy	Treatment	Results
		Pat(f)	Ctrl(f)	Pat	Ctrl			
Scherfler et al. [27]	MRI 1.5 T/ VBM & DTI	16(4)	12(5)	56.8 ± 10.1	59.8 ± 4.4	All	10	Alterations of hypothalamus, midbrain, fronto-temporal and cingulate areas
Menzler et al. [33]	MRI 1.5 T/ DTI	8(7)	12(9)	49.5 ± 12.7	56.8 ± 10.6	All	All	Alterations of hypothalamus (correl. with subjective severity), brainstem, caudate, fronto-temporal and cingulate areas
Nakamura et al. [34]	MRI 1.5 T/ DTI	24(9)	12(6)	27.7	29.8 ± 2.2	12	0	Alterations in amygdala and fronto-parietal areas in narcolepsy with cataplexy, but not without cataplexy
Ellis et al. [35]	^{1}H-MRS	12(6)	12(6)	33 ± 13	33 ± 11	All	0	No change in NAA/Cr in pons
Lodi et al. [37]	^{1}H-MRS 1.5 T	23(10)	10(4)	38 ± 16	37 ± 14	10	0	Reduced NAA/ Cr ratio in hypothalamus
Kim et al. [42]	^{1}H-MRS 3.0 T	17(3)	17(5)	25.1 ± 4.6	26.8 ± 4.8	All	0	Increased GABA concentrations in medial prefrontal cortex. Effect was greater in narcolepsy without nocturnal sleep disturbance than in narcolepsy with nocturnal sleep disturbance
Tonon et al. [38]	^{1}H-MRS 1.5 T	16(8)	10(nr)	40 ± 18	40 ± 12	All	0	Reduced NAA/ Cr ratio in hypothalamus
Poryazova et al. [39]	^{1}H-MRS 3.0 T	14(7)	14(7)	30.6 ± 2.3	31.4 ± 2	All	0	Reduced mI/Cr ratio in amygdala

Structural neuroimaging studies of narcolepsy. From left to right: reference of the study, brain imaging analysis technique, number of patients and controls studied, mean age of patients and controls, number of patients with a history of cataplexy, number of patients exposed to medication for narcolepsy at the time of the imaging procedure, and main results of the study

^{1}H-MRS, a-m, age-matched; proton magnetic resonance spectroscopy; ctrl, healthy control; correl, correlated; CoTh, cortical thickness; CoVo, cortical volumetry; Cr, creatine-phosphocreatine; DTI, diffusion tensor imaging; f, number of females; inf, inferior; mI, myo-inositol; MRI, magnetic resonance imaging; MVol, manual volumetry; NAA, *N*-acetylaspartate; nr, not reported; pat, patient; VBM, voxel-based morphometry

Table 13.2 Functional neuroimaging studies of narcolepsy

Study	Technique	Target	Functional state	Number of participants		Mean age (years ± SD)		Cataplexy	Treatment	Results
				Pat(f)	Ctrl(f)	Pat	Ctrl			
Asenbaum et al. [46]	SPECT ^{99m}Tc-HMPAO	rCBF	rWk & SOREMP	6(3)	0	40.5 ± 12.5	–	All	1	No change between SOREMP sleep and wakefulness. Parietal activation during REM sleep
Joo et al. [48]	SPECT ^{99m}Tc-ECD	rCBF	rWk	25(8)	25(8)	31	31	All	0	Reduced cerebral perfusion in hypothalami, caudate, pulvinar, paracentral and cingulate cortices
Hong et al. [51]	SPECT ^{99m}Tc-ECD	rCBF	Cataplectic episode	2(1)	0	25 and 64	na	All	0	Increased perfusion in limbic areas, basal ganglia, thalami, sensorimotor cortices and brainstem. Decreased perfusion in prefrontal cortex and occipital lobe
Chabas et al. [52]	SPECT ^{99m}Tc-ECD	rCBF	Cataplectic episode	1(1)	0	68	na	1	0	Increased perfusion in cingulate cortex, orbitofrontal cortex, temporal cortex and right putamen
Joo et al. [49]	PET ^{18}F-FDG	CMRglu	rWk	24(8)	24(8)	32	32	21	0	Reduced CMRglu in hypothalami, thalamic nuclei and fronto-parietal cortices
Dauvilliers et al. [50]	PET ^{18}F-FDG	CMRglu	rWk & cataplectic episode ($n = 2$)	21(11)	21(11)	40.2 ± 18.1	40.6 ± 17.8	All	14	Increased CMRglu in cingulate and visual association cortices during wakefulness. During cataplexy, CMRglu increase in parietal and decrease in hypothalami
Schwartz et al. [54]	fMRI 3.0 T	BOLD contrast	Humour judgment	12(6)	12(6)	32.6 ± 8.3	33.8 ± 6.9	All	0	Hypoactivation of hypothalamus and hyperactivation of amygdala

(continued)

Table 13.2 (continued)

Study	Technique	Target	Functional state	Number of participants		Mean age (years ± SD)		Cataplexy	Treatment	Results
				Pat(f)	Ctrl(f)	Pat	Ctrl			
Reiss et al. [53]	fMRI 3.0 T	BOLD contrast	Humour judgment & cataplectic episode ($n=1$)	10(7)	12(7)	29.8 ± 6.5	25.9 ± 4.1	All	0	Hyperactivation of hypothalamus, nucleus accumbens and inferior frontal gyri during humour response. Hypothalamic hypoactivity during cataplexy
Ponz et al. [58]	fMRI 3.0 T	BOLD contrast	Monetary incentive-delay task	12(7)	12(7)	30.5 ± 7.98	32 ± 7.43	All	0	Hyperactivation of amygdala. Lack of activation in ventral midbrain and medial prefrontal cortex
Ponz et al. [59]	fMRI 3.0 T	BOLD contrast	Classical aversive conditioning	9(5)	9(5)	33.78 ± 8.36	34.66 ± 8.15	All	0	Lack of activation of amygdala. Lack of negative coupling between amygdala and medial prefrontal cortex during conditioning

Functional neuroimaging studies of narcolepsy. From left to right: reference of the study, brain imaging analysis technique, neurophysiological target, sleep-wake or state or task, number of patients and controls studied, mean age of patients and controls, number of patients with a history of cataplexy, number of patients exposed to medication for narcolepsy at the time of the imaging procedure, and main results of the study.

^{18}F-FDG, ^{18}F-fluorodeoxy glucose; ^{99m}Tc-ECD, 99mTc ethyl cysteinate dimer; ^{99m}Tc-HMPAO, ^{99m}Tc-hexamethylpropyleneamineoxime; BOLD, blood-oxygen-level dependent; CMRglu, cerebral metabolic rate of glucose utilization; ctrl, healthy control; f, number of females; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; na, not applicable; pat, patient; PE, positron emission tomography; rCBF, regional cerebral blood flow; rWk, resting wakefulness; SOREMP, sleep onset rapid-eye-movement period; SPECT, single photon emission computed tomography

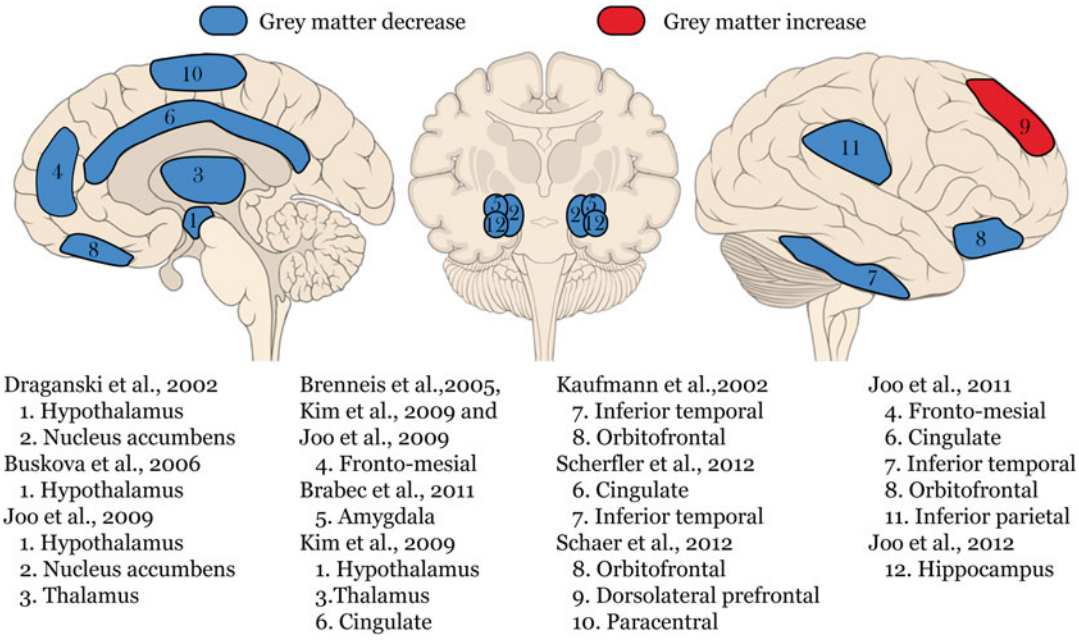

Fig. 13.1 Grey matter volumetric alterations in narcolepsy. VBM and cortical thickness studies have most consistently shown grey matter decreases in the hypothalamus [20–23] and fronto-mesial regions [22, 23, 26, 28]. Other cortical areas showing consistent volumetric decreases are the cingulate [23, 27, 28], inferior temporal [25, 27, 28] and orbitofrontal [25, 28, 29] cortices. One study found a volumetric increase in narcoleptic patients with respect to healthy controls, in the dorsolateral prefrontal cortex [29]. Prepared with illustrations by Patrick J. Lynch and C. Carl Jaffe. http://creativecommons.org/licenses/by/2.5/

Cortical thickness measures have also been applied to MRI scans to detect subtle changes in the narcoleptic cerebral cortex compared to controls (Fig. 13.1). A first study found cortical thinning in the cingulate, inferior parietal and fronto-temporal cortices [28], while a second study showed thinning in the paracentral lobule and the orbitofrontal cortex [29]. Additionally, thinning of the inferior parietal and orbitofrontal cortices was inversely correlated with subjective disease severity in the respective studies. These results are in accordance with the aforementioned VBM data showing grey matter decrements in fronto-temporal cortices, possibly related to narcoleptic cognitive dysfunction. Interestingly, the latter study also detected a cortical thickening of the dorsolateral prefrontal cortex in narcoleptic patients with respect to controls; these data were instead proposed to reflect compensatory activity in reaction to cognitive challenges. Also of interest, global cortical thinning was greater for early-onset (<16 y.o.) than for late-onset (>16 y.o.) narcoleptic patients, which may represent a chronic effect of the disease or, alternatively, a differentiation between two etiological subtypes of narcolepsy [29]. The global cortical decrements observed in structural studies led Joo and colleagues [30] to hypothesize that memory function may be affected in narcolepsy, and they turned their attention to the hippocampus. Using manual volumetry, they determined that hippocampal volumes were indeed smaller in a sample of 36 narcoleptic patients, even though their visual or verbal memory performances were not significantly different from 36 age- and sex-matched controls (Fig. 13.1). Furthermore, shorter sleep and REM sleep latencies on the MSLT (which are objective markers of disease severity) were associated with smaller hippocampal volume in narcoleptic patients. Narcolepsy may thus have a detrimental effect on cognition in the hippocampus and fronto-temporal cortices,

which is masked by compensation from other brain areas, such as the dorsolateral prefrontal cortex. Manual volumetry was also applied to describe structural changes in the amygdala [31] (Fig. 13.1). This MRI study found that the amygdala was reduced in volume in narcoleptic patients, which is possibly related to emotional dysregulation in narcolepsy (see functional studies below).

White Matter Alterations

Microstructural changes in axonal integrity can be quantified from MRI scans using DTI. This analytical technique is able to track the direction of diffusion of water molecules through the brain volume [32]. The directional organization of white matter tracts constrains water molecule diffusivity in an anisotropic (uneven) manner, the extent of which can be measured by a scalar value, fractional anisotropy (FA). FA is sensitive to the organization, integrity and myelination of white matter axons. In addition, mean diffusivity (MD) of water molecules provides an indirect measure of neuronal loss by quantifying the extracellular fluid space in grey and white matter. Applied to narcoleptic patients, DTI revealed decreases in FA [33] and increases in MD [27] in the hypothalamus compared to controls, in corroboration with VBM studies implicating this area in narcoleptic pathophysiology. FA decreases likely signified a pathological reduction in the number and coherence of axons in the area, while increased MD signified neuronal loss. FA decreases concomitant with MD increases provide strong evidence for neurodegenerative effects, since the erosion of white matter should be followed by an increase in extracellular fluid space. Combined MD increases and FA decreases were found in the fronto-orbital and anterior cingulate cortices, possibly explaining attentional deficits in narcolepsy [27]. Other brain areas showing reduced FA only were the midbrain and medulla oblongata [33], as well as frontotemporal cortices [27, 33], areas which receive hypocretinergic projections from the hypothalamus and which may thus have undergone secondary neuronal loss. MD increases without FA decreases were found in the dorsal raphe nuclei and the ventral tegmental area, which are also afferented by hypothalamic hypocretin neurons [27]. Curiously, FA increases were found in the pons, pre- and postcentral gyri and corona radiata, which may be explained by compensatory processes [33]. A number of objective and subjective measures of disease severity were associated with FA decreases in the hypothalamus and brainstem, but none of these correlations survived Bonferroni correction for multiple comparisons [33]. Still, trends towards significance were found in the positive correlation between FA values in the hypothalamus and the Epworth Sleepiness Scale (ESS), a subjective marker of disease severity, and in the negative correlation between the ESS and FA values in the medulla oblongata [33]. A recent DTI study examined structural differences between two narcoleptic subtypes: narcolepsy with cataplexy and narcolepsy without cataplexy [34]. While narcolepsy with cataplexy showed differences with respect to healthy controls, notably in the inferior frontal gyrus and the amygdala, narcolepsy without cataplexy displayed no significant differences from controls. The authors concluded that narcolepsy with and without cataplexy may constitute two distinct etiologies.

Spectroscopy

Proton MRS (^{1}H-MRS) allows a noninvasive assay of specific molecular concentrations in the brain. By measuring localized ratios of cell metabolites, ^{1}H-MRS can provide evidence of neuronal damage in specific areas of the brain. An early ^{1}H-MRS study examined concentrations of *N*-acetylaspartate (NAA) and creatine-phosphocreatine (Cr-PCr) in the ventral pons [35]. NAA is thought to provide a sensitive index of cell mass, while Cr-PCr, metabolites of oxidative phosphorylation, are believed to be relatively constant in the brain [36]. A decrease in the NAA/Cr-PCr ratio can thus be understood as net neuronal loss in the observed brain region. Examining this ratio in the pons revealed no change between

narcoleptic patients and healthy controls, anticipating results later obtained in MRI studies of the pons [17, 18]. With the eventual discovery of hypocretin's role in narcolepsy, two more ^{1}H-MRS studies from Plazzi and colleagues targeted the hypothalamus and indeed found that NAA/Cr-PCr ratios were lower in this region for narcoleptic patients than for healthy controls [37, 38]. Reduced NAA/Cr-PCr in the hypothalamus is evidence of neuronal loss, in agreement with the autoimmune destruction of hypocretinergic neurons in this area. In the latter of these two studies [38], researchers hypothesized that brain regions innervated by hypothalamic hypocretin neurons may show signs of secondary neuronal loss (a common finding in the aforementioned VBM studies). They examined two of these regions, the thalamus and parietal-occipital cortex, but found no difference between narcoleptic patients and controls. A recent ^{1}H-MRS study from another research group sought to corroborate findings in the narcoleptic hypothalamus, while also examining the amygdala and ponto-mesencephalic junction, but contrary to previous results, no change in NAA/Cr-PCr ratios was detected in either of these regions when compared to controls [39]. Instead, they found that myoinositol/Cr-PCr ratios were lower in the narcoleptic amygdala, which the authors propose may be due to changes in amygdalar cell signalling, possibly in relationship with emotional dysregulation (see functional studies). Results from these MRS studies corroborate some MRI findings in the pons and hypothalamus, but also add to the inconsistencies in the literature concerning these regions, as well as the thalamus and cerebral cortex. Furthermore, the apparent reversibility of NAA/Cr-PCr ratio decreases in the recovery from acute brain pathology [40] has called into question its link with neuronal loss, instead suggesting it may be indicative of neuronal dysfunction [41]. Neurotransmitter concentrations have also been studied with MRS. Using a 3.0-T MRS scanner, absolute gamma-aminobutyric acid (GABA) concentrations were assessed in a sample of 17 narcolepsy–cataplexy patients versus 17 healthy controls [42]. It was found that patients had significantly higher GABA concentrations in the medial prefrontal cortex (mPFC) than did normal controls. Moreover, narcoleptic patients without nocturnal sleep disturbances had higher mPFC GABA levels than those with nocturnal sleep disturbances, and both groups had higher mPFC GABA levels than controls. According to the authors' interpretation, elevated GABA may act as a compensatory mechanism in narcolepsy, whereby nocturnal sleep disturbances are alleviated. In line with this interpretation, GABA levels were reduced in MRS studies of insomniacs, for whom nocturnal sleep disturbances are chronic [43, 44].

In sum, while definite trends pervade the structural neuroimaging literature for narcolepsy, more evidence is needed to stem the still widespread inconsistencies, even within the same imaging modalities (Table 13.1). Nonetheless, a number of anatomical studies convergently support hypothalamic damage in narcolepsy–cataplexy, which is compatible with a loss of hypocretinergic neurons, whose cell bodies are located exclusively in the hypothalamus [13]. Alterations in fronto-temporal regions were another common finding, which may relate to cognitive and mood disturbances in narcolepsy. Also of note, correlations between subjective disease severity and neuroanatomical alterations were discovered, including a correlation between hypothalamic damage and the Ullanlinna Narcolepsy Scale score [23] and between ESS and cortical thickness measurements [28, 29]. These results, though still uncertain, can be considered in tandem with functional neuroimaging data to provide a clearer picture of narcoleptic neuropathology.

Functional Imaging in Narcolepsy

Baseline Conditions

Few neuroimaging studies have described baseline activity in the narcoleptic brain (Table 13.2). An early SPECT study scanned narcoleptic patients and healthy controls after radioactive ^{133}Xe inhalation, during both resting wakefulness and sleep [45]. Waking activity in narcolepsy

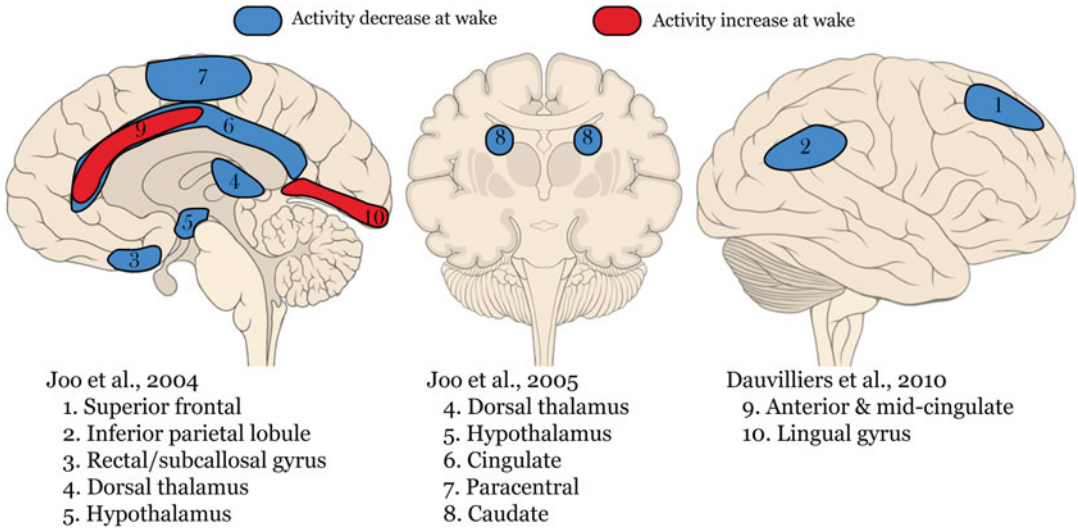

Fig. 13.2 Blood flow and metabolic differences during resting wakefulness in narcolepsy. Few studies have examined narcoleptic brain activity at baseline. Among them, recurrent findings are activity decreases in the dorsal thalamus and the hypothalamus during resting wakefulness [48, 49]. Contrary to these studies, Dauvilliers et al. [50] detected activity increases during resting wakefulness, in the cingulate cortex and lingual gyrus. Prepared with illustrations by Patrick J. Lynch and C. Carl Jaffe. http://creativecommons.org/ licenses/by/2.5/

displayed decreased regional cerebral blood flow (rCBF) in the brainstem area, in comparison with controls. After sleep onset (SOREMP in 3 out of 13 cases), rCBF increased in all regions, which the authors interpreted as increased dreaming activity specific to narcolepsy. More recent SPECT studies have also characterized rCBF during baseline states in narcolepsy (Fig. 13.2). A study using ^{99m}Tc-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) compared wakefulness and SOREMPs in six narcoleptic patients [46]. No significant difference was detected in ^{99m}Tc-HMPAO uptake between states, but interestingly, the researchers reported high perfusion in parietal regions, which is uncharacteristic of normal REM sleep [47]. Further functional studies during narcoleptic REM sleep are needed to explore this phenomenon. Another SPECT study used ^{99m}-technetium ethyl cysteinate dimer (^{99m}Tc-ECD), to evaluate rCBF differences in waking activity between 25 patients with narcolepsy–cataplexy and 25 healthy controls [48]. Decreased perfusion was observed throughout the brain, notably in bilateral hypothalami, caudate nuclei, pulvinar nuclei of the thalamus, cingulate gyrus and fronto-parietal cortices. These areas of decreased activity correspond to regions of hypocretinergic projection and are thus in line with structural studies, indicating a loss of hypothalamic neurons in narcolepsy.

Two PET studies have also examined waking activity in narcolepsy compared to controls, using ^{18}F-fluorodeoxy glucose (^{18}F-FDG) as a radiotracer for the cerebral metabolic rate of glucose utilization (CMRglu) (Fig. 13.2). The first study of 24 narcoleptic patients and 24 healthy controls found reduced CMRglu in the hypothalami, thalami and fronto-parietal cortices [49]. In stark contrast, the second study found no areas of hypometabolism in 21 narcoleptics compared to 21 controls, but instead found hypermetabolism of the cingulate and visual association cortices during wakefulness [50]. The authors of this latter study attribute the discrepancy between both PET studies to differences in scanning conditions, sample inclusion criteria and patient treatment history.

As an interim summary, imaging studies examining baseline narcoleptic brain activity have been few, but some concordance exists between observations of reduced activity in the

hypothalamus, thalamus and fronto-parietal cortices. Strikingly, there is a lack of well-characterized and recent imaging data for sleep in narcolepsy. New studies of narcoleptic sleep using modern imaging techniques will be crucial to understanding the disease, particularly its disruptive effects on nocturnal sleep.

Cataplexy

Cataplectic attacks, by their nature, are unpredictable and difficult to capture with neuroimaging. Researchers have resorted to eliciting cataplexy with emotional stimulation, for instance, by telling a funny story, but they have had limited success [50]. Consequently, neuroimaging studies of cataplexy are few and have diminutive sample sizes (Table 13.2). A first such study captured cataplectic episodes in two narcoleptic patients using ^{99m}Tc-ECD SPECT [51]. Compared with baseline wakefulness and REM sleep, the cataplectic state was characterized by hyperperfusion in limbic areas (including the right amygdala), thalami, basal ganglia, brainstem and parietal cortices, and hypoperfusion in prefrontal and occipital cortices. A case study using the same imaging modality instead found hyperperfusion throughout the cerebral cortex, specifically in the orbitofrontal, temporal, cingulate and right putamen [52]. The authors likened this activation to a REM sleep state, albeit without usual pontine, occipital or amygdalar activation. An ^{18}F-FDG PET study managed to capture cataplectic episodes in two narcoleptic patients and found metabolic increases in the pre-postcentral gyri and the somatosensory cortex as well as a decrease in hypothalamic metabolism [50]. Lastly, a cataplectic attack was captured during an fMRI scan and showed marked hypoactivation of the hypothalamus [53]. Little can be concluded from these limited data, but the repeat finding of hypothalamic hypoactivity [50, 53] is promising, in light of structural data. It will be important for researchers to develop improved procedures for eliciting cataplectic attacks in the laboratory.

Emotional Stimulation

Because cataplexy is often triggered by strong emotions, it can also be informative to examine how narcoleptic patients respond differently to emotional stimuli. A few studies have employed emotional stimulation paradigms during fMRI scans to capture these differences (Table 13.2). The fMRI scanner measures changes in the blood-oxygen-level-dependent (BOLD) signal between task and baseline conditions as an index of event-related brain activity. In two independent studies, funny pictures or cartoons were displayed to narcoleptic–cataplectic patients and healthy controls undergoing fMRI scans. One of these studies showed enhanced activity in the emotional network, including the hypothalamus and nucleus accumbens, when comparing patients to controls [53]. The second study, in contrast, showed reduced activity in the hypothalamus, concomitant with heightened amygdalar activity [54]. Together, these studies suggest a dysregulation of the hypothalamic-amygdalar emotional network in narcolepsy with cataplexy. Interestingly, the first study reported that narcoleptic–cataplectic patients were less likely than controls to rate a cartoon as funny, although this effect was not replicated in the second study.

The neuropeptide hypocretin modulates more than just sleep–wake patterns. It is also believed to be involved in reward-related behaviours, motivation, feeding and addiction [55–57]. Hence, hypocretin deficiency in narcolepsy may also lead to anomalous responses to reward and aversive stimulation. Following this rationale, Ponz and colleagues probed both the narcoleptic reward and fear conditioning systems in two fMRI studies. In the reward study [58], researchers presented patients and controls with the monetary incentive-delay task, which is known to recruit the mesolimbic and midbrain reward system in normal subjects. While performing this task in the scanner, patients recruited vastly different regions from healthy controls. Instead of activating the ventral pathway (ventral tegmentum, ventromedial prefrontal cortex and nucleus accumbens), narcoleptic patients showed enhanced activity in the amygdala and dorsal

striatum in response to positive outcomes, in agreement with previous studies showing increased amygdalar activation in intense emotional states [51, 54]. Interestingly, ventral-medial prefrontal cortex activation positively correlated with disease duration in the narcoleptic group, suggesting that alternate pathways may be learned by patients over the years to compensate for the lack of input from the ventral midbrain pathway. In the fear conditioning study [59], patients and controls were presented with pictures in synchronization with a painful electric shock, in a classical conditioning paradigm. It was found that normal amygdalar response to aversive conditioned stimuli was reduced in narcoleptic patients. Furthermore, the normal functional coupling between the amygdala and medial prefrontal cortex during conditioning was observed in controls but not in patients.

Data from fMRI studies, though still sparse, are well aligned in demonstrating abnormal emotional processing in narcolepsy. Reward conditioning, aversive conditioning and humour judgement are three paradigms which represent various facets of emotional reactivity, and each has been shown to be altered in narcolepsy ([58], [59] and [54], respectively). These studies, buttressed by anatomical studies reporting alterations in the amygdala [31, 34, 39], support dysfunctional emotional network activity in narcolepsy-cataplexy, which may be linked to global hypocretin depletion.

Neurotransmission

Acetylcholine (ACh) is known to be an important neurotransmitter in the control of REM sleep [60, 61] and was hypothesized to be dysregulated in narcolepsy. However, a PET study using the radioligand ^{11}C-*N*-methyl-4-piperidyl-benzilate (^{11}C-MPB) found no difference in cholinergic binding between narcoleptic patients and healthy controls [62].

Serotonin (5-HT) has also been proposed as showing disturbance in narcolepsy, based on animal studies linking it with the suppression of REM sleep [63]. A PET study using 4-(2′-methoxyphenyl)-1-[2′-(*N*-2″-pyridinyl)-*p-18F-fluorobenzamido*]ethylpiperazine (^{18}F-MPPF) to study 5-HT$_{1A}$ receptor binding reported increased ^{18}F-MPPF binding affinity in the anterior cingulate and temporal cortices during sleep compared to wakefulness in patients with narcolepsy [64]. However, the omission of a control group limits the study's implications for narcoleptic pathophysiology.

Dopamine became a neurotransmitter of interest in narcolepsy research when increased dopamine receptor D2 binding was shown in postmortem studies of deceased narcoleptic patients [65, 66]. A series of PET and SPECT studies ensued, using various radioligands to characterize presynaptic and postsynaptic dopamine binding (e.g. [^{123}I](*N*)-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane [^{123}IPT] with SPECT, and ^{11}C-raclopride in PET, respectively). Only one SPECT study of seven patients found a correlation between D2 binding in the striatum (using [^{123}I](*S*)-2-hydroxy-3-iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl] methyl)benzamide [^{123}IBZM]) and the frequency of cataplectic and sleep attacks [67]. Six other PET and SPECT studies were unable to replicate this finding [68–73]. It may be that increased dopamine binding in the postmortem studies was the result of life-long medication use on behalf of the deceased patients rather than constituting an intrinsic feature of pathophysiology of narcolepsy [41]. Altogether, neurotransmission studies of narcolepsy have not uncovered any neurotransmitter-specific abnormalities. A more detailed description of these neurotransmission studies can be found in [74]

Summary

The expanding brain imaging literature in narcolepsy is showing remarkable convergences. Of prime interest, functional, anatomical and spectroscopic data concordantly show atrophy and dysfunction of the hypothalamus in narcolepsy–cataplexy, in agreement with the pathophysiological theory of narcolepsy–cataplexy as a disease affecting hypocretinergic neurons in the

hypothalamus. In line with this theory, several brain regions receiving major or moderate hypocretinergic projections from the hypothalamus [13] also show signs of neurodegeneration and altered function, notably the thalamus, amygdala and fronto-temporal cortices. The limbic system, particularly the amygdala, shows altered responding in functional studies, paralleled by signs of damage from some structural studies. These changes may relate to the emotional disturbances observed in narcolepsy–cataplexy as well as to the triggering of cataplectic attacks by intense emotional events. Cortical and subcortical anatomical changes, notably in the hippocampus and prefrontal cortices, may explain specific cognitive dysfunctions in narcolepsy. Lastly, reduced thalamic volume and activity may be responsible for narcoleptic sleep fragmentation.

A paucity of functional research has characterized brain activity in narcolepsy during sleep. Further research in this area may provide valuable insights into normal and pathological sleep–wake neurophysiology and may help to explain the little-researched but debilitating symptom of sleep fragmentation in narcolepsy. Studies of neurotransmission in narcolepsy have yielded few positive results, having largely focused on the dopaminergic system. New techniques for imaging hypocretin binding in PET (see Wang et al. [75] for hypocretin-2) or SPECT will be invaluable in understanding the extent of narcoleptic pathophysiology. Finally, some methodological considerations may curb the variability of results in brain imaging studies. Given that narcolepsy is a relatively rare condition and participants are difficult to find, strict controls on sampling and procedures are crucial for obtaining reliable results. In structural studies, this may be achieved by standardized data preprocessing, to facilitate valid cross-study comparisons. Furthermore, in light of abundant associations between the extent of neural abnormalities and indices of disease severity [23, 28–30, 33], age of disease onset [29] and symptomatology [34], it will be important to consider possible phenotypic and etiological heterogeneities within the narcolepsy population, with particular attention to the differentiation between narcolepsy with and without cataplexy.

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Part III

Psychosocial Considerations

Quality of Life and Psychosocial Issues in Narcolepsy: Implications for Management

14

Meeta Goswami

Introduction

Changing medical technology and novel treatment modalities have increased life expectancy with a concurrent rise in chronic illnesses. Improved management techniques enable patients to cope better with their illnesses, thus generating demands and expectations to lead satisfying lives despite having chronic illnesses or disabilities. These dynamics have propelled a vigorous interest in improving the QOL of patients with chronic medical illnesses and, more recently, those with sleep disorders [1].

Despite successful relief of physical symptoms, patients may report psychosocial symptoms such as depressed mood, inability to accomplish activities of daily living, decrements in social and recreational activities, and low self-esteem. QOL assessments allow researchers to compare differences in well-being in different conditions and detect subtle changes in patients' responses to medical or psychosocial interventions. Studies on QOL provide valuable information for evaluating health outcomes, identifying problems and needs, and tailoring the management plan to suit patients' needs. Furthermore, results from these studies may be applied to enhance communication between patient and professional and improve overall quality of care for patients. New information could be valuable for family members who care for the disabled in helping them to understand the patient's disability and provide an effective support system [2]. Data generated from QOL studies are important in conducting cost-benefit analyses, evaluating health programs, making appropriate changes in program development, and justifying funding.

QOL, Health-Related Quality of Life, and Health Status

The World Health Organization has a generic definition of QOL; namely, it is individuals' perceptions of their positions in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [3]. Health-related quality of life (HRQOL) refers to domains that affect the health of a person. Researchers generally consider the domains of physical functioning (including pain), emotional state (including concentration and memory), performance of social roles, intellectual function, and general feelings of well-being or life satisfaction [4–6]. Subjective well-being, health, and welfare [7] are noteworthy areas under consideration as are social performance and social well-being [8]. These social variables are investigated by developing measures of social support and social adjustment.

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Veenhoven described four components of quality of life: life chances, life ability, appreciation of life, and utility of life [9]. Wilson and Cleary (1995) proposed a model incorporating several measures of health outcome, including biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life. It is argued that these different factors have a causal relationship among them, and since no one single instrument can capture all dimensions of health, a combination of instruments is suggested [10].

Scholars pursue methodologies and seek data that are measurable, quantifiable, and amenable to statistical analysis to enable meaningful comparison among studies. Although this concept is scientifically sound, many of us can attest that often highly functional people are dissatisfied with their lives, whereas some who have disabilities are quite happy. Thus, disability itself may not produce decrements in QOL. Moreover, levels of contentment, happiness, satisfaction, and patients' perspectives of what is salient in their lives, domains that could be meaningful to the patient, are not captured by these measures. Clearly, the measurement of function alone cannot fully express the meaning of QOL to different individuals. Furthermore, the importance of these domains is determined by professionals. Although not explicitly stated, the values of the researcher influence the construction of indices. Individualized QOL measurement methods and instruments offer the patient or research participant the chance to indicate those domains that are salient or meaningful to them. Dijkers (2003) reviewed such measurements, e.g., the Patient-Specific Index, the Flanagan Quality of Life Scale, Schedule for the Evaluation of Individual Quality of Life, Individual Quality of Life Interview, and the Duggan–Dijkers Approach, among others. These instruments give subjects the opportunity to select domains, specify aspirations, and record their feelings or opinions on various domains. The construction of these indices is time and effort intensive, and the subject has the responsibility of domain selection. Moreover, proxy measures cannot be used as in HRQOL indices [11]. Finally, issues with cognition and communication in some cases are likely to hinder verbalization of preferences, or the patients may not have pondered the topic of preferences of life's major concerns.

Ware (2003) proposed a conceptual paradigm that incorporates the construction, scoring, and interpretation of "role participation" as distinct from the physical and mental aspects of health to "facilitate studies of the implications of differences in physical and mental capacities for an individual's participation in life activities." The application of item response theory and computerized adaptive testing-based methods can be useful in attaining assessments that are more precise and practical [12].

Of note is a paradigm shift from focusing on negative disease states as indicators of health to developing measures of well-being and positive functioning. The 2010 Behavioral Risk Factor Surveillance Survey System (BRFSS) study obtained a total of 18,622 responses from New Hampshire ($N=3139$), Oregon ($N=2289$), and Washington ($N=13{,}194$). Validated questionnaires assessed physical (satisfaction with energy levels), mental (satisfaction with life, life domains, and happiness), and social facets (frequency of social support) of well-being. Results indicated that well-being differed by sociodemographic variables and health variables such as marital status, age, employment, health behaviors, and disability status [13].

The sociocultural environment may affect one's perception of quality of life. A study in India on cancer patients showed that nearly two-thirds of the respondents believed that peace of mind, spiritual satisfaction, and social satisfaction were very important for a high QOL of life; level of individual functioning was not one of the top five important factors [14]. These results may reflect the influence of cultural practices, religious beliefs, and spirituality on one's perception of quality of life. The study points to the importance of social support and spirituality in measuring QOL.

According to US national surveys, 95 % of Americans believe in God or a universal spirit

and indicate that religious or spiritual beliefs are important in their lives. Studies suggest that religiosity and spirituality may indeed be related to positive health behaviors and satisfaction with life [15–17]. Often, religiosity is measured by church attendance. This indicator may not capture intrinsic spirituality, a deeper sense of an all-pervading universal power. One study measured the relationship of a person's health, physical pain, and intrinsic spirituality [18]. The Index of Core Spiritual Experiences (INSPIRIT) measured intrinsic spirituality, and the Dartmouth Primary Care Cooperative Chart assessed overall health and pain. With a response rate of 95 % (442 patients), results showed overall health was significantly related to spirituality. Significant differences were found in overall health and physical pain across levels of spirituality: high, moderate, and low. A study at Duke University showed that lifetime religious social support and current religious attendance were positively correlated at every level of impairment. Those who reported higher lifetime religious social support received more instrumental social support, irrespective of current attendance. Healthy behaviors were associated with both God Helped and lifetime religious social support. Cost of religiousness (a measure of the occurrence of physical, emotional, and interpersonal losses and difficulties associated with one's past religious life) predicted depressive symptoms and impaired social support. Family history of religiousness was unrelated to late-life health [19].

Research shows that religious and spiritual coping may affect the immune system [20]. One review found evidence from randomized interventional trials of the beneficial physiological impact of meditation (primarily transcendental meditation) to physiological processes. The reviewers concluded that available evidence is generally consistent with the hypothesis that religiosity/spirituality is linked to health-related physiological processes, including cardiovascular, neuroendocrine, and immune function [21]. Physiological mechanisms could mediate the relationship between religion/spirituality and health [22].

The beneficial role of spirituality warrants closer examination of this dimension of health and its incorporation in assessing overall QOL.

Although QOL is accepted as a critical end result in biomedical research, little consensus exists pertaining to the definition of the construct of QOL and its differentiation from the concept of health status. Health status and QOL are separate concepts, since people may attribute high scores to their QOL despite having a disorder or disability depending on their attitudes toward pain and disability, their coping strategies, social networks and support, their expectations from family and friends, and varying levels of spirituality. Often, health status has been described as QOL [23, 24]. A meta-analysis of the relationships between the constructs QOL and perceived health status and three domains (i.e., mental, physical, and social functioning) in 12 chronic disease studies illustrated that, from the patient's perspective, QOL and health status are distinct constructs. When rating QOL, patients gave greater emphasis to mental health than to physical functioning, whereas appraisals of health status showed physical functioning was more important than mental health. Surprisingly, social functioning did not have a major impact on either construct [23]. The meaning of QOL is dynamic, and as individuals fulfill their basic needs of physical, mental, and social well-being, other concerns gain prominence as observed in a recent survey in Australia where one-third of the respondents reported safety, dignity, and independence as the most important contributing factors to their overall QOL [25].

Consistent with QOL research in adults, adolescents differentiate between these two constructs, and their QOL ratings were more strongly correlated with the mean number of poor mental health days than the mean number of poor physical health days [26]. This analysis indicates that many health status instruments may be inappropriate for measuring QOL. Evaluations of the effectiveness of medical treatment may be affected depending on whether QOL or health status is the study outcome.

Measuring Health-Related Quality of Life (HRQOL) in Narcolepsy

The Short Form 36 (SF-36)

The most commonly used generic measures developed from the Medical Outcomes Study are SF-36, SF-12, and SF-8. Generic instruments may not be responsive to clinical changes in specific patients and may not be as sensitive to change as disease-specific ones [27, 28].

The SF-36 is the most comprehensive [29, 30] and has been tested extensively in the USA and other countries and has been translated into many languages. It is suitable for a range of disorders and for the general population to elicit normative data for comparison among different disorders. It is considered the current acceptable standard measure for HRQOL with high reliability and validity. The instrument measures eight domains: physical functioning, role functioning-physical, role functioning-emotional, mental health, social functioning, vitality, bodily pain, and general health. It does not ask questions about sleep and uses vitality as a proxy—a term that can be misinterpreted by the respondent. Vitality is included in the mental health summary score but correlates significantly with both mental and physical health [31]. The SF-36 version 2, a new modification, has improved wording and instructions, better internal consistency and reliability, and reduced floor and ceiling effects compared to the older version, thus improving its sensitivity to change and its precision (differentiation among groups) [32, 33].

Shorter versions of the SF-36, i.e., SF-12 and SF-8, are available to ensure easy administration in less time [34].

Sickness Impact Profile (SIP)

The SIP is a generic measure designed to evaluate functional status of patients with chronic diseases. It is a behaviorally based evaluation of dysfunction due to sickness. The aim was to create a sensitive, appropriate, and valid instrument to discern differences in health status and aid in evaluating the outcome of health services [35]. It includes 136 items grouped in 12 categories, namely, sleep and rest, alertness behavior, work, mobility, ambulation, body care and movement, eating, recreation and pastimes, home management, communication, social interaction, and emotional behavior. It has high test–retest reliability ($r=0.92$) and internal consistency ($r=0.94$). Clinical validity was determined by assessing the relationship between clinical measures of the disease and the SIP scores [36]. It may lack face validity for those who define themselves as well [33].

Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ is a disease-specific, 35-item instrument that assesses the impact of excessive daytime sleepiness on physical, mental, and social functioning in daily activities. It measures activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome. The instrument is reported to have content validity, internal consistency, test–retest reliability, construct validity with the Epworth Sleepiness Scale, as well as concurrent validity with the SIP and SF-36 [37]. A Norwegian version showed satisfactory internal consistency, test-retest reliability, and construct validity [38].

The FOSQ is not as comprehensive as the SIP or the SF-36 as it does not include burden of symptoms and overall well-being [33]. It could serve as an adjunct to the SF-36 in assessing HRQOL in narcolepsy. Disease-specific instruments are focused on distinct diseases and are clinically relevant. Items that are not relevant to the specific disorder or disease should not be included in the instrument [39]. Scores cannot be compared to the general population or used to make comparisons across treatments for different diseases; also, it may not pick up effects due to other coexisting conditions [39].

Points to Consider in Critical Appraisal of Research on HRQOL in Narcolepsy

While evaluating studies in HRQOL, it is important to bear in mind the reliability and validity of the measuring instruments, their appropriateness for the aim of the study, and the external validity (generalizability) of the instrument. Consider, also, ordering and method of administration of the instrument. There may be a difference in responses when questionnaires are administered face-to-face by the researcher or by mail or telephone [40]. To reduce bias from ordering of administration of any instrument, the generic instrument should precede the disease-specific one, because subjects are likely to exclude their responses to the disease-specific measure from the responses to the generic measure [41]. Furthermore, the method of subject selection must be considered to avoid institutional bias and self-selection. Finally, patients are often confused between the symptoms of sleepiness and fatigue, and questionnaires may have items that are not mutually exclusive, thus confounding the results [42, 43]. Bailes et al. (2006) found that the measures on all four popular sleepiness and fatigue scales (Stanford Sleepiness Scales, Epworth Sleepiness Scale, Chalder Fatigue Scale, and Fatigue Severity Scale) were highly correlated, indicating that the constructs of sleepiness and fatigue are confounded. To eliminate the effects of confounding factors, the authors developed a six-item sleepiness scale and a three-item fatigue scale by selecting those items that were not significantly correlated. The sleepiness items were related exclusively to a subject's chances of dozing during daytime activities; the fatigue items were related to perceptions of lack of energy, weakness, or tiredness resulting from engaging in physical exercise and other daytime activities. There was good test-retest reliability in the scales, although retest was done at 4 h [42]. It is important to make a distinction between mental and physical fatigue.

Quality of Life in Narcolepsy

Most professionals and lay people know little about the pervasive effects of the symptoms of narcolepsy on the life of the individual. In fact, studies show that diagnosis may be delayed by as long as 10 or more years from the time the symptoms first appeared (reviewed in Chap. 5). During this time, the affected individual may drop out of school, lose a job, and develop relationship problems with family, friends, or teachers because of the inability to keep awake.

Narcolepsy has negative effects on the QOL of patients with deleterious effects on work, education, recreation, sexual life, interpersonal relations, memory, personality, and marital life [44–48]. Approximately 25 % of the patients with narcolepsy report sexual dysfunction possibly due to cataplexy, comorbid diabetes mellitus [49], or the medications prescribed for cataplexy such as tricyclic antidepressants [50]. Adderall® (amphetamine-dextroamphetamine) at high doses, sometimes prescribed for narcolepsy, may lead to hyperactivity. Symptoms of hyperactivity, hyperthermia, tachycardia, tachypnea, mydriasis, tremors, and seizures in humans and animals are reported [51]. QOL in narcolepsy may also be affected by comorbid medical and sleep disorders [52]. The presence of obesity is reported by several investigators [53–55], and extremely obese subjects are also reported to have poor sleep quality, mood disturbances, and poor QOL [56]. Clinical observation shows obesity can also have psychosocial consequences of self-consciousness, poor self-image, and social isolation. Disturbed sleep among patients with narcolepsy is indicated by the presence of movement disorders and can affect QOL [54, 57]. In France, pain was reported at least monthly by one-third (32.8 %) of those who had narcolepsy with cataplexy (NC), with a significantly higher frequency and impact than controls (17.9 %) and independent of the patients' narcolepsy medication. Moreover, depression and amount of sleep were determinants for pain, and chronic pain had significant impact on sleep quantity, depression, and QOL in NC [58].

High divorce (18 vs. US 7.3 %) [59] and unemployment rates (16 vs. US 7.5 %) [60] were reported in a study in New York City [61]. Respondents expressed need for counseling, transportation services, homemaker and home care services. Patients reported pervasive feelings of tiredness and low levels of energy and motivation.

Narcolepsy patients have poor driving records and high rates of automobile accidents [62, 63] as well as accidents at home and at work. In a survey of members of the American Narcolepsy Association using a mailed questionnaire (539 members responded, 68 % response rate out of $n=783$ members), about one-third (165) reported accidents at work or at home. The most frequent accidents were falls, followed by burns from objects other than cigarettes, cuts, breaking things, cigarette burns, and spills. The study did not differentiate between accidents that occurred before or after treatment for narcolepsy [64].

The economic costs of having narcolepsy can be high and is comparable to diseases such as Parkinson's disease [65], Alzheimer's disease [66], epilepsy [67], and stroke [68]. In a study in Germany [69] on 75 patients diagnosed with narcolepsy, information on the symptoms of narcolepsy and their economic impact was obtained through a standardized telephone interview and a mailed questionnaire to assess health-related QOL (SF-36 and EQ-5D). The total annual cost of having narcolepsy was $15,410 per patient, and direct cost amounted to $3310. Total annual indirect costs of $11,860 per patient were due to early retirement because of narcolepsy. Thirty-two out of seventy-five patients reported narcolepsy as the cause of unemployment.

Depression is a common feature in narcolepsy [70–72]. It is reported that 49 % of patients have depression versus 9–31 % of the normal population [73] and a rate of 20 % by Ohayon [52]. A rate of 56.9 % was revealed in a survey of narcolepsy patients in the UK [74]. Memory and concentration problems as well as depression were noted by Sturzenegger and Bassetti (2004) [70] in a prospective study including 57 subjects with narcolepsy and cataplexy (N), 56 patients with non-narcoleptic hypersomnia (*H*), and 40 normal controls (No). Comparisons were made with 12 hypocretin-deficient narcolepsy subjects (N-hd). There were significant differences between those with narcolepsy and cataplexy (N) and those who had narcolepsy without cataplexy or possible cataplexy (NpC), including mean sleep latency on MSLT, but none between N and N-hd. People with narcolepsy and possible cataplexy had a less severe form of narcolepsy as measured by standardized scores. The Epworth Sleepiness Scale (ESS) was significantly higher in N (17 ± 5) than in H (15 ± 4, $p=0.003$). Problems with concentration (78 %), problems with memory (68 %), and depression (50 %) were frequent in N and H (79, 61, and 60 %) but not in No (30 %, $p<0.001$; 33 %, $p=0.001$; 23 %, $p=0.01$) [70]. The variability in depression rates may reflect methodological differences in the study design, and whether the patients were on medications for narcolepsy or other medical conditions.

Psychopathology was noted by Kales and Krishnan [75, 76]. However, a study in the UK conducted on 45 patients with narcolepsy and 50 matched normal controls found that narcolepsy was neither associated with psychiatric disorders nor with diagnosable depressive disorders. Thirty-six patients were on modafinil without stimulants. No significant differences were found between patients and controls for depression or neurotic symptoms. These surprising results could be due to differential effects of medications taken over the years (amphetamines in the past and modafinil at the time of the study), differences in sample size, lack of standardized measures of symptoms, selection bias, and confusing hypnagogic hallucinations of narcolepsy, especially auditory hallucinations, with schizophrenia [77].

Cognitive deficits in narcolepsy have received the attention of researchers. Rieger et al. reported impairment in the vigilance attention network as well as impairment in the executive attention network in subjects with narcolepsy [78]. Researchers in Germany found a pattern of slower information processing for patients with narcolepsy on more complex cognitive tasks that require a higher degree of executive function. The results indicated a mild verbal deficit and a

consistent impairment in executive function in the narcolepsy group in comparison with matched controls [79]. Most of the patients were on medications (Ritalin or Vigil), and their confounding effect is not known. In a study in Korea, patients with narcolepsy showed impairment of vigilance, attention, and execution [80]. A computerized neurocognitive function test (Vienna Test System) on 24 subjects with narcolepsy with cataplexy and 24 controls matched on age, gender, and IQ showed that narcolepsy subjects responded more slowly than controls to acoustic and visuo-acoustic stimuli. In the vigilance test, the number of both omission and commission errors was much higher for subjects with narcolepsy ($p<0.05$), probably, it is suggested, due to a qualitative deficit in information processing. The response time in narcolepsy subjects was slower than healthy controls, and this difference was more pronounced in complex tasks. Contrary to our clinical observation of memory problems in day-to-day activities in the lives of most patients with narcolepsy, even when they are attentive, this study showed no significant difference in the maximum memory function between the narcolepsy and control subjects. Appropriate measuring instruments that assess memory function in normal daily activities would be helpful in accurately eliciting information on memory problems. The small sample size reduces the external validity of this study.

In one meta-analysis [81], reduction across different psychological functions was found in 22.9 % of persons with insomnia, 34.6 % in narcolepsy, and 36.9 % of those who had sleep-related breathing disorders (SRBD). Research was undertaken in Germany [82] to elucidate daytime differences of performance in psychological tests along with subjective measures of sleepiness and tiredness in narcolepsy (NAR), treated and untreated obstructive sleep apnea (OSAS), psychophysiological insomnia (INS), and a control group (CON). All participants were free of drugs acting on the central nervous system except for those in the NAR group who took medication for cataplexy. The NAR group showed consistently higher levels of impairment in alertness, selective attention, and subjective ratings of tiredness/sleepiness. The dominant pattern was curvilinear. In all three measures of cognitive functioning, performance decreased between 08:00 h and 14:00 h and increased again or leveled off. Subjective ratings showed increasing tiredness/sleepiness from morning to early afternoon followed by a decrease in the late afternoon hours. Sleepiness/tiredness was correlated with higher self-rated depression scores and was more pronounced in untreated patients than in control subjects. Small sample size (ten subjects in each group) may limit the external validity of the results. The authors point out other limitations of the study, i.e., semi-random selection of subjects and training and adaptation effects due to repeated measurement design.

In a survey of 129 members of the Australian narcolepsy support group, the Psychosocial Adjustment of Illness Subscale–Self-Report (PAIS-SR) total score revealed more adjustment problems for men than for women and more vocational adjustment problems for younger than older respondents with narcolepsy, probably due to the older group's better acceptance and management of their condition. Medication status significantly affected adjustment in the social environment. The stimulant medication group was better adjusted than the no medication group and the stimulants + tricyclics group. People with narcolepsy in this study reported more adjustment problems in comparison to cardiac, mixed cancers, and diabetes patients [83]. Because of a self-selected sample and different measuring instruments, the results of this study are difficult to compare with other studies.

Health-Related Quality of Life

Health-related quality of life (HRQOL) was examined in a national investigation to study the effects of modafinil on wakefulness [84]. Data were collected in two similar 9-week double-blind studies including 558 persons with narcolepsy from 38 centers. Subjects were randomized into one of three groups: placebo, 200 mg modafinil, and 400 mg modafinil. A questionnaire comprised of the SF-36 and supplemental

narcolepsy-specific scale was administered to assess QOL changes with treatment. These two instruments were pretested on narcolepsy patients in two sleep centers [85]. People with narcolepsy (PWN) were more affected in vitality, ability to perform usual activities due to physical and emotional problems, and social functioning compared to the general population. HRQOL effects were worse among PWN than among those with migraine headaches with one exception: bodily pain. PWN experienced HRQOL effects as bad as or worse than those with Parkinson's disease and epilepsy in several HRQOL areas.

In the UK, treated PWN had significantly lower scores than treated obstructive sleep apnea–hypopnea syndrome (OSAHS) patients for mental health and general health as measured by the SF-36 [72]. No significant differences were found between treated PWN and untreated OSAHS patients in the eight domains of the SF-36. Treated PWN were sleepier than untreated OSAHS patients with a greater impact on activities of daily living. PWN had difficulties in relation to leisure activities; subjects reported falling asleep in class (50 %), at work (67 %), and losing or leaving a job because of narcolepsy (52 %). This study suggests that treatment and management of narcolepsy are not optimal.

In a mailed questionnaire survey of 305 members of the United Kingdom Association of Narcolepsy (UKAN), respondents scored significantly lower on all domains of the SF-36 than age- and sex-matched normative data and particularly poorly in the physical, energy/vitality, and social functioning domains. The psychosocial questions developed for this study showed that narcolepsy affected education, work, relationships, activities of daily living, and leisure activities. There was no difference among groups receiving different medications. Normal health status was not restored with medications, again suggesting that pharmacological management of narcolepsy is inadequate [74]. The diagnosis of narcolepsy was not clearly established, and subjects were self-selected members of the UKAN.

In a study in Italy, narcolepsy patients were compared with idiopathic hypersomnia and sleep apnea patients. The SF-36 was self-administered. The narcolepsy patients scored lower in all domains, except bodily pain, than the Italian norm. Some of the variance was explained by excessive daytime sleepiness (inverse relation) and disease duration (direct relation, probably due to adaptation) [86].

A cross-sectional study of 77 members (with narcolepsy and cataplexy) of the Norwegian Association for Sleep Disorder (NASD) showed that respondents had significantly lower scores on all domains of the scale of the SF-36, with the exception of the vitality domain, when compared with the normal population. Treatment with medication for narcolepsy did not affect any domain in the study. The SF-36 was mailed to the respondents. According to the authors, differences in results from other studies could be due to a difference in mindset or public education in Norway or to access to support and relevant educational material due to their membership with the NASD [87].

The FOSQ was administered in a randomized trial with 285 patients with narcolepsy to study the effectiveness of sodium oxybate on HRQOL. The medication produced significant dose-related improvements in the total FOSQ score from baseline. Similar improvements were observed in the activity level, general productivity, vigilance, and social outcome subscales ($p<0.01$). Intimacy and sexual relationship subscale was not affected [88].

The following two studies administered the sickness impact profile (SIP) to evaluate functional health status. In a study conducted by mail on 81 patients with narcolepsy [43], 62.5 % reported severe fatigue, and fatigued patients reported higher use of stimulant medication than those not reporting severe fatigue (64, 40 %, $p=0.02$). Fatigue was differentiated from sleepiness and was measured by a 20-item checklist individual strength (CIS) questionnaire. Patients with CIS-fatigue score > 35 were compared with those without severe fatigue. Daytime sleepiness did not differ in the two groups, indicating a differentiation between fatigue and sleepiness. Fatigued patients were more likely than non-fatigued patients to report less control over symptoms and "catastrophic thoughts." Severe

fatigue also significantly increased functional impairment (SIP) and resulted in low quality of life (SF-36). Perhaps fatigue is partially caused by stimulant medications [43]. The questionnaire was mailed to 127 patients with narcolepsy and the response rate was 65 %.

Ton et al. in their research on 226 patients with narcolepsy conducted personal interviews and elicited information on their health status. The percent of total dysfunction (SIP mean 10.3) was significantly correlated with the Epworth Sleepiness Scale (0.33, $p<0.001$) and the Ullanlinna Narcolepsy Scale (0.41, $p<0.001$). Total dysfunction score on the SIP (mean % = 13.2) was higher than the general population score (mean % = 3.6). Psychosocial aspect was more dysfunctional (mean = 13.2) than the physical one (mean = 5.0). The mean percent of dysfunction was in the following areas: sleep and rest (23.6), alertness behavior (22.6), recreations and pastimes (20.6), and work (15.3). Areas of concern to patients included social isolation, reduced sexual activity, and forgetfulness [89].

How Do Patients Adjust to a New Way of Life After Successful Treatment of Narcolepsy?

The amelioration or, in some cases, the removal of the negative psychosocial impact of a chronic illness may have far-reaching and diverse effects on the lives of patients receiving these treatments. Psychosocial adjustment to a new way of "normal" life may pose challenges requiring psychosocial and acquisition of coping techniques. Adjustment problems during adaptation to normal life following seizure surgery are illustrated [90]. Persons with narcolepsy face similar posttreatment adjustment experiences as those who have epilepsy according to a study conducted in Australia [91]. Researchers evaluated the "burden of normality" in 33 successfully treated patients with narcolepsy (Nar) and compared the results with 31 patients with epilepsy (Epi) who had successful epilepsy surgery. The Austin CEP interview has been validated with epilepsy patients who underwent antero-temporal lobectomy (ATL) but not with narcolepsy patients. Content analysis of the responses showed perceptions of posttreatment changes that were significant. Identity transformation was the most frequently reported psychological adjustment occurring in both groups (Nar 79 %; Epi 87 %), followed by increased expectations by self and others (Nar 70 %; Epi 71 %). Both groups described grief over missed opportunities and years "lost" because of limitations posed by a chronic illness [Nar 33 %; Epi 71 % ($p<0.01$)]. Nar patients were more frustrated than Epi patients over the delay in effective treatment (Nar 45%; Epi 0 %). This may be related to delay in diagnosis of narcolepsy and ineffective medication in some cases. Major behavioral manifestations of posttreatment adjustment were excessive activity levels (Nar 54 %; Epi 42 %) and shirking/avoidant behavior (Nar 52 %; Epi 65 %). Major sociological features of adjustment were the need to structure relationships (Nar 55 %; Epi 65 %), new vocational/educational goals (tNar 33 %; Epi 45 %), and new social horizons (Nar 9 %; Epi 42 %; $p<(0.01)$. This study documents the need for psychosocial support services after successful treatment of narcolepsy.

Can a Disability Have Any *Positive Consequences* for the Individual and the Family?

No study has addressed this topic in narcolepsy; however, research in other medical disorders suggests that an illness could be a catalyst for positive growth. Stress-related growth is the phenomenon of discovering or experiencing positive personal enhancement in a situation that is initially negative and devastating. In a study of women with HIV/AIDS in New York City, 83 % of the respondents reported an array of positive changes in their lives [92] including relationships, health behaviors, career goals, view of self, value of life, and spirituality. Factors promoting stress-related growth may include sociodemographic variables, inner resources, type of stress, and availability of support. The variables, positive reappraisal coping and emotional support,

were associated with higher levels of growth, whereas depressive affect was negatively associated with growth [93]. This relatively new area of research suggests that, even in the face of great stress, an overwhelming majority of human beings can still locate a silver lining. Further research with different stressors and different disorders will shed more light on the phenomenon of stress-related growth.

The Value of Social Support

Social support is the degree to which a person's basic needs are satisfied through a social network. These basic needs may be emotional (affection, sympathy, understanding, acceptance, and esteem from significant others) or instrumental (advice, information, assistance with responsibilities, and economic help) [94]. Others have defined social support as the information, alliance, aid, and esteem derived from interactions with family, friends, peers with similar concerns or problems, and professionals [95]. *Social network* refers to the social relations with family, friends, and colleagues [96]. Social support can influence coping mechanisms [97] and promote health [98]. Emotional support may promote cognitive resilience, while social ties provide cognitive reserve that protects against impaired cognition [99]. Social factors affect health status and thus influence QOL [100–102]. Social support, particularly tangible social support, may affect the immune system and was positively associated with the antibody response to vaccination with pneumococcal polysaccharides [103]. Social network variables significantly affect overall health status of patients with chronic diseases [104, 105] and are reported to have a direct relationship with mortality rates [101]. People who are more socially active function better than those with few social ties [106]. Well-integrated persons report higher levels of social (OR 4.07; CI 1.96–8.47) and role functioning (OR 3.59; CI 1.6–8.02) as well as higher emotional well-being (OR 8.57; CI 3.59–20.46) [107]. The absence of only one social support or one social network is reported to be associated with a degradation of health [108], and in one study that conducted hierarchical multiple regression analyses ($n=168$), higher levels of optimism were significantly associated with fewer anxious and depressive symptoms, less hopelessness, and better QOL; increased perception of social support was also significantly associated with better QOL, and, notably, optimism moderated the relationship between social support and anxiety [109]. Level of education, "living in couple," occupational status, and net income per household were related to HRQOL independent of effects of age and gender [110]. Finally, strong social network is positively associated with quality of sleep [111]. Thus, incorporating social support and positive experiences in the management plan is likely to improve QOL of patients.

Support Groups

Support groups differ from self-help groups and psychotherapy groups. *Self-help groups* are run by patients who share knowledge acquired through a common experience with an illness (Surgeon General C. Everett Koop's report by Mary Huber 1987). Patients control the group and there is no charge, but donations are often encouraged. *Support groups* are led by a professional facilitator [112]. The mission is to provide mutual aid in a small group structure to serve the core needs of the members, which includes sharing information and providing advocacy, support, and affirmation as well as the opportunity to socialize [113]. Traditional *psychotherapy groups*, on the other hand, focus on personal exploration in a group setting with the aim of producing personal change and modifying interpersonal relationships by observation, reflection, and awareness [114]. Sivesind DM and Baile WF (1997) offer the following four major differences between support groups and psychotherapy groups [112]:

- Support groups offer concrete guidance, whereas psychotherapy groups do not.
- Support groups are run for an indefinite period of time and the members change frequently,

whereas psychotherapy groups are time limited and have a consistent group membership.
- Support group members are identified by a common problem, whereas members of a psychotherapy group are not.
- Support groups help patients cope with the effect of an illness/disorder and decrease a sense of isolation of group members. In contrast, psychotherapy groups focus on making personal changes through insight to improve interpersonal skills or relieve intrapsychic distress.

Studies have shown the positive effects of support groups in chronic illnesses, including cancer, [115], diabetes [116], cardiac conditions [117], and in child birth [118]. Mothers at risk for depression were more satisfied with postpartum doulas than peer telephone support [118]. Results from the Longitudinal Aging Study Amsterdam (LASA) show that emotional support is a more important determinant of loneliness than instrumental support. Subjective assessment of support affects cognitive functioning [119]. Investigation of psychosocial resources (positive support, active coping) and psychosocial constraints (negative support, avoidant coping) as predictors of improvement in health following surgery revealed that psychosocial constraints, namely, negative support and avoidant coping, encountered by patients were strong predictors of poor recovery [120].

Who Can Provide Support?

In addition to professional support, the assistance of family members, friends, and experientially similar others can be mobilized to provide comfort and support to a person with severe/chronic illness with or without comorbidities; however, respondents in one study reported 30 % more difficulties discussing health issues [incidence rate ratio (IRR) = 1.30; 95 % CI = 1.11, 1.53] and 44 % more barriers to providing support (IRR = 1.44; 95 % CI = 1.18, 1.75) to depressed relatives/friends when compared to responses for non-depressed relatives/ friends [121]. The most commonly enlisted supporters are parents and significant others who offer emotional and instrumental support, reminders for taking medications, and assistance in self-management strategies [122].

The underlying mechanisms in peer support are experiential knowledge, social support, social comparison, and helper therapy [123]. Peer supporters have greater experience with the healthcare system and management strategies that they can share with members with similar disabilities. Improved physical and mental well-being through social support and relationships include social influence/social comparison, role-based purpose and meaning, social control, self-esteem, belonging and companionship, sense of control, and perceived support availability; stress buffering processes are also influential [124].

Narcolepsy and Support Groups

In a qualitative study, narcolepsy patients reported several benefits of attending support groups [125]. Diagnosed narcolepsy patients are registered with the Narcolepsy Institute for counseling, behavior modification, and case management. All participants volunteer to attend these groups. Fifteen frequent members attend most of the groups and about 15 others attend infrequently. Considering that 75 members in New York City had registered for the Family Support Program in 2000–2001, the attendance rate was 40 %. Frequent members have developed a bond and a spirit of camaraderie. They welcome new members and often offer suggestions and advice. Older members show compassion toward younger members and narrate their own experiences with narcolepsy when they were in their teens or twenties. The facilitator sometimes has to intervene if the discussion assumes a negative tone or diverges from the topic and steers the group unobtrusively toward a supportive and positive note. A questionnaire with structured and open-ended questions designed to assess patients' satisfaction with services, their needs, and perceptions of support groups was administered to 15 group members at the Narcolepsy

Institute in 2000. This information is valuable in making appropriate changes in program development. Content analysis of patients' responses to the questions related to benefits of support groups at the Narcolepsy Institute and their perceptions of reasons why some members do not attend support groups is presented. All responses to an open-ended question on benefits of attending support groups were classified into three categories: emotional benefits, information, and services received from the Narcolepsy Institute.

Emotional support indicated by the following comments: "The give and take"; I learn to share; received genuine love and caring; I am not alone; it helps me to be stronger; I feel optimistic; I get guidance; I derive emotional strength and information from other people's experience; they have changed my life and provide continuous support.

Information or instrumental support indicated by the following comments: I receive very good information on medications, diet, and nutrition (most responses). My understanding of how narcolepsy affects my own life has been broadened immeasurably, thanks to these sessions. I learn about living with a disorder and concern for others. I learned to keep an organized schedule. I adopted good food habits that are helpful in staying awake.

Services: satisfaction with services is indicated by the following responses:

Counseling is very good.
I like the support groups.
Support from other patients is very helpful.
I like the newsletter.
Staff has a positive approach.
I get personal attention.
Staff members treat me well.
They are always there to help me [125].

Patients' responses reveal that they derived invaluable benefits from group meetings. The most commonly stated benefit was the amount of information they received about managing symptoms, various treatments, and new research on narcolepsy. Some felt that the group provided the drive they needed to move on with their lives. Many felt that the sincerity and friendship of the group was particularly important to them. Others expressed great relief at meeting those who have a similar disorder and sharing experiences with them. A few members expressed more self-confidence since participating in groups; others found the sessions on nutrition were particularly relevant to their condition. Emotional support and strength from other people's experiences and valuable information on medications, diet, organizing tasks, and learning to keep awake were other benefits expressed by members.

Support groups provide a forum for information exchange, acceptance and understanding by peers who are similarly affected, and also access to pertinent resources in a supportive and caring environment. Patients feel reassured and develop confidence and hope. Thus, counseling and support are important in the comprehensive management of narcolepsy. A support group setting provides unique features not found in psychotherapy groups. Group cohesion develops from a sense of understanding, compassion, and acceptance from group members providing a "significant other" and reduces isolation and passivity that many persons with narcolepsy experience. Helping others in the group lends meaning and dignity to their lives. Mutual benefits in a cohesive group environment led by a professional are likely to operate synergistically to enhance the quality of the group experience.

Why Do Some Members Not Attend Support Group Meetings?

The services provided by the Narcolepsy Institute are free for eligible members; however, many members do not avail themselves of the opportunity of the group experience. The reasons given by patients for not attending are:

- Lack of transportation
- Inability to find a companion to accompany them to the meeting
- Difficulty traveling in the subway because of sleepiness and frequently missing the destination stop
- The discomfort of traveling or staying awake in the group due to the severity of narcolepsy and cataplexy

- The perception that they do not need support from a group
- Self-perceived need for a psychotherapy group
- Lack of motivation: Would like to attend but can't get self to meetings
- Inability to attend because of work and conflicting time schedules
- Lack of knowledge about the benefits derived from a support group

These responses reflect difficulty in utilizing public or private transportation due to narcolepsy, low motivation, lack of time, and lack of understanding about what support groups have to offer.

What Characteristics Differentiate Those Who Attend Support Groups from Those Who Don't?

Knowledge about variables affecting support group participation can assist in the formation and development of successful support groups. Researchers in Sweden [126] found that among patients with cardiac disease, non-attendees reported a more relaxed attitude to life and a more positive view of themselves than attendees. Attendees were more likely to report close relationships as a source of information compared to non-attendees; they scored higher than non-attendees on emotional satisfaction and degree of autonomy in their relationships and were more likely to indicate similarity of values in their network. Perhaps non-attendees are more independent minded and have less need for support groups. In a recent study, a higher "active emotion-oriented" style of coping, higher levels of overall treatments, and unemployment were predictors of self-help group participation [127].

Support Groups/Self-Help Groups and the Internet

The Internet presents a widely accessible, 24-h modality to promote chronic disease management. Consequently, there is a growing trend on the part of individuals to resort to the Internet for information and support. Online support groups can serve as an adjunct to professional care by providing a forum to vent feelings and provide mutual support. Internet participation removes the barriers of the difficulty of traveling because of disability and to obtaining transportation and the time constraints often encountered by patients. Support group participants report both positive and negative experiences online. Positive experiences include access to information and advice, connecting with others who understand, interaction with health-care professionals, treatment-related decision making, and improved adjustment and management. Negative aspects included reading about the negative experiences of others, feeling like an outsider [128], information overload and misinformation, inability to connect physically, and declining relationships [129]. Unmoderated sites are likely to present misleading information about therapies compared to moderated sites [130]. Age and low economic status (SES) could be a barrier to utilization of Web-based support. Older persons or those with less education were less likely to use the Internet as a forum for support in a study in Australia [131].

Telephone-Based Peer Support Groups

Telephone support and follow-up provide a cost-effective way of managing patients by removing constraints of time, inclement weather, and expense for both patient and supporters. Recent studies show the benefits of telephone peer support. Supporters report increased self-esteem and well-being; challenges include supporting someone with negative emotions and poor prognosis and striking a balance between detachment and concern [132].

Recent Advances in Facilitating Social Well-Being

Recently, an innovative approach to networking, Circles of Health, has been tested. Multidimensional medical evaluations standardized to

the International Classification of Functioning, Disability, and Health are incorporated into corresponding medical health records. These data are utilized to generate multidimensional indicators that are then integrated into Circle of Health's social environment. This allows the monitoring of patients' health statuses based on a comprehensive profile [133]. The Happiness Route is another innovative approach to improve the well-being of socially isolated people with impairments and a low SES. It focuses on positive psychology versus problem-based approach with questions such as "How do you want to live your life?" [134].

Implications for Management of Narcolepsy

Review of studies on QOL in narcolepsy in the USA and other countries documents extensive negative effects of narcolepsy on physical health, mental health, work, and social health of patients. Keeping in mind that there are differences in methodology in different studies, a pattern of reduced function in narcolepsy is evident. Notably, PWN were sleepier than untreated OSAHS patients, with a greater impact on activities of daily living [72]. They reported more adjustment problems when compared to patients with cardiac disease, mixed cancers, and diabetes [83]. The economic burden of illness was comparable to Parkinson's disease, Alzheimer's disease, epilepsy, and stroke [69]. They reported significantly higher levels of impairment in alertness, selective attention, and subjective ratings of tiredness/sleepiness when compared with OSAS, insomnia patients, and controls [82]. Emerging studies indicating the presence of medical and sleep comorbidities in narcolepsy present further challenges to the management of an already complex disorder. Furthermore, the developmental aspects of narcolepsy and its comorbidities pose another set of issues in the diagnosis and management of narcolepsy. Treatment of narcolepsy is not optimal [72], and even after successful treatment, patients may have adjustment problems [91]. Finally, social support provides many benefits and enhances individuals' ability to cope with their disabilities and improve the quality of their lives [125]. Social support can be provided by a professional to individuals, families, or in a support group. Recent studies on online and telephone-based self-help groups provide insights on the value of these modalities in assuaging dissonance and discomfort and reducing the loneliness of people with chronic illnesses.

This review indicates that pharmacological management of symptoms is not sufficient although it is necessary in most cases. Successful management of objective and observable clinical features may be affected by other complaints of narcolepsy patients, such as low level of energy and fatigue, problems with memory, depressed mood, adjustment problems, and perception of lack of security in the environment. Patients need relief from the negative impact of narcolepsy on their mental and social lives. Medical treatment should be supplemented with behavior modification, lifestyle changes, and psychosocial support and counseling.

Social Support and Counseling

People with narcolepsy are often socially isolated. Even if the disorder is well controlled or not severe, patients may avoid social events because of low energy level, sleepiness, fear of embarrassment or potential injury, depression about their condition, or lack of motivation.

Many patients benefit from obtaining information and counseling from a professional in order to cope with interpersonal relationships, marital problems, genetic issues, career selection, career growth, memory problems, and time management. Long-term psychosocial support is essential to the total management of narcolepsy and is best addressed by a team approach in which physician and psychologist, social worker, or qualified counselor work together in the best interests of the patient. Patients with severe coping problems should seek the assistance of a psychiatrist for more intensive counseling and therapy. Interpersonal relations are greatly affected in narcolepsy. Even families

who are knowledgeable about the disorder may face significant problems. Misunderstandings, frustrations, and anger may build between parents and children. Parents with narcolepsy may worry about the possibility that their children will inherit the disorder. Support and counseling by a sensitive professional individually or in support groups will clarify misunderstandings, improve communication, and enhance the quality of relationships.

Sharing information about clinical symptoms, medications and their effects, and coping strategies in managing the psychosocial impact of narcolepsy is an important group process enabling patients to develop a positive outlook. Many emotional burdens are reduced by discussing the experiences of different group members. Social support may strengthen individual's coping behavior by increasing morale or self-esteem [125]. Support groups facilitate active involvement by patients in their health care and have a unique value in the total care of a patient, thus enhancing their quality of life. Perhaps referral by professionals and explanation of benefits derived from participation in support groups will encourage more patients to engage actively in support groups.

In view of recent data on stress-related growth, timely and appropriate psychosocial interventions and access to social resources to promote stress-related growth are likely to improve the quality of life of patients with narcolepsy.

Transportation

Some persons with narcolepsy cannot drive and may avoid public transportation, fearing they will fall asleep or get cataplexy. Many do not wish to be dependent on others for transportation. In support group meetings at the Narcolepsy Institute, patients report sleeping on the train or bus and missing their destination stops, missing a highway exit while driving and entering another state, and sleeping at the airport and missing their flights. The support of a companion while traveling and access to special transportation services for the disabled will ensure safety and facilitate timely and punctual visits to their professionals.

Employment

Because education for persons with narcolepsy often is either inadequate or interrupted, career goals may need to be changed or adjusted. Excessive daytime sleepiness (EDS) may not only hinder job progress but may also result in job loss. Advocacy by a professional may be needed to enlighten employers about narcolepsy so that appropriate adjustments to working conditions can be made, such as providing intermittent work breaks for a rest or brief nap. Potential approaches that may ensure job opportunities and continued employment of valuable and valued workers are (1) flexible work schedules that allow brief nap times and take advantage of the employee's best functioning periods; (2) work assignments that will not be hazardous to the employee or to others; (3) work assignments that do not require either rotating shifts or performance of sedentary monotonous tasks that contribute to EDS; and (4) work that provides mental stimulation as well as physical activity. To alleviate fear of job loss, to assure equity of employment, and to promote a comfortable work atmosphere, both employers and employees should be educated about narcolepsy, its symptoms, and the limitations it may place on certain job aspects. Employees and employers should be aware of legislation that prevents discrimination in hiring and employment practices. Narcolepsy is classified legally by the United States federal and state governments as a disability and in New York State as a developmental disability. The Americans with Disabilities Act provides protection for people with disabilities [135]. With support from their health-care professionals, disabled individuals can request accommodations in the work place.

As patients weave the experience of having narcolepsy into the fabric of their personal and social lives, sensitive health-care professionals may enhance the healing process by timely psychosocial interventions or referrals for such services. Determination of the adequacy of social support in the management of narcolepsy will enable professionals to facilitate accessibility of support services. A person-centered approach in the management strategy would consider the

person's perceived needs and developing goals with a choice in medical and psychosocial interventions. Furthermore, inasmuch as religion and spirituality are the most prevalent and powerful coping mechanisms that lend value and meaning in the experience of stress and/or illness, professionals should become aware of the various resources that can be accessed by patients.

Research Implications

Tiredness and sleepiness are different symptoms, and lack of differentiation between the two symptoms in the measuring instrument may confound the results. Combining different instruments or administering different measures for symptoms, health status, and QOL may elicit more valid results. Studies that combine standardized HRQOL instruments, individualized instruments, and subjective qualitative data may procure richer data, and qualitative data may explain some of the processes (why and how) for making cognitive and behavioral changes to enhance the QOL. Longitudinal studies are needed to determine the process involved in the correlation between the domain selected and perception of satisfaction with life. How do patients rate the importance of different domains? Are individuals' levels of expectations and aspirations realistic? Are they equipped with the necessary skills to adjust their expectations when life's circumstances thwart the fulfillment of these expectations? The beneficial role of spirituality warrants closer examination of this dimension of health and its incorporation in assessing overall quality of life.

W hat determines self-perceived recovery in narcolepsy? Do physical factors (symptoms) play a more important role than social or mental factors in the recovery process? Do social and mental factors mediate the recovery process? Longitudinal studies in group processes in narcolepsy are needed to study the underlying mechanism of change in health behaviors to enhance the QOL. A study of characteristics of persons with narcolepsy that differentiate those who attend support groups from those who don't would offer valuable information on psychological and social variables that can be manipulated to promote and enhance participation in the counseling process and in leading successful support groups. A comparison of costs and benefits of interventions could yield information on improving the QOL of patients. Multicenter clinical, translational, and longitudinal studies will equip clinicians and researchers with knowledge to treat and manage the whole patient and offer a person-centered and family-centered approach to delivering high-quality clinical care. Finally, the concept of critical health literacy employs a multidimensional approach to engage individuals with health information derived from evidence-based medicine, media studies, medical sociology as well as epidemiological studies that could lead to better understanding of the social determinants of health and to better health outcomes [136].

In conclusion, a person-centered and family-centered comprehensive management approach must be designed to address narcolepsy, its disabling effects, and the role of social stressors and social supports on the QOL of the individual and the family. Tangible progress can be attained by a concerted effort to manage this disorder comprehensively by a team of professionals. Comprehensive care implies active participation by the clinician, patient, and family in treating the whole person, thus maintaining the independence and dignity of the individual while adhering to sound scientific principles coupled with humanistic care.

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Narcolepsy, Intimacy, and Sexuality

15

Gila Lindsley

Introduction

Intimacy is an intrinsically important and personal part of every individual's life. In the mental health community, it is often said that everyone—patient and clinician alike—seeks intimacy. Human beings are social creatures. The extensive work of Harry Harlow in the mid-twentieth century, at the University of Wisconsin Primate Laboratory, demonstrated clearly the adverse outcomes of social isolation. In humans, social isolation can lead to feelings of severe loneliness which, according to some authors, can over time literally kill. Because the symptoms of narcolepsy can significantly interfere with the development and maintenance of personal relationships of all kinds, it is a neurological disorder that has the strong potential of leading to just this kind of social isolation and loneliness, as well as clinical depression. It is not unusual for a person with narcolepsy not to know one other person with narcolepsy, one who will truly understand the experience, someone with whom they can feel the bond of genuine friendship and can confide in regarding how the symptoms of narcolepsy have affected their lives.

Significant advances in understanding narcolepsy's pathophysiology and the increasing sophistication of pharmacological treatments to mitigate the severity of this disorder's symptoms are important factors in improving the lives of those with narcolepsy. Hopefully, the progress in researching its pathophysiology and the development of medications to control symptoms will continue.

However, even with the availability of these forms of help, the person with narcolepsy continues to face narcolepsy-specific symptoms in the realm of intimacy and sexuality.

The ability to achieve and maintain intimate relationships is understood as being essential to any person's health and well-being. The successful realization of these kinds of relationships is of interest to all of us—as witness, the popularity of the book *The Dance of Intimacy* [1]. The degree of interest in this has been followed up with numerous excellent scholarly publications on the topic. For instance, John Cacioppo, Ph.D., University of Chicago, has dedicated his entire career to the study of loneliness. He is especially focused on what he refers to as the toxic effects of perceived social isolation [2]. Judith Shulevitz in a recent article in The New Republic [3] writes elegantly about the need for personal relationships, beginning with citing Frieda Fromm-Reichmann's writings on the topic in the late 1950s. Psychology Today published online an article

In memory of LF.

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entitled *The Dangers of Loneliness*, stating "In fact, evidence has been growing that when our need for social relationships is not met, we fall apart mentally and physically" [4].

But to reiterate, in the case of narcolepsy, additional and significant challenges are superimposed. This chapter will look at the challenges to the development and maintenance of several different kinds of intimate relationships for those with narcolepsy: the non-sexualized intimate parent–child and friendship relationships; intimate relationships with spouse or partner, both nonsexual and sexual aspects; and the intimate relationship with oneself.

There already have been some excellent publications about the impact of narcolepsy on quality of life in general and on interpersonal relationships more specifically [5–15]. However, there are very few publications which explicitly focus on intimacy issues from which to draw on in the development of this chapter. It, therefore, relies primarily upon sources of information other than peer-reviewed journals or texts. Specifically, the content of this chapter has been largely drawn from anecdotal data derived from professional contact with a large number of people with narcolepsy, and from online first-person reports—a new source of information made available by a significant increase in the utilization of cyberspace. A synthesis of the main themes that emerged and several illustrative anonymized (to maintain confidentiality) case studies will be presented.

Clinicians, in having available deeper insight into the way narcolepsy can impact upon intimate relationships, hopefully will attain a broadened base and more explicitly conceptualized parameters to work from to better help guide people with narcolepsy toward satisfying solutions.

Definitions

Intimacy The working description of intimacy to be used here is the ability of one individual to be close to another. This requires that the person be able safely to make him- or herself vulnerable to the other person and that the sense of self is sufficiently well developed that there is neither fear of disclosing oneself nor of being engulfed by the other person [16]. The greater the identity development, the greater the ability to achieve and maintain healthy intimate relationships.

Narcolepsy Narcolepsy is a neurological disorder. The current understanding is that it arises from degeneration of the hypothalamic hypocretin/orexin system [17], which is one of the major arousal systems of the brain. Therefore, a person with narcolepsy is not a psychiatric patient. Nonetheless, she or he is an individual who may need psychosocial help managing the challenges of this chronic medical condition. The symptoms of narcolepsy described below, which when not under control can secondarily lead to numerous obstacles for establishing and maintaining intimate relationships, are as follows:

Excessive daytime sleepiness and lingering fatigue even in the absence of true sleepiness. This is perhaps the most disabling of all the symptoms of narcolepsy.

Cataplexy. This is the sudden loss, partial or complete, of skeletal muscle tone, usually in the presence of conscious awareness and usually in response to an affective stimulus

Hypnagogic/hypnopompic hallucinations. These are hallucinations which occur with sleep onset or sleep offset and are generally visual, auditory, or both. They are understood to be REM sleep dream events, but displaced from REM to partial wakefulness. While the hallucinations are occurring, they are perceived as actual events. However, once the person is fully awake, the events are usually (although not invariably) recognized as hallucinations.

Automatic Behavior. This refers to episodes in which the person with narcolepsy appears to be carrying out waking behaviors, but is amnestic to having done so. The automatic behavior can be as simple as repeatedly deleting text just typed into a word-processing program to as complex as driving a car for many miles and arriving at a destination with no memory of how the destination was reached.

Sleep Paralysis. This term refers to a flaccid paralysis of skeletal muscle, understood as the displacement of the normal atonia of REM sleep out of sleep entirely, to the interface between sleep and wakefulness. Because the person with this symptom is therefore at least partially awake, the paralysis is accompanied by cognizance of it. Should sleep paralysis occur upon a sudden awakening caused by a dangerous event, that event is especially fearful because the person cannot move and do something about it. Hypnagogic/hypnopompic hallucinations often co-occur with sleep paralysis, as does the experience of being unable to breathe. Aptly, the phenomenon is embedded in the folklore of Newfoundland as the "Old Hag phenomenon," wherein it was understood to have been caused by an old hag (a hallucinatory event) sitting upon one's chest. It is similarly embedded in Japanese folklore as Kanashibari, meaning literally "bound or fastened in metal," with similar implications for perceived difficulty breathing [18].

Impact of Symptoms as a Function of Developmental Stage

That these symptoms have an impact on intimacy appears to be independent of age or gender. However, the way the impact manifests itself does differ as a function of whether or not the individual has been diagnosed with narcolepsy and especially as a function of developmental stage. It is this latter progression that will be developed here. Life-span developmental stages by which manifestation of narcolepsy symptoms is organized are preteen and early adolescence, later adolescence and early adulthood, adulthood and nonsexual aspects of intimacy, adulthood with focus on nonsexual aspects of marriage/committed long-term relationship, and adulthood and sexual aspects of intimacy.

Preteen and early adolescence At this stage of life-span development, early diagnosis, the psychological issue of separation-individuation, and the psychosocial issue of inclusion/exclusion from a peer group are central.

Diagnostic Issues Numerous young people with emerging narcolepsy were initially erroneously diagnosed with depression, a personality disorder, a neurotic disorder, or an adjustment reaction [19]. Anecdotal data also suggest a high probability of an attention deficit hyperactivity disorder (ADHD) diagnosis. The result is that youngsters with undiagnosed narcolepsy, often treated for one or several of these other disorders, experience difficulties neither they, their parents, friends, teachers, nor their health-care professionals understand.

The hypnagogic/hypnopompic hallucinations pose a particular problem with respect to diagnosis and potentially inappropriate treatment. Whether as yet diagnosed with narcolepsy or not, the child may be completely unwilling to confide in anyone about hallucinatory experiences for fear of being labeled "crazy." Further compounding the problem and as pertinent in this context, available anecdotal data indicate that if the health-care professional treating the young person is unaware of narcolepsy as a possibility and the child does describe hallucinations, a psychotic diagnosis can at least be entertained. The result can be erroneous (and ineffective) treatment with powerful psychopharmacological medications.

Separation-Individuation Separation-individuation is an important factor especially during the preteen and early adolescent years. Although there is documentation of onset before the age of 10, the typical age of onset for narcolepsy is also the second decade of life. This timing of narcolepsy's typical age of onset is especially significant since the preadolescent/early adolescent period corresponds to a stage of psychological developmental termed "second individuation" [20]. According to certain schools of psychological thought (e.g., object relations theory), it is the developmental stage during which the ability to establish intimate relationships (platonic friendships) with same-sex peers begins to emerge.

The psychological construct of "second individuation" builds upon Mahler's characterization [21] of the early childhood "separation-individuation" process. In Mahler's terms, "separation and individuation" refers to the process by which the toddler emerges from a symbiotic relationship to his or her caregiver (separation) and embarks upon individual achievements defining his or her identity (individuation). "Second individuation" refers to a reemergence of this process during adolescence.

The ability to negotiate the "second individuation" developmental task of adolescence is understood to bear heavily upon whether or not a youngster is able to establish intimate relationships outside the family. For instance, one study [22] found in adolescents that the rate of emotional separation from parents predicted the rate by which an adolescent was able to develop intimacy with a same-sex friend.

One of the necessary preconditions for this milestone period of individuation is that the youngsters have the *opportunity* to separate and individuate and that the child has the opportunity to make some of his or her own decisions and then to experience the consequences be they positive or negative. A booklet published by the Narcolepsy Network, *Questions and answers by and for young persons who have narcolepsy* [23], addresses the particular obstacles a young person with diagnosed narcolepsy may face in developing his or her own independent sense of self.

Narcolepsy Network is a national organization which has been a prominent catalyst and advocate for the recognition of this neurological disorder by the school, legal, health-care, and pharmaceutical communities. The organization is run by, and for the benefit of, people with narcolepsy. Details about the organization including the various types of support additional to what it offers can be found on its website: http://www.narcolepsynetwork.org.

In this particular publication of the Network, a chapter entitled "Why don't my parents let me lead my own life?" first notes that this of course is a general complaint among young people. However, the chapter then goes on to identify additional parental restrictions that may be placed on autonomous decision-making for young people with narcolepsy. The additional restrictions arise out of the quite legitimate parental fear that certain activities may be risky because of the ever-present possibility of a cataplectic attack or uncontrollable sleep attack, but taken to the extreme, such additional restrictions may actually inhibit the youngster's ability to develop autonomy. The youngster may also self-impose these same limitations and for the same reason. These restrictions, especially if severe, may inhibit the child from learning independently what can and cannot be done safely, within the realm where making a decision to do something will not put the child in imminent danger. Under these conditions, she or he therefore remains dependent, unable to separate and individuate.

Case History: MAG

MAG is a 25-year-old woman with narcolepsy who has just learned to drive a car. She is still uncomfortable driving alone, so will go out in the car only if there is another trusted adult with her and only for short drives on very familiar streets. She has just moved into her own apartment and that with a great deal of trepidation. The move was accompanied by her opening her own checking account for the first time. Although her apartment is just a few blocks from her parents' home, her choice has been to see them infrequently. She describes that while she was growing up, her parents would not allow her to participate in any activities with peers unless they had completely vetted not only the friends, but also their parents and each specific activity. Humiliated by this, she began to decline social invitations. Once she graduated high school, her life was limited to the confines of her home. She did not get a job. She did not go to college. Her parents provided her with the basic needs of life. "I was afraid of the world, had no idea how to take care of myself, and it never really occurred to me that I could." She describes that one day, very abruptly, she decided she needed to make her own life. This

was triggered by her having read a succession of local articles about high school friends' marriages and then childbirths. "The world was leaving me behind." Poorly prepared to be out on her own, she nonetheless made the decision to do so, this with support from a counselor she was seeing. Her avoidance of her parents was akin to the moving away from one's parents that normally would have occurred during her teen years. She is still shaky, but quite determined. Currently she is on disability and fortunately in a state where numerous support systems are available through the program. Her great hope is that she will be able to learn enough life skills to be able to go to college, begin a career, go off disability, and eventually have her own family. Based upon what she has already accomplished, this is a realistic hope.

Inclusion/Exclusion from a Peer Group If the youngster is able to separate from family and begin moving toward his or her peer group, the issue of acceptance by that peer group arises. This is especially true in contemporary American culture where preadolescents and young adolescents begin to place a higher value on relationships with peers than with family members. Finding a peer group where they "fit in" is of paramount importance.

Yet, sleepiness and the ever-present possibility of a cataplectic episode when laughing at a joke can pose what may seem like insurmountable barriers to fitting in with peers. Defenses against these possibilities include learning to contain emotions to avoid cataplexy and trying to hide pervasive sleepiness. One approach to hiding the sleepiness is to keep moving around, trying to stay awake, possibly the basis for young people with undiagnosed narcolepsy erroneously carrying the diagnosis of ADHD.

Finally, as described above in a different context, having hypnagogic hallucinations is also a secret a young person with narcolepsy may keep, one more aspect of "self" which may not be disclosed to another peer. These hallucinations pose other psychosocial problems as well. Anecdotal reports indicate that some young people with narcolepsy at times were not believed by people in their lives privy to the existence of these hypnagogic hallucinations, e.g., when they described specific events to a parent who knew about the hallucinations' existence. Some of the youngsters whose reports contributed to this chapter indicated that at times what they told their parents was discarded as "one of your hallucinations" rather than being dealt with appropriately with efforts to ascertain if what the youngster said might actually be true and if determined not to be with parents helping the youngster to differentiate between what is and what is not real. Perhaps even more insidious is that sometimes a young person with narcolepsy is him- or herself unsure whether or not a particular event occurred. In a similar vein, dreams may be remembered as real memories, creating another potential problem for the young person with narcolepsy[1] and hence their belief in their own reality testing.

And before narcolepsy is diagnosed in a youngster? The emergence of symptoms can lead to considerable confusion and under some circumstances significantly erode a developing sense of self.

For instance, from the Experience Project Blog:

> I first had my sleep paralysis when I was 12 years old and then the sleepiness & sleep paralysis got sooooo bad in my teen years. I couldn't figure out what was wrong with me, I just thought I was either demon possessed or super lazy. I went to several different doctors and none of them could figure out what was wrong with me. They all gave me a diagnosis of depression because I was physically very healthy. They just couldn't figure out why I'd feel so tired and suffer from nightmares (sleep paralysis) other than through the diagnosis of depression [24].

Keeping secrets about themselves, containing emotions, at times being unsure what is real and what is not—this set of defenses and insecurities is antithetical to young people being able to become close to a peer or peer group and even to themselves. The potential problem is further exacerbated if the diagnosis of narcolepsy has not yet been made. It is eased at least to some degree when the correct diagnosis is made and appropriate psychosocial support is available.

[1]This set of problems is true for adults with narcolepsy as well.

Trust and Self Disclosure Another section of the Narcolepsy Network booklet entitled "Who to tell about your narcolepsy?" focuses on trust and self-disclosure. Kids who stand out as atypical (e.g., "weird" or "odd") are at risk for being rejected from evolving peer groups. It is unlikely that any child in this subculture wants to be perceived that way. A rational explanation to a hoped-for friend about narcolepsy may possibly defuse the "odd" label, allowing the desired inclusion with a peer or peer group. On the other hand, to share this with someone else means to allow oneself to be vulnerable—a key element of intimacy. Young people with narcolepsy may worry and ask themselves, "But what if the other child laughs?" or "What if my explanation of narcolepsy adds fuel to the "weird" fire?" So the questions of who to tell, determining who can and cannot be trusted, are often a concern for the young person with narcolepsy. The associated psychosocial support would minimally involve helping the youngster make the necessary discrimination between who can and cannot be trusted.

Case History: RIL

RIL was 17 years old when he described his experiences prior to his narcolepsy diagnosis. Now happily looking forward to beginning college, he recalls how difficult things were for him from about age 12 or so, when he was just beginning middle school. He'd been a reasonably good student until that time, but then his grades started to fall. He realized part of his problem was note-taking. When he went home to study his notes, he saw that at some point in class he had started writing nonsense, his words "dribbling down and off the page" (automatic behavior). He also described that at times during the school day, it was as if he were seeing things under "stroboscopic light" (micro-sleeps). He'd see bits and pieces of events, but sometimes these just didn't hold together. He eventually realized he was drifting in and out of sleep, but did not dare share that with anyone. He just kept fidgeting and moving around, mostly trying to stay awake. In the gym locker room, as his friends were beginning to bond by telling off-color jokes, he'd begin to feel a "dippy feeling" in his knees (partial cataplexy) and slowly learned to drift away when the jokes were told. He was therefore increasingly more separated from his peer group. At home, his parents told him to stop sleeping all the time and study, then maybe his grades would improve. As a product of all of this, the then 12-year-old became more and more depressed. Eventually he was "coded" as having a learning disability and ADHD. He had begun seeing a psychiatrist for antidepressant medication (which, serendipitously, seemed to help the skeletomuscular weakness—i.e., cataplexy) and was mortified to have to see a special education resource counselor. He was frankly thrilled when finally diagnosed with narcolepsy, the sleep work-up initiated by his resource counselor. For the first time, he was able to understand what had been going on. But that did not happen until he was about 15 years old. With understanding came action on his part. Slowly, he found he was able to explain to a few chosen friends what had been going on and began to find his place in his peer group. By age 17, he felt academically and socially prepared for college.

Later Adolescence and Early Adulthood

As later adolescence then early adulthood begin, potential problems relating to dating become central.

The question "who to tell" described for younger people continues to be an issue in later adolescence and early adulthood, but now can affect dating relationships. For instance, a young adult may become so sleepy during a date that the person's companion can take it as boredom or rudeness. Should the relationship nonetheless continue and light sexuality become involved, there is the possibility that she/he may fall asleep with the onset of sexual activities. Perhaps the young adult with narcolepsy may deal with the situation by finding a way to end the relationship. Alternatively, he or she may choose to explain to

the partner what is actually going on, revealing more as the partner also begins to share more personal things. It is a risk, of course. If the partner is able to be understanding and genuinely cares for the person with narcolepsy, this kind of disclosure can result in the couple becoming closer. On the other hand, the disclosure can have the opposite effect, leading the partner to back off.

Another variation on the theme encountered by young adults with narcolepsy whose cataplexy is incompletely controlled is that they might have a cataplectic attack as sexual excitement increases. Again, the question of appropriateness of self-disclosure arises as the adolescent questions who to tell and under what circumstances.

Of course, if the self-disclosure is *not* made, some difficult situations can arise! For instance, as written on the Family Life (FML) Blog by an anonymous contributor:

"Today, I learned that my boyfriend has narcolepsy when we were having sex and he passed out on top of me." This was followed by her response when one of the blog participants asked what narcolepsy is: "It's a disease where you just randomly pass out unconscious" [25].

Adulthood and Nonsexual Aspects of Intimacy

Serious dating and then the formation of a long-term intimate relationship are often important milestones in adulthood.

Serious Dating As young adulthood progresses and the possibility of committed long-term relationships and marriage enter the picture, new obstacles are faced, especially if the symptoms are not wholly controlled. The possibility of an automatic behavior episode poses one potential obstacle to a young adult with narcolepsy. Understanding that behaviors can occur *without awareness*, the person with narcolepsy can entertain all manner of fears. The fears revolve around whether he or she might do something without being aware and which would be inappropriate or offensive to the prospective partner. Such fears may stand in the way of the person with narcolepsy even allowing the possibility of an intimate relationship.

Or dream material stored as "real" memories can affect one's ability to be intimate with another person. For instance, perhaps in waking life, a woman with narcolepsy fears she may be taken advantage of by a man should the strong feelings he elicits trigger a cataplectic episode. Such a fear has a rational basis. Although studies have not been done to establish the prevalence rate of people with narcolepsy having been sexually violated, raped, or assaulted and whether such incidents are sleep related, there are published reports indicating that such abusive events do occur and are sleep related (see "Adulthood and Sexual Aspects of Intimacy"). Thus, a woman who begins to feel close to a man may *fear* this could happen to her, even in the absence of suggestive behavior on his part. This worry can be integrated into a dream in which her prospective mate does take advantage of her. If that dream material becomes stored as a "real" memory, it can negatively affect an incipient intimate relationship if this is not discussed.

Case History: PR

PR is a newly married man. He awakened—or so he believed at the time—in the middle of the night and heard his wife say she didn't love him anymore. He was devastated, especially since he never truly believed that a woman could love him. Weeks went by, during which he waited for his wife to bring this up during their waking time. But she said nothing. He did not understand how his wife could go about business as usual after this horrible admission. He finally confronted her, only to learn that she did very much still love him and had not told him during the night that she did not love him. Since he knew well that she did not talk in her sleep, it finally dawned on him that what he had experienced was a hallucination or perhaps a dream disguising itself as a true memory—a trick of his own mind.

Finally, if the person with narcolepsy has successfully entered into and maintained an intimate

relationship to the point that marital plans are discussed, fear of what might happen once they are married can lead to a last-minute decision to break an engagement. The person might become frightened that because of the narcolepsy the marriage might not work out.

Adulthood with Focus on Nonsexual Aspects of Marriage/Committed Long-Term Relationship

Once a person with narcolepsy does enter into a committed long-term relationship, other issues arise that need to be anticipated and managed.

One important issue has to do with choosing a long-term partner a person with narcolepsy can rely upon and trust. This obviously is important for anyone considering a long-term relationship. However, the importance is very significantly magnified in a person with narcolepsy because of the many accommodations that will be needed.

The blog Life Transformed by Narcolepsy is comprised of sequential entries by one individual. With respect to the above issue, she writes, in her blog titled "My romantic relationships changed dramatically after diagnosis," that "If you are dating a jackass when you are diagnosed, let this be your reason to pack up and go. Because if you have even suspected your partner of being self-centered before, you know that you haven't seen anything yet…. I cannot express to anyone strongly enough how important it is for a persona dealing with a disabling illness to choose a partner that is capable of caring for another person…. A person who is inherently selfish will find your diagnosis beyond their abilities" [26].

For instance, for many adults with or without narcolepsy, living a normal life includes the desire to have a family. The decision to have a child is based on a wide range of considerations for all couples. If one member of the couple has narcolepsy, additional considerations are present. A concern about genetic transmission of narcolepsy can play a prominent role in family planning. Pertinent here is that although in the canine model, narcolepsy is known to be genetically transmitted [27]; for humans it is not yet clear whether the same is true [28]. If the couple is highly concerned, fear of an unwanted pregnancy can interfere with intimacy. This fear needs to be made explicit and discussed.

If the decision is made to have a child, potentially serious adverse effects of the pregnant woman's narcolepsy medications on the developing fetus need also be taken into account. The prevailing medical practice is that before attempting to conceive, the woman should withdraw from those medications. This means that throughout her pregnancy, her premedication sleepiness, cataplexy, and other narcoleptic symptoms are likely to reemerge. A genuine concern for the couple can be whether or not the marriage or union is strong enough to sustain 9 months of her being sleepy most of the time and of the increased likeliness that she will have a cataplectic episode in response to strong emotions (e.g., loving emotions, anger, joy). Even if the woman was very clear prior to their marriage about her narcolepsy and what the symptoms were like before diagnosis and pharmacological treatment, a possible fear is that her partner still may not be prepared when these symptoms actually occur. For this reason, too, there can be a fear of pregnancy with the potential of affecting intimacy.

Persistent sleepiness (readiness to sleep) and tiredness (not sleepy, but just no energy) have the potential of dissolving an already established marital relationship even when pregnancy is not involved. If the partner poorly understands narcoleptic sleepiness, for instance, and the sleepiness is not effectively controlled by medication, it is possible that the partner may call it "laziness" on occasion, as has been described by numerous people whose reports contributed to the construction of this chapter—a painful epithet and one that can create distance between the two people. Or, even worse, an epithet such as this was reported by one person to have been used with such persistent frequency and intensity that it bordered on emotional abuse. Even under the best of conditions, when the partner is aware and accepting of the person with narcolepsy's incompletely controlled sleepiness, simply the rate at which it might occur can wear on the relationship.

Cataplexy plays an important role in a context different from what was described above as well. Inevitably, in any relationship, there will be disagreements, conflicts, and even anger. Conflict resolution, with a particular focus on communication, is a central issue in couples therapy [29]. Poor communication can occur if one member of the couple is unable or unwilling to communicate a troubling situation or issue to their partner, rendering conflict resolution impossible since one partner is unaware of the problem. A traditional intervention in couple therapy, therefore, is to teach each partner to express his or her concerns to the other, to stand up for him- or herself.

When one partner in the relationship has narcolepsy, the process can be more complex because the anger a conflict might engender can be a powerful precipitant of cataplexy. As a consequence, some percentage of people with narcolepsy have learned to avoid even the possibility of confrontation or conflict, many shutting down entirely rather than addressing the issue at hand. The therapist working with a couple when narcolepsy is involved needs to be especially aware of this and be able to help the couple recognize the accommodations each of them must make so that effective communication and peaceful conflict resolution become possible.

Another challenge to a long-term committed relationship revolves around the issue of psychiatric depression. One concern has to do with the issue of misdiagnosis. If narcolepsy has not yet been diagnosed, the excessive daytime sleepiness of narcolepsy may be mistaken for the lethargy of depression. The consequence: If the diagnostician does not include narcolepsy in the differential diagnosis, an erroneous diagnosis of depression may in fact be made. Anecdotal reports indicate that some people whose narcolepsy was not diagnosed until adulthood were subjected to increasingly more aggressive treatments for "depression" because of apparent refractoriness to the just-prior treatment. Erroneous labeling of the adult with still undiagnosed narcolepsy as an intractable, severe depressive has been reported to impair significantly the person's desirability as a continuing long-term committed partner.

Even if narcolepsy has been correctly diagnosed, another consideration is that depression can be comorbid with it [19, 30, 31]. Often, the depression is secondary to frustration at being unable to do what used to be possible. Over time, unresolved symptoms of narcolepsy can result in job loss due to incremental difficulty carrying out the work. Under certain circumstances, the person with narcolepsy can pursue and obtain legal disability benefits [32], but being put on disability itself can further undermine a person's self-esteem. Depression secondary to job loss and forced disability status is more likely when narcolepsy develops late, after a person has already established her- or himself professionally, since she may have lost a well-established career. The comorbid depression can put additional stress on the relationship, loosening and possibly dissolving the relationship's bonds. This is especially true if the person with narcolepsy who has a comorbid depression refuses to seek treatment for it.

Case History: Mrs. L.

Mrs. L. was in her late 40s when her husband divorced here. Onset of narcolepsy symptoms for her was late, beginning at about 25 years old. She was not actually diagnosed until another 5 years had passed. By then, her first marriage had dissolved, in large part because she "was sleeping all the time." However, she had the good fortune of having a long-time male friend and whom she began dating. The two had worked for the same company where they became friends. They subsequently married. Her husband entered the marriage with his eyes wide open, completely aware of all aspects of his wife's narcolepsy, having seen it during all the years of their friendship. By the time they got married, she had cycled through first reaching a high level of middle management, then becoming increasingly more symptomatic and slowly losing the team working under her, to finally being released from the company and put on disability. Despite her job loss, her husband-to-be was able financially to support both of them. He was highly empathic with her disability.

In fact, he literally supported her as she began a cataplectic episode while they were walking down the aisle at their marriage ceremony. For the first several years of marriage, her husband increasingly took over function in recognition of his wife's difficulties. He was not, however, prepared for her to be in bed "almost all the time," for her more and more often falling asleep on the couch and not sharing their marital bed. He was even less prepared for this formally vital, intellectually keen, and resourceful woman to become overwhelmingly self-absorbed, "having almost constant pity parties." Realizing that what he was seeing was incremental depression in his wife, he asked then begged her to seek psychotherapeutic help. After "too many years" of her refusing to do so, feeling tremendously sad, he finally asked her for a divorce. He rued the life he believed they can have had together, "growing old with each other." And for a very long time, he continued to have pervasive feelings of guilt, always wondering what else he could have done.

Even under the best of circumstances, unresolved sleepiness of the narcoleptic partner can stress not only the relationship but can as well stress the non-narcoleptic partner as an individual. That partner may genuinely love and be extremely supportive of the person with narcolepsy, but may also feel too guilty to acknowledge the partner's chronic sleepiness as a significant stressor. If the partner without narcolepsy is a married woman, for instance, she may keep entirely to herself how often she feels as if she were single. She may not disclose how her husband is unable to be a true companion to her or to their friends. The woman may stoically accept all of the domestic, social, and financial responsibilities that fall on her shoulders. However, the cumulative effect over the years of keeping these stresses to herself out of guilt can have a tremendous impact on her well-being. Once again, we see the detrimental effect of keeping secrets.

Words written by the wives of narcoleptics, in a blog called The Narcoleptic's Wife [33], provide considerable insight into the kinds of emotional dilemmas the wives may be facing and some of the secrets they may keep from their husbands with narcolepsy and perhaps from everyone. On this blog site, as with many others, the anonymous participants speak frankly and openly. The originator of the blog states at the beginning of each new blog, "I love my husband but I hate his illness. I'm trying to learn how to help my family thrive despite my husband's narcolepsy, and I hope this blog also helps anyone living under the weight of this disease."

Some relatively recent examples:

- Guilt. From a Friday, August 27, 2010 entry. A Narcoleptic's guilt. [34]

  > My husband apologizes a lot…. He apologizes sincerely, because he feels guilty. He feels guilty because his illness is a weight that prevents him from being the husband he envisions in his own head…. it isn't your fault, so why feel guilty? … as if the weight of narcolepsy wasn't enough to bear, he has the added burden of guilt. Hopefully my bearing some of the load will allow him to breathe.

- Isolation. From a Monday, August 13, 2012 entry in The Narcoleptic's Wife. "The isolation of narcolepsy" [35]

  > I feel a little down today…. Sometimes I decline invitations because I just don't want to deal with narcolepsy in a social setting. I don't want to nudge my husband awake, wake him when he begins to snore, or watch him worriedly as he fights to control a laugh. It can be exhausting, so at times I'd just rather stay home.

- Keeping passion alive in the relationship. From a Monday, December 30, 2013 entry. "How to keep passion alive in a relationship with a narcoleptic" [36]

  > Take the lead… Keep it simple … have a backup plan … spontaneity is OK … be flexible… Do something everyday … be patient with your spouse…. And yourself…. Narcolepsy is incredibly frustrating. And unpredictable. And inconvenient … every marriage should be based on mutual love and attraction, so work hard to make sure that narcolepsy doesn't rob you of yours….

With good communication and the personal decision *not* to keep these kinds of secret, quite a good outcome is possible. When a wife, let us say, is able openly to acknowledge, talk about, and work through with her husband the effects of

his narcolepsy on her she will more wholeheartedly be able to support him. A potential result is that later in life, should she fall ill, her spouse will more likely be available to support her.

Case History: Mr. B.

Mr. B. is a 79-year-old man with narcolepsy, married for over 55 years to his high school sweetheart. They grew up in the same town. Their immediate and extended families not only knew each other but were social friends. He recalls that his symptoms of narcolepsy probably started around the time he and his now-wife began dating. However, in those years, there were no sleep disorder centers. Despite his tendency to fall asleep at awkward moments, and events which were probably the early stages of partial cataplexy, so close were the families that his symptoms were simply accepted as part of him. He described the trajectory of his and his wife's many decades together, how wonderful the acceptance of his wife and both their families had been of him as his symptoms progressed, and what a relief it was when finally he had a sleep evaluation and was diagnosed with narcolepsy and pharmacological treatment initiated. He then described his experience as his wife became ill in her mid-70s, especially his sadness to see his lifelong companion becoming so very ill. But the strength of their marriage combined with strong family and community allowed him to emerge with the strength he needed to offer her the same kind of loving support she had offered him for so many years.

Critical variables in all the instances described are openness in communication, maturity, and effective, informed, appropriate psychosocial support.

Adulthood and Sexual Aspects of Intimacy

Marriage (or a committed relationship between two people) almost invariably involves sexual intimacy. The difficulties people with narcolepsy can have with sexual intimacy, therefore, need also to be considered.

A textbook chapter by Karacan and his colleagues [37] describes sexual dysfunction in men with narcolepsy. The article provides case studies centering on loss of sexual interest in men because of sleepiness, cataplexy induced by sexual arousal, and erectile dysfunction induced especially by the stimulant medications intended to control sleepiness. Amphetamine, in particular, is identified as a drug whose chronic use can produce erectile failure, ejaculatory problems, and decreased libido in men.

If the person with narcolepsy is also depressed and psychopharmacological treatment is warranted, one possibility is that the antidepressant will be a selective serotonin reuptake inhibitor (SSRI). Possible sexual side effects of SSRIs, including loss of libido and/or loss of ability to successfully engage in sex, are now well documented [38]. Thus, while the potential for interpersonal intimacy may increase as the depression lifts, with this class of medication, the potential for sexual intimacy may decrease. On a positive note, effective antidepressant medications without sexual side effects are becoming available.

On quite a different note, a review paper [39] describes several case studies wherein the female patient either had hallucinations of being sexually abused or was actually sexually abused during an episode of cataplexy. In one case, the subject was described as having first been raped by a policeman and then several years later at a party given by her manager at work. In both situations, she described having been aware of what was happening, but because of her cataplectic paralysis, she was unable to fight either man off or to scream out for help. This kind of history can give a woman second thoughts about sexualized intimate contact with a man.

Cataplexy can directly affect a woman's sexual intimacy with her partner as well, even in the absence of a cataplexy-related sexual abuse history. For instance, a woman's partner may be unaware during a sexually intimate occasion that she is in the midst of a cataplectic episode, continuing his sexual engagement with her despite

the advent of her cataplectic attack. It is also possible that he actually *may* be aware but decides to proceed with sexual contact despite it. Either situation can raise a dilemma for the woman who will have been aware but unable to respond during the sexual encounter. Depending upon the solidity of interpersonal intimacy and communication between the two, she may be left trying to decide if she were being taken advantage of in a particularly distasteful way—or if her mate simply accepted her, cataplexy and all.

Unresolved daytime sleepiness can also have an impact on sexual intimacy. The person with narcolepsy might find him- or herself often in a state of being neither truly awake nor truly asleep during the usual wake-time hours. This would be equivalent to the experience any sleeper has when beginning to fall asleep, during the "hypnagogic period." The hypnagogic period (stage 1 non-REM sleep) is a time when one's thoughts begin to drift. Experientially input from external stimuli (e.g., the sound of rain) is interspersed with dreamlike cognitions and images. However, in the case of narcolepsy with unresolved sleepiness, this state can be present throughout the daytime, not just at the interface between daytime wakefulness and nighttime sleep. Per the report of one individual, "A sleepy consciousness in a sexually charged situation can lead a person into some very unpredictable situations."

Another theme that emerges revolves around the fact that for a very large percentage of the population, sex and sleep occur in the same place—in bed, when the couple is recumbent, and often at night. The ensuing sleepiness for a person with narcolepsy would directly interfere with sexual intimacy. One solution to this is that the couple set things up so that sexual intimacy is reserved for afternoons or mornings, not at nighttime; and so it occurs at any place in the house but in their bed and bedroom.

While not explicitly sexual, the closely related problem a person with narcolepsy may encounter in sharing a bed with his or her partner for purposes of sleeping is addressed here. Sharing the bed may, for one reason or another, lead to a less than restful night for the partner with narcolepsy. Impairment to the restfulness of nighttime sleep can, in turn, exacerbate daytime narcoleptic symptoms. This can pose a difficult choice for people with narcolepsy regarding intimacy. Sleeping together and cuddling, in the same bed, and waking up with that person in the morning is an expression of intimacy, such that choosing to sleep in separate beds might deprive the couple of it. On the other hand, if sleeping in the same bed also means she/he is less wakeful the next day, *that* can negatively impact on the person with narcolepsy's ability to be intimate with his or her partner. The clinician working with the couple can help them make this dilemma explicit and then assist them with communicating about it until they reach a satisfactory resolution.

Timing of intimate sexual relations relative to nighttime medication intake can also present a problem. For instance, if the person with narcolepsy is taking sodium oxybate (Xyrem®) at bedtime, sleepiness will quickly ensue[2]. It is therefore important that the couple keep this in mind, planning so that their initiation of intimate sexual contact occurs before the sodium oxybate bedtime dose is taken.

The blog Always Sleepy [40] has participants of all ages, living in all different kinds of situations, offering their day-to-day experiences as they negotiate the challenges of narcolepsy in their lives. One particular entry, March 28, 2007, is entitled "An exclusive look into the secret sex lives of Narcoleptics" [41]. It is well worth reading in its entirety. It identifies all the factors highlighted above—and more. Its being written as a first-person account makes it especially compelling.

As with all things involving the maintenance of intimate relationships, communication about this extremely personal and intimate part of life for people with narcolepsy and their significant others is necessary. In order for such communication, certain obstacles need to be overcome. For

[2]Sodium oxybate, currently indicated for excessive daytime sleepiness and cataplexy in the context of narcolepsy, is taken in two doses: at bedtime and 4 h later.

instance, many people are hesitant to discuss intimate issues under any circumstances. Or, for the person with narcolepsy who must take a nighttime dose of sodium oxybate such that there must be explicit planning about the timing of lovemaking, there may be the concern that this kind of planning runs counter to the desire for spontaneous sexual intimacy. As such, this is a concern potentially interfering with the willingness to discuss coordination between the timing of sexual intimacy and bedtime medication. Even if the willingness is there, external factors may interfere. If, as an example, both members of the couple work, the part of the couple with narcolepsy may be especially exhausted at the end of a work day. The result would be an insufficient amount of useful awake time available *for* that discussion at day's end. A solution would be to have this conversation before the work day begins—or on a non-work day.

Concluding Comments

The willingness first to enter into an intimate relationship, and then to establish and maintain it, can be difficult for many people. What have been described here are the additional and significant superimposed challenges to intimacy a person with narcolepsy may face. Each of the symptoms of narcolepsy, if not under control, can pose problems independent of age and gender. The ways such potential problems manifest themselves as a function of developmental stage in particular have been described.

Not all people with narcolepsy experience these challenges, but the clinician does need to be aware of the possibility. Drawing their patients out on the kinds of things identified in this manuscript, if their patients do not spontaneously volunteer these kinds of concerns, is quite important. The following are key to whether or not narcolepsy's symptoms will present such challenges which can have become obstacles: (1) whether or not, and at what point in life, narcolepsy has been diagnosed, (2) the degree to which the symptom is under control, generally by pharmacological agents possibly complemented by psychosocial support, and (3) the maturity of the person(s) with whom the person with narcolepsy care(s) to become intimate.

In detail:

1. Whether or not, and at what point in life, narcolepsy has been diagnosed: One result of increasing awareness on the part of school systems and health-care professionals is that narcolepsy is to some extent being identified far earlier in a person's life. In the not-so-distant past, it was not unusual for a diagnosis of narcolepsy to be delayed until a person was in their third or even fourth decade of life. Importantly, early recognition and early treatment can minimize or obviate the significant damage to self-esteem, the ability to establish intimate relationships with a peer group (and ultimately with a life partner), and the possibility of a youngster with narcolepsy being treated for the wrong diagnosis (e.g., ADHD or depression). Unfortunately, the general consensus is that narcolepsy continues to be underdiagnosed in school-aged children. Continuing efforts are being made to rectify this.
2. The degree to which symptoms are under control: With respect to pharmacological control of symptoms, new medications are now available for the most intrusive narcoleptic symptoms: excessive daytime sleepiness and cataplexy. Some of the potential obstacles to intimacy described above, therefore, can at least be mitigated pharmacologically. However, the following caveats must be recognized: (1) Not all people have access to these medications. (2) Even when these medications are available to a person with narcolepsy, the medications do not invariably (if at all) wholly eliminate narcoleptic symptoms. Residual symptoms, if present, can lead to the obstacles to intimacy delineated above. (3) For various reasons, a person may need to discontinue their medications for a period of time. The discontinuation of medication during pregnancy has already been described. Also, some people with narcolepsy develop

tolerance to stimulants very quickly and must take a medication holiday every weekend in order to get the benefit of the stimulant during the following work week. These individuals often sleep away the entire weekend, depriving the family, partner, and/or spouse of time together that can be critical to maintaining a healthy relationship. (4) The medication(s) may be discontinued entirely because of noxious side effects.

3. Maturity, self-acceptance, open communication: Some form of psychosocial support, such as participation in the numerous anonymous blogs now available in cyberspace, self-help groups, individual psychotherapy, couple therapy, and/or family therapy, is often useful. Psychosocial support can, variously, focus on self-acceptance, on appropriate disclosure of symptoms, and on assisting with open communication, problem solving, and conflict resolution.
4. The acceptance by a narcoleptic person that narcolepsy is a part of his or herself *and* that it does not define who she or he is. Reaching this level of self-acceptance, depending upon the degree to which it might have been undermined in formative years, can be a challenge. The earlier the diagnosis is established, and the more supportive those around the person are, the less of a difficulty this will become for them in later life.
5. Open communication between the person with narcolepsy and his or her prospective or actual intimate partners and also with people who could be in a position to help (e.g., family, friends, work associates, therapists). This facilitates self-acceptance as well as the development of genuine relationships among people who can be trusted.

The ability to be willing and able to enter an intimate relationship is an important aspect of an individual's life in our culture. This chapter has been written in the hope that it will offer the health-care professionals who treat people with narcolepsy an increased ability to assist in their care. Hopefully in the years to come, a chapter similar to this can be grounded in systematically collected empirical data. Here, we have synthesized the information that is available—primarily from first-person reports of those with narcolepsy and of their families and significant others, and from numerous on-line blogs.

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Memory and Cognition in Narcolepsy

16

Christian Bellebaum and Irene Daum

This chapter addresses the issue of cognitive deficits associated with the sleep disorder of narcolepsy. In the first section, the main symptoms and pathophysiological mechanisms in narcolepsy will be summarised to the extent in which they are relevant for the development or mediation of neuropsychological impairments accompanying narcolepsy. These impairments are outlined in more detail in the following section. In the final section of this chapter, the findings will be discussed in terms of the possible neurocognitive mechanisms underlying the neuropsychological impairments in narcoleptic patients.

Main Symptoms of Narcolepsy

The most prominent symptom of narcolepsy is excessive daytime sleepiness [1]. During their normal everyday activities like working, eating, etc., most patients experience two or more sleep attacks during the day. Together with cataplexy and sleep paralysis accompanied by hallucinations, sleepiness forms part of the "narcoleptic tetrad" (see [2] and [3]). Cataplexy refers to a sudden reduction or complete loss of skeletal muscle tone affecting single body parts or even the whole body. These attacks are frequently triggered by emotional experiences and may last several minutes. The patients are fully conscious, while being unable to move. Similarly, the narcolepsy sufferer is awake and unable to move during sleep paralysis. But this symptom usually occurs only during periods of falling asleep or waking up. It can last up to ten minutes and is often accompanied by visual hallucinations, which can also occur independently.

Dysfunction of the Hypocretin System in Narcolepsy

Narcoleptic symptoms have consistently been associated with dysfunctions of the hypocretin system, with two hypocretin neuropeptides, hcrt-1 and hcrt-2, being generated from a single precursor and synthesised by neurons in the lateral hypothalamus. In narcoleptic patients with cataplexy symptoms, the number of hypocretin neurons is dramatically reduced [4]. Accordingly, low hypocretin levels are found in these patients [5] but not in narcoleptic patients without cataplexy (see [2]). Extensive screening revealed that—unlike the mechanism in dogs—mutations in human hypocretin-related genes are not the

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cause of hypocretin deficiency [6]. A genetic predisposition for an autoimmune response targeting the hypocretin neurons is thought to be responsible for the disease in human subjects ([7]; see [2]).

Structural and Functional Changes in the Brain

Hypocretin neurons in the lateral hypothalamus project to many different parts of the brain (see [8]). Hypocretin deficiency may thus lead to structural (and functional) changes in many different brain areas, as documented by grey and white matter differences between narcolepsy patients and controls in different subregions of the temporal and frontal cortex and other direct and indirect target areas of hypocretin neurons such as the ventral tegmental area, nucleus accumbens, hippocampus and others ([9, 10, 11, 12, 13], but see [14]). In addition, neurotransmitter function may be affected, with evidence of disruption of cholinergic and monoaminergic neurotransmission in narcolepsy patients [15]. Drugs affecting monoaminergic systems also affect single symptoms of narcolepsy. For example, activation or blockade of the cholinergic system exacerbates or reduces cataplexy, and anticholinergic antidepressant medication is used to successfully treat cataplexy. In addition, findings of altered receptor binding in the amygdala, globus pallidus, putamen and nucleus caudatus along with increased levels of monoaminergic metabolites also indicate neurotransmitter dysfunction in narcolepsy [15, 16], which may be linked to dysfunction of the hypocretin system [17].

Cognitive Deficits in Narcolepsy

Memory

Memory problems are among the most frequent complaints in self-reports of narcolepsy patients. In an early investigation, patients reported forgetfulness and problems in following conversations [18]. More systematic investigations in larger samples corroborated these first observations. Nearly 50 % of 180 patients from different continents (Asia, Europe and North America) complained about memory problems, predominantly affecting memory for recent events [19, 20]. In a large sample of narcoleptic sufferers, approximately 40 % of the patients reported at least mild memory problems [21].

In the light of these self-report data, it is surprising that memory assessment by standardised tests did not consistently yield significant impairments. Earlier studies, for example, did not find significant group differences on immediate and delayed recall for verbal and visual memory between narcoleptic patients and healthy control subjects [22, 23]. Mild memory deficits have been linked to impaired perceptual encoding [24]. Along similar lines, low performance on recall of a prose passage or word lists of patients compared to control subjects was observed at immediate recall, with no further loss across a 30 min retention period [25]. The results of the study by Naumann et al. [25] also suggested a modality-specific effect, with more pronounced problems for verbal compared to visual memory.

More recent investigations suggest potential mechanisms responsible for impaired memory encoding in narcolepsy. Using a face memory test, Allen and colleagues [26] reported reduced recognition performance in a single patient with narcolepsy. Functional neuroimaging during encoding revealed abnormally low activity in the frontal cortex, particularly the pre-supplementary motor area and the right middle frontal gyrus, and hyperactivity in the left and right hippocampus, compared to a large sample of healthy control subjects. Normalisation of both brain activity and performance under medication (modafinil) confirmed that the underlying pathology in narcolepsy indeed affects memory encoding. A related study found structural alterations in the hippocampus of narcolepsy patients. Both left and right hippocampal volumes were reduced compared to healthy controls [10]. This finding is in line with reduced hippocampal glucose metabolism in narcolepsy under rest [27] and has been linked to alterations in hippocampal projections

from the region of the medial septum/diagonal band of Broca, which controls hippocampal theta rhythm [28] and receives projections from hypocretin-containing neurons [6]. Memory performance was, however, not reduced in the patients and did not correlate with hippocampal volume [10]. It is thus conceivable that enhanced hippocampal activity during memory encoding, as observed by Allen et al. [26] in a single patient, reflects a compensatory strategy for reduced frontal activity and/or reduced hippocampal volume, which may or may not suffice to keep memory performance in the normal range. In summary, although there is evidence of reduced memory performance in narcolepsy sufferers compared to healthy controls, the impairments tend to be mild, which is in clear contrast to the subjective complaints of significant or severe forgetfulness. Patients may be able to enhance their cognitive function for brief periods of time by "investing" more attentional resources, which might lead to near-normal performance on memory tests in laboratory environments. It has also been proposed that laboratory tests are just not sensitive enough to detect the subtle deficits in narcolepsy patients [10]. In everyday life with its multiple and unpredictable distractions, the patients may fail to keep up a higher level of arousal for an extended period of time, leading to fluctuations in memory and—in some circumstances—to severe retention problems. At the same time, there is evidence of structural and functional changes in the hippocampus in narcolepsy, probably induced by the dysfunction of the hypocretin system.

Alternative mechanisms that might contribute to memory disturbances in narcolepsy are related to adverse effects of disturbed sleep patterns on memory consolidation on the one hand and to excessive daytime sleepiness on the other. If sleepiness as such is the underlying cause of memory dysfunction in narcoleptics, similar impairments would be expected for other sleep disorders such as obstructive sleep apnoea (OSA) and insomnia. Experimentally induced sleep deprivation should also lead to comparable deficits. For insomnia, however, the majority of studies did not yield memory impairments [29]. Findings on subjective sleepiness in insomnia are mixed. Some studies reported elevated levels of subjective sleepiness in insomnia, but others did not (see [29]). Objective measures such as the Multiple Sleep Latency Test (MSLT) imply that insomniacs are not particularly sleepy, as they do not fall asleep earlier than control subjects, when given the opportunity to sleep during the day. Since difficulty with falling asleep is one of the core symptoms of insomnia, the MSLT may, however, not adequately reflect sleepiness in insomnia patients.

Studies on the influence of disturbed nocturnal sleep on memory consolidation more consistently yielded impairments in insomnia. Backhaus and colleagues [30], for example, reported reduced memory for previously learned declarative material after a night of sleep in insomniac patients relative to controls, probably related to reduced slow-wave sleep in the patients. No such effect was seen for a procedural memory task, although other studies also found reduced consolidation for this type of memory in insomnia patients [31]. There is clear evidence of memory consolidation during sleep in healthy subjects. Plihal and Born [32] found sleep-induced consolidation for both declarative and procedural memory, related to different sleep stages. Declarative memory was enhanced after early sleep intervals (the first hours during the night) and procedural memory after late sleep. This finding reflects the differential involvement of rapid eye movement (REM) and non-REM sleep in consolidation for the different types of memories, with REM sleep supporting procedural memory and non-REM sleep, in particular slow-wave sleep, underlying declarative memory consolidation [33]. In accordance with this, naps solely containing non-REM sleep selectively enhanced declarative memory [34].

Nocturnal sleep is clearly disrupted in narcolepsy sufferers. The patients often fall asleep readily, but they wake up again after a brief period, and they have difficulty falling asleep again. In a 24 h day, overall many patients do not sleep longer than healthy subjects. Sleep-onset REM periods (i.e. the time period between sleep onset and the first onset of REM sleep which

typically occurs after about 90 min in healthy subjects) of less than 15 min are a diagnostic criterion for narcolepsy (see Nishino [35]). Transitions between states of wakefulness and sleep and between different sleep states are presumably disrupted in narcoleptics, with disruption of memory consolidation as a secondary effect. The pattern of memory problems reported above would, however, not support the hypothesis of deficient memory consolidation, since impairments appear to be most pronounced immediately after encoding, before consolidation has been established. On the other hand, there is recent evidence that disturbed sleep also affects memory encoding. A single night of total sleep deprivation led to a significant reduction of hippocampal activity during encoding and impaired retention of visual material studied under sleep deprivation [36]. Experimentally induced reduction of slow-wave activity and deep sleep was found to cause impaired hippocampal activation during encoding as well as memory deficits, despite normal total sleep duration [37, 38]. Moreover, van der Werf and colleagues [37] showed that impaired encoding specifically affected declarative memories. It is thus conceivable that the disturbed sleep patterns in narcolepsy rather than daytime sleepiness per se are responsible for impaired memory, mainly due to effects on encoding. This notion needs to be corroborated by further research in larger samples of narcoleptic patients.

Attention

As reported above, daytime sleepiness is one of the most striking symptoms in narcolepsy. The patients experience the urgent need to nap, and they frequently fall asleep despite their efforts to stay awake. It is not surprising that around 40 % of narcolepsy patients complain about concentration difficulties as a prominent cognitive impairment. In psychological terms, it is difficult to determine the nature of the problem which patients experience as concentration problems. The term concentration as used in everyday life encompasses a range of different processes and presumably most closely matches the psychological term attention or sustained attention. Attention is not a unitary concept and involves several distinct subcomponents, such as alertness, vigilance and selective or divided attention [39]. In contrast to the memory domain, subjective reports of concentration problems tend to be corroborated, at least partly, by the results of standardised neuropsychological attention tests.

Alertness refers to a subject's ability to engage in and sustain a state of preparation for the detection of highly relevant stimuli. Vigilance shares similarities with alertness, but usually refers to the maintenance of alertness over an extended time period. In narcoleptic patients, alertness/vigilance has frequently been assessed with the critical flicker fusion (CFF) test. This test provides a more indirect measure of attention. The CFF is the minimal frequency at which flickering lights induce the perception of a constantly flashing light. The higher the CFF, the more alert the subject is considered to be. Applying this measure, Levander and Sachs [40] reported lower alertness in narcolepsy patients than in healthy controls; alertness was enhanced by the administration of central stimulants. In a study by Rieger et al. [41], tonic alertness was assessed in terms of speed of responding to a target stimulus, and phasic alertness was assessed in terms of forewarned reaction times (RT), that is, the ability to increase the alertness level in expectation of the target stimulus. Narcolepsy patients showed slower RTs than controls, suggesting a general alertness deficit. Similar to healthy control subjects, however, narcoleptics responded faster in the phasic alertness condition, when the target was preceded by a warning stimulus. This pattern suggests that phasic alertness mechanisms are intact, while the general speed of information processing is slowed. Using the same task, Naumann and colleagues did not replicate the finding of generally slowed reactions in narcoleptic patients [25], while Bayard [42], analysing tonic and phasic alertness separately, found slower and more variable responses in narcoleptic patients with cataplexy, while patients without cataplexy were unimpaired. Moreover, both reaction times (RTs) and variability increased in the

second task block compared to the first. Along similar lines, a recent study yielded impairments in narcoleptics based on the psychomotor vigilance task. The deficits were comparable to those in patients with hypersomnia but more severe than in patients with insufficient sleep [43].

The sustained attention to response task (SART) has also been administered to assess vigilance in patients with sleep disorders. This task requires subjects' fast responses to the appearance of all digits on the screen with one exception, for which the response needs to be withheld. It was shown that the overall error score in this task (omission and commission errors) separates narcolepsy patients and controls as well as measures of sleepiness do [44]. While sleepiness and performance on the SART did not correlate significantly, comparable performance levels were found for different disorders involving increased sleepiness [45]. It has to be noted, however, that the SART also taps into processes related to selective attention as in Go/NoGo tasks, questioning whether the underlying deficit is related to a basic or "higher" attentional function (see below).

The assessment of the ability to sustain attention across an extended time period yields a more consistent impairment pattern in narcolepsy patients. In a study which applied the CFF test every 15 min for a total duration of 10 h, general alertness levels did not differ between patients and controls, but patients showed a significantly increased performance variability throughout the day [46]. This pattern was interpreted in terms of a high level of alertness fluctuations over time, a finding which has been corroborated by several other studies. Similar to patients with obstructive sleep apnoea, narcoleptics perform poorer than controls on driving simulation tasks [47], with increasing problems with increasing duration of the assessment [48]. Comparable vigilance impairments have been reported for a variety of other tasks, which required high levels of attention up to 1 h ([49]; see [50]). Patients may be able to compensate alertness problems when performing a task for a brief period of time in the range of seconds or a few minutes. However, such compensatory mechanisms cannot be upheld for an extended time period, and performance differences between patients and controls become more pronounced with passing time. In addition, performance on vigilance tasks tends to be more variable in narcolepsy patients, reflecting high alertness fluctuations [51].

Although the data basis is as yet sparse, more demanding attention mechanisms, such as the ability to efficiently divide attentional resources between different tasks at hand, appear to be more severely affected than alertness. Two studies administered the same divided attention task which requires subjects to simultaneously monitor both visual and auditory stimuli and to respond to target stimuli in both channels. In the earlier study, narcoleptic patients missed more targets and showed longer and more variable RTs than control subjects [41]. Slow RTs were, however, also observed during task conditions in which the patients had to respond to visual or auditory stimuli only and RT slowing was thus not specific to the divided attention condition. A tendency for reduced accuracy in the divided attention compared to the single stimulus condition, on the other hand, would support the hypothesis of a specific divided attention impairment. In the more recent study, there was evidence for a speed-accuracy trade-off in the patients, with intact accuracy scores being accompanied by prolonged RTs [25]. As was reported in a recent placebo-controlled crossover design study, intranasal hypocretin does not only reduce the number of wake-REM sleep transitions and the total REM sleep duration but also enhances divided attention performance in narcoleptics, adding evidence that divided attention is affected by the underlying pathology in narcolepsy [52].

Other attention subcomponents, which share features with "executive functions" (see next section), have also been assessed in narcoleptic patients. Considerable between-study differences in the tasks used and also in the labelling of the attentional subcomponents often do not allow a direct comparison of the results. The majority of the studies reported significant impairments in narcoleptic patients. Visual search tasks, also referred to as focused attention, yielded evidence of speed-accuracy trade-offs, with one study reporting reduced accuracy and normal RTs [53],

while another found the opposite pattern: intact accuracy and prolonged RTs [41]. Similarly, Naumann et al. [25] observed slower performance speed of narcoleptics on a cancellation task, while performance accuracy did not differ from control subjects. For selective attention assessed with a Go/NoGo task, significant impairments in terms of slowed responding were seen in narcolepsy patients compared to patients without cataplexy and to controls [42].

Taken together, the available evidence does not support the notion of a general impairment of attentional functions in narcoleptic patients. Attention appears to be particularly affected on tasks (a) which require cognitive processing across an extended period of time or (b) which are characterised by increased information processing demands such as the ability to focus or to divide attentional resources. In situations with relatively low demands as in simple RT tasks, narcoleptic patients seem to be able to compensate for arousal fluctuations by phasic increases in alertness which can be upheld for a short period of time. In a similar way, patients might be able to cope with more demanding tasks, but the need to use effort to keep up high arousal levels leads to speed-accuracy trade-offs, with the patients either performing less accurately or more slowly than control subjects. Finally, some of the tasks used for the assessment of attentional functions as Go/NoGo tasks and the SART also tap into processes like inhibition that are typically seen as higher cognitive or executive function. Thus, impairments cannot always be ascribed to attentional functions per se.

Executive Functions

The term executive functions refers to superordinate cognitive control processes, which allow the efficient coordination of information processing and action control [54, 55]. Executive functions do not describe a unitary process, but generally come into play when, for example, limited attentional resources have to be allocated to different sensory input channels or when different actions have to be coordinated during multitasking conditions. Executive control is also necessary for the temporary inhibition of predominant, but currently inadequate, response tendencies or when information has to be constantly updated as in working memory tasks. The interest in executive functions in narcoleptic patients has increased in recent years. One of the most recent studies [42] focused on three independent executive function components which had been outlined in a model by Miyake and colleagues [56]: information updating, set shifting/cognitive flexibility and inhibition.

In the category of information updating, the assessment of working memory, i.e. the ability to hold and to process new information for a limited period of time, did not consistently yield group differences between narcoleptic patients and control subjects, at least when simple digit backward tasks were administered [22, 23, 25, 50, 57]. Naumann et al. [25] did, however, observe prolonged RTs in narcoleptic patients in a 2-back task, while performance accuracy was intact. A recent investigation corroborated this finding in narcolepsy patients with cataplexy [42]. Moreover, this study revealed more variable RTs and higher error rates in the patients compared to controls. Error rates were also enhanced in narcoleptics without cataplexy.

The results for cognitive flexibility are also mixed. For example, verbal fluency tasks have been administered as a measure of rule-guided cognitive search and flexibility. While one recent study did not find impairments in all subtests [57], a previous study did [25]. Importantly, a deficit in cognitive flexibility would be reflected in a disproportionate impairment in a switching condition, which requires subjects to alternate between two categories. Such a pattern was found in neither of the two studies. Instead, Naumann et al. [25] reported a significant impairment of narcolepsy patients on the Hayling Sentence Completion test, with the patients needing longer to retrieve suitable words from memory and having more difficulties in inhibiting a predominant but in the current context unsuitable response tendency. Although the study by Rieger et al. [41] focused on attention, the results derived from a flexible attention task are also of interest for the

executive function domain. In this task, subjects are presented two stimuli, a digit and a letter, each being presented on one side of the screen, left or right. Subjects have to indicate the location of the target stimulus with a left or right button press, but the target—letter or digit—changes from trial to trial. Thus, performance on this task would reflect cognitive flexibility. Narcolepsy patients did not only take longer to perform this task, they also made more errors. It remains to be clarified, whether this problem can be interpreted in terms of an increased susceptibility to interference. Applying the same task, RTs were longer in narcoleptics with cataplexy relative to patients without cataplexy and to healthy controls [42]. Both groups of patients showed more variable RTs than controls and an elevated number of errors, suggesting that flexibility was impaired in narcolepsy, at least to some degree, irrespective of cataplexy. Using different tasks, two other recent studies did [58] and did not [57] report problems with cognitive flexibility in narcolepsy, so that the overall picture remains inconsistent.

As was already noted in the section on attention, some attention tasks also tap into executive processes. For example, Go/NoGo tasks are often referred to as measures of selective attention, while they also assess the ability to inhibit irrelevant stimuli. Different versions of these tasks consistently yielded at least mild impairments in narcolepsy patients, starting from simple tasks with one go- and one nogo-stimulus each [42], to the SART, where one nogo-stimulus is shown in the context of several go-stimuli [44], and finally to complex tasks, in which go- and nogo-stimuli are defined by feature combinations [57].

Despite rising interest in this domain, the data basis for executive function assessments in narcoleptic patients is still small, and further research is clearly needed, before firm conclusions can be drawn. Recent research suggests that narcoleptic patients do suffer from some degree of executive function impairments, especially in the domain of inhibition. By definition, executive function tasks are demanding. It is conceivable that the mechanism of breakdown shares some similarities with the problems observed during the performance of demanding attention tasks. Narcoleptic patients may have to allocate a considerable proportion of their attentional and cognitive resources to the continuous maintenance of alertness. The resulting reduction of processing resources may not suffice to perform demanding tasks as fast and as accurately as control subjects. Potential mechanisms for executive function impairments will be discussed in more detail in the last section of this chapter.

Decision-Making, Reward-Related Behaviour and Emotional Processing

Findings of hypocretin neuron projections to areas involved in reward-related behaviours such as the ventral tegmental area, nucleus accumbens and ventral striatum have led to the proposal that, apart from promoting wakefulness, one of hypocretin's functions may be related to reward processing and decision-making [8, 59, 60]. Accordingly, Ponz et al. [61] observed altered activation patterns in reward-associated brain areas in humans with narcolepsy applying functional neuroimaging. Activations in the ventral midbrain and the ventral striatum were reduced in the patients relative to controls during reward anticipation and reception, respectively. Amygdala and dorsal striatal activations were enhanced for positive outcomes. Other, more recent studies showed that decision-making is affected in narcoleptics, which appears to be in accordance with the imaging findings. Consistent deficits were seen for decision-making under ambiguity as assessed by the Iowa Gambling Task [57, 62–64], whereas no changes compared to control subjects were seen for decisions under risk [62, 64, 65]. Interestingly, the impairment for decisions under ambiguity did not depend on medication with psychostimulants, as both treated and untreated patients scored lower than controls. Changes in reward processing have also been linked to other types of reward-associated behaviours in narcolepsy. For example, a higher incidence of binge eating or other eating disorders [65, 66] and depressive symptoms was found in narcoleptic patients [67]. Other potential associations

with impulsivity, gambling or substance abuse could not clearly be established (see [63]).

Finally, the specific deficit in the Iowa Gambling Task has been discussed in the context of findings on partly differential neural mechanisms for decisions under ambiguity and decisions under risk, with the former involving also limbic structures such as the amygdala (see [62]). As pointed out above, enhanced amygdala activation was seen for reward processing in narcolepsy [61]. In another study, Ponz and colleagues corroborated altered amygdala function in narcoleptics, albeit this time with reduced activations compared to controls in an aversive conditioning task [68]. These and other findings strongly suggest that the amygdala plays an important role in the pathophysiology of narcolepsy. However, findings on the processing of emotional stimuli, one of the core functions of the amygdala, are inconclusive. For example, altered reactions to emotional stimuli have been reported by Tucci et al. [69], while there was no difference between patients and controls on the recognition of emotions in facial expressions [70].

Mechanisms Responsible for Cognitive Dysfunction in Narcolepsy

Although the empirical database on cognitive function in narcolepsy is still sparse and although there are considerable between-study inconsistencies, the general pattern does seem to indicate that the majority of narcoleptic patients suffer from cognitive problems. Attention appears to be the most affected cognitive domain, but recent evidence also involves memory, executive function and decision-making impairments.

On the one hand, the finding of impaired attention complicates the interpretation of results from other cognitive domains, since adequate attentional functions are a prerequisite for successful performance on any kind of task. Attentional impairments emerged particularly during the performance of demanding or longer-lasting tasks, which led to the suggestion that patients need to allocate a considerable proportion of their attentional resources to the maintenance of alertness [25]. The remaining resources may be sufficient for the performance of short and simple but not complex or demanding tasks. This hypothesis would thus link the cognitive problems in narcolepsy mainly to elevated levels of sleepiness as it would involve not only attentional problems but also memory or executive dysfunction. In an attempt to control for the effect of sleepiness, healthy subjects were sleep-deprived to the same level of sleepiness as narcolepsy patients, which was achieved after 36 h of sleep deprivation, i.e. the subjective sleepiness ratings were comparable [71]. Control subjects still outperformed the narcolepsy patients on an attention task. Although this result does seem to argue against sleepiness as the primary cause of cognitive problems in narcolepsy, it is possible that subjective ratings do not reflect the real level of sleepiness in narcoleptics. More objective sleepiness measures such as the MSLT do in fact show that narcolepsy is accompanied by increased levels of sleepiness [72], whereas subjective measures might underestimate the level of sleepiness.

The neuropsychological profile of narcoleptic patients might thus be at least partly linked to the disruptive effects of sleepiness. In fact, sleepiness induced by sleep deprivation in healthy human subjects is associated with changes in task-related brain activity in distinct cortical regions. Increased activity in frontal and parietal brain regions in different attention and memory tasks was interpreted in terms of "compensatory recruitment" [73–76]. Chee et al. [77] examined neural activity in rested and sleepy subjects on lapses of attention in a selective attention task. Compared to lapses after a normal night of sleep, lapses in sleep-deprived subjects were associated with decreased frontoparietal, visual cortex and thalamic activity. Most interestingly, the neural responses associated with very fast correct responses did not differ between rested and sleep-deprived subjects. Compensatory recruitment may thus lead—from time to time—to "normal" or even increased activations of task-related brain areas, enabling the subject to perform in the normal range.

As was outlined above, structural and functional changes in different brain regions have been reported in narcolepsy, providing a potential underlying mechanism for cognitive deficits. With respect to memory performance, the association between altered hippocampal structure and function and performance in narcolepsy still has to be determined in detail by future research. One mechanism directly linking hypocretin to memory relates to the disturbed sleep patterns caused by hypocretin deficiency (see above). While initially it was thought that slow-wave sleep is responsible for consolidation, evidence is accumulating that it might also underlie encoding, especially for declarative memories (see above), which could explain the encoding deficits frequently seen in narcolepsy.

The pattern of hypocretin neuron projections also suggests a role in reward processing and thus decision-making [8]. For example, the dopamine neurons in the midbrain and the ventral striatum including the nucleus accumbens, both belonging to the so-called reward system of the human brain, are targeted by hypocretin neurons, as was described above. Accordingly, decision-making problems are quite consistently found in narcoleptics.

In order to examine the relative contributions of hypocretin deficiency and subjective sleepiness, the comparison of narcolepsy patients with and without cataplexy is a promising approach, as only the former show very low levels of hypocretin [78]. Only few studies to date systematically examined these two groups of patients in comparison to healthy controls. One such study on executive attention revealed that simple attentional functions were specifically impaired in patients with cataplexy, whereas more complex functions involving aspects of executive control were impaired in both types of patients [42]. As the two groups were matched according to MSLT scores, sleepiness might be the underlying factor for these aspects of executive function. However, more research on similarities and differences in the neurobiological mechanisms of narcolepsy with and without cataplexy is clearly needed.

To summarise, cognitive impairment in narcolepsy seems to be at least partly caused by neural mechanisms triggered by and compensating for sleepiness. It is likely, however, that factors more directly related to the disorder and its pathology such as hypocretin deficiency in the hypothalamus and its effects on other brain areas and neurotransmitter systems also contribute to the cognitive disturbances.

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Psychoanalysis and Narcolepsy

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J.F. Pagel

Psychoanalysis and Narcolepsy

Psychoanalytic theory reasonably proposes that sets of mental dynamics underlie cognitive functioning. This theory, first published in 1895 in a series of papers by the Viennese Neurologist Sigmund Freud, went further to propose that blocks and dysfunctions in these mental dynamics led to the various forms of psychiatric illness [1].

Just a decade before, in 1880, Gelineau had published the first medical description of narcolepsy. He referred to the illness as a "neurosis" [2].

Narcolepsy and psychoanalysis were discovered/developed at almost the same time, in the same area of the world. They have a long, bidirectional, sometimes complementary, yet somewhat dysfunctional history of interaction. Freud's first book on dreaming, published in 1900, startled and changed the fields of both neurology and psychiatry and led to a psychoanalytic fascination with the dreamlike epiphenomena of narcolepsy [3]. Narcolepsy as a disease is phenomenologically defined by sleepiness and dreamlike epiphenomenon. Freud's theory was developed during an era in which sleep was often viewed as "a nirvana state of the intrauterine life, while awakening symbolizes painful birth" [4]. The new physiologic insights into narcolepsy were incorporated into psychoanalytic theory. The dreamlike epiphenomenon of narcolepsy seemed to support this association suggesting the possibility that dreams might function as proposed by Freud and others as "protectors of sleep" [3]. If dreaming protected sleep and narcoleptics with their bizarre dreamlike behaviors were extraordinarily sleepy, then narcolepsy was a disorder reflecting disordered mental dynamics. Among psychoanalysts, dreams were often perceived as equivalent to the dream-associated epiphenomena of narcolepsy. When defined, dreams were considered to be similar to these bizarre, hallucinatory behaviors that occurred in both waking and sleep [5].

Post-Freud, psychoanalytic approaches were among the primary therapeutic modalities utilized in the treatment of patients diagnosed with narcolepsy. Narcolepsy, with its symptoms of extreme sleepiness developing during the psychologically and sexually stormy years of adolescence, was perceived psychoanalytically as an illness based on the psychodynamics of sexual repression. Despite the growing evidence that narcolepsy had a physical and neurological basis, this psychosexual perspective of narcolepsy patients and their appropriate therapy continued

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in major published presentations on the diagnosis until the late twentieth century. Remnants of that psychoanalytic perspective of narcolepsy persist today in perceptions that affected patients are lazy, misbehaving, and sexually engrossed teenagers, poorly motivated, and prone to psychiatric disorders.

The discovery of rapid eye movement sleep (REMS) occurred in the mid 1960s during a time in which Freudian psychodynamics dominated the integrated fields of neurology and psychiatry. In 1975, Hobson and McCarley published their theory of activation synthesis and extended psychoanalytic theory into the modern era by proposing that all cognitive behaviors, both conscious and nonconscious, reflect the biological and physiological activity occurring in the central nervous system (CNS) [6]. If as many understood at that time, REMS was equivalent to dream sleep, the cognitive activity of dreaming reflected the electrical EEG, neuroanatomical and neurochemical activation occurring in the CNS during REMS. Equating REMS with dreaming, despite the large volume of evidence to the contrary, was belief based, in part, on Freudian mental dynamic views of dreaming as an expression and "activation" of the primitive aspects of the brain. REM sleep/dreaming was considered to be a psychodynamically primitive state of CNS activation parodying the psychoanalytic "Id." This requirement that REMS = dreaming became a conceptual framework at the basis of almost all neuroscientific theories of consciousness. This perspective, of REMS as the neuroscientific and psychoanalytic equivalent of dreaming, persists in almost all of today's widely accepted theories of neuroconsciousness.

These perspectives of psychoanalysis are not just historical artifacts. They continue to affect research, patient care, and social perspectives toward dreaming and patients with the diagnosis of narcolepsy. Narcolepsy, as a diagnosis, provides an excellent case example for the effects of a century of acceptance of psychoanalytic theory on neurology and psychiatry as well as the persistent effects of that perspective on the epistemology of sleep and dream science.

Psychoanalytic Narcolepsy

Narcolepsy is a very strange illness—as strange as either epilepsy or schizophrenia, illnesses that through much of human history were viewed spiritually as evidence of demons or the manipulation of contrary gods and witches. The diagnosis of narcolepsy, included from the very first, the bizarre dreamlike phenomena of sleep-onset hallucinations, sleep paralysis, and cataplexy. To many, this illness seemed to be clearly appropriate for treatment with the new psychoanalytic techniques of the early psychoanalysts. Freud addressed sleep paralysis in *The Interpretation of Dreams*, postulating that the sensation of inhibited motor movement represented a "conflict of will" [1]. It is unclear whether Freud himself treated narcolepsy. Rumors of an unpublished and untranslated paper persist.

Freud was not developing his theories in a vacuum. Gelineau (1880) in describing narcolepsy as a "neurosis" placed it clearly within the purview of psychoanalysis [2]. At the time diseases now known to have clear neurological basis, such as epilepsy, were classified among the psychoses and neurosis.

Among Freud's insights into the association between sleep and dreaming was the concept of dreams as protectors of sleep: "all dreams are in a sense dreams of convenience: they are the purpose of prolonging sleep instead of waking up, because they are the guardians of sleep and not its disturbers" [7]. "Thus the wish to sleep, must in every case be reckoned as one of the motives for the formation of dreams and a successful dream is the fulfillment of that wish" [8]. Based on this psychoanalytic perspective, sleep was often described as an escape mechanism [9]. The view of sleep as a temporary escape from harsh reality into a memory of protected intrauterine nirvana would lead to a series of psychodynamic explanations for narcolepsy as a disease of psychological regression [10, 11]. The concept of sleep as "momentary suicide" was adopted by some schools of psychoanalytic thought [12]. Jones (1936) highlighted the potential role of psychological factors in the etiology of narcolepsy

in a 22-year-old patient: "It seems logical to suppose that the sleep attacks have developed from the previous states of dissociation. The faints, the cataplexies, amnesias and sleeps may then be regarded much the same in function, in giving the patient a temporary escape from reality" [13].

Dream analysis is intrinsic to the therapeutic process of psychoanalysis. Narcoleptics, with frequent and bizarre dreamlike experiences associated with their illness, seemed to be ideal subjects. In a Freudian sense, reported dreams are the process by which we deal with or at least review within the shelter of our mostly unconscious dream state, repressed and suppressed experiences and emotions, as well as/or in light of all our positive and negative experiences and memories. Freud posited that repressed feelings, especially of loss, may inspire either repression or sublimation, which could be utilized by a therapist to foster higher cultural achievement [14]. For the Freudian psychoanalyst, dreams include repressed memories and emotion that can be brought into waking consciousness through the techniques of free association and dream analysis. Once the dream is reported and available for waking analysis, the dream can provide useful insights into the patient's and the therapist's psychodynamics. Dreams were viewed somewhat differently by Carl Jung, with emphasis on shared symbols and archetypes. In a Jungian sense, dreams can "facilitate 'transcendent' function by integration of opposing trends to work toward an ideal good…the unconscious expression of a desire for wholeness is found in dreams" [15]. Jungian psychoanalysts focused on the symbolism and fascinating condensation of ideas to be found in dreams, using the content of impactful, significant dreams in the attempt to understand an individual's personality and emotional conflicts [16].

Treating Narcolepsy with Psychoanalysis

In the early 20th century, treatment options were limited for individuals diagnosed with narcolepsy. It is not surprising that psychoanalysis was used to treat narcolepsy, particularly during an era in which alternative treatment modalities for narcolepsy included electroshock therapy, insulin-induced hypoglycemic coma, and psychosurgery [17–19]. Narcolepsy was often managed by psychological methods including analytic explorations into the background causes for the attacks of unwanted sleep [20]. Narcolepsy was viewed as one of the pathological states of sleep and consciousness disturbances, "basically…a form of neurosis to be treated by psychotherapeutic means" [21]. Before and after the use of activating medications for narcolepsy became accepted in the 1930s, many narcoleptics underwent extensive psychoanalysis of their bizarre dreams and their dream-associated behaviors.

Freud proposed that psychic structures and their dynamics could be inferred from the psychoanalytic interpretation of dreams. This information could then be used to develop a treatment plan for psychiatric symptoms. The extraordinarily bizarre dreams of narcolepsy patients provided fertile ground to be utilized in psychoanalytic therapy for the illness. It became widely accepted that for narcolepsy, "…the psychogenic element is large and important, and the condition must properly be regarded as basically a form of neurosis to be treated by psychotherapeutic means" [21]. Among psychotherapists, narcolepsy was often viewed as a disease of repression: "repression and dissociation are at the root of the disorder and reintegration alone can effect a true cure" [21]. In case reports, narcolepsy was postulated to occur in particular patients with "difficulties in realistic adjustments in personal relationships with others" [22]. The origin of that repression could be parental conflict: "…the passive experience of the death of the patient as retribution for a death wish against a hated parent or person" [23]. However, the psychodynamic bases for the symptoms of narcolepsy were often viewed to have an origin based on interior sexual conflicts. Obendorf in 1916 indicated that, "…uncontrollable attacks of drowsiness were interpreted as an escape from intense shame attendant upon a masturbation conflict in which fantasies of incest with the mother played an important role. The drowsy spells at the same time provided a

substitute for autoneurotic activity" [24]. Schulte in 1942 proposed that the symptoms of narcolepsy occurred secondary to "homosexual inversion" [25]. Coodley in 1948 noted that for one of his patients: "His narcoleptic attacks may be conceived of as regressive phenomena, the result possibly of the unconscious wish to return to an incestuous relationship with his sister during a somnolent state." Coodley went further to postulate that cataplectic attacks were, "a version of, "self-castration, in which the entire body—equated with the penis—goes limp" [26].

Such perspectives have extended into the modern era, "The psychogenic fraction of narcolepsy is centered about unacceptable impulses and defenses they provoke. In cataplexy episodes, sexual and aggressive actions and fantasies are blocked on a neuromuscular level. A sleep attack is far more complicated and some aspects may be compared to a classical psychoneurosis because the symptom provides not only defense but simultaneous disguised gratification of a wish" [27]. More recent studies into the dreams of narcolepsy patients (1976) utilize the same rationale: "Data obtained from a study of dreams of narcolepsy patients clearly demonstrates the force of sexual drive and aggressive instinct in these individuals. These drives are so strongly suppressed and guilt ridden during wakefulness that the representations and affects that could express these drives do not attain consciousness. In certain circumstances, however, that which is repressed and suppressed tends to reappear at the conscious level and it is this situation that the narcoleptic or cataplectic attack appears" [28].

It seems appropriate to point out that only a subset of narcolepsy patients were treated with psychoanalysis. There are major psychoanalytically based texts of psychiatry that do not even mention the diagnosis of narcolepsy or cataplexy [16, 29]. Gill in 1941 noted in the Lancet: "There is no case yet on record where the whole picture has been altered or improved materially by psychotherapy, even deep paralysis" [30]. Some psychotherapists began to reevaluate the psychogenic origins of the state, frustratingly suggesting that the psychodynamic of narcolepsy might rather be secondary to the patient's refusal to listen to their therapist: "The narcoleptic symptoms seemed to function in some way to protect the patients from a threatened resolution of their difficulties along realistic lines which they are not prepared to accept" [16]. However, today, community and medical conceptions of narcolepsy continue to be affected by its psychogenic history. Patients and families may view the diagnosis as one based on suppressed, guilt-ridden, sexual drives. This conceptual association can contribute to social and medical handicaps for some narcolepsy patients [31]. Narcolepsy patients complain of physicians and cohorts demonstrating a lack of understanding and on occasions taking a moral stance in labeling them as "lazy, unable to work, or unable to face the vicissitudes" [32].

Narcolepsy and Neuroscientific Theory

In 1964, Rechtschaffen and Dement determined that in patients with narcolepsy associated with cataplexy, both sleep paralysis and hypnagogic hallucinations occurred in association with REMS periods. This finding led to their hypothesis that consciousness could best be described as occurring during three relatively independent neurophysiological states—wakefulness, sleep, and the paradoxical state of REMS [33] (Fig. 17.1). The theory of activation synthesis built on this model postulates that all cognitive behaviors, both conscious and nonconscious, reflected the biological and physiological activity occurring in

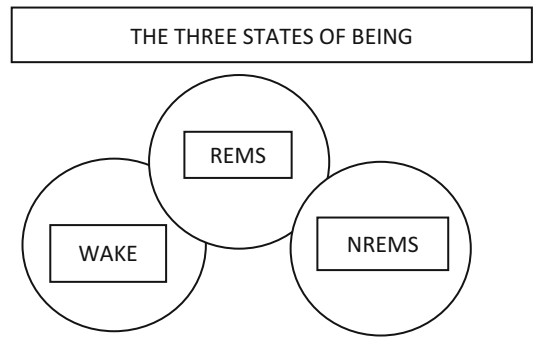

Fig. 17.1 The hypothesized three states of consciousness (Rechtschaffen and Dement 1969 [33])

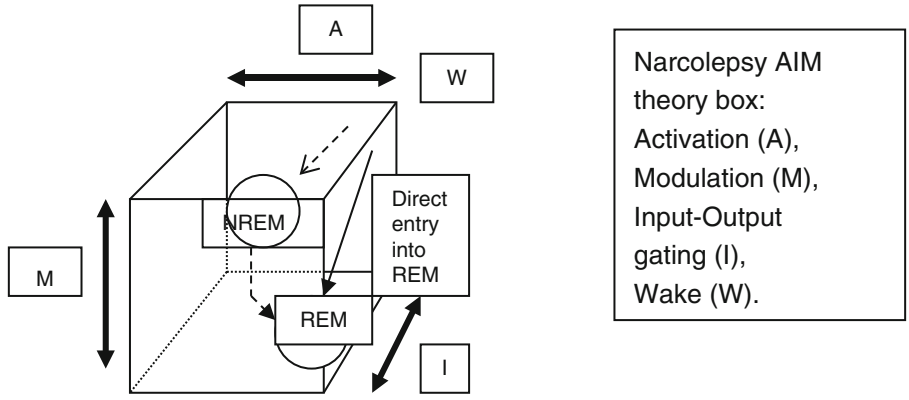

Fig. 17.2 AIM theory. Disorders related to input–output gating: narcolepsy—"Instead of traversing the NREM domain of the AIM conscious state space (*dotted line*) en route to REM sleep, patients with narcolepsy are pulled directly into it. They can thus experience all or part of REM sleep behavioral complex at the edge of waking. This is why they have sleep-onset REM periods" (Hobson 1999 [41] p. 201)

the brain [9]. The primary proof for this theory was the apparent finding that REMS was the CNS dreaming state. The authors proposed that the cognitive activity of dreaming was based on CNS activation developed in the brain stem during REM sleep. This primitive electrophysiological state of activation is integrated with upper cerebral cognitive processes to create dreams. This postulate remains at the basis of current neuroscientific theories of consciousness including activation synthesis and the derivative offspring: activation-input-modulation (AIM), reverse learning, neural net theory, search attention theory, and most recently protoconsciousness theory [34, 35]. These theories are all based on the postulate that dreaming is equivalent to or has a special relationship with REMS. These neuroconsciousness theories have been extended to levels of exceeding complexity. If REMS is dreaming, animal models and brain scanning studies of REM sleep can be utilized to describe the cognitive state of dreaming. A large body of work has utilized brain slice studies, fMRI, PET, SQUIB, and micropipette techniques to experimentally describe the neuroanatomical, neurochemical, electrophysiological, and neuropsychiatric characteristics of REMS. Much of this work is presented as dream research [36]. Psychodynamically based interpretations of narcolepsy-associated symptoms, particularly sleep paralysis, continue to be published [37, 38]. The dream-associated epiphenomena of narcolepsy continue to be considered as representative of the dreaming state [39, 40]. The conception of REM dreaming as bizarre and REM sleep as a psychodynamically primitive state of CNS activation parodying the psychoanalytic "Id" persists in modern versions of activation-synthesis theory including AIM [41] (Fig. 17.2).

Psychodynamic, neuroanatomical, and neurochemical postulates as to the pathophysiology of narcolepsy have been based on this theoretical construct [41]. A research paradigm was developed, called the narcolepsy approach paradigm (NAP), and used to study dreaming associated with sleep-onset REMS periods [42]. This model was then utilized as a model for the psychological and physiological characteristics of the dream state. Narcolepsy-associated postulates based on this model include:

1. "In narcolepsy full blown, REMS replaces waking consciousness" [41].
2. "The emotionally based symptoms of narcolepsy, temporal lobe seizures, and normal dreaming result from unchecked paroxysmal discharges of limbic lobe neurons" [41].
3. "Narcolepsy exaggerates the normally partial dissociations of waking and dream consciousness. While having hallucinatory experiences within dreams is analogous to

psychosis, having them while awake is identical to psychosis" [41].

4. "Narcolepsy is a disorder of the reticular activating system, the system controlling REMS and the system considered to be the primary center for the control of sleep and wakefulness" [43].

The status of many of these postulates based on AIM theory can now be compared to actual data based on PET and fMRI scans as well as recent genetically based research into the neurochemistry and neural interconnections involved in the disease state of narcolepsy. This data demonstrates that the neurochemistry and neuroanatomy of narcolepsy and cataplexy may vary markedly from many of such postulates based on neuroconsciousness theories such as AIM.

Narcolepsy-Based Psychoanalytic Perspectives of Dreaming

The association between narcolepsy and dreaming has altered the definition of dream. Based on the perception that the REMS phenomena of narcolepsy are equivalent to dreaming, the phenomenology of narcolepsy-associated dreamlike epiphenomena has been applied to our understanding of dreaming in normal individuals. Both psychoanalysts and neuroscientists have stretched the definition of dreaming to include the REMS-associated states of narcolepsy, defining dreams as bizarre, hallucinatory mental activity that can occur in either a sleep or a wake state [5]. This has become the most generally accepted psychoanalytic definition of dreaming. The dreams of narcoleptics due to their association with hypnagogic hallucinations and sleep paralysis can on some scales be considered more "bizarre" than other dreams [39, 44–46] (Table 17.1). Today, there are some authors who suggest that mentation occurring during sleep that does not meet such "bizarreness" criteria is not dreaming. It is suggested that this non-bizarre mentation be referred to as sleep-associated thought rather than as dreaming [47]. Based on this perspective, dreaming, defined as bizarre hallucinatory mentation, occurring outside REM sleep indicates that REM sleep must occur covertly outside what is polysomnographically defined as REM sleep. This perspective requires that both sleep and sleep stages be redefined, so that when dreams are reported, REMS is considered to have occurred. This theory would account for the dream reports from other sleep stages and for dreamlike mentation reported while awake. Both could be viewed as evidence for "covert" episodes of REMS. It should, however, also be noted that, based on the most widely accepted scale for bizarreness developed by primary supports of "covert" REMS theory at Harvard, sleep-onset hallucinations score as less bizarre

Table 17.1 Hypnagogic hallucinations. Formal characteristics, assessment of bizarreness, and thought

Formal characteristics
• Primarily visual hallucinations perceived as potentially real
• Coherent dream stories
• High recall
• Potential lucidity
• Impression of falling (association with sleep starts)
• Intense anxiety (association with PTSD and hypnagogic sleep paralysis)
• Recurrent (reality based in patients with PTSD)
Bizarreness
[Hobson scale]
Discontinuities—high
Incongruities—low
Uncertainties—low
[Hunt scale]
Hallucinations—high
Clouding/confusion—high
General—high (emotion, bizarre personification)
Rational
Thought processing [Wolman and Kozmova]
• Analytical—low
• Perceptual—high
• Memory and time awareness– high
• Affective—high
• Executive—low
• Subjective—high
• Intuitive/projective—low
• Operational—low

Bizarreness scale assessment based on Hobson (1987) [44] and Hunt (1989) [45]; rational thought processing assessment based on Wolman and Kozmova (2006) [46]

than REMS dreams due to their short length and less developed story lines [44] (Table 17.1).

Since dreams are almost universal cognitive experiences, there has been a clear tendency for each individual to presume that what he or she considers to be a dream is the same for each other person. Unfortunately, what is a dream to someone with psychoanalytic training (bizarre mentation in either sleep or wake) is antithetical to the individual with a background in the study of sleep (any mentation reported as occurring in sleep) [5, 48]. In dream research, this has been a particular problem, since most authors fail to define their definition for the topic of study in their work [49]. This has led to a confused situation in which the topic of study in one paper (dream—undefined) while identified in the same manner is actually a totally different topic from another paper addressing what is apparently the same topic (dream—undefined).

Some neuroconsciousness theorists have extended the postulate that dreams are bizarre, hallucinatory mental activity to support the theory that dreams are a form of visual hallucination. Dreams have some qualities of hallucinations, in that they feel like what is unfolding in the dream is real and happening to us or to someone else that we are observing. This perspective is based on formal characteristics of the dreaming process that can be considered hallucinatory: visual and motor hallucinations, the delusional acceptance of hallucinoid experience as real, extremely bizarre spatial and temporal distortion, strong emotion, and the failure to remember—findings that may be more characteristic of sleep paralysis and hypnagogic hallucinations than normal dreaming. These authors suggest that the dream is a hallucination because the dreamer has a "delusional" acceptance during dreaming of the dream experience as being real [41]. This view of dreaming as hallucinatory and delusional has contributed to the view of dreaming as a valid model for psychosis.

The concept of dream as hallucination has been widely incorporated into modern dream theory. Vogel (1960) postulates that "the purpose of the pathological sleep is not only to defend, but also to provide the ego repression necessary for hallucinatory wish fulfillment through dreaming" [50]. If dreaming is basically a perceptual hallucination, it is easier to consider dreaming as a simple, meaningless perceptual state based on primitive brain stem activity (REM sleep) of the self-referenced mind [41]. Viewed as a process of perceptual hallucination, dreaming can be postulated to be one of the processes utilized by the CNS during sleep to detoxify the system of unwanted memories of potentially pathological nature such as obsessions, hallucinations, and delusions. The hallucination theory of dreaming has been so utilized in supporting the "erasure" theory of Crick and Mitchison (1983) [51]. Extending this view to its logical conclusions, sleep itself can be considered as a state independent of waking conscious, a state of unconsciousness or coma, as well as a state of perceptual dislocation. In other words, sleep could also be considered a hallucinatory state in which actual perceptions (external objects) are negated by the CNS perceptual system [52]. For patients with narcolepsy, this perspective can lead to misdiagnosis and less than optimal care when inappropriate antipsychotic medications with extensive side effects are used to treat their schizophrenic-like hallucinations [53].

Discussion

The use of psychoanalysis as a treatment option for narcolepsy was based on theory. Psychoanalysis was also less likely to induce harm for the patient than some of the other available treatment options in the early twentieth century such as psychosurgery and electroshock therapy. There is little evidence, even based on anecdotal case studies, that psychoanalysis led to an improvement in patient symptoms or affected the course of the illness for individual patients in any positive fashion. In the current era, narcolepsy is clearly a neurological illness with well-defined genetic, electrophysiological, and neurotransmitter basis. For more than a generation, psychoanalysts used dream interpretation to make diagnoses and form treatment plans. In an era in which there were few alternative

treatments available for psychiatric illness, psychoanalysis became the treatment of choice. Unfortunately, the psychoanalytic era of psychiatry turned into one of long-term institutionalized therapy in which there were more hospitalized psychiatric patients than those with medical diagnoses. The other psychodynamic and medical approaches that eventually became available for the treatment of psychiatric illnesses have proven far more effective and much less costly. Today, psychoanalysis-based therapy is rarely used in the treatment of narcolepsy. However, this psychoanalytic history continues to affect social and medical attitudes toward patients with the diagnosis.

Patients with narcolepsy often have symptoms of fatigue, emotional flattening, anxiety, weight gain, and sleep disturbance—symptoms that could be based on a psychiatric disorder. For most of the last century, psychopathic personality structures, and sexual deviations were considered by many as the underlying basis for narcolepsy. Even without this history of psychogenic origin, the experience of having the disease of narcolepsy is often personally, socially, and psychologically distressing. Currently, psychiatric comorbidities continue to be associated with the diagnosis of narcolepsy: primarily the diagnoses of depression, psychosis, personality, sexual and eating disorders, and anxiety [54]. However, studies that have removed the symptom criteria for fatigue and sleep disorders from diagnostic tests for depression have failed to support the reported high prevalence of depression in patients with narcolepsy [55]. Despite the presence of hallucinations in both disorders, there is little evidence for an association between narcolepsy and schizophrenia [56]. It now seems apparent that most of the "psychiatric" symptoms associated with narcolepsy are symptoms of the disease itself.

The best evidence for a psychiatric comorbidity in narcolepsy is for the eating disorders of bulimia and binge eating [54]. Metabolic abnormalities are known to occur in patients with narcolepsy that are likely to affect appetite and weight [57]. Based on the medical/psychoanalytic history of narcolepsy, however, such correlations should be made with caution. Narcolepsy patients who viewed their psychotherapists as bemused and misguided, if not confused and potentially dangerous, were totally correct. Significant harm did result. Historically, patients and families were confronted with misguided accusations of sexual conduct, and soldiers were released from duty and even punished for their hysteric symptoms [58].

The effects of psychoanalytic theory on the epistemology of sleep and dream science has been even more persistent. Integrated through psychoanalytic theory, the dreamlike epiphenomena of narcolepsy have been incorporated into popular and theoretical conceptions of dreaming, sleep, and consciousness. It is clear that psychoanalysis failed as a treatment and psychopathogenesis model when applied to narcolepsy. Yet psychoanalytic theory has been preserved in modern cognitive state definitions and neuroscientific theories of consciousness such as AIM. Because these theories have been based on and applied in studies of narcolepsy, current scientifically based insights into the pathogenesis of the disease state of narcolepsy provide a useful measuring stick as to the predictive value of such hypotheses.

With the deconstruction of psychoanalysis, the loss of the REMS = dreaming correlate as a basis for neurobiological theories of dreaming, and with the realization that many studies have not clearly defined their topic of study, the field of dream science has entered a postapocalyptic era. Almost all studies of dream content have been psychoanalytically based. Most were detailed studies of individual patients with no control groups, topic definition, or attempts to control major competing variables likely to affect reported content, such as transference and researcher bias.

The association between REMS and dreaming remains poorly defined. Currently, it is unclear whether any form of "special" relationship exists between REMS and dreaming [59]. Based on this lack of clarity, it now seems factious to apply our extensive understanding of the electrophysiology, neuroanatomy, and neurochemistry of REMS to the cognitive state of dreaming. The medical field of sleep medicine rarely considers dreaming,

relegating the cognitive state to pathologic subtypes of parasomnia for limited analysis and study. In the United States, there is little, if any, available funding for further basic work, and research into the dream state has gone into a nadir of activity. The percentage of scientific papers on the topic of dreaming is at a modern low [60].

There are areas of dream science that have maintained validity after the collapse of these belief systems. Consistent variables affect dream and nightmare recall [52]. Standardized and computerized content analysis can be utilized to minimize transference and researcher bias, but it is perhaps unsurprising that based on such controlled study techniques, waking life experience (continuity) is the primary variable affecting dream content [61]. It is currently unclear as to whether sans REMS, the cognitive state of dreaming contributes to emotional and memory processing [62, 63]. Sans psychoanalysis, there is little in current dream science that can be cogently utilized to explain the meaning, significance, or the psychodynamics of dreaming. Recent works on dreaming document steady incremental increases in the understanding of the state, rather than breakthrough insights into the meaning of existence and the origin of consciousness. This recent work reveals dreaming as an exceedingly complex state occurring in different forms throughout sleep, with dreamlike states occurring frequently during waking [36]. There are electrophysiological, neurochemical, anatomic, and physiological systems of dreaming, with each of these systems affected by a wide variety of medical, psychological, sleep, and social variables [52]. Currently, without recourse to psychoanalytic theories of psychodynamics, such mind-based characteristics of the dream state as meaning, significance, self-reflection, inspiration, innovation, and empathy are rarely, if ever, scientifically addressed.

Today, we understand less about dreaming than we understand about most other cognitive states. After 6000 years of human interest and study, dreaming still eludes our attempts at explanation. Beyond REMS, the role that the cognitive state of dreaming plays in narcolepsy is unclear. It remains unclear as to whether the dreams and dreamlike epiphenomena of patients with narcolepsy are the same as the dreams and parasomnias of individuals who do not have narcolepsy. Beyond the continuity of narcoleptic dreams with the waking experience of having the disease of narcolepsy, it is psychodynamically unclear as to their meaning.

Conclusion

The twentieth century of intertwined interaction between psychoanalysis and narcolepsy continues to affect research, patient care, and social perspectives toward patients with the diagnosis of narcolepsy. Narcolepsy and psychoanalysis are intertwined in primary patterns of interaction:

1. Narcolepsy and psychoanalysis were discovered/developed in the same era, with each contributing bidirectionally in their development, one as a disease process and the other as a theory of psychodynamics.
2. Psychoanalysis was applied for many years as one of the primary therapies utilized in the treatment of narcolepsy. Perspectives based on that approach to the narcolepsy patient continue to affect patient care and social perspectives toward patients with the diagnosis of narcolepsy—often in a negative fashion.
3. Sleep and dream science fields of study have incorporated psychoanalytically based definitions for dreaming derived from the study of narcolepsy into their epistemology. This has contributed to perspectives of dreams as nonfunctional hallucinations as well as confusion as to the appropriate working definition for dream for use in research.
4. Neuroconsciousness theories (starting with activation synthesis) have incorporated psychoanalytic perspectives of narcolepsy into their constructs—equating REMS with dreaming viewed psychodynamically as an activation of primitive structures of the CNS/psyche. Current scientifically based insights into the pathogenesis of narcolepsy provide a useful measuring stick as to the predictive value of such hypotheses.

Narcolepsy, as a diagnosis, continues to provide an excellent case example for the effects of a century of acceptance of psychoanalytic theory on neurology and psychiatry as well as the persistent effects of that perspective on the epistemology of sleep medicine and dream science.

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Dreaming in Narcolepsy

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Erin J. Wamsley

Dreaming in Narcolepsy

In addition to objective sleep abnormalities [1–5], narcolepsy is associated with unusual subjective experiences during sleep. Hypnagogic and hypnopompic hallucinations are perhaps the most dramatic examples of this and are one of the defining symptoms of narcolepsy [6]. Yet beyond the sleep-wake transition, narcolepsy patients also experience definite abnormalities of nocturnal dream experience [7–13], which may directly result from disrupted sleep neurobiology in this population. Here, we will focus on dreaming during nocturnal and daytime sleep, as opposed to the more fleeting hypnagogic and hypnopompic hallucinations that occur during the transitions between sleep and wakefulness.

Our understanding of dreaming in narcolepsy remains unfortunately incomplete. Despite decades of research investigating sleep abnormalities in narcolepsy, there have been surprisingly few well-controlled, detailed laboratory studies of dream content in this population. A selection of the available evidence is reviewed below. In summary, these investigations have revealed that narcolepsy patients report experiencing unusually frequent [11–14], intense, and emotional dreams [11, 12, 15] and that patients are prone to mistake vivid, realistic dreams for memories of waking experience [12, 16, 17]. Yet self-report measures of dream experience have not been entirely consistent with laboratory-based studies of dreaming, which suggest that intensified dream experiences may largely be restricted to early-night sleep [7, 8, 10], perhaps associated with fragmented, early-onset REM (rapid eye movement) sleep and indistinct boundaries between sleep states.

Understanding dreaming in narcolepsy is important clinically, as dream experiences can contribute to patient distress and dysfunction and is also valuable to basic science, in that the cognitive characteristics of patients' sleep experience may shed light on underlying abnormalities of sleep neurobiology.

Dream Recall

Narcolepsy patients appear to recall more dreaming than the general population, particularly during early-night sleep. Patients consistently report remembering dreams more often than controls when asked to self-report their typical dream recall frequency [11–14]. Some laboratory evidence corroborates this self-report data. For example, in the laboratory, narcolepsy patients recall more dreams from MSLT (multiple sleep latency test) naps than other sleep-disordered patients [18]. But in contrast, laboratory studies

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of overnight sleep have not confirmed globally increased dream recall in narcolepsy. Fosse collected dreams throughout the night from a sample of narcolepsy patients and controls, and found that patients did *not* recall more dreams than controls when experimentally awakened from REM sleep, nor were the dreams of narcolepsy patients on average any longer than those of controls [9]. Schredl similarly failed to find any difference in the amount of dreaming recalled by narcolepsy patients and controls in the laboratory setting [11]. These studies highlight a disconnect between narcolepsy patients' own judgments about their dreaming, as compared to what patients actually report experiencing when prompted to verbalize their dreams during experimental awakenings in the laboratory setting.

These observations may be reconciled by other studies suggesting that although narcolepsy patients do not recall more dreaming than the general population overall, they do report more dreaming during early-night REM sleep (the first 1st REM period). In multiple studies, Cipolli's group has found that although narcolepsy patients do not recall REM dreams more frequently than controls, the length of dream reports elicited from the first REM period is significantly greater in narcolepsy patients, independent of whether a SOREMP (sleep-onset REM period) occurred [7, 8]. Thus, it could be that patients' perception of frequent dreaming is driven by salient experiences of long, intense dreams during early-night REM sleep.

In all studies of dreaming, it is difficult to determine the extent to which we are measuring the *experience* of a dream during sleep, as compared to the completeness with which that experience is *remembered and reported*. In the case of narcolepsy, it is unclear whether patients are actually generating "more" dreaming during sleep than the general population or, alternatively, whether they might simply be better able to remember and report their experiences. For example, the repeated awakenings characterizing fragmented sleep in narcolepsy [1, 4] could prompt patients to awaken and remember dreaming more frequently than controls, despite similar processes of dream generation (as would be suggested by the arousal-retrieval model of dream generation [19, 20]). As we will discuss below, personality-related factors can also influence the recall and reporting of dreams. Alternatively, altered sleep neurobiology in narcolepsy may actually increase the amount of subjective experience generated by the sleeping brain, for example, by increasing arousal levels during sleep, altering functional patterns of brain activation, or increasing the fragmented intrusion of REM sleep processes into the early night.

Regardless of the mechanism, anecdotes suggest that in some patients, recalling frequent and intense dreaming can itself become a bothersome symptom of narcolepsy. Although there is little systematic data available on the degree to which increased dream recall causes clinically significant distress in this population, below we turn to clinically relevant evidence that independent of the *amount* of dreaming experienced, narcolepsy patients may be prone to suffer from intense and disturbing dreams [11, 13, 14, 21].

Qualities of Dream Experience

Dreaming may not only be more frequent in narcolepsy but also differ qualitatively from dreaming in the general population. Of particular concern are anecdotal reports that narcolepsy patients are prone to suffer from intense and disturbing dreams, including nightmares. Indeed, there is evidence that negative emotion is especially prevalent and/or intense in the dreams of narcolepsy patients, again perhaps driven by early-night REM sleep. In studies using retrospective questionnaires, narcolepsy patients report experiencing more emotion in dreams than age-matched controls [11, 12, 15] or other hypersomnolent patients [15]. In particular, patients rate themselves as experiencing more *negative* dream emotions [11, 15], which is consistent with the fact that narcolepsy patients also report experiencing nightmares more frequently than the general population [13, 14, 21, 22]. But here again, at least one study suggests that emotion is more frequent and intense selectively during early REM sleep, in this case during sleep-onset

REM periods [10]. This may explain why another laboratory study found no difference in dreamed emotion between patients and controls using a procedure where dream reports were elicited only in the morning following polysomnographic evaluation and not from early-night REM [11]. Although the number of studies is small, these few observations suggest the hypothesis that increased reports of nightmares and negative dream emotion in narcolepsy could be driven by early-night REM abnormalities.

Other qualitative features of dreaming may also be altered in narcolepsy. For example, the dreams of narcolepsy patients are typically characterized as complex and vivid, two qualitative features often assessed in studies of dreaming. But empirical studies are few and far between, and the data available are not entirely consistent. Although several studies have described particularly vivid dreaming in narcolepsy [12, 22, 23], one careful laboratory study has found that the vividness of recalled dreams was if anything actually decreased in narcolepsy, compared to control subjects [9]. Dreams have also been reported to be both more [11] and less [9] "bizarre" than those of age-matched controls. These inconsistencies may in part be explained by a lack of standardized content measures used across multiple studies, in which constructs like dream "bizarreness" and "vividness" are often measured in very different ways by different investigators.

Lucid Dreaming in Narcolepsy

The concept of "lucid dreaming" was once largely relegated to the realm of new-age pseudoscience. But psychophysiological and neuroimaging studies have now definitively established that certain individuals can be aware that they are dreaming during sleep and are even able to remember and execute simple commands from the sleep state [24–28]. For example, during a dream, proficient lucid dreamers are able to signal from sleep by moving their eyes in a predetermined pattern that can be read on the electrooculogram [24–28]. Emerging evidence suggests that narcolepsy patients experience lucid dreaming[1] more commonly than the general population. Indeed, this increased meta-awareness may be one of the primary qualitative features that distinguishes dream experience in narcolepsy from that in controls.

As early as the 1970s, Gerald Vogel noted an unusually high degree of self-awareness in the dreams of narcolepsy patients [29]. More recently, several studies have measured "reflective consciousness" and "self-reflective awareness" in the dreams of narcoleptic patients and found that patients report a higher degree of such awareness during the dream state than do control participants [9, 30]. Following up on these reports, two recent studies have directly examined the experience of lucid dreaming in narcolepsy, finding that patients report a much greater frequency of lucid dreaming than age-matched controls [13, 14]. Dodet et al. confirmed this observation in the laboratory, demonstrating that narcolepsy patients were much readily able to produce a "signal-verified" lucid dream (in which the participant indicates awareness using a predefined eye movement signal) in comparison to non-narcoleptic control participants [14].

Together, these data demonstrate enhanced metacognition during sleep in narcolepsy. Like other peculiarities of dream experience in this population, lucid dreaming in narcolepsy may be related to altered REM sleep. Although most common in REM, typical dreaming can occur in any sleep stage [31–36]. In contrast, lucid dreaming occurs almost exclusively during REM sleep [37, 38]. Thus, increased lucid dreaming in narcolepsy more directly suggests a REM abnormality than does generally enhanced dream recall.

Because narcolepsy patients do not typically have an overall increased amount of REM sleep, enhanced dream lucidity might instead be caused by heightened arousal or regional brain activation abnormalities within REM sleep. Recent evidence in controls suggests that lucidity may be caused by increased activation in select cortical regions, including prefrontal cortex, which is

[1] Defined as an awareness, during the dream, that the participant is in fact asleep and dreaming.

normally relatively inactive during REM [25, 28]. This cognitive evidence suggests that REM in narcolepsy patients may be associated with different patterns of functional brain activation, in which regions typically deactivated during REM sleep show abnormally heightened activation.

Source Memory Confusion

Memory for dream experiences is not only particularly strong in narcolepsy but is also easily *confused* with the memory of waking experience. This peculiar phenomenon has been vividly illustrated in several case studies of narcolepsy patients who have, for example, made serious accusations of sexual assault based on what was later determined to have been a vivid dream experience [16, 17].

We recently undertook the first systematic study of these "dream delusions" in narcolepsy, uncovering a strikingly high incidence of confusions in which dream experiences were misinterpreted as representing real, highly significant life events, leading to sustained delusions that persisted for hours, days, weeks, or longer [12]. Overall, we found that 83 % of narcolepsy patients reported that they had confused dreams with reality (compared to 15 % of control subjects), with two-thirds of these reporting in a follow-up interview that this occurs with a frequency of at least once a week [12].

Even healthy college students report the occasional, benign confusion of dream experience with reality [39, 40], but the experience of narcolepsy patients is characterized by a much a more serious and profoundly disruptive form of memory confusion. For example, one man dreamed that a young girl had drowned in a nearby lake and subsequently asked his wife to turn on the local news, expecting to see coverage of this incident. Another participant believed that she had been unfaithful to her husband, until a chance encounter with the "lover" prompted her to realize that she had merely dreamed of sexual encounters with this individual that had not actually occurred. Overall, we found that the confusion of dreams with reality is a common and highly distressing experience for narcolepsy patients [12], which differs in kind from the everyday memory mistakes that we all experience.

While the neurobiological origin of these "dream delusions" is uncertain, they could be secondary to enhance dream recall and/or increase vividness and intensity of dreaming in narcolepsy described above. If narcolepsy patients routinely experience very realistic and visually vivid dreams, the nature of these experiences themselves could render them less easily distinguished from reality. However, we found that among narcolepsy patients, self-reported vividness and frequency of dreaming were unrelated to the experience of dream delusions [12]. We have alternatively proposed that these delusions could result from an abnormal encoding of dream memories caused by disruption of normal sleep state neurobiology underlying narcolepsy.

A Note on Ernest Hartmann's "Boundaries of the Mind"

In the general population, many of the dream features described here—high dream recall, frequent nightmares, vivid dreaming, lucid dreaming—tend to go together. Individuals who experience any one of these dream characteristics are likely to also experience others. Thus, rather than being independently affected in narcolepsy, it may be that all of these traits are altered as a result of some underlying factor that characterizes the population. Below, we will discuss possible neurobiological origins of altered dreaming in narcolepsy. But also relevant is Ernest Hartmann's proposal that these sleep experiences are related to a distinct *personality*. Hartmann has characterized individuals who move easily between states of consciousness and have a decreased distinction between self and other as having a "thin" boundary personality type, associated with open-mindedness, creativity, and fantasy-proneness [41, 42]. A number of studies using Hartmann's assessment tool [41] have confirmed that the thin boundary personality construct is a strong predictor of dream recall, nightmares, and dream lucidity [41, 43–45].

We used Hartmann's boundary questionnaire to compare narcolepsy patients and control participants and found that patients scored much higher on the Boundary Questionnaire than age-matched controls, indicating that narcolepsy patients have particularly "thin" boundaries, according to Hartmann's construct [12]. In light of this, it should be considered whether personality factors related to more global characteristics of mental life might contribute to the unique aspects of dream experience in narcolepsy.

Effects of Pharmacological Treatment

Although the effects of medication on dreaming in narcolepsy remain poorly understood, pharmacological treatment in some cases can reduce the frequency and intensity of dreaming. In one recent study, narcolepsy patients reported that dream recall frequency and nightmare frequency both decreased after starting medication [13]. This was true when examining all medications combined and also when specifically questioning those who had begun taking sodium oxybate. In children, one study reported a decrease in "terrifying dream experiences" with sodium oxybate treatment [46], and in adults, a retrospective study similarly reports reduced nightmares among a small sample of narcoleptics under treatment with medications including selective serotonin reuptake inhibitors, modafinil, and sodium oxybate [21]. In our own study on delusional confusion of dreaming with reality, several patients volunteered that this symptom of "dream delusions" had subsided following treatment [12]. Although hardly conclusive, these few observations suggest that unpleasant dreams may decrease after beginning pharmacological treatment for narcolepsy and particularly with sodium oxybate. However, it is important to note that an increase in nightmares and unusual dreams has also been reported as a side effect of sodium oxybate use in both children and adults [47–49].

Because sodium oxybate increases slow wave sleep and decreases sleep fragmentation [50], it is not surprising that patients would report a decrease in the frequency and intensity of dreaming following the start of treatment. Although dreaming can occur during slow wave sleep [33, 34], dream reports are most common during REM sleep [31, 32], becoming increasingly scarce during deeper stages of sleep. Furthermore, sleep fragmentation has long been proposed to promote increased dream recall [51], which is consistent with reports that subjects with high dream recall have decreased arousal thresholds and decreased ERP response thresholds during sleep [19, 52, 53]. Thus, we might hypothesize that any drug which increases slow wave activity and decreases sleep fragmentation could similarly decrease dream recall frequency. Future research probing the effects of narcolepsy treatment on dreaming will be necessary to come to more firm conclusions about the extent to which treatment may normalize the dream characteristics described here.

Conclusions

Despite the small number of studies available, we can begin to draw some tentative conclusions about the nature of dreaming in narcolepsy. First, patients' assessment of their own dream experience using retrospective methods [11–15] is partially inconsistent with the findings of laboratory studies [9–11]. Narcolepsy patients report dreaming more frequently than controls, and they report experiencing dreams that are more vivid, emotional, and bizarre than controls. Yet studies sampling dreams using experimental awakenings in the laboratory suggest that dreams of narcolepsy patients and controls differ primarily during the sleep-onset period or early night, with no consistently observed differences later in the night. It may be that patients rely heavily on salient early-night or sleep-onset experiences when making retrospective judgments about their typical dream experience and that retrospective studies primarily reflect abnormally frequent and intense dreaming during this early-night period.

So what accounts for reports of frequent and intense dreaming in narcolepsy? Particularly if this effect turns out to be restricted to the early

night, it is tempting to ascribe these dream abnormalities to the well-known presence of sleep-onset REM periods in narcolepsy patients. Yet this conclusion would be premature. First, it is well established that dreams are frequently experienced outside of REM sleep [31, 32, 35, 54, 55], and thus there is no a priori reason to suppose that intense early-night dreaming must be a result of early-night REM sleep. Second, two of the studies reviewed above suggested that although narcolepsy patients showed frequent and intense dreaming primarily during early sleep, this effect was *not* related to the presence of SOREMPs [8, 18]. That is, dreams elicited from early nocturnal sleep or MSLT naps differed between patients and controls, regardless of whether patients experienced a SOREMP [8, 18]. Although there have been no studies examining dreaming during NREM sleep in narcolepsy, it may be that dream experience is altered in narcolepsy patients even in the absence of PSG-defined REM. Although sleep-onset REM periods are a clearly defined sleep architecture abnormality in this population, there are more subtle alternations of sleep physiology which also might account for altered dreaming. For example, there is evidence that sleep in narcolepsy may be characterized by a "state instability," in which more time is spent in transitional states, with sleep stages "bleeding into one another" more than is typical [56, 57]. This more global alteration of sleep architecture is one example of an equally plausible neurobiological explanation for altered dreaming. As discussed above, frequent and intense dreaming might also be related to sleep fragmentation or a generally increased arousal level during sleep.

In conclusion, the examination of dreaming in narcolepsy brings us to several insights about the nature of this disorder. First, for the clinician, understanding the unique qualities of narcoleptic dreams provides a more complete picture of a patient's symptom profile. Dream-related symptoms can be among those which contribute to a patient's distress and to disruption of their everyday lives [12, 23]. Although perhaps less tangible than other sleep abnormalities, the features of a patient's dreaming should be given special attention both as a possible area of distress and as a metric of improvement with treatment. Second, as we continue to advance our understanding of the underlying neurobiology of narcolepsy, the characteristics of dreaming in these patients may assist us in developing new hypotheses and distinguishing between rival hypotheses. As described above, sleep-onset REM does not necessarily provide a full explanation for intensified in narcolepsy, and as we move forward, studying altered cognition during dreaming may provide further clues to the underlying neurobiology at work.

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Narcolepsy and Mental Illness

19

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Narcolepsy with cataplexy (NC) is a rare, debilitating complex sleep disorder that affects approximately 0.026 % of the general population. The disorder is characterized by excessive daytime sleepiness (EDS), fragmented nocturnal sleep, dissociated manifestation of rapid eye movement sleep phenomena such as sleep paralysis and hypnagogic hallucinations, and cataplexy (i.e., abrupt and reversible axial or bilateral muscle weakness in the presence of awake electroencephalographic [EEG] activity most frequently elicited by emotions). Narcolepsy with cataplexy is also associated with cognitive alterations, mood symptoms, and reduced quality of life. NC is caused by loss of lateral hypothalamic neurons producing hypocretin.

Hypocretin-1 and hypocretin-2 are involved in a variety of physiological processes such as arousal, maintenance of waking, feeding behavior, and energy metabolism. Hypocretins in the mesolimbic pathways regulate emotion, reward processing, and addiction. Therefore, NC provides a window to the mechanisms involved in human behavioral regulation.

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Performance in Narcolepsy

Sleepiness

Sleepiness or daytime sleepiness refers to a sleep propensity. Sleep propensity is a measure of a subject's tendency at a particular time to doze or fall asleep, at least briefly. This means entering Stage 1 sleep as defined by the EEG, whether or not it progresses to Stage 2 and to other stages [1].

Johns has postulated a four-process conceptual model of sleep and wakefulness that takes into account the powerful behavioral influences on sleep propensity [2]. A basic tenet of this model is that whether we are awake or asleep at any particular time depends on the relative strengths of two mutually inhibiting drives, the wake drive and the sleep drive, not on the absolute strength of either drive alone. It is further postulated that each of these drives has a primary and a secondary component. The primary components are derived mainly from the intrinsic activity in different neuronal groups within the central nervous system; the secondary components are homeostatic and behaviorally influenced.

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The functions of these drives can be outlined hypothetically as follows:

- The primary wake drive arises from intrinsic activity in some or all of several neuronal centers in the central nervous system (CG) whose action promotes wakefulness [3]. This activity varies with a circadian rhythm, usually entrained to have its peak at 7–9 p.m. and its trough at 4–5 a.m. Behavioral and environmental influences would set the phase of such a rhythm but would not generate it. This primary wake drive is reflected in core temperature, cortisol secretion, melatonin secretion, and REM sleep, although each of the variables also has other central mechanisms. The primary wake drive is the equivalent of Borbely's process C [4].
- The secondary wake drive is due to the additive effects of inputs to the central neurons system from postural muscles, joints, and other enteroceptive nerve tracts, as well as from visual and other exteroceptive inputs, with collaterals to the thalamic projection system and the limitric system. This secondary wake drive is partly under voluntary control.
- The primary sleep drive arises from intrinsic activity in various neuronal centers whose coordinated action promotes non-REM sleep. It may have low-amplitude circadian and ultradian rhythms. Its peak of activity would usually be between 10 p.m. and midnight [3].
- The secondary sleep drive is the equivalent of Borbely's process. It increases progressively during wakefulness and is discharged during non-REM sleep. Its buildup is prevented by frequent naps during the day [4].

It is postulated that the primary and secondary wake drives have additive effects which together would constitute the total wake drive. Similarly, the total sleep drive would result from the additive effects of the primary and secondary sleep drives. These sleep and wake drives would naturally inhibit each other to produce an oscillator of the "flip-flop" type. Awake would occur whenever the total wake drive exceeded the total sleep drive and asleep when the sleep drive exceeded the wake drive. Once asleep, progression from Stage 1 to Stage 2 probably requires further active inhibition of the wake drive by the sleep drive. The sleep-onset process takes some time and is not instantaneous. Other processes during sleep would control the interaction between non-REM and REM sleep.

Under most circumstances, it is the magnitude of the secondary wake drive that is the single most important determinant of whether we fall asleep or stay awake at any particular time. Changes in the secondary wake drive are partly under voluntary control, e.g., when we choose to lie down in bed, relax, and close our eyes.

Other changes in sleep propensity which are affected by the time of day (due to changes in the primary wake and sleep drives) and the duration of prior wakefulness (due to changes in the secondary sleep drive) are not under much voluntary control but do influence our choice of when to go to bed each night as part of our sleep habits.

However, this four-process model may be unable to account for factors such as motivation, fatigue, boredom, or mood that may all impact on sleepiness states.

The brain, which is a complex dynamic system, works by interactions on multiple temporal and spatial scales which enable adaptive behaviors appropriate to environmental stimuli. These interactions are accomplished not only by specific network activities that produce organismal responses to stimuli but also by the general state of the system which is most clearly represented in the shift of state from wake to sleep. Thus, system-wide dysfunctions can occur not only in the networks responsible for specific functional responses to the external world but also in the less well-understood networks responsible for the maintenance of and switching between neural states and the timing of the neural states within the 24 h light/ark (LD) cycle.

Therefore, abnormalities that occur in this system can be at multiple levels with complex interactions resulting in a clinical picture that can vary in temporal and spatial scales.

In narcolepsy/cataplexy, a cardinal symptom of the disorders is excessive daytime sleepiness (an insurmountable urge to sleep) which manifests

itself primarily when the subject falls asleep at inappropriate times ("sleep attacks"). This is the result of an inability to maintain a consolidated awake period characterized by abrupt transitions to NREM sleep (i.e., dysregulation of NREM-sleep onset).

A 10-year longitudinal study performed by Bruck and Costa indicated that the impact of excessive daytime sleepiness on the ability to carry out day-to-day activities showed minor increases in severity over a 10-year period which could not be attributed to major changes in medication status [5]. Bruck argued that the underlying severity of excessive daytime sleepiness does not increase with time, but rather that the interaction of excessive daytime with the aging process increases its detrimental impact [5].

Attention and Memory

Early case reports in narcolepsy/cataplexy patients described concentration problems and forgetfulness, independent of the degree of sleepiness [6]. Later studies indicated that 40–50 % of narcolepsy patients complained of memory problems [7]. Concentration and learning difficulties were reported by a significant proportion of narcolepsy sufferers [8].

In contrast to self-report findings, standardized neuropsychological assessment of memory abilities mostly yielded intact short- and long-term memory in narcoleptics [9]. Mild verbal memory problems observed in one study were attributed to deficient perceptual encoding [10]. Antinarcoleptic medications generally did not affect memory performance [10].

There is little empirical evidence for a genuine memory deficit in narcolepsy. Factors such as affective changes and psychosocial adjustment difficulties might influence the subjective complaints of memory deterioration [11]. Mild memory deficits in narcoleptic patients observed only in a few studies could have been due to use of different tasks [12].

Attention networks carry out the functions of alerting, orienting, and executive control [13]. The anatomical structures related to alerting are locus coeruleus and right frontal and parietal cortex; to orienting are superior parietal, temporal parietal junction, frontal eye fields, and superior colliculus; and to executive attention are anterior cingulate, lateral verbal prefrontal, and basal ganglia. The neuromodulators for alerting, orienting, and executive attention are norepinephrine, acetylcholine, and dopamine, respectively.

- Alerting is defined as achieving and maintaining a state of high sensitivity to incoming stimuli.
- Orienting is the selection of information from sensory input. This may be overt as when eye movements accompany movements of attention or may occur covertly without eye movements.
- Executive control involves the mechanisms for monitoring and resolving conflict among thoughts, feelings, and responses.

Executive control encompasses the ability to select information from a certain source or a certain content and to set priorities in information processing to enable an individual to make optimal use of limited capacities [14]. It comprises the ability to select and integrate stimuli and/or contents as well as the ability to focus on and change between such stimuli and contents [15].

The concept of executive control is strongly connected with the concept of limited capacity. If attention would not be limited, selectivity would not make any sense [16]. Executive control also shows a relation to the concept of attention control. To apply attention selectively, a person must be able to control his or her attention to the task at hand.

Three important sub-aspects of selective attention are:

- Focused attention (i.e., the ability to attend to relevant stimuli)
- Divided attention (i.e., the ability to share attention between different sources of information)
- Flexible attention (i.e., the ability to change the focus of attention) [15]

Assessment of attention yielded deficits in vigilance and sustaining attention as well as

high fluctuations of alertness in narcolepsy, in particular during long and repetitive tasks [17]. Performance on briefer, more challenging tasks was intact in most cases [18], and deficits have only rarely been observed [19]. It is possible that altered sleep regulation mechanisms affect the ability to sustain attention at a high level over longer periods of time and, thereby, interfere not only with attention but also with memory or executive function [20].

Cognitive functions or cognitive regulatory systems include three broad categories of functions:

- Inhibitory functions (the ability to suppress one response in favor of another)
- Working memory (the ability to maintain and manipulate multiple pieces of information at the same time)
- Cognitive flexibility (the ability to adjust response or attention quickly on the face of changing demands) [21]

Problem solving and planning typically build upon a combination of these three components.

As a regulatory capacity, executive functioning is central to a range of normal and abnormal behavior. It can overlap with emotional regulation processes. There is evidence that neural circuity which supports executive functioning and emotional regulation is largely overlapping. Cognitive regulation of behavior and emotions is supported by several circuits in the prefrontal cortex. The prefrontal cortex is responsible for maintaining an internal representation of current goals and modulating activity in brain regions responsible for perception or action in order to flexibly achieve these goals. In order to accomplish this, the prefrontal cortex must be able to maintain a representation of goals in the face of distraction, update representations as new information is received through multiple sensory modalities, and provide a feedback signal that can select the neural pathways appropriate for the current task context [22].

The regions implicated in executive functioning across a range of tasks are two well-conserved cognitive control networks: a frontal parietal network containing the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortices and a cingulo-opercular network containing the dorsal anterior cingulate cortex (dAcc), anterior insula, and the anterior prefrontal cortex. A set of regions including the inferior frontal gyrus, supplementary motor area, and subthalamic nucleus which have been implicated in response inhibition specifically, and the default mode network comprised of medial prefrontal, medial and lateral parietal, and medical temporal regions [23].

Concomitant with engagement of the frontoparietal and cigulo-opercular networks, the default mode network deactivates. Momentary impairments in this coordination between activation in the frontoparietal and cigulo-opercular networks and deactivation on the default mode network are associated with lapses in attention and behavioral performances [24]. Conversely, internally oriented mentation, such as self-reflection and autobiographical memory, activates the default mode network [25], further suggesting that the balance between the cognitive control networks and the default mode network is important for flexible transitioning from an internal focus of attention to externally focused attention-demanding tasks.

The evidence for cognitive dysfunction in narcolepsy has been sparse, and the results are often contradictory [20]. Executive functions were impaired across general executive control subcomponents [26]. In contrast to an earlier study [9], narcolepsy patients showed reduced verbal fluency, a task which reflects cognitive flexibility and the efficiency of role-guided memory search and retrieval strategies. Letter, semantic fluency, and alternating fluency assessed by Naumann et al. [27] are linked to distinct cognitive and neuronal mechanisms [26].

The finding that narcolepsy patients showed reduced fluency independent of the specific task and processing features suggests a more general dysexecutive problem which may be related to a general reduction of availability of resources necessary for the guidance of efficient search and retrieval strategies [27]. The HSCT requires fast retrieval from semantic memory and fast monitoring and evaluation of retrieved information [28].

Narcolepsy patients needed longer than controls to retrieve information in the initiation condition which is consistent with the verbal fluency findings. When having to inhibit the dominant response, patients needed longer and made more errors than control subjects, a result which reflects deficient inhibition and high susceptibility to interference from the dominant response. Therefore, the general pattern of cognitive dysfunction in narcolepsy is consistent with a reduction or limitation of cognitive processing resources [27]. It is also conceivable that a need to monitor and stabilize fluctuating vigilance levels may contribute to the cognitive changes in narcolepsy.

Disruption of the hypocretin system is associated with a deficient regulation of cortical activity and deficient vigilance. Instability of cortical activation is likely to disrupt the efficiency of cognitive control processes as current information processing occurs simultaneously with compensatory regulation processes which are necessary to maintain a sufficiently high vigilance level [27].

Mood Disorders

Anxiety and Depression

As many as 19.2 % of the narcoleptic patients had major depressive disorder compared to 6.4 % in the matched general population [29]. Social anxiety disorders were also highly prevalent among narcoleptic participants (21 %). Panic disorder and posttraumatic stress disorder were observed in more than 10 % of the narcoleptic participants. However, these 2 disorders were only significant among women, while attention-deficit/ hyperactivity disorder in childhood was only significant among boys. When the timeline of the disorders was examined, it was found that only 13.5 % of narcolepsy patients with MDD had the disorder before the onset of narcolepsy [29].

For anxiety disorders, the order of appearance varied; obsessive-compulsive disorder and social phobia were present before the onset of narcolepsy in approximately half the cases, 50 % and 46.4 %, respectively. Panic disorder and simple phobia all developed after the onset of narcolepsy. Posttraumatic stress disorder, generalized anxiety disorder, and agoraphobia were present before the onset of narcolepsy in 21.6 %, 16.7 %, and 21.4 % of cases, respectively [29].

Hypocretins act primarily as excitatory neurotransmitters to control monoaminergic and cholinergic neuron activities. Hypocretin deficiency induces a cholinergic-monoaminergic imbalance with primary effect on vigilance as well as on other functions including mood regulation. Hypocretins are also involved in neuroendocrine functions and stress reactions through stimulation of the hypothalamus pituitary adrenal axis [30]. Hypocretin deficiency per se may trigger mood disturbances and psychological alterations through diverse pathways [31].

High levels of psychopathology were frequently reported in cross-sectional studies in narcolepsy with a high rate (from 15 to 37 %) of moderate to severe self-reported depressive symptoms [32]. A case–control study found mood disorder symptoms in one-third of narcolepsy patients but with similar frequency of formal mood disorder diagnosis [33]. In a 5-year cohort study of patients with narcolepsy/cataplexy, mood symptoms remained relatively stable, with 25 % of patients showing constant moderate to severe mood symptoms across assessments [34].

One large cross-sectional narcolepsy study found that depressive symptoms (using the BDI-11) were associated with greater EDS severity, greater alterations in physical and mental health quality of life, as well as increased frequency of REM-sleep manifestations such as cataplexy, hypnagogic hallucinations, and sleep paralysis [32]. In addition, it was noted that anticatapletics at doses prescribed for cataplexy management were ineffective in treating depressive symptoms.

Emotional Processing and Anhedonia

The amygdala plays a major role in the interpretation of emotionally significant stimuli with strong projections to the hypocretin area [35].

As in patients with amygdala lesions, patients with narcolepsy/cataplexy failed to exhibit startle potentiation during unpleasant stimuli [36]. A psychophysiological investigation in narcolepsy/cataplexy also revealed an attenuated reaction to unpleasant pictures [37].

Recent functional MRI studies examined brain activation patterns on patients with narcolepsy/cataplexy when shown humorous materials. One of these studies revealed an enhanced ventral striation and hypothalamus response on patients with narcolepsy/cataplexy when shown humorous cartoons [38]. In contrast, positive humorous pictures elicited reduced hypothalamic response together with pronounced activity in amygdala in another narcolepsy/cataplexy study [39]. These findings suggest an amygdala involvement in the pathophysiology of narcolepsy which would result in abnormal emotional processing under both pleasant and unpleasant conditions.

As indicated above, executive functioning networks are implicated in the regulation of emotions. Emotions themselves are complex, coordination phenomena that involve behavioral, cognitive, and physiological changes, activate action tendencies, and create subjective feelings [40]. Emotion regulation includes an array of processes varying from the deliberate and effortful deployment of cognitive resources to alter an emotional reaction [40] to the uncued spontaneous use of "automatic" (i.e., implicit) processes that occur entirely outside of awareness [41]. Consistent with the fact that explicit emotional regulation requires deliberate and effortful deployment of cognitive resources, neuroimaging studies have found that it is also associated with activation in the frontoparietal and cingulo-opercular cognitive control networks implicated in executive functioning more broadly along with decreased activation in the amygdala [42].

Understanding and remediating deficits in core components of executive functions has bearing on both executive functioning and explicit emotional regulation. Implicit emotional regulation involves the ventral anterior cingulate cortex which regulates emotional conflict by dampening amygdala activity without involvement of activation in executive functioning-related cognitive control networks.

A recent study indicated that narcolepsy patients with depressive symptoms were more hedonistic than patients with depression. This outcome was interesting because anhedonia is a cardinal symptom of major depression, and the experience of enjoyment is the typical trigger of a cataplexy episode. Patients who maintain a good level hedonic experience are more prone to experience cataplexy. However, it is not yet known if narcolepsy patients differ from control in the range of hedonic levels. The possibility that narcoleptic patients with depression are prone to an atypical depression is an interesting likelihood which needs further confirmation.

Psychosis

Psychosis is very unusual in narcolepsy, except during treatment with amphetamines. The risk of psychosis appears to be dose related although it is likely that some subjects are more susceptible to this complication than others [43]. Psychosis is usually predominately paranoid. Psychotic symptoms in narcolepsy may appear during sodium oxybate treatment. Hallucinations resemble those seen in schizophrenia. However, the insight that symptoms are delusional is usually preserved [44].

Other Psychological Aspects

Dreams and Hallucinations

Up to one-third of normal individuals experience visual hallucinations prior to falling asleep or immediately following arousal. These hypnagogic and hypnopompic hallucinations occur in a variable frequency, last a few seconds to minutes, and may be as simple as spots of light or geometric patterns to complex images such as faces, figures of real or bizarre humans or animals, objects, or scenery. Associated emotional reaction to these complex images may be neutral, pleasant, or sometimes extremely frightening [45].

Perceptual disturbances are a hallmark of severe mental disorders, and complex visual hallucinations are a common finding in psychiatric settings. In schizophrenia and other psychoses, complex visual hallucinations accompany auditory hallucinations. These hallucinations often present throughout waking hours and have less insight and more paranoia.

Two different pathophysiological mechanisms to explain the phenomenology of visual hallucinations as a result of a wide variety of conditions have been proposed. Visual hallucinations in the context of visual sensory deprivation, migraines, and epilepsy seem to be caused by direct excitation of the visual cortex or by deafferentation. Visual hallucinations related to narcolepsy, peduncular lesions, Parkinson's disease, Alzheimer's disease, delirium, schizophrenia, and those occurring as drug effects would be caused by pathology and dysfunction of the ascending brainstem cholinergic pathways [46].

Sleep disturbances are common in patients with vivid formed hallucinations. Normal individuals usually do not experience their first REM-sleep period within the 90 min after sleep onset. Patients with narcolepsy frequently enter REM sleep within 20 min of sleep onset. Hallucinations are related to this first REM especially if its onset is rapid and not to later REM episodes or total REM time which is normal in narcolepsy [47, 48]. In normal individuals, the first REM epoch arises out of deep non-REM sleep. Hallucinations may be a manifestation of going into REM from a relatively higher level of arousal [49]. This would explain why these hallucinations only occur in the first REM epoch.

Most cases of the narcolepsy syndrome are constitutional, but some are secondary to lesions of the pons and midbrain overlapping considerably with those causing peduncular hallucinosis [50]. In these two situations, hallucinations may share a similar pathophysiological basis. In idiopathic narcolepsy, there is evidence of altered brainstem function. Increased brainstem blood flow has been shown during sleep, the reverse of that in normal individuals [51]. During hypnagogic hallucinations, an increase has also been shown especially in the right parietal, occipital, and posterior temporal cortex [52]. The hallucinations are often in color with vivid sounds as well as with taste, smell, and pain. There is often a sensation of levitation, including flying. These hallucinations may merge into wakefulness and are often sufficiently realistic for the subject to be unsure whether they represent reality or not. This transient loss of contact with reality can be embarrassing and can lead to a lack of confidence.

Narcolepsy is also associated with the REM-sleep behavior disorder in which dreams with an aggressive or vigorous content are physically enacted. Characteristically, the dreams are of being chased or attacked by strangers or animals or less commonly of attacking or chasing people. The narcoleptic may retaliate and, thereby, injure himself/herself or partner [53].

Pain

Pain is generally considered to be a symptom of narcolepsy. But several studies have shown that generalized bodily pain appears to be more frequent in those with narcolepsy than normal subjects [54]. This is particularly a feature in those with severe narcolepsy [55]. Whether this is due to physiological abnormalities in pain pathways or to increased awareness of painful sensations or even to a recognized organic cause for the pain is uncertain.

Food Cravings and Weight Gain

Narcolepsy has been linked with olfactory dysfunction [56]. It has been suggested that olfactory dysfunction may be a predictor of local degeneration of hypocretinergic mucosa cells. Olfactory dysfunction is one of the first signs of a neurodegenerative disorder. In line with this finding, a French study showed that patients with Parkinson's disease could suffer from sleep-onset REM and REM-sleep behavior disorder [57]. Loss of hypocretin cells has been reported in Parkinson patients.

The discovery of a hypocretin deficiency in individuals with narcolepsy and its role in coordinating food seeking and feeding behaviors has promoted interest into eating behaviors and attitudes of individuals with narcolepsy. Hypocretin-expressing neurons in the lateral hypothalamus act as metabolic sensors and modulate energy homeostasis, hedonic pleasure, decision-making to make optimal adaptive choices, and reward-seeking [58]. A close interaction between the hypocretinergic and dopaminergic systems in satiety control is supported by data showing that hypocretin in the posterior ventral pallidum can enhance liking for sweet rewards as with mu-opioid stimulation [59]. Therefore, it would be expected, given their hypocretin deficiency that narcoleptic individuals would have smaller appetites and consume less food and drink in comparison to the general population. However, research to date investigating the eating patterns and behaviors of narcoleptics/cataplexic is largely inconsistent with a hypocretin deficiency explanation. Narcoleptic/cataplexic individuals are associated with excessive weight gain particularly at disease onset and in children [60], with a global increased frequency of obesity also in adults [60]. Weight gain in narcoleptics/cataplexics appears not related to excessive daytime sleepiness (inactivity) or to higher food intake from controlled diary study [61, 62]. Medication is not a factor contributing to weight gain in narcoleptic/cataplexic individuals [63].

Sleep-related disorder (SRED) is a non-rapid eye movement parasomnia defined by recurrent episodes of involuntary eating and drinking during arousals from the main sleep period. A recent study found SRED was significantly associated with narcolepsy/cataplexy. However, SRED in narcolepsy and cataplexy was not associated with weight gain suggesting a possible primary effect of hypocretin deficiency. Finally, no difference was found in the current prevalence of eating disorders (i.e., bulimia nervosa, binge eating disorder, or anorexia nervosa) nor was the frequency of eating attacks higher in the narcolepsy group [64].

Narcolepsy and Disruption to Social Functioning

Research indicates that the clinical symptoms of narcolepsy have a profoundly negative effect on the quality of life of those diagnosed as narcoleptic. It seems that narcoleptic patients experience a higher rate of work, home, and driving accidents, greater unemployment, lower job satisfaction and performance, and lower educational outcomes than their non-narcoleptic counterparts [65]. It is not uncommon for people living with the disorder to be labeled as lazy or irresponsible in work and school settings or seen as emotionally unstable [66].

Issues regarding interpersonal relationships and psychological well-being in narcoleptic patients are also well documented with problem areas including sexual dysfunction, depression, low levels of self-esteem, anxiety, social and emotional withdrawal, poor psychosocial adjustment, and irritability [67]. The relatively low community profile of narcolepsy, the stigma attached to the diagnosis, and the treatments prescribed (stimulants) contribute to the complexity of the impact of living with the disorder, often resulting in negative attitudes toward narcoleptic patients [67]. Furthermore, the incessant nature of the symptoms means that the patients seldom experience respite.

On September 24, 2013, the US Food and Drug Administration (FDA) held a public meeting to hear perspectives from people living with narcolepsy about their disease, its impact on their daily lives, and the effectiveness of currently available therapies. FDA conducted the meeting as part of the agency's Patient-Focused Drug Development initiative, an FDA commitment under fifth authorization of the Prescription Drug User Fee Act to more systematically gather patients' perspectives on their condition and available therapies to treat their condition.

The report underscored the chronic and debilitating effect that narcolepsy had on patient's lives. Several key themes emerged from this meeting:

(a) Excessive daytime sleepiness (EDS) was identified by most participants as the most significant symptom affecting their daily

lives. Because of EDS, they constantly battle "brain fog" and other cognitive impairments, automatic behaviors, and chronic sleep deprivation.

(b) For those who experience cataplexy, hallucinations, or sleep paralysis, the uncontrollable and often unpredictable loss of control can be terrifying for some patients. Others related that symptoms such as insomnia, weight gain, mood fluctuations, and depression have a significant negative impact on their lives.

(c) Narcolepsy patients' symptoms often changed over time. Participants identified an apparent cyclical (e.g., seasonal, monthly) nature of their symptoms, particularly with respect to their ability to sleep. For some, their symptoms, even when treated, had consistently worsened over time. Others had developed new symptoms (such as cataplexy).

(d) Narcolepsy is a debilitating condition that can exert a significant social, emotional, and financial toll on patients and their families. Participants described their difficulty in maintaining a job or attending school, caring for their households, engaging in social situations, and maintaining relationships. For some, the stigma of being labeled lazy, careless, or incapable by colleagues, health-care professionals, and others is very frustrating.

(e) Almost all participants use prescription medications to treat their condition. For many, these drugs have drastically improved their symptoms. The side effects of these drugs, however, have a significant impact on many patients' lives. Some have had to give up a beneficial drug because of intolerable side effects or because of the development of tolerance. Nondrug therapies such as scheduled naps, diet modifications, and exercise play an important role in helping narcolepsy patients manage their condition. These mechanisms, however, can be challenging to sustain.

(f) Participants stressed the importance of recognizing the broader challenges people with narcolepsy face including proper diagnosis and treatment and the support they need in their schools, workplaces, and communities.

(g) Patients see a continued need to enhance the treatment armamentarium given current challenges with variability in effectiveness, tolerability, and access to currently available treatments.

Conclusion

Narcolepsy with cataplexy is associated with a high comorbidity of both medical condition and psychiatric disorders. The symptoms of narcolepsy with cataplexy can overlap with many other disorders at times leading to misdiagnosis and inappropriate treatments. The inclusion of patients, family members, caregivers, and/or support groups is of utmost importance and would enormously be useful in gathering in-depth information about the personal issues, social problems, and treatment efficiency and adherence and compliance aspects. Multidisciplinary approach to the treatment and management offers better therapeutic benefits to the individuals affected by narcolepsy with cataplexy.

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Narcolepsy, Driving and Traffic Safety

20

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Introduction

Excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis, and nocturnal sleep disturbances are the best known symptoms of narcolepsy. Although less well described, but important in the context of driving, disturbed vigilance is also a very important symptom of narcolepsy [1]. About 4–12 % of general population suffers from EDS. Daytime sleepiness may result in reduced alertness and thus affects driving ability. The 2002 Gallup survey [2] revealed that 37 % of drivers reported that they have nodded off or fallen asleep at least once in their driving career. The Sleep in America Poll [3] showed that 91 % of respondents acknowledged that less sleep may increase the risk for injuries, but 51 % of them reported that they did drive while sleepy. Powell and colleagues [4] reported that an increase of 1 unit on the Epworth Sleepiness Scale (ESS) was associated with a 4.4 % increase of having at least one accident ($p<0.0001$). Fulda and Schulz [5] reviewed the literature concerning cognitive functioning of patients with narcolepsy. A total of 14 studies revealed narcolepsy is characterized by reduced alertness, poor performance on divided attention and tracking tasks, and reduced vigilance.

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Narcolepsy and Accident Risk

Broughton et al. [6] performed a survey among 180 patients with narcolepsy. When compared to matched controls, patients reported more often falling asleep at the wheel (66 %) and had ever near or actual accidents (67 %). Cataplexy (29 %) and even sleep paralysis (12 %) while driving were reported. These high numbers were gathered by subjective patient reports about their driving behavior. More recent studies also reported a significantly increased traffic accident risk for patients with narcolepsy [7].

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Driving Performance of Untreated Narcolepsy Patients

Findley et al. [8] examined driving performance of 10 patients with untreated narcolepsy. In the Steer Clear driving simulator, subjects observe a car driving on a two-lane drawn highway. Now and then during the 30-min task, obstacles (i.e., cartoon bulls) appear on the road. By pressing the space bar, the car changes lane and a collision is avoided. When compared to matched controls, narcolepsy patients hit a higher percentage of obstacles. Poor performance on the Steer Clear was associated with a higher reported traffic accident rate in the patients with narcolepsy.

Using the same computerized simple RT driving simulation task, Findley and colleagues [9] compared performance of 16 patients with narcolepsy with that of 31 untreated sleep apnea patients and 14 healthy controls. The number of collisions was measured in six 4-minute periods of simulated driving. Narcolepsy and sleep apnea patients had significantly more collisions than healthy controls. Interestingly, the inter-subject variability in errors among the narcoleptic patients was fourfold that of the apnea patients, and 100-fold that of the control volunteers, pointing at the great difference in impairment levels among narcoleptic patients.

George and colleagues [10] compared performance of 21 patients with sleep apnea, 16 narcolepsy patients, and 21 healthy controls. Using a simple driving simulator, participants were tested for 20 min. Tracking error was much worse in narcolepsy patients when compared to controls. The relationship between the multiple sleep latency test (MSLT) and tracking in either patient group was weak.

Kotterba and colleagues [11] compared driving simulator performance and neuropsychological test results in narcolepsy patients in order to evaluate their predictive value regarding driving ability. Thirteen patients with narcolepsy and ten healthy control subjects performed a 60-min driving simulator test (Computer-Aided Risk Simulator, CAR), including different weather and daytime conditions. Also, occasionally obstacles were present on the road. The number of accidents (crashes with other cars, pedestrians, or obstacles on the road) was recorded. Concentration lapses (e.g., disregarding traffic lights or speed limit, driving at night with switched off headlights) were counted manually. Patients with narcolepsy had significantly more accidents than healthy controls. No differences were found on the number of concentration lapses.

Philip et al. [12] examined performance of nine narcoleptic patients and ten idiopathic hypersomnia patients in a 40-min driving simulator test. Outcome measure was the number of inappropriate line crossings. Patients were either treated or untreated. Unfortunately, patients were grouped according to their sleep latencies on the MWT, and the data was not analyzed by patient group. The results were compared to 14 healthy controls and revealed that patients with pathological MWT scores, defined as having a sleep latency between 0 and 19 min, showed significantly more inappropriate line crossings than the other groups.

Treatment Effects on Driving Performance

Currently, gamma-hydroxybutyrate (sodium oxybate) is the first-line treatment option for narcolepsy patients who suffer from both EDS and cataplexy. However, up to now, the effects of sodium oxybate on driving performance of narcolepsy patients have not been examined.

Modafinil and methamphetamine are also often used to improve symptoms of EDS. The effect on driving of the stimulant drug methamphetamine has been studied in narcolepsy patients [13]. Methamphetamine was administered daily to eight narcoleptic patients (0, 20, or 40–60 mg) and eight healthy controls (0, 5, or 10 mg) for 4 days for each dosage, separated by 3 days of washout (drug-free). A test in the Steer Clear driving simulator was performed on the last day of each treatment condition. In addition, the MSLT was performed to determine sleep tendency. Sleep latency increased from 4.3 min (placebo) to 9.3 min (highest dose) in narcoleptic patients.

In healthy controls sleep latency increased from 10.4 (placebo) to 17.1 min (highest dose). In line with this, error rate on the driving task decreased from 2.53 % (placebo) to 0.33 % (highest dose) for narcoleptic patients. In healthy controls, the error rate decreased from 0.22 % (placebo) to 0.16 % (highest dose). When taking a high dose of methamphetamine, the performance of narcoleptic patients did not differ significantly from healthy controls receiving placebo. This study illustrates that stimulant drugs cause a dose-dependent decrease in daytime sleep tendency and improvement in performance.

Two healthy volunteer studies confirm improvement of driving performance after stimulant drug use. Ramaekers and colleagues [14] examined the effects of 3-4-methylenedioxy methamphetamine (MDMA) (75 mg), methylphenidate (20 mg), and placebo on driving performance in 18 recreational MDMA users. On-the-road driving tests were performed 3–5 h after drug use and the next day (27–29 h after intake) to examine possible withdrawal effects. The first driving test measured the weaving of the car while participants tried to maintain a steady lateral position within the right traffic lane and a constant speed. Primary parameter of the test is the standard deviation of lateral position (SDLP), i.e., the weaving of the car. A second driving task, also performed on a public highway in normal traffic, comprised of following a lead car. Main parameters in this task were time to speed adaptation (TSA) and break reaction time (BRT). Both MDMA and methylphenidate significantly improved driving performance as indicated by reduced weaving. However, MDMA affected performance negatively in the car following test, whereas performance after using methylphenidate did not differ significantly from placebo. During withdrawal, no significant differences from placebo were found.

Verster and colleagues [15] examined the effects of methylphenidate on driving performance in adults with attention deficit hyperactivity disorder (ADHD). After a training session and withdrawal of methylphenidate for at least 4 days, patients participated in a double-blind trial and performed an on-the-road driving test after intake of placebo or their regular dose of methylphenidate. In line with Ramaekers' findings, driving performance after using methylphenidate was significantly improved when compared to placebo. Given these findings, it can be expected that stimulant drugs will also improve driving in patients with narcolepsy.

Philip et al. [16] studied the effects of modafinil (400 mg) in 27 patients with central hypersomnia. Of them, 13 had narcolepsy and 14 suffered from idiopathic hypersomnia. In this study, patients performed a driving test on a public highway in normal traffic. Outcome measures were SDLP and the number of inappropriate line crossings. The outcomes did not differ significantly between patients with narcolepsy and idiopathic hypersomnia. For both groups combined, relative to placebo treatment, modafinil improved driving performance: it reduced SDLP ($p = 0.06$) and the number of inappropriate line crossings ($p < 0.05$). However, when treated with modafinil, the number of inappropriate line crossings in patients remained significantly higher when compared to healthy controls.

Interpretation of Driving Simulator Results

Various studies have shown that untreated narcolepsy patients have impaired cognitive functioning, especially on domains of attention and vigilance [5]. Excessive daytime sleepiness impairs performance and successful treatment should diminish these symptoms. Besides the fact that the number of driving studies examining narcolepsy treatment is limited, there are some methodological issues that should be taken into account when interpreting the results and conclusions of these studies.

First, although a relationship between daytime sleepiness and driving performance has been reported [16], the simple fact that successful treatment reduces daytime sleepiness does not automatically imply that driving is safe. Second, predicting actual driving from laboratory tests measuring attention, vigilance, and other isolated psychological skills and abilities

is often inaccurate [17]. Driving is an example of skilled but complex behavior in which various skills and abilities are integrated. These can be tested in isolation, but the results do not sum up in a predictive score of actual driving performance. Third, various driving simulators were used in the studies discussed in this chapter. Especially the older driving simulators such as the Steer Clear are in fact divided attention tasks. Subjects are seated behind a computer screen and use the computer keyboard to control a drawn car on the computer screen. These tests do not differ from other divided attention tests when it comes to predicting actual driving.

The aim of the study by Kotterba and colleagues [11] was to see whether performance on a neuropsychological test battery correlates significantly with driving simulator performance in patient with narcolepsy. If this was the case, the extensive testing methods could be replaced by a simple and shorter driving simulator test. Unfortunately, there was no correlation between driving performance and neuropsychological test results. Also, there was no significant correlation between driving simulator performance and excessive daytime sleepiness. Surprisingly, Kotterba and colleagues conclude that the driving simulator is suitable to access fitness for driving and state that "On-road evaluation may be unnecessary especially in cases with ambiguous neuropsychological test results."

The obviously artificial environment of simple driving simulators is evident to participants of experiments, and this will affect their performance accordingly. In contrast to driving in actual traffic, the tests are often experienced as a game. For example, in real life accidents may have serious consequences while this is not the case in a driving simulator. Subjects may therefore differ in risk-taking behavior in the simulator when compared to actual driving. Newer more advanced driving simulators such as the STISIM are more promising and try to make the driving test more realistic. Subjects are seated in a real car and a driving scene can be presented on a curved screen surrounding the front of the car. These newer driving simulators also include other traffic—an essential perquisite to test driving performance in a more realistic manner. Up to now, the on-the-road driving test is the gold standard to examine driving performance [18]. Performing the test on a public highway in real traffic ensures its ecological validity.

Taken together, although often claimed, there is little direct scientific evidence that treatment of narcolepsy improves driving performance. Future studies should be executed to examine driving performance of patients with narcolepsy, preferably using the on-the-road driving test during normal traffic.

Decisions on Fitness to Drive

There is no standard list of criteria or assessment scale to assess fitness to drive in people with narcolepsy. Commonly, physician and psychiatrists rely on their own clinical experience and base their decision on the presence and severity of narcolepsy symptoms. Unfortunately, decisions whether a narcolepsy patient is suitable to drive a car are not always uniform, given differences between physicians in interpretation of the assessment criteria. Ingravallo [19] reported that agreement on driving license decision ranged from 73 to 100 %. The decision correlated significantly with age, number of daytime naps, sleepiness, cataplexy, and quality of life. A survey among sleep specialists who attended the 2007 WorldSleep conference confirmed that there is disagreement whether or not narcolepsy patients should drive a car and that this depends greatly on the amount of daytime sleepiness experienced by patients [20] (see Fig. 20.1).

Currently, most European countries do not include EDS among the specific medical conditions to be considered when judging whether or not a person is fit to drive. A unified European Directive seems desirable [21]. In addition, there is a need for a social awareness program to educate the public about the potential consequences of narcolepsy and EDS in order to reduce impaired driving and the number of traffic accidents [22].

The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) states that the decision

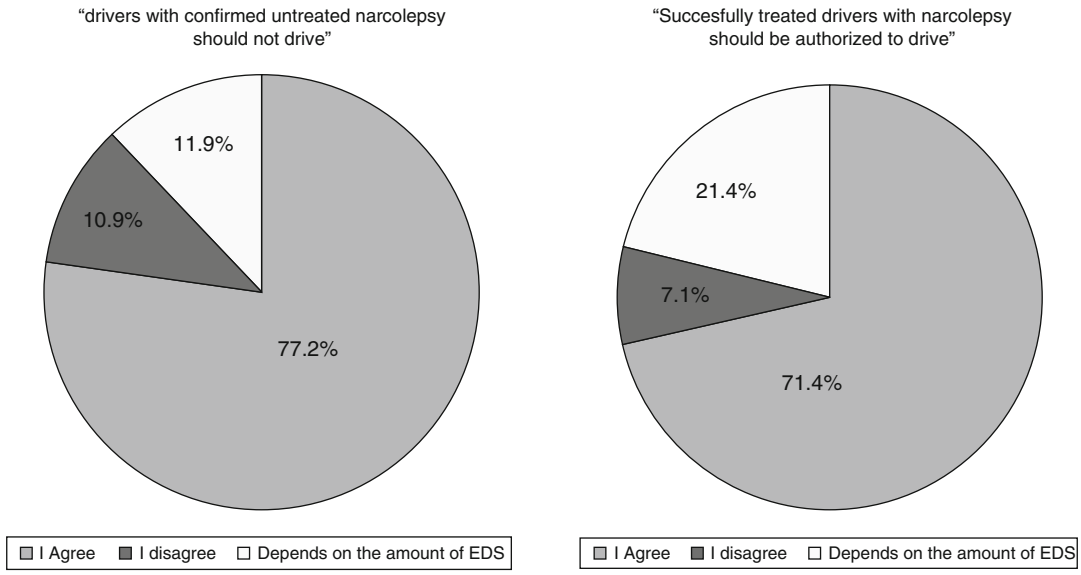

Fig. 20.1 Results from a survey conducted among attendants of the 2007 WorldSleep conference in Cairns, Australia ($N = 125$) [20]

whether or not it is safe to drive (irrespective of the condition or treatment) should be based on the results of driving tests performed in actual traffic, preferably combined with additional evidence from driving simulators and laboratory test results that examine driving-related skills and ability in isolation.

From this chapter it is evident that untreated narcolepsy may significantly impair driving ability and may increase the risk of becoming involved in traffic accidents.

More systematic epidemiological studies are needed to calculate the traffic accident risk of both treated and untreated patients with narcolepsy. Given the great variability in symptom severity between narcolepsy patients (e.g., the presence and severity of daytime sleepiness), this should be taken into account when determining whether narcolepsy patients are fit to drive or not.

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Part IV

Management

Overview of Management of Narcolepsy

21

Seiji Nishino and Nozomu Kotorii

Introduction

Narcolepsy is characterized by excessive daytime sleepiness (EDS), cataplexy, and other dissociated manifestations of rapid eye movement (REM) sleep (i.e., hypnagogic hallucinations and sleep paralysis). Non-pharmacological treatments (i.e., by behavioral modification) are often reported to be useful additions to the clinical management of narcoleptic patients. Regular napping usually relieves sleepiness (for 1–2 h) and is the treatment of choice for some patients, but this often has negative social and professional consequences. Exercising to avoid obesity, keeping a regular sleep-wake schedule, and having a supportive social environment (e.g., patient group organizations and support groups) are also helpful. In almost all cases (more than 90 % of diagnosed patients), however, a pharmacological treatment is needed.

The treatment for EDS includes the use of amphetamine-like central nervous system (CNS) stimulants and modafinil (and its *R*-enantiomer), which are new non-amphetamine wake-promoting compounds. Due to the high safety and low side effect profiles, modafinil rapidly became the first-line treatment of choice for EDS associated with narcolepsy. These compounds do not improve cataplexy and other dissociated manifestation of REM sleep, and antidepressants (monoamine uptake inhibitors) are additionally used for the treatment of cataplexy and REM sleep abnormalities. Although anticataplectic medications do not improve EDS, some monoaminergic uptake inhibitors with dopaminergic uptake inhibition are wake promoting and are occasionally used for the treatment of EDS. Caffeine may also be used in the patients with mild EDS or before the diagnosis are made. Gamma-hydroxybutyrate (GHB, a short-acting sedative, sodium oxybate is the approved formula in the USA) given at night improves EDS and cataplexy, and the number of patients treated with sodium oxybate is also increasing in the USA.

The major pathophysiology of human narcolepsy has been revealed in association with the discovery of narcolepsy genes in animal models: about 90 % of human narcolepsy–cataplexy has been found to be hypocretin/

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orexin ligand deficient. The discovery directly led to the development of new diagnostic tests (i.e., CSF hypocretin-1 measures). Hypocretin replacement is also likely to be a new therapeutic option for hypocretin-deficient narcolepsy, but this is still unavailable in humans.

In this review, we first describe clinical symptoms of narcolepsy, followed by an overview of the management of these symptoms. Both pharmacological and non-pharmacological treatments are discussed. We also discuss prospects on the new treatments. The mechanisms of actions of these pharmacological compounds are detailed in the second chapter.

Symptoms of Narcolepsy

Narcolepsy is a syndrome of unknown etiology (prevalence = 1 in 2000 [1, 2]) characterized by EDS that is often profound. About 95 % of narcoleptic cases are sporadic, but it also occurs in familial forms. Narcolepsy usually occurs in association with cataplexy and other symptoms and signs, which commonly include hypnagogic or hypnopompic hallucinations, sleep paralysis, automatic behavior, and disrupted nocturnal sleep [3]. Symptoms most often begin during adolescence or young adulthood. However, narcolepsy may also occur earlier in childhood or not until the third or fourth decade of life. Quality of life studies suggests that the impact of narcolepsy is equal to that of Parkinson's disease [4]. Although EDS is not specific for narcolepsy and is seen in other primary and secondary EDS disorders (such as sleep apnea syndrome), cataplexy is generally regarded as pathognomonic. Occurrence of cataplexy is tightly associated with loss of hypocretin neurotransmission [5], and it rarely occurs as an isolated symptom. Cataplexy occasionally occurs in conjunction with other neurological conditions such as Niemann–Pick type C disease, myotonic dystrophy, and Prader–Willi syndrome, but the pathophysiological links in these neurological conditions with the hypocretin abnormalities are not well established yet [6].

Sleepiness or Excessive Daytime Sleepiness

As with the sleepiness of other sleep disorders, the EDS of narcolepsy presents itself with an increased propensity to fall asleep, nodding or easily dozing in relaxed or sedentary situations, or a need to exert extra effort to avoid sleeping in these situations [7]. Additionally, irresistible or overwhelming urges to sleep commonly occur from time to time during wakeful periods in untreated narcolepsy patients. These so-called sleep attacks are not instantaneous lapses into sleep, as is often thought by the general public, but represent the episodes of profound sleepiness experienced by those with marked sleep deprivation or other severe sleep disorders. In addition to frank sleepiness, EDS of narcolepsy (as in other sleep disorders) can cause related symptoms including poor memory, reduced concentration or attention, and irritability. Narcoleptic subjects feel refreshed after a short nap, but this does not last long and they become sleepy again within a few hours. Narcolepsy may therefore consist of an inability to maintain wakefulness combined with the intrusion of REM sleep-associated phenomena (hypnagogic hallucinations, sleep paralysis, and possibly cataplexy; see below) into wakefulness.

Cataplexy

Cataplexy is the partial or complete loss of bilateral muscle tone in response to a strong emotion [7]. Reduced muscle tone may be minimal, occurring in a few muscle groups and causing minimal symptoms such as bilateral ptosis, head drooping, slurred speech, or dropping things from the hand, or it may be so severe that total body paralysis occurs, resulting in complete collapse. Cataplectic events usually last from a few seconds to 2 or 3 min but occasionally continue longer [8]. The patient is usually alert and oriented during the event despite their inability to respond. Positive emotions such as laughter more commonly trigger cataplexy than negative

emotions; however, any strong emotion is a potential trigger [9]. Startling stimuli, stress, physical fatigue, or sleepiness may also be important triggers or factors that exacerbate cataplexy. Children with narcolepsy often (about 1/3 of patients) present with a previously unrecognized description of cataplexy that we coined "cataplectic faces," consisting of a state of semipermanent eyelid and jaw weakness [10].

The current international classification of sleep disorders (ICSD-III) [3] for narcolepsy does not require cataplexy for diagnosing narcolepsy if REM sleep abnormalities [i.e., sleep onset REM sleep periods (SOREMPs) during multiple sleep latency test (MSLT)] are objectively documented. According to epidemiologic studies, cataplexy is found in 60–100 % of patients with narcolepsy. The percentage affected with cataplexy is reported to be in a large range because the definitions of narcolepsy vary among studies (and different diagnostic criteria are used). The onset of cataplexy is most frequently simultaneous with or within a few months of the onset of EDS, but in some cases, cataplexy may not develop until many years after the initial onset of excessive daytime sleepiness [8].

Hypnagogic or Hypnopompic Hallucinations

These phenomena may be visual, tactile, auditory, or multisensory events, usually brief but occasionally continuing for a few minutes, occurring at transitions from wakefulness to sleep (hypnagogic) or from sleep to wakefulness (hypnopompic) [7]. Hallucinations may contain combined elements of dream sleep and consciousness and are often bizarre or disturbing to patients.

Sleep Paralysis

Sleep paralysis is the inability to move, lasting from a few seconds to a few minutes, during the transition from sleep to wakefulness or from wakefulness to sleep [7]. Episodes of sleep paralysis may alarm patients—particularly those who experience the sensation of being unable to breathe. Although accessory respiratory muscles may not be active during these episodes, diaphragmatic activity continues, and air exchange remains adequate.

Other commonly reported symptoms include automatic behavior ("absent-minded" behavior or speech that is often nonsensical which the patient does not remember) and fragmented nocturnal sleep (frequent awakenings during the night).

Hypnagogic hallucinations, sleep paralysis, and automatic behavior are nonspecific to narcolepsy and occur in other sleep disorders (as well as in healthy individuals); however, these symptoms are far more common and occur with much greater frequency in narcolepsy [7].

Treatments of Narcolepsy

Pharmacological Treatment of Daytime Sleepiness with Amphetamine-Like Compounds

Non-pharmacological treatments (i.e., behavioral modification such as regular napping and work accommodations) are often helpful (see Rogers [11], Roehrs et al. [12], and Garma and Marchand [13]) (Table 21.1). Regular napping usually relieves sleepiness for 1–2 h [12] and is the treatment of choice for some patients, but this often has negative social and professional consequences. Exercising to avoid obesity and keeping a regular sleep–wake schedule are also helpful. Referral to patient support groups (e.g., narcolepsy network) and giving directives regarding driving and other potentially dangerous activities are critical until the patient achieves a better understanding and control over the disorder. Characteristics of other non-pharmacological treatments for narcolepsy are summarized in Table 21.1.

However, in a survey by a patient group organization [14], 94 % of all patients reported using pharmacological therapies, mostly stimulant medications. Sleepiness is usually treated using amphetamine-like CNS stimulants or modafinil, a novel wake-promoting compound unrelated to the

Table 21.1 Non-pharmacological approaches to the treatment of narcolepsy

Management	Description	Therapeutic target	References
Structured nocturnal sleep Avoid deprivations and shifts in sleep schedule Regular timing of nocturnal sleep (e.g., 10:30 p.m. to 7 a.m.) Relaxation techniques prior to nocturnal sleep [131] Avoidance of intense stimulation prior to nocturnal sleep	Maintain a structured bedtime and arising time, despite the quality or continuity of the nocturnal sleep. If you wake up during the night, and find it difficult to go back to sleep, you can take a short break and do a sedentary activity such as reading for a brief time. But you should return to bed and attempt to sleep. The time scheduled for nocturnal sleep should be 8 h or more	Reduction of daytime sleepiness attacks	[131]
Daytime sleep schedules Strategically timed naps 15-min naps at 12:30 and 17:00 p.m. are significant on MWT [132] Efficacy of nap: single long nap > multiple short naps > no nap [133] (single long nap: 24 % of whole sleep; multiple short naps: 4.8 % of whole sleep × 5; sleep per 24 h was held constant) 15- and 30-min naps on the 1600-h latency test are equally effective [12] Narcoleptic persons have no significant sleep inertia effects [133] Planning napping strategies before using medications	Daytime naps provide a critical part of treatment for the daytime sleepiness associated with narcolepsy. Naps may range from 15 to 20 min to longer than 1 h. Many find short naps (<30 min) refreshing, but others require longer naps. Generally, narcoleptic persons have no significant sleep inertia effects whereas increased nap duration (>15 min) provided no additional benefits. At least one nap, and usually two, proves very beneficial for almost all persons with narcolepsy. Additionally, morning impairment (steady decline in performance from time of awakening) might be curtailed by addition of a single short morning nap)	Reduction of daytime sleepiness attacks	[12, 132, 133]

Other intervention strategies within the cognitive behavioral treatment approach [134] Systematic desensitization The patient and therapist imagine a set of situations that the former typically fears, specifying as many details as possible. Then, while the patient is in a deep state of relaxation, patient is guided to imagine these scenes based on the degree of anxiety associated with them Stimulus control This technique uses the reinforcer that maintains cataplectic behavior in a continuous manner until its effect is lost. Imagery rehearsal therapy Working with the imagination while awake affects daydreaming due to the continuity of fantasies. Testing or reviewing a new dream while awake reduces nightmares Muscle relaxation [135] This technique seeks to relax the muscle groups, starting with the distal part of a limb, passing after a few seconds to another segment. The process proceeds to cover the whole body Lucid dreams [136] Remember recent hallucinations Develop intention through self-instruction Visualize recent hallucinations Repeat the above steps "Bring back" the mind to the present moment	It was proposed that CBT for narcolepsy should have three components. (a) The behavioral component begins with specific techniques aimed at changing sleep-disordered behaviors or sleep-related disorder variables that are not compatible (e.g., sleep satiation and nap training). (b) The cognitive component is aimed at modifying beliefs, motivations, and emotions that might play an important role in maintaining narcolepsy and emphasizing the psychosocial effect of the disorder. (c) The educational component seeks to instruct the patient regarding the nature of the disease, the mechanism of drug action, and precautions regarding the use of medication to achieve an overall understanding of the problem. Within the CBT approach, symptomatic strategies that have served for other disorders closely related to an emotional and physiological component have been proposed. For example, systematic desensitization is used to address cataplexy. The main characteristic of this cognitive-behavioral technique is the successive approximation of situations that increase the frequency and intensity of dysfunctional behaviors, emotions, or cognitions. Given the characteristics of cataplexy, CBT becomes a starting point for patients with narcolepsy to cope with emotions. Imagery rehearsal therapy is used effectively for nightmares and might be used among patients with narcolepsy to control sleep paralysis and hypnagogic hallucinations. Lucid dreaming decrease episodes of hypnagogic hallucinations; however, this technique should be used with caution because of the sleep fragmentation caused by training in this technique. The progressive muscle relaxation used in one case report were useful in addressing an acute problem. A larger controlled study should be performed to test these effectiveness	Reduction of cataplexy attacks Reduction of cataplexy attacks Reduction of hypnagogic hallucinations and the ability to cope with them Reduction of anxious situations that can assist in maintaining symptoms or impair patient quality of life Reduction of hypnagogic hallucinations and the ability to cope with them	[134–136]
Hypnosis [137] A physiological mechanism through which a direct suggestion is accepted by internalized self-instructions. For this to happen, four things are needed: A focus of attention; A shock; The suggestion itself; and No criticism of the suggestion	When these requirements are met, the suggestion takes root and is externalized in motor function. Thus, the suggestion has overcome the mind. Data monitoring suggests that this approach might reduce narcolepsy. A follow-up assessment at 2 months showed improvement in symptoms of sleepiness	Reduction of sleep paralysis	[137]

(continued)

Table 21.1 (continued)

Management	Description	Therapeutic target	References
Dietary practice Taking nonprescription stimulants(tea, coffee, mate, etc.) at scheduled times The caffeine content of six cups of strong coffee has about the same stimulant effect as 5 mg of dexamphetamine [113] Abstinence or minimal use of alcohol The process proceeds to cover the whole body	Little is known about the effects of diet on alertness and sleep with narcolepsy, but good dietary practices are useful in insuring good sleep hygiene. Some nonprescription stimulants such as tea and coffee are not considered as drugs, but these beverages should be prepared in a consistent manner. Use of the tablet form of caffeine permits more precise dosage monitoring	Insuring good sleep hygiene and reduction of daytime sleepiness attacks	[138]
Counseling or other assistance Counseling for reorganization of lifestyle Counseling for reconsideration of the type of work Individual or group psychotherapies [138] Assist scheduling of alertness-requiring activities Advocacy by a professional against employers	A recent study of more than 500 narcoleptics revealed that they suffer from decrease in quality-of-life measures similar to those experienced by patients with Parkinson's disease. Most victims of narcolepsy will require special considerations at work or school. Most narcoleptics will find shift work or changes in work schedule extremely difficult. Daytime work is strongly recommended. There is also much need for counseling about the psychosocial impact so that patients can optimize their adaptation to the disease and be realistic in their expectation	Improving quality of life	[138]

Table 21.2 Current pharmacological treatment for EDS associated with human narcolepsy

Compound	Usual daily doses	Half life (h)	Side effects/notes
Wake-promoting compounds for EDS:			
Sympathomimetic stimulants:			
D-amphetamine sulfate (II)	5–60 mg	16–30	Irritability, mood changes, headaches, palpitations, tremors, excessive sweating, insomnia
Methylphenidate HCl (II)	10–60 mg	~3	Same as amphetamines, less reduction of appetite or increase in blood pressure
Pemoline (IV)	20–115 mg	11–13	less sympathomimetic effect, milder stimulant slower onset of action, occasionally produces liver toxicity
Non-amphetamine wake-promoting compounds:			
Modafinil (IV)	100–400 mg	9–14	No peripheral sympathomimetic action, headaches, nausea
Armodafinil (IV)	100–300 mg	10–15	Similar to those of modafinil
Compounds improving disturbed night-time sleep and EDS			
GHB (I), Sodium oxybate (III)	20–40 mg/kg/night	~0.3	Overdoses (a single dose of 60–100 mg/kg) induces dizziness, nausea, vomiting, confusion, agitation, epileptic seizures, and hallucinations and coma with bradycardia and respiratory depression evidence of withdrawal syndrome

All compounds in the list are scheduled compounds and the class is listed in the parentheses
The half-life of s-enatiomer of modafinil is short and 3–4 h, and thus half-life of racemic modafinil mostly reflects the half-life of armodafinil (*R*-enantiomer)

amphetamines (Table 21.2). The most commonly used amphetamine-like compounds are methamphetamine, D-amphetamine, methylphenidate (all are schedule II compounds), pemoline, and mazindol (both are schedule IV compounds) (Table 21.2). The most important pharmacological property of amphetamine-like stimulants is their release of catecholamines, mostly dopamine and norepinephrine [15, 16] (see the next chapter).

The clinical use of stimulants in narcolepsy has been the subject of the American Academy of Sleep Medicine (AASM) [formerly, the American Sleep Disorders Association (ASDA)] Standards of Practice publications [17, 18]. Typically, the patient is started on a low dose, which is then increased progressively, to obtain satisfactory results (Table 21.2). Studies have shown that subjectively, daytime sleepiness can be greatly improved, but that sleep variables are never completely normalized by stimulant treatments [19]. Low-efficacy compounds/milder stimulants (such as modafinil or, more rarely nowadays, pemoline) are usually tried first. More effective amphetamine-like stimulants (i.e., methylphenidate, D-amphetamine, and methamphetamine) are then used if needed. The final dose of stimulant medication used varies widely from patient to patient (from no stimulant treatment to very high doses), depending on tolerance, personality, efficacy, and lifestyle. Patient input and work environment are very important. Some patients prefer to use high doses of long-acting, slow-release preparations to stay awake all day long, while others combine lower doses and short half-life derivatives (e.g., methylphenidate) with scheduled napping. Stimulant compounds are generally well tolerated in narcoleptic subjects. Minor side effects such as headaches, irritability, nervousness, tremors, anorexia, palpitations, sweating, and gastric discomfort are common (Table 21.2). Cardiovascular impact such as increased blood pressure is possible considering sympathomimetic effects of these classes of compounds established in animals but which

have been remarkably difficult to document in human studies [20]. Surprisingly, tolerance rarely occurs in this patient population, and "drug holidays" are not recommended by the American Academy of Sleep Medicine [17]. Stimulant abuse is rare for the well-defined narcolepsy subjects [21–24], and a compliance study had shown about half of patients who received stimulants to reduce or withdraw stimulant medications by themselves [25]. Exceptionally, psychotic complications may be observed, most often when the medications are used at high doses and chronically disrupt nocturnal sleep.

Amphetamine was first used to treat narcolepsy in 1935 [26], only 8 years after Alles recognized the stimulant activity of amphetamine [27]. Both the L-isomers and D-isomers have been used for the treatment of narcolepsy, either in isolation or as a racemic mixture (available in the USA). The D-isomer is a slightly more potent stimulant (see Parkes and Fenton [28] and Parkes [29]) and is most generally used. L-amphetamine is occasionally used in some European countries (dose range 20–60 mg) (see Parkes [30]). It is well absorbed by the gastrointestinal tract and is partially metabolized in the liver using aromatic and aliphatic hydroxylation. This process yields parahydroxyamphetamine and norephedrine, respectively, both of which are biologically active [31]. Amphetamine is metabolized into benzoic acid (23 %), which is subsequently converted to hippuric acid or to parahydroxyamphetamine (2 %). This in turn is converted to parahydroxynorephedrine (0.4 %). Thirty-three percent of the oral dose is excreted unchanged in the urine. Importantly, urinary excretion of amphetamine and many amphetamine-like stimulants is greatly influenced by urinary pH. Amphetamine is a weak base, and at the physiological pH, it exists mainly as a charged amine [RNH3]+, which is poorly reabsorbed in the renal tubules. Acidifying the urine thus favors the excretion of the charged form of the amine (see Beckett, Rowland, and Turner [32]), increases urinary excretion versus liver catabolism, and reduces the half-life. At urinary pH of 5.0, the elimination half-life of amphetamine is very short (about 3–5 h), but at pH 7.3, it increases to 21 h [32]. Sodium bicarbonate will delay excretion of amphetamine and prolong its clinical effects, whereas ammonium chloride will shorten the duration of amphetamine toxicity. Finally, D-amphetamine is available as a sulfate base derivative or as spansule (slow-release) capsules.

Methamphetamine is the most efficacious and most potent amphetamine derivative available. This compound is extremely useful in subjects with severe sleepiness who need high doses. The addition of a methyl group makes this derivative more lipophilic, thus increasing CNS penetration and providing a better central over peripheral profile. The widespread misuse of methamphetamine has led to severe legal restriction on its manufacturing, sales, and prescription in many countries (see Parkes [30]), but it is available in the USA.

Methylphenidate was introduced for the treatment of narcolepsy by Yoss and Daly almost 50 years ago [33]. It is now the most commonly prescribed amphetamine and amphetamine-like stimulant in the USA, with 46 % of narcoleptic patients using the compound on a regular basis [14]. Part of its popularity is due to its relatively short duration of action (approximately 3–4 h). This property allows narcoleptic patients to use the compound on an "as needed" basis while still keeping the possibility of napping open. The compound is also reported to produce fewer psychotic complications at high doses [34]. A slow-release formulation is available but less frequently used.

Pemoline is generally better tolerated than methamphetamine or D-amphetamine, but it is also less efficacious and less potent. Pemoline has been withdrawn from the market in several countries, including the USA, because of liver toxicity. After taking a therapeutic dose of pemoline (40 mg), peak levels in serum are reached within 4–6 h. The half-life is 16–18 h. Pemoline is partially metabolized by the liver. Metabolites include pemoline conjugates, pemoline dione, and mandelic acid. After oral administration of 40 mg of pemoline, 35–50 % of the dose is excreted in the urine within 32 h, and only a minor fraction is present as metabolites [35]. The long duration of action of pemoline may be

associated with a better compliance in narcoleptic patients [25]. Pemoline most selectively blocks dopamine reuptake and only weakly stimulates dopamine release. Fatal hepatotoxicity has been reported and may be dose related [36, 37]. Pemoline should thus not be prescribed to patients with impaired hepatic function, and hepatic function should be carefully monitored during chronic drug administration. The recent introduction of modafinil, a novel wake-promoting agent with a similar profile and less side effects, has greatly diminished the use of this compound in narcolepsy.

Modafinil and Armodafinil

Racemic modafinil, a compound structurally distinct from amphetamines, was approved in the USA in 1998 (schedule IV compounds) for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy. The compound has also been explored increasingly to treat other conditions, and clinical uses for residual sleepiness in treated obstructive sleep apnea syndrome (OSAS) and EDS associated with shift work sleep disorder (SWSD) were also approved by the FDA.

Modafinil has been available in France since 1986, and long-term follow-ups suggest no remarkable side effect profile and low abuse potential. Clinical trials in France and Canada have shown that 100–300 mg of modafinil is effective for improving daytime sleepiness in narcoleptic and hypersomnolent subjects without interfering with nocturnal sleep [38–40]. Double-blind trials on 283 narcoleptic subjects in 18 centers in the USA and 75 narcoleptic subjects in 11 centers in Canada revealed that 200 and 400 mg of modafinil significantly reduced sleepiness and improved patients' overall clinical condition [41, 42]. A systematic review and meta-analysis of the efficacy of modafinil in narcolepsy including nine trials involving 1054 patients in comparison with placebo revealed that modafinil brings significant benefit in terms of elimination of EDS as assessed by Epworth Sleepiness Scale (ESS; −2.73 points), MSLT (1.11 min), and MWT (2.82 min) [43]. A small increase in sleep latency may represent clinically significant improvements in wakefulness; however, it was also reported that patients who have previously been treated with methylphenidate may respond more poorly to modafinil [42]. It may have limited efficacy on cataplexy and the symptoms of abnormal REM sleep [38–40] but was not different from placebo in the number of attacks of cataplexy per day in the meta-analysis. Modafinil is well tolerated by these subjects, and adverse experiences with modafinil use occur at rates comparable to placebo [41, 42]. Of note, the European Medicines Agency has recently recommended the use of modafinil be restricted to the treatment of narcolepsy due to serious psychiatric side effects and skin reactions such as Stevens-Johnson syndrome [44].

In humans, modafinil exhibits a linear pharmacokinetic profile for doses ranging from 50 to 400 mg, with a terminal elimination half-life (t1/2) of 9–14 h [45]. Modafinil is extensively metabolized into two major pharmacologically inactive metabolites, modafinil acid and modafinil sulfone, which are renally excreted. Less than 10 % of the oral dose of modafinil is excreted unchanged, and 40–60 % is excreted as the unconjugated acid in urine [45].

Armodafinil is the *R*-enantiomer of modafinil (racemic), with a considerably longer half-life of 10–15 h (verses 3–4 h for the *S*-enantiomer) [46, 47]. Armodafinil was approved by the FDA in June 2007 for the treatment of EDS with narcolepsy, OSAS, and SWSD, for the same indications for those of modafinil.

The exact mode of action of modafinil is still uncertain. Some of the actions proposed are detailed in the next chapter. Similarly, the modes of action of armodafinil are still uncertain.

Several factors make modafinil an attractive alternative to amphetamine-like stimulants, and modafinil rapidly became the first-line treatment for EDS associated with narcolepsy.

First, animal studies suggest that the compound does not affect blood pressure as much as amphetamines do [48] (potentially resulting from its lack of effects on adrenergic release or reuptake). This suggests that modafinil might be

useful for patients with a heart condition or high blood pressure. Second, animal data suggest no neurotoxic effects and no or less rebound hypersomnolence upon withdrawal. Third, data obtained to date suggest that tolerance and dependence for this compound is limited [38], although a recent animal study reports a cocaine-like discriminative stimulus and reinforcing effects of modafinil in rats and monkeys, respectively [49]. Finally, clinical studies suggest that the alerting effect of modafinil might be qualitatively different from that of amphetamine [38]. In general, patients feel less irritable and/or agitated with modafinil than with the amphetamines [38]. In animal experiments, modafinil did not induce behavioral excitation, as measured by lack of locomotor activation [50].

The efficacy profile of armodafinil has demonstrated that it has longer wake-promoting effects than modafinil. Despite similar half-lives (9–14 h), plasma concentration following armodafinil administration lasts longer than that following modafinil administration, resulting in a more prolonged effect during the day and potential improvement in sleepiness throughout the day in patients with narcolepsy [51]. Once-a-day treatment with modafinil may not be adequate in some patients who have not been able to maintain a sufficient level of wakefulness throughout the day. Lower doses of armodafinil, 150 and 250 mg, were used in a phase III trial [52], whereas earlier modafinil trials used 200 and 400 mg. Armodafinil is available at lower doses than modafinil, indicating the potential for an improved safety profile.

Other Wake-Promoting Agents

Mazindol (2–8 mg daily), a sympathomimetic anorectic agent, is less frequently used due to its weaker stimulant activity (see Iijima et al. [53]). At these doses, mazindol produces central stimulation, a reduction in appetite, and an increase in alertness, but has little or no effect on mood or the cardiovascular system. It is a weak releasing agent of dopamine, but it also blocks dopamine and norepinephrine reuptake with high affinity (see Nishino et al. [54]). Mazindol is effective for both excessive daytime sleepiness and cataplexy [53]. Mazindol is absorbed quantitatively at a medium rate from the gastrointestinal tract, and the peak blood concentration is reached after 2–4 h. The half-life of clearance from blood was estimated to be 33–55 h [55].

Bupropion is a DA reuptake inhibitor that may be useful for the treatment of EDS associated with narcolepsy (100 mg t.i.d.) [56, 57]. It may be especially useful in cases associated with atypical depression [57]. Convulsion is a dose-dependent risk of bupropion (0.1 % at 100–300 mg and 0.4 % at 400 mg).

Caffeine, a xanthine derivative, may be the most popular and widely consumed stimulant in the world. The average cup of coffee contains about 50–150 mg of caffeine. Tea (25–90 mg/5 oz), cola drinks (35–55 mg/12 oz), chocolate (15–30 mg/1 oz), and cocoa (2–20 mg/5 oz) also contain significant amounts of caffeine. Taken orally, caffeine is rapidly absorbed, taking 47 min to reach maximum plasma concentration. The half-life of caffeine is about 3.5–5 h [58]. A slow-release soft gelatin caffeine capsule is also available with a mean delay in peak plasma concentration of 4 h [58]. The behavioral effects of caffeine include increased mental alertness, faster and clearer flow of thought, increased wakefulness, and restlessness [59]. Fatigue is reduced, and the need for sleep is delayed [59]. Physical effects of caffeine include palpitations, hypertension, increased secretion of gastric acid, and increased urine output [59]. Heavy consumption (12 or more cups a day or 1.5 g of caffeine) can cause agitation, anxiety, tremors, rapid breathing, and insomnia [59]. The mechanism of action of caffeine involves antagonism of an adenosine (nonspecific) receptor and of adenosine-induced neuronal inhibition [59] (see details in the next chapter). Considering the fact that 100 mg of caffeine is roughly equivalent to one cup of coffee, caffeine does not possess the efficacy to counteract the pathological sleepiness seen in narcolepsy. Nevertheless, caffeine can be bought without a prescription in the form of tablets (No Doz®, 100 mg caffeine; Vivarin® 200 mg caffeine) and is used by many patients with narcolepsy prior to diagnosis [60].

Caffeine is metabolized into three active metabolites, paraxanthine, theobromine, and theophylline. Recently, it was demonstrated that paraxanthine significantly promoted wakefulness and proportionally reduced NREM and REM sleep in both control and narcoleptic mice [61]. The wake-promoting potency of paraxanthine (100 mg/kg p.o.) is greater than that of the parent compound, caffeine (92.8 mg/kg p.o.), and comparable to that of modafinil (200 mg/kg p.o.) [61]. High dose of caffeine and modafinil induced hypothermia and reduced locomotor activity, while paraxanthine did not [61]. In addition, behavioral test revealed that the compound possessed lesser anxiogenic effects than caffeine [61]. Although further evaluation in human should be needed, paraxanthine may be a better wake-promoting agent for normal individuals, as well as patients suffering hypersomnia, including narcolepsy.

Sodium Oxybate and Treatment of Disturbed Nocturnal Sleep

Insomnia is a major complaint in narcoleptic subjects. Several studies reported that benzodiazepine hypnotics are effective in consolidating nighttime sleep in patients with narcolepsy [62]. GHB, a compound with remarkable REM- and SWS- inducing properties, has also been used for consolidating nighttime sleep, an effect that leads to decreased sleepiness and cataplexy the following day [63–66]. Due to its positive effects on mood and libido, its SWS-enhancing properties, and a subsequent increase in growth hormone release, the drug is widely abused by athletes and other populations [67, 68]. In addition, because of its euphorigenic, behavioral disinhibitive, and amnestic properties, coupled with simple administration (i.e., high solubility, colorlessness, and tastelessness of drink), the abuse/misuse of GHB as a recreational substance and as a so-called date-rape drug has risen sharply in recent years, leading to an increased number of overdoses and intoxications for which no specific antidote exists [69, 70].

However, recent large-scale double-blind placebo-controlled clinical trials in the USA lead to reestablish sodium oxybate (sodium salt of GHB) as a first-line treatment for narcolepsy–cataplexy [71–74] (see also Morgenthaler et al. [18]). In the USA, sodium oxybate is the approved formula of GHB and classified as a schedule III compound, while GHB itself is classified as a schedule I drug that currently has no accepted medical use for treatment in the USA.

The compound is especially useful in patients with severe insomnia and cataplexy who do not tolerate well the side effects of antidepressant medication on sexual potency. Although improvement in sleepiness occurs relatively quickly, anticataplectic effects appeared 1–2 weeks after the initiation of the treatment. Sodium oxybate has demonstrated statistically significant improvements in both symptoms EDS and cataplexy, either as monotherapy or in combination with modafinil, in clinical trials [75]. The recommended starting dose is 4.5 g a night divided into two equal doses of 2.25 g, which may be adjusted up to a maximum of 9 g per night in increments of 1.5 g per night at 1- to 2-week intervals. The benefit was significant after 4 weeks, highest after 8 weeks and was maintained during long-term therapy [76]. The modes of actions of sodium oxybate on sleep and sleep-related symptoms are largely unknown (see the next chapter). The compound has also been reported to increase periodic leg movements in narcoleptic patients [77].

Sodium oxybate is absorbed 15–20 min after oral ingestion, and peak plasma concentration occurs at 60–120 min. The elimination half-life is 20 min [78, 79]. Exogenous sodium oxybate is almost completely eliminated by oxidative biotransformation to carbon dioxide and water; less than 5 % is detected unmetabolized in the urine [78, 79]. At low doses, sodium oxybate is an anxiolytic and myorelaxant. At intermediate doses, sodium oxybate increases slow-wave sleep and REM sleep [80]. However, due to the short half-life of the compound, its effects on sleep architecture are short lasting (about 3–4 h), and administration thus has to be repeated two to three times during the night (20–40 mg/kg/night).

Overdoses (a single dose of 60–100 mg/kg) induce dizziness, nausea, vomiting, confusion, agitation, epileptic seizures, hallucinations, and coma with bradycardia and respiratory depression [81].

There was no evidence of rebound cataplexy upon discontinuation after long-term treatment [72]. There is little evidence of withdrawal syndrome after prescribed usage of sodium oxybate [82]; however, withdrawal symptoms following excessive use can be severe [83, 84].

Antidepressants and the Pharmacological Treatment of Cataplexy

Amphetamine stimulants and modafinil have little effect on cataplexy, and additional compounds are most often needed to control cataplexy if the symptom is severe enough to warrant treatment. Since the 1960s, it has been known that imipramine is very effective in reducing cataplexy [21]. Together with protriptyline and clomipramine, these tricyclic antidepressants are now the most commonly used anticataplectic agents [14] (Table 21.3). Other antidepressant compounds of the tricyclic family have also been used with some success (Table 21.3). The use of tricyclic antidepressants in the treatment of cataplexy is, however, hampered by a number of problems. The first one is the relatively poor side effect profile of most tricyclic compounds. These are mostly due to their anticholinergic properties, leading to dry mouth (and associated dental problems), tachycardia, urinary retention, constipation, and blurred vision (see Table 21.3). Additional side effects are weight gain, sexual dysfunction (impotence and/or delayed orgasm), tremors, antihistaminergic effects leading to sedation, and occasionally orthostatic hypotension due to the alpha-1 adrenergic blockade effects of some compounds. In this respect, protriptyline is often preferred, due to its previously reported mild stimulant effect (see Henry et al. [85]). Nighttime sleep might also become more disturbed due to increased muscle tone and leg movements [86, 87]. The cardinal pharmacological property of tricyclic antidepressants is their ability to inhibit the reuptake of norepinephrine (and epinephrine) and serotonin (see Baldessarini [88]). The degree of uptake inhibition of norepinephrine and serotonin is quite variable depending on the compound and the existence of active metabolites (mostly active on adrenergic uptake) (see Baldessarini [88]). Additionally, some tricyclic compounds, such as protriptyline, are also weak dopamine reuptake inhibitors [88].

The introduction of newer antidepressants with selective serotonergic uptake inhibition properties (e.g., SSRIs) and no anticholinergic effects, such as fluoxetine, fluvoxamine, paroxetine, sertraline, femoxamine, zimelidine, and trazodone, has raised hope that the control over cataplexy could be achieved with fewer side effects. In general, however, clinicians have been less impressed with the potency of the serotonergic compounds on cataplexy [89–91]. This experience parallels experiments in canine narcolepsy suggesting that adrenergic, and not serotonergic, uptake inhibition mediates the anticataplectic effects of most antidepressant medications [92, 93] (see the next chapter). Among the SSRIs, fluoxetine is a viable alternative to tricyclic compounds [89]. Fluoxetine has a good side effect profile and may induce less weight gain, a significant advantage for some patients. It is to be noted that there is a risk of prolonged rebound cataplexy after withdrawal of tricyclic antidepressants and SSRIs [94, 95]. Venlafaxine, a novel serotonergic and noradrenergic reuptake inhibitor (SNRI), has also been used recently with good success. Recently, a pilot study of duloxetine, a new SNRI, was conducted in three patients with narcolepsy/cataplexy [96]. A rapid and powerful anticataplectic activity, strongly associated with EDS improvement with few side effects, was observed. Finally, the introduction of reboxetine, a specific adrenergic reuptake blocker, may offer a novel and more effective alternative to SSRIs and tricyclic antidepressants based on animal data.

In addition to the antidepressants listed in Table 21.3, GHB (or sodium oxybate), a hypnotic compound discussed in greater detail in the section on disrupted nocturnal sleep, has been shown to alleviate cataplexy during long-term administration.

Table 21.3 Currently used anticataplectic agents

Antidepressants compound	Usual daily doses	Half-life (h)	Notes/side-effects
Tricyclics:			
Imipramine	10–100 mg	5–30	Dry mouth, anorexia, sweating, constipation, drowsiness
Desipramine	25–200 mg	10–30	(NE>>5-HT>DA) a desmethyl metabolite of imipramine, effects and side effects similar to those of imipramine
Protriptyline	5–60 mg	55–200	(NE>5-HT>DA) reported to improve vigilance measures anticholinergic effects
Clomipramine	10–150 mg	15–60	(5-HT>NE>>DA) Digestive problem, dry mouth, sweating, tiredness, impotence. Anticholinergic effects. Desmethyl-chlomipramine (NE>>5-HT>DA) is an active metabolite
SSRIs:			
Fluoxetine	20–60 mg	24–72	No anticholinergic or antihistaminergic effects good anticataplectic effect but less potent than clomipramine. Active metabolite nor fluoxetine has more adrenergic effects
Fluvoxamine	50–300 mg	15	No active metabolite, pharmacological profile similar to fluoxetine less active than clomipramine, gastrointestinal side effects
SNRIs:			
Venlafaxine	150–375 mg	4	New serotonergic and adrenergic uptake blocker; no anticholinergic effects, effective on cataplexy and sleepiness, nausea
Milnaciplan	30–50 mg	8	New serotonergic and adrenergic uptake blocker; no anticholinergic or antihistaminergic effects, effective on cataplexy
NRI:			
Atomotetin	40–60 mg[a]	5.2	Normally indicated for Attention Deficit Hyperactivity Disorder (ADHD)
Compounds improving disturbed night-time sleep and cataplexy			
GHB, Sodium oxybate	20–40 mg/kg/night	~0.3	Overdoses (a single dose of 60–100 mg/kg) induce dizziness, nausea, vomiting, confusion, agitation, epileptic seizures, and hallucinations and coma with bradycardia and respiratory depression no cataplexy rebound reported upon discontinuation

SSRI selective serotonin reuptake blocker, *NSRI* norepinephrine/serotonin reuptake inhibitor, *NRI* norepinephrine reuptake inhibitor

Reboxetine is another NRI, but is not available in the USA

[a]Doses for treatments for ADHD are suggested to be lowered when starting anticataplectic treatment. Gamma hydroxybutyric acid is available as Sodium Oxybate in the USA and classified as Scheduled III compounds

MAOIs (monoamine oxidase inhibitors) are known to potently reduce REM sleep and are therefore excellent candidate anticataplectic agents. However, these compounds are less often used due to their poor safety profile. Selective or reversible MAOIs have recently become available, but large-scale clinical trials on these compounds are still not available (see Nishino and Mignot [7]).

Treatment of Sleep Paralysis and Hypnagogic Hallucinations

The treatment of these two symptoms is not well codified. Hypnagogic hallucinations can be quite bothersome and often occur in patients who also suffer from frequent nightmares. As they are a manifestation of sleep onset REM sleep, the compounds that suppress REM sleep are usually

Table 21.4 Evaluations of hypocretin ligand replacement therapy in the animal model of narcolepsy

Approaches	Animal models	Methods	Effect on cataplexy	Effects on sleep	References
Peptide replacement					
	Ligand deficient narcoleptic dog	IV	Very short lasting anticataplectic effect	NA	[100]
	Ligand deficient narcoleptic dog	Intrathecal	No effect	NA	[101]
	Ligand deficient mice	ICV	Improve	Wake-promoting	[102]
Gene therapy					
	Ligand deficient mice	Diffuse expression of ligand (TG with beta-actin promoter)	Improve		[102]
	Ligand deficient mice	Transient expression of ligand (with AAV vector) in the LH	Improve		[139]
Cell transplantation					
		Cells transplanted (LH from 10-day old rats) survive for a short period (up to 36 days)	NA	NA	[140]

IV intravenous, *ICV* intracerebroventriclular, *AAV* adeno-associated virus, *TG* transgenic, *LH* lateral hypothalamus

helpful in alleviating this symptom, and tricyclic antidepressant treatment has been reported to have some beneficial effects [97]. Sleep paralysis only rarely requires treatment, but tricyclic antidepressants are also very effective for preventing this symptom. Recently, high doses (60 mg qd) of fluoxetine have been advocated as a very active treatment for isolated sleep paralysis [98]. GHB is also effective in suppressing hypnagogic hallucinations, sleep paralysis, and cataplexy [99].

Future Treatment Options

Since a large majority of human narcolepsy patients are hypocretin ligand deficient, hypocretin replacement therapy may be a new therapeutic option. This may be effective for both sleepiness (i.e., fragmented sleep/wake pattern) and cataplexy. Animal experiments using ligand-deficient narcoleptic dogs suggest that stable and centrally active hypocretin analogs (possibly non-peptide synthetic hypocretin ligands) will need to be developed in order to be peripherally effective [100, 101] (Table 21.4). This is also substantiated by a mice study that found normalization of sleep/wake patterns and behavioral arrest episodes (equivalent to cataplexy and REM sleep onset) in hypocretin-deficient mice knockout models supplemented by central administration of hypocretin-1 [102] (Table 21.4). In addition, orexin gene therapy (injection of an adeno-associated viral vector coding for prepro-orexin plus a red fluorescence protein into the medipbasal hypothalamus) markedly improved the maintenance of wakefulness in orexin/ataxin-3 narcoleptic mice [103].

These results demonstrate that cell transplantations and gene therapy may be developed in the future (see Table 21.4). One of the concerns for this option is that the hypocretin peptides do not cross the brain barrier (BBB) well. Intranasal delivery is a noninvasive method of bypassing the BBB to deliver therapeutic agents to the brain and spinal cord. Recent reports in both rhesus monkeys and humans show some effects using intranasal hypocretin-1 administration [104, 105]. A recent double-blind, randomized,

placebo-controlled crossover design study on seven patients with narcolepsy/cataplexy and matched healthy controls showed that intranasal hypocretin-1 restores olfactory function in narcolepsy/cataplexy patients [104]. But unfortunately, no data exist concerning potential effects on daytime sleepiness and cataplexy at this time.

Another concern is the receptor function in ligand-deficient narcolepsy. A significant degree of ligand deficiency is already evident at the disease onset. Life-long treatment of narcolepsy is required, and thus preserved receptor functions, many years after the loss of ligand, are essential for the replacement therapy. In order to evaluate changes in hypocretin receptors in hypocretin-deficient narcolepsy, Mishima et al. [106] recently studied hypocretin receptor gene expressions of ligand-deficient narcolepsy in mice, dogs, and humans. Substantial decline (by 50–71 %) in the expression of hypocretin receptor genes was observed in both ligand-deficient humans and dogs. The result in the mice study suggested that decline is progressive over age. However, about 50 % of the original expression was still observed in old human subjects. It is unknown if this is beneficial for the patients. However, since narcoleptic Dobermans heterozygous for hypocretin receptor 2 mutation (supposed to express 50 % of hypocretin receptor 2 genes and normal levels of hypocretin [107]) are asymptomatic, it is likely that an adequate ligand supplement prevents narcoleptic symptoms of hypocretin-deficient patients.

Beside hypocretin replacement, preclinical and clinical trials for new classes of compounds are also in progress. Some histaminergic compounds may be used for wake promotion. Histamine has long been implicated in the control of vigilance, and H1 antagonists are strongly sedative. The downstream effects of hypocretins on the histaminergic system (hcrtr2 excitatory effects) are likely to be important in mediating the wake-promoting properties of hypocretin [108]. In fact, brain histamine and CSF histamine contents are reduced in narcoleptic subjects [109]. Reduction of histamine contents is also observed in human narcolepsy and other hypersomnia of central origin [109, 110]. Although centrally injected histamine or histaminergic H1 agonists promote wakefulness, systemic administrations of these compounds induce various unacceptable side effects via peripheral H1-receptor stimulation. In contrast, the histaminergic H3 receptors are regarded as inhibitory autoreceptors and are enriched in the central nervous system. H3 antagonists enhance wakefulness in normal rats and cats [111] and in narcoleptic mice models [112]. Histaminergic H3 antagonists might be useful as wake-promoting compounds for the treatment of EDS or as cognitive enhancers [113], and several histaminergic H3-receptor antagonists/inverse agonists are currently being investigated.

Pitolisant (previously called BF2.649 and tiprolisant, Bioprojet Ltd., Paris, France) was the first clinically used inverse agonist of the histamine H3 autoreceptor that increases histamine release in the hypothalamus and cortex. In a pilot single-blind study on 22 patients with narcolepsy/cataplexy, pitolisant 40 mg in the morning reduced excessive daytime sleepiness [114]. Recent double-blind phase III trials on 95 narcoleptic subjects in 32 sleep disorder centers in five European countries revealed that pitolisant (10, 20, or 40 mg a day) once a day was efficacious on two major symptoms of narcolepsy, EDS and cataplexy, compared with placebo and well tolerated compared with twice-a-day modafinil (100, 200, or 400 mg a day) [115]. If these findings are substantiated in further ongoing studies, H3-receptor inverse agonists including pitolisant could offer a new treatment option for patients with narcolepsy.

Another possible area that currently gathers less pharmaceutical interest is the use of thyrotropin-releasing hormone (TRH) direct or indirect agonists. TRH itself is a small peptide, which penetrates the blood–brain barrier at very high doses. Small molecules with agonistic properties and increased blood–brain barrier penetration (i.e., CG3703, CG3509, or TA0910) have been developed, partially thanks to the small nature of the starting peptide [116]. TRH (at the high dose of several mg/kg) and TRH agonists increase alertness and have been shown to be

wake promoting and anticataplectic in the narcoleptic canine model [117, 118], and it has excitatory effects on motoneurons [119]. Initial studies had demonstrated that TRH enhances DA and NE neurotransmission [120, 121], and these properties may partially contribute to the wake-promoting and) anticataplectic effects of TRH. Interestingly, recent studies have suggested that TRH may promote wakefulness by directly interacting with the thalamocortical network; TRH itself and TRH receptor type 2 are abundant in the reticular thalamic nucleus [122]. Local application of TRH in the thalamus abolishes spindle wave activity [123], and in the slice preparations, TRH depolarized thalamocortical and reticular/perigeniculate neurons by inhibition of leak K+ conductance [123].

Other pathways with possible applications in the development of novel stimulant medications include the adenosinergic system (more selective receptor antagonists than caffeine), the dopaminergic/adrenergic system (e.g., DA/NE reuptake inhibitors), the GABAergic system (e.g., inverse benzodiazepine agonists), and the glutamatergic system (ampakines) (see Mignot and Nishino [124]).

It is also interesting to evaluate anticataplectic effects of D2/D3 antagonists in humans, since experiments in canine narcolepsy have suggested that dopamine D2/D3 receptor mechanisms may be more specifically involved in regulation of cataplexy (and sleep-related motor control) than of REM sleep [125].

Narcolepsy with cataplexy is currently thought to be an autoimmune disorder targeting hypothalamus hypocretin neurons. An autoimmune basis for the hypocretin cell loss in narcolepsy has been suspected due to its strong DQB1*0602 association, association with T-cell receptor polymorphisms [126], and recently reported tribble autoantibodies [127]. Based on the autoimmune hypothesis of narcolepsy, immune-based therapy such as steroids (in one patient), intravenous immunoglobulins (IVIg), and plasmapheresis have been proposed, with some promising results in a few cases [128, 129]. Recently, the case of narcolepsy with cataplexy with undetectable CSF hypocretin-1 level that completely reversed shortly after disease onset was reported [130]. Although needing replication in well-designed trials, these results suggest that immune-based therapy could become a new treatment option for patient with narcolepsy/cataplexy at disease onset.

Conclusion

Non-pharmacological treatments (i.e., behavioral modification such as regular napping and work accommodations) are often helpful. Nevertheless, over 90 % of diagnosed narcoleptic patients are reported to take medications to control symptoms.

Amphetamine-like stimulants have been used in the treatment of EDS in narcolepsy and various other conditions for decades. Amphetamines are sympathomimetic amines and induce various side effects. Amphetamines are also classified schedule II compounds.

Racemic modafinil, a compound structurally distinct from amphetamines, was developed and approved for treatment for EDS associated with narcolepsy (in 1998 in the USA). Due to the high safety and low side effect profiles, modafinil rapidly become the first-line treatment choice for EDS associated with narcolepsy. The mode of action of the modafinil remains controversial and may involve dopaminergic and/or non-dopaminergic effects. Whatever its mode of action is, the compound is generally found to be safer and to have a lower abuse potential than amphetamine stimulants. Amphetamines and modafinil do not improve cataplexy and dissociated manifestation of REM sleep, and antidepressants (monoamine uptake inhibitors) are additionally used for the treatment of cataplexy and REM sleep abnormalities.

Tricyclic antidepressants potently reduce REM sleep and have been used for treatments of cataplexy and other REM sleep abnormalities, but these classes of compounds induce various side effects (anticholinergic and antihistaminergic). The second-generation antidepressants, SSRIs, are also very commonly used as anticataplectics

in human. This is mostly due to their better side effect profiles, but the anticataplectic effects of these compounds are rather modest. Recently, selective NE and NE/5-HT reuptake inhibitors were introduced, and evaluations of these are in progress and may bring profound beneficial insights.

GHB, a compound with remarkable REM- and SWS-inducing properties, has also been used for consolidating nighttime sleep, an effect that leads to decreased sleepiness and cataplexy the following day. Recent large-scale double-blind placebo-controlled clinical trials in the USA lead to reestablish sodium oxybate (sodium salt of GHB) as a first-line treatment for narcolepsy–cataplexy. It should be noted that the therapeutic window for the compound is narrow, and overdose may induce fatal side effects.

Other classes of compounds/systems with possible applications in the development of novel stimulant/anticataplectic medications include the histamine system (especially H3-receptor antagonists), TRH system (TRH analogs), D2/3 antagonists (for cataplexy), reversible and selective MAOI, the adenosinergic system, the dopaminergic/adrenergic system (e.g., some DA/NE reuptake inhibitors), the GABAergic system (e.g., inverse benzodiazepine agonists), and the glutamatergic system (ampakines).

Finally, hypocretin replacement therapy may be more straightforward and efficient for the treatment of both cataplexy and sleepiness, but the development of small molecular weight peptide agonists or method of bypassing the BBB to deliver therapeutic agents to the brain and spinal cord is essential. If these are effective in humans, cell transplantation and/or gene therapy and immune-based therapy may also be developed in the near future.

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22 Modes of Action of Drugs Related to Narcolepsy: Pharmacology of Wake-Promoting Compounds and Anticataplectics

Seiji Nishino and Nozomu Kotorii

Introduction

More than 90 % of patients diagnosed with narcolepsy receive pharmacological treatments. The pharmacological treatments of excessive daytime sleepiness (EDS) include amphetamine-like central nervous system (CNS) stimulants and modafinil (and its *r*-enantiomer). Other less often used stimulants are compounds with dopamine uptake inhibitions. Caffeine is the most commonly consumed CNS stimulant in humans through coffee and various food and drinks containing products derived from the kola nut or from cacao, and caffeine may also be effective for mild EDS cases. These compounds do not improve cataplexy and other REM sleep abnormalities (hypnagogic hallucinations and sleep paralysis), and antidepressants (monoamine uptake inhibitors) are additionally used for the treatment of cataplexy and REM sleep abnormalities. Gamma-hydroxybutyrate (GHB, a short-acting sedative; sodium oxybate in the USA) given at night reduces both EDS and cataplexy.

A series of pharmacological experiments, especially using the canine models of narcolepsy, revealed the major mode of wake-promoting action of amphetamines, amphetamine-like compounds, and monoamine uptake inhibitors: wake-promoting effects of these compounds are mediated by presynaptic enhancement of dopaminergic neurotransmission. This mechanism may also be the major mode of action of modafinil, but this is still debated.

Modes of action of anticataplectic compounds have also been revealed by animal experiments in a same way, and an enhancement of noradrenergic transmission is primarily involved in the therapeutic action of monoamine uptake inhibitors. Mechanisms of actions of GHB, however, are largely unknown and remain to be studied.

In this review, the modes of actions proposed for the therapeutic compounds for narcolepsy are discussed.

Neurobiology of Wakefulness and Modes of Action of Amphetamines and Modafinil on EDS

Amphetamine was first synthesized in 1897, but its stimulant effect was not recognized until 1929, by Alles. In 1935, amphetamine was used for the

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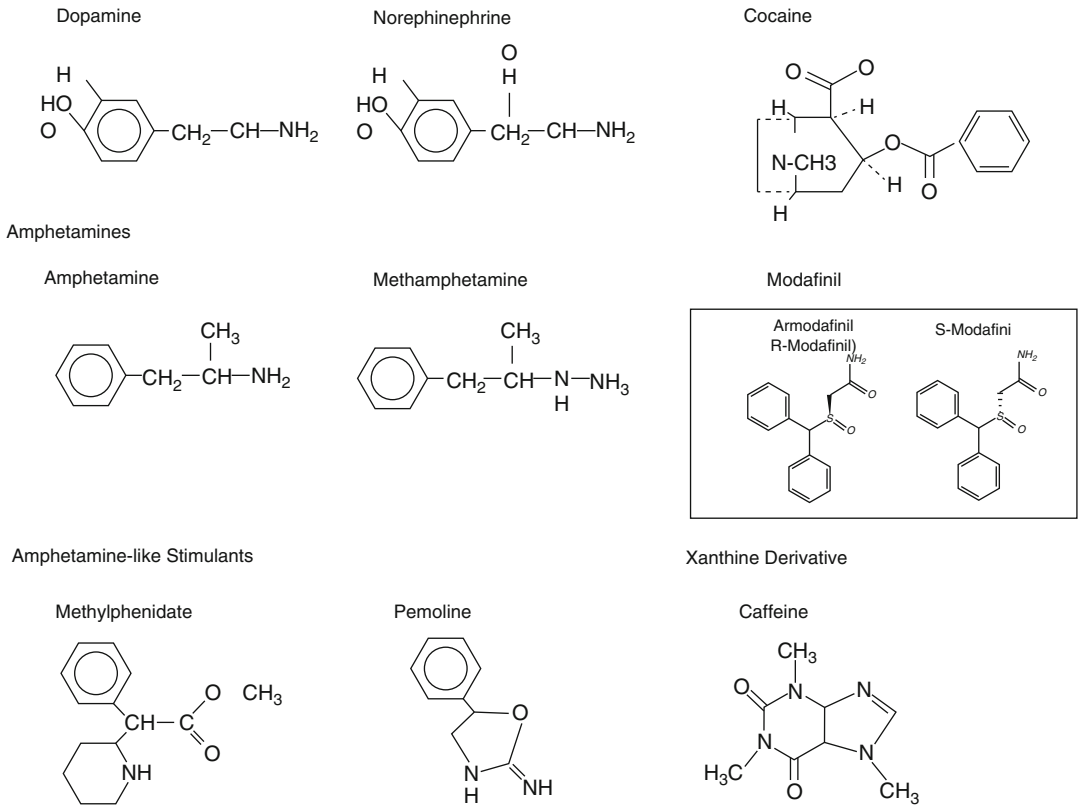

Fig. 22.1 Chemical structures of amphetamine-like stimulants, cocaine, modafinil, armodafinil, and caffeine (a xanthine derivative), as compared to dopamine (DA) and norepinephrine (NE)

first time for the treatment of narcolepsy. Narcolepsy was possibly the first condition for which amphetamine was used clinically. It revolutionized therapy for the condition, even though it was not curative. The piperazine derivative of amphetamine, methylphenidate, was introduced for the treatment of narcolepsy in 1959 by Yoss and Daly, but both compounds share similar pharmacological properties.

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) is a chemically unique compound developed in France (Fig. 22.1). Modafinil has been available in France since 1984 on a compassionate mode and was approved in France in 1992. Modafinil has been approved (and its *R*-enantiomer in 2007) in 1998 in the USA for the treatment of narcolepsy, shift work disorder, and residual sleepiness in treated patients with sleep apnea syndrome.

To understand how these compounds promote wakefulness, it is helpful to first review some of the basic anatomical and physiological pathways that promote wakefulness.

Neurobiology of Wakefulness

Sleep/wake is a complex physiology regulated by brain activity, and multiple neurotransmitter systems such as monoamines, acetylcholine, excitatory and inhibitory amino acids, peptides, purines, and neuronal and non-neuronal humoral modulators (i.e., cytokines and prostaglandins) [1] are likely to be involved. Monoamines are perhaps the first neurotransmitters recognized to be involved in wakefulness [2], and the monoaminergic systems had been the most common pharmacological targets for wake-promoting

compounds in the past years. On the other hand, most hypnotics target the gamma-aminobutyric acid (GABA)ergic system, a main inhibitory neurotransmitter system in the brain [3].

Cholinergic neurons also play critical roles in cortical activation during wakefulness (and during REM sleep) [1]. Brainstem cholinergic neurons originating from the laterodorsal and pedunculopontine tegmental nuclei activate thalamocortical signaling, and cortex activation is further reinforced by direct cholinergic projections from the basal forebrain. However, currently no cholinergic compounds are used in sleep medicine, perhaps due to the complex nature of the systems and prominent peripheral side effects.

Monoamine neurons, such as norepinephrine (NE)-containing locus coeruleus neurons, serotonin (5HT)-containing raphe neurons, and histamine containing tuberomammillary neurons, are wake-active and act directly on cortical and subcortical regions to promote wakefulness [1]. In contrast to the focus on these wake-active monoaminergic systems, researchers have often underestimated the importance of dopamine (DA) in promoting wakefulness. Most likely, this is because the firing rates of midbrain DA-producing neurons [ventral tegmental area (VTA) and substantia nigra] do not have an obvious variation according to behavioral states [4]. In addition, DA is produced by many different cell groups [5], and which of these promote wakefulness remains undetermined. Nevertheless, DA release is greatest during wakefulness [6], and DA neurons increase discharge and tend to fire bursts of action potentials in association with significant sensory stimulation, purposive movement, or behavioral arousal [7]. Lesions that include the dopaminergic neurons of the VTA reduce behavioral arousal [8]. Recent work has also identified a small wake-active population of dopamine-producing neurons in the ventral periaqueductal gray that project to other arousal regions [9]. People with DA deficiency from Parkinson's disease are often sleepy [10], and dopamine antagonists (or small doses of dopamine autoreceptor (D2/3) agonists) are frequently sedating. These physiologic and clinical findings clearly demonstrate that DA also plays a role in wakefulness.

Wakefulness (and physiology associated with wakefulness) is essential for the survival of creatures and, thus, is likely to be regulated by multiple systems, each likely having a distinct role. Some arousal systems may have essential roles for cortical activation, attention, cognition, or neuroplasticity during wakefulness, while others may only be active during specific times to promote particular aspects of wakefulness. Some of the examples may be motivated behavioral wakefulness or wakefulness in emergency states. Wakefulness may thus likely be maintained by many systems with differential roles coordinating in line. Similarly, wake-promoting mechanism of some drugs may not be able to be explained by a single neurotransmitter system.

Modes of Action of Amphetamines

Phenylisopropylamine (amphetamine) has a simple chemical structure resembling endogenous catecholamines (Fig. 22.2). The pharmacological effects of most amphetamine derivatives are isomer specific. D- (or S-) Amphetamine, for example, is a far more potent stimulant than the L- (or R-) derivative. In EEG studies, D-amphetamine is four times more potent in inducing wakefulness than L-amphetamine [11]; not all effects are, however, isomer specific. For example, both enantiomers are equipotent at suppressing REM sleep in humans and rats [11] and at producing amphetamine psychosis. The relative effects of the D- and L-isomers of amphetamine on NE and DA transmission may explain some of these differences (for details, see the pharmacology section).

Amphetamine-like compounds, such as methylphenidate, pemoline, and fencamfamine, are structurally similar to amphetamines; all compounds include a benzene core with an ethylamine group side chain (Phenethylamine derivatives: Fig. 22.1). Both methylphenidate and pemoline were commonly used for the treatment of EDS in narcolepsy, but pemoline has been

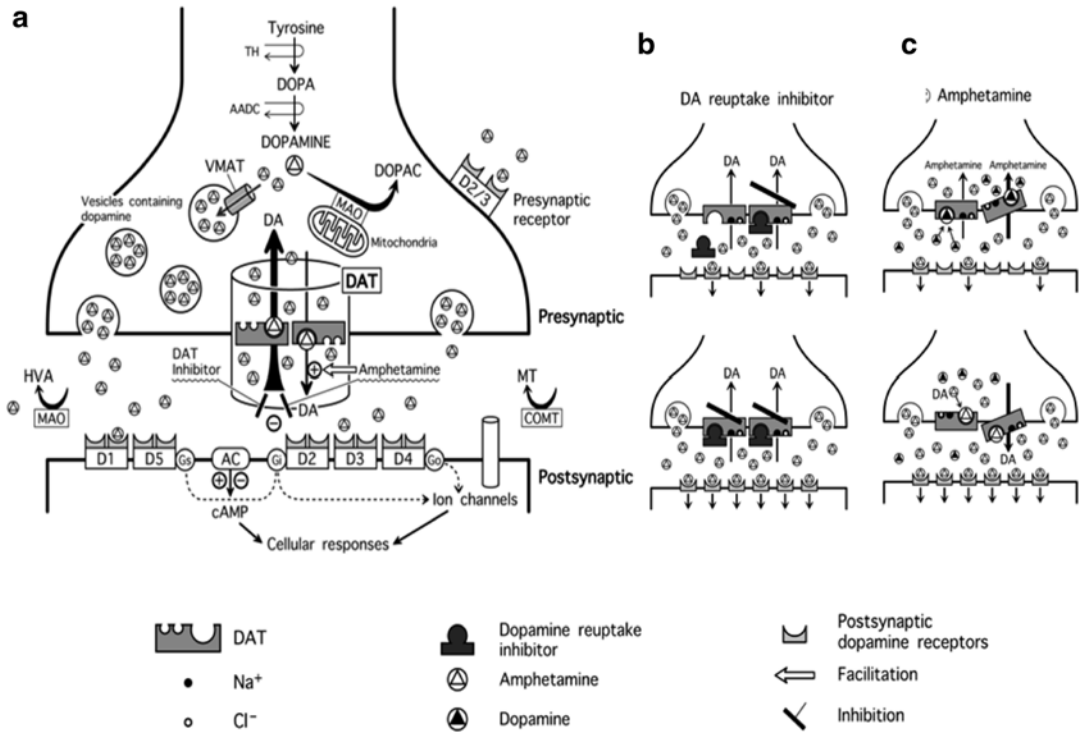

Fig. 22.2 (**a**) Schematic representations of dopaminergic terminal neurotransmission in relation to modes of action of dopamine (DA) reuptake inhibitors and amphetamine. (**b**) Effects of dopamine reuptake inhibitors at the dopaminergic nerve terminal. (**a**) DA transporter (DAT) is one of the most important molecules located at the dopaminergic nerve terminals and regulates dopaminergic neurotransmission. (i) Amphetamine interacts with the DAT carrier to facilitate DA release from the cytoplasm through an exchange diffusion mechanism (**c**). At higher intracellular concentrations, amphetamine also (ii) disrupts vesicular storage of DA and (iii) inhibits monoamine oxidase (MAO). Both these actions increase cytoplasmic DA concentrations. (iv) Amphetamine also inhibits DA uptake by virtue of its binding to and transport by the DAT. AADC, aromatic acid decarboxylase; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; COMT, catechol-*O*-methyltransferase; D1–D5, dopamine receptors 1 through 5; DA, dopamine; DAT, dopamine transporter; DOPA, 3,4-dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid; Gi, Go, and Gs, protein subunits; HVA, homovanillic acid; MAO, monoamine oxidase; TH, tyrosine hydroxylase; VMAT, vesicular monoamine transporter. (**b**) Sodium and chloride bind to the DAT to immobilize it at the extracellular surface. This alters the conformation of the DA binding site on the DAT to facilitate substrate (i.e., DA) binding. DAT reuptake inhibitors bind to DAT competitively and inhibit to DA–DAT bindings, resulting increasing DA concentrations in the synaptic cleft. (**c**) Amphetamine, in competition with extracellular DA, binds to the transporter. Substrate binding allows the movement of the carrier to the intracellular surface of the neuronal membrane, driven by the sodium and amphetamine concentration gradients, resulting in a reversal of the flow of DA uptake. Amphetamine dissociates from the transporter, making the binding site available to cytoplasmic DA. DA binding to the transporter enables the movement of the transporter to the extracellular surface of the neuronal membrane, as driven by the favorable DA concentration gradient. DA dissociates from the transporter, making the transporter available for amphetamine and thus another cycle

withdrawn from the market in several countries because of liver toxicity. The most commonly used commercially available form of methylphenidate is a racemic mixture of both the D- and L-enantiomers, but D-methylphenidate mainly contributes to clinical effects, especially after oral administration. This is due to the fact that L-methylphenidate, but not D-methylphenidate, undergoes a significant first-pass metabolism (by de-esterification to L-ritalinic acid).

Molecular Targets of Amphetamine Action

The molecular targets mediating amphetamine-like stimulant effects are complex and vary depending of the specific analog/isomer and the dose administered. Amphetamine per se increases catecholamine (DA and NE) release and inhibits reuptake. These effects are mediated by specific catecholamine transporters [12] (Fig. 22.3). The DA transporter (DAT) and the NE transporter (NET) have been cloned and characterized. The DAT and NET proteins are about 620 amino acid proteins with 12 putative membrane-spanning regions. Amphetamine derivatives inhibit the uptake and enhance the release of DA, NE, or both by interacting with these molecules. The DAT and NET normally move DA and NE, respectively, from the outside to the inside of the cell. This process is sodium dependent; sodium and chloride bind to the DA/NET to immobilize it at the extracellular surface and to alter the conformation of the DA/NE binding site, thereby facilitating substrate binding. Substrate binding induces movement of the carrier to the intracellular surface of the neuronal membrane, driven by sodium concentration gradients. Interestingly, in the presence of some drugs such as amphetamine, the direction of transport appears to be reversed (Fig. 22.3) [14]. DA and NE are moved from the inside of the cell to the outside through a mechanism called exchange diffusion, which occurs at low doses (1–5 mg/kg) of amphetamine, and this mechanism is involved in the enhancement of catecholamine release by amphetamine. A recent in vitro experiment has shown that amphetamine transportation causes an inward current, and intracellular sodium ion becomes more available, thereby enhancing DAT-mediated reverse transport of DA [14, 15].

At higher doses, other effects are involved. Moderate to high doses of amphetamine (>5 mg/kg) interact with the vascular monoamine transporter 2 (VMAT2) (see [12]). The vesicularization of the monoamines (DA, NE, serotonin, and histamine) in the CNS is dependent on VMAT2, and the VMAT2 regulates the size of the vesicular and cytosolic monoamine pools. Amphetamine is highly lipophilic and easily enters nerve terminals by diffusing across several membranes, which leads to a diffusion of the native monoamines out of the vesicles into the cytoplasm along a concentration gradient, and it acts as a physiological VMAT2 antagonist that releases the vascular DA/NE into the cytoplasm. These mechanisms, as well as the reverse transport and the blocking of reuptake of DA/NE by amphetamine, all lead to an increase in NE and DA synaptic concentrations (see [12]). High doses (higher than a clinical dose) of amphetamines are also shown to inhibit monoamine oxidase (MAO) and prevent catecholamine metabolism.

Various amphetamine derivatives have slightly different effects on all these systems. For example, methylphenidate also binds to the NET and DAT and weakly enhances catecholamine release, but has less effect on the VMAT granular storage site than amphetamine. Similarly, D-amphetamine has proportionally more releasing effect on the DA versus the NE system when compared to L-amphetamine. Of note, other antidepressant medications acting on catecholamines including both DA and NE (e.g., bupropion or mazindol) tend to exert their actions by simply blocking the reuptake mechanism.

Dopaminergic Neurotransmission and EEG Arousal

How amphetamines and other stimulants increase EEG arousal has been explored using a canine model of narcolepsy and DAT knockout mice models. Canine narcolepsy is a naturally occurring animal model of the human disorder [16]. Similarly to human patients, narcoleptic dogs are excessively sleepy (i.e., shorter sleep latency), have fragmented sleep patterns, and display cataplexy [16]. The pharmacological results demonstrated here are obtained mostly from the experiments using familial narcolepsy in Dobermans in which [17] hypocretin neurotransmission was disrupted by loss of function of hypocretin receptors (i.e., hypocretin receptor 2). In contrast, sporadic (non-familial) form of narcoleptic dogs is found to be ligand deficient,

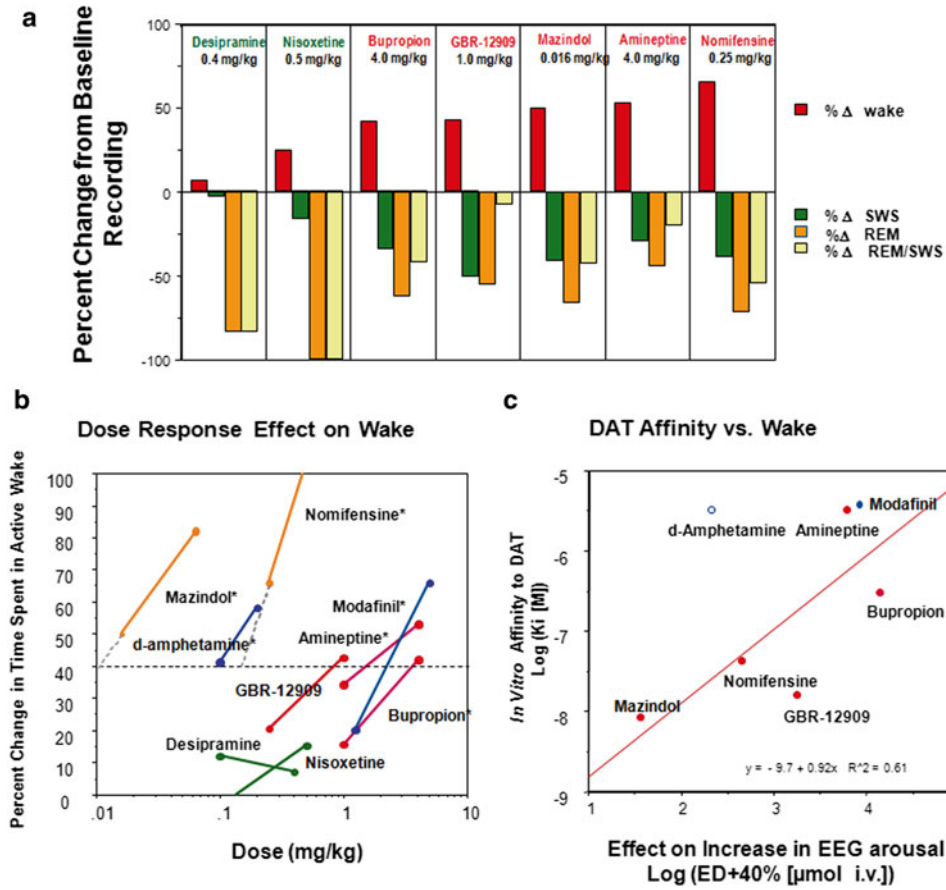

Fig. 22.3 (**a**, **b**) Effects of various DA and NE uptake inhibitors and amphetamine-like stimulants on the EEG arousal of narcoleptic dogs and (**c**) correlation between in vivo EEG arousal effects and in vitro DA transporter binding affinities. (**a**, **b**) The effects of various compounds on daytime sleep were studied using 4-h daytime polygraphic recordings (10:00–14:00) in 4–5 narcoleptic animals. Two doses were studied for each compound. All DA uptake inhibitors and CNS stimulants dose-dependently increased EEG arousal and reduced SWS when compared to vehicle treatment. In contrast, nisoxetine and desipramine, two potent NE uptake inhibitors, had no significant effect on EEG arousal at doses that completely suppressed cataplexy. Compounds with both adrenergic and dopaminergic effects (nomifensine, mazindol, D-amphetamine) were active on both EEG arousal and cataplexy. The effects of the two doses studied for each stimulant were used to approximate a dose–response curve; the drug dose that increased the time spent in wakefulness by 40 % above baseline (vehicle session) was estimated for each compound. The order of potency of the compounds obtained was mazindol > (amphetamine) > nomifensine > GBR 12,909 > amineptine > (modafinil) > bupropion. (**c**) In vitro DAT binding was performed using [3H]-WIN 35,428 onto canine caudate membranes. Affinity for the various DA uptake inhibitors tested varied widely between 6.5 nM and 3.3 mM. In addition, it was also found that both amphetamine and modafinil have low but significant affinity (same range as amineptine) for the DAT. A significant correlation between in vivo and in vitro effects was observed for all 5 DA uptake inhibitors and modafinil. Amphetamine, which had potent EEG arousal effects, has a relatively low DAT binding affinity, suggesting that other mechanisms, most probably monoamine-releasing are also involved. In contrast, there was no significant correlation between in vivo EEG arousal effects and in vitro NE transporter binding affinities for DA and NE uptake inhibitors. These results suggest that presynaptic enhancement of DA transmission is the key pharmacological property mediating the EEG arousal effects of most wake-promoting CNS stimulants (adapted from Nishino, S., et al., *Increased dopaminergic transmission mediates the wake-promoting effects of CNS stimulants.* Sleep Res Online, 1998. 1(1): p. 49–61 [13], with permission of the World Sleep Federation)

similar to most human narcolepsy, but both forms of narcoleptic dogs exhibit similar symptoms and react to the pharmacological compounds in a similar way [16]. Although amphetamine-like compounds are known well to stimulate catecholaminergic transmission, the exact mechanism by which they promote EEG arousal is still uncertain. Stimulation of either or both adrenergic and dopaminergic transmission has been suggested to play a role.

In order to address this question, the effects of ligands specific for the DA (GBR12909, bupropion and amineptine), NE (nisoxetine and desipramine), or both the DA and NE (mazindol and nomifensine) transporters, as well as amphetamine and a non-amphetamine stimulant, modafinil, were studied in narcoleptic and control Dobermans [13] (Fig. 22.3). DA uptake inhibitors such as GBR12909 and bupropion dose-dependently increased EEG arousal in narcoleptic dogs, while nisoxetine and desipramine (two potent NE uptake inhibitors) had no effect on EEG arousal at doses which almost completely suppressed REM sleep and cataplexy (see [13]). Most strikingly, the EEG arousal potency of various DA uptake inhibitors correlated tightly with in vitro DAT binding affinities (Fig. 22.3), while a reduction in REM sleep correlated with in vitro NET binding affinities [13]. These results strongly suggest that DA uptake inhibition is critical for the EEG arousal effects of these compounds.

It should be noted that D-amphetamine has a relatively low DAT binding affinity but potently (i.e., need for a low mg/kg dose) promotes alertness (Fig. 22.3). It is also generally considered to be more efficacious (i.e., can produce more alertness at a higher dose) than pure DAT reuptake inhibitors in promoting wakefulness. However, as described earlier, D-amphetamine not only inhibits DA reuptake, but it also enhances DA release (at lower doses by exchange diffusion and at higher doses by antagonistic action against VMAT2) and inhibits monoamine oxidation to prevent DA metabolism. The DA-releasing effects of amphetamine are likely to explain the unusually high potency of amphetamine in promoting EEG arousal.

The effects of various amphetamine analogs (D-amphetamine, L-amphetamine, and L-methamphetamine) on EEG arousal and their in vivo effects on brain extracellular DA levels in narcoleptic dogs were compared [18], in order to further differentiate the DA and NE systems' involvement in the mode of action of amphetamine derivatives. In vitro studies have demonstrated that the potency and selectivity for enhancing release or inhibiting uptake of DA and NE vary between amphetamine analogs and isomers [19]. Amphetamine derivatives thus offer a unique opportunity to study the pharmacological control of alertness in vivo. Hartmann and Cravens previously reported that D-amphetamine is four times more potent in inducing EEG arousal than L-amphetamine, but that both enantiomers are equipotent at suppressing REM sleep in humans and rats [11]. Enantiomer-specific effects have also been reported with methamphetamine; L-methamphetamine is much less potent as a stimulant than either D-methamphetamine or D- or L-amphetamine (Fig. 22.4) (see [19]). Similarly, in canine narcolepsy, D-amphetamine is three times more potent than L-amphetamine and 12 times more potent than L-methamphetamine in increasing wakefulness and reducing slow wave sleep (SWS) [18].

To further study what mediates these differences in potency, the effects of these amphetamine derivatives on DA release were examined in freely moving animals using in vivo microdialysis. Amphetamine derivatives (100 μM) were perfused locally for 60 min. through the dialysis probe implanted in the caudate of narcoleptic dogs (Fig. 22.4) [18]. The local perfusion of D-amphetamine raised DA levels nine times above baseline. L-Amphetamine also increased DA levels by up to seven times, but peak DA release was only obtained at the end of the 60-min. perfusion period. L-Methamphetamine did not change DA levels under these conditions. These results suggest that D-amphetamine is more potent than L-amphetamine in increasing caudate DA levels, while L-methamphetamine had the least effect; this is in agreement with data obtained in other species using the same technique [19]. NE was also measured in the frontal

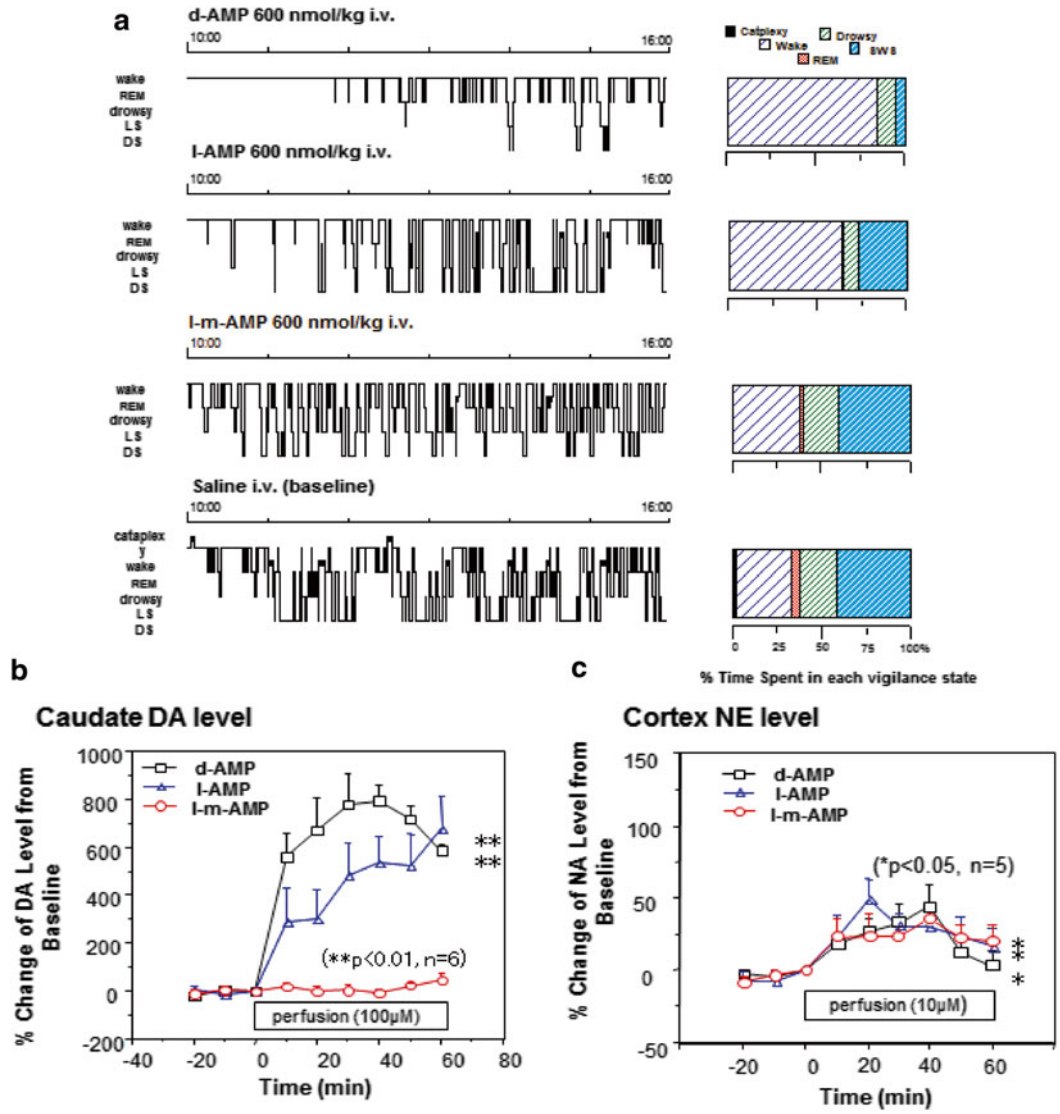

Fig. 22.4 Effect of amphetamine derivatives on sleep parameters during 6-h EEG recording. (**a**) Typical effects of amphetamine derivatives on sleep architecture in a narcoleptic dog (600 nmol/kg i.v.) Representative hypnograms with and without drug treatment are shown. Recordings lasted for 6 h, beginning at approximately 10:00 a.m. Vigilance states are shown in the following order from *top* to *bottom*: cataplexy, wake, REM sleep, drowsy, LS, and DS. The amount of time spent in each vigilance stage (expressed as % of recording time) is shown on the *right side* of each hypnogram. D-AMP was found to be more potent than L-AMP, and L-m-AMP was found to be the least potent, while all isomers equipotently reduced REM sleep. Local perfusion of amphetamine derivatives: (**b**) effects on caudate DA and (**c**) cortex NE levels. Local perfusion of D-AMP (100 μM) raised DA levels eight times above baseline. L-AMP also increased DA levels up to seven times above baseline, but this level was obtained only at the end of the 60-min perfusion period. L-m-AMP did not change DA levels under these conditions. In contrast, all three amphetamine isomers had equipotent enhancements on NE release. These results suggest that the potency of these derivatives on EEG arousal correlated well with measurements of DA efflux in the caudate of narcoleptic dogs, while effects on NE release may be related to REM suppressant effects

cortex during perfusion of D-amphetamine, L-amphetamine, and L-methamphetamine. Although all compounds increased NE efflux (i.e., net effects of release and uptake inhibition), no significant difference in potency was detected among the three analogs (Fig. 22.4.).

The fact that the potency of amphetamine derivatives on EEG arousal correlates with effects on DA efflux in the caudate of narcoleptic dogs further suggests that the enhancement of DA transmission by presynaptic modulation mediates the wake-promoting effects of amphetamine analogs. This result is also consistent with data obtained with DAT blockers (see Fig. 22.3). Considering the fact that other amphetamine-like stimulants (such as methylphenidate and pemoline) also inhibit DA uptake and enhance release of DA, the presynaptic enhancement of DA transmission is likely to be the key pharmacological property mediating wake promotion for all amphetamines and amphetamine-like stimulants.

The role of the DA system in sleep regulation was further assessed using mice lacking the DAT gene. Consistent with a role of DA in the regulation of wakefulness, these animals have reduced non-REM sleep time and increased wakefulness consolidation (independently from locomotor effects) [21]. DAT knockout mice have also proven to be a powerful tool to help dissect the molecular mechanisms mediating the effects of nonselective monoaminergic compounds. Using these animals, DAT was shown to be involved in mediating locomotor activation after amphetamine and cocaine administration. Indeed, no locomotor stimulation is observed in these mice after cocaine or amphetamine. Interestingly, NET knockout mice are more sensitive to the locomotor stimulation of amphetamine, suggesting that NET may play a feedback control role on amphetamine-induced dopaminergic effects [22]. With regard to sleep, the most striking finding was that DAT knockout mice were completely unresponsive to the wake-promoting effects of methamphetamine, GBR12909 (a selective DAT blocker), and modafinil. These results further confirm the critical role of DAT in mediating the wake-promoting effects of amphetamines and modafinil (Fig. 22.3) [21] (see also modafinil section). Interestingly, DAT knockout animals were also found to be more sensitive to caffeine [21], suggesting functional interactions between adenosine and DA systems in the control of sleep/wakefulness (see also caffeine/adenosine section).

Anatomical Substrates of Dopaminergic Effects

Anatomical studies have demonstrated two major subdivisions of the ascending DA projections from mesencephalic DA nuclei (VTA, SN, and retrorubral [A8]): (1) The mesostriatal system originates in the SN and retrorubral nucleus and terminates in the dorsal striatum (principally the caudate and putamen) [5]. (2) The mesolimbocortical DA system consists of the mesocortical and mesolimbic DA systems. The mesocortical system originates in the VTA and the medial SN and terminates in the limbic cortex (medial prefrontal, anterior cingulated, and entorhinal cortices). Interestingly, DA reuptake is of physiological importance for the elimination of DA in cortical hemispheres, limbic forebrain, and striatum, but not in midbrain DA neurons. It is thus possible that DA uptake inhibitors (and amphetamine and modafinil) act mostly on DA terminals of the cortical hemispheres, limbic forebrain, and striatum to induce wakefulness. Local perfusion experiments of DA compounds in rats and canine narcolepsy have suggested that the VTA, but not the SN, is critically involved in the regulation of EEG arousal [23]. DA terminals of the mesolimbocortical DA system may thus be important in mediating wakefulness after DA-related CNS stimulant coadministration.

Modes of Action of Modafinil/Armodafinil

The mechanism of action of modafinil/armodafinil is highly debated. There are limited numbers of studies addressing the mode of action of armodafinil, and this section mostly discusses the action of racemic modafinil.

Modafinil/armodafinil has not been shown to bind to or inhibit any receptors or enzyme of known neurotransmitters [24, 25]. The list includes serotonin, dopamine, adenosine, galanin, melatonin, melanocortin, hypocretin/orexin, orphanin, benzodiazepines, transporters for GABA, norepinephrine, choline, catechol-*O*-methyltransferase, GABA transaminase, and tyrosine hydroxylase [26–29] (see also [30] for a review). In vitro, modafinil/armodafinil binds to the dopamine transporter and inhibits dopamine reuptake [13, 24]. These binding inhibitory effects have been shown to be associated with increased extracellular dopamine levels in the striatum in rats and dog brain [21, 31].

Nevertheless, an interaction and involvement of adrenergic α-1 systems were initially suggested because of the ability of the α-1 antagonist, prazosin, to antagonize modafinil-induced increases in motor activity in mice [29] and wakefulness in cats [27]. However, modafinil does not bind to α-1 receptors in vivo (Ki $>10^{-3}$ M, obtained from prazosin binding using canine cortex) (see [32]). The hyperlocomotion produced by amphetamine largely depends on the α-1b receptor because mice lacking this receptor have much less hyperactivity. Modafinil in contrast does not increase locomotor activity beyond that seen with normal wakefulness. Furthermore, previous studies in the canine model of narcolepsy have shown that adrenergic α-1 agonists are potent anticataplectic agents [33] and have significant acute hypertensive effect. Modafinil has no anticataplectic activity and lacks hypertensive effects, suggesting that its alerting properties are not derived from adrenergic α-1 stimulation. These preclinical observations generally argue against a direct effect of modafinil on adrenergic receptors. Clinical observations provide an even stronger evidence that modafinil is neither a direct nor indirect sympathomimetic. Amphetamine causes dilation of the pupils by increasing NE signaling, but modafinil has no effect on the pupils. Some studies have noted slight increases in heart rate or blood pressure with high doses of modafinil. However, these changes were small and the majority of clinical studies on modafinil, including a meta-analysis of seven large clinical trials of modafinil which is the most comprehensive study on this issue, have found no changes in heart rate or blood pressure. These clinical observations suggest that at the usual clinical doses, modafinil does not increase adrenergic signaling in humans.

A serotonergic 5HT2 receptor-mediated change in GABAergic transmission was suggested next [26]. Modafinil increases 5HT metabolism in the striatum and reduces GABA flow to the cortex [26]. The effect on GABA release is blocked by ketanserin (a 5HT2 antagonist) but not by prazosin [26]. Furthermore, muscimol, a GABAergic agonist, blocks the effect of modafinil on wakefulness in cats [27]. Although serotonergic/GABAergic interaction may be involved in the mode of action of modafinil, the effects described may be indirect and additional work is needed to substantiate this hypothesis. As for the 5HT2 receptor, modafinil does not bind serotonergic receptors in vitro.

Regarding the in vitro binding affinities of modafinil, a systematic receptor screening revealed that modafinil binds to the DAT with IC50 of 10^{-6} M [24]. This binding affinity is low, but is not negligible since modafinil does not bind to any other known receptors and since clinical doses of modafinil are high (up to several mg/kg in human).

With regard to modes of action of modafinil on sleep, the most striking finding was that DAT knockout mice were completely unresponsive to the wake-promoting effects of methamphetamine, GBR12909 (a selective DAT blocker), and modafinil. These results further confirm the critical role of DAT in mediating the wake-promoting effects of amphetamines and modafinil and that an intact DAT molecule is required for mediating the arousal effects of compounds [21]. It was recently shown that modafinil was effective in noradrenaline-depleted (by DSP-4 administration) [34] and histamine-deficient (i.e., HDC KO mice) mice [35], also suggesting the importance of the dopaminergic system in wake promotion of modafinil.

Other investigators have shown, however, that modafinil can be distinguished pharmacologically from most other compounds by presynaptic

dopaminergic activity. For example, modafinil does not produce stereotypic behavior at high doses. Additionally, agents that inhibit dopaminergic function such as D1 blockers, D2 blockers, and tyrosine hydroxylase blockers have no effect on modafinil's locomotor-enhancing effects in mice. Finally, an in vitro voltammetry study found that modafinil did not increase the catechol oxidation peak height (an indirect measure of dopaminergic activity), suggesting a lack of presynaptic dopaminergic involvement in modafinil activity. Ferraro et al. [28], however, reported that systemic administration of modafinil (30–300 mg/kg) dose-dependently increased DA release in the nucleus accumbens of rats (as we also observed that modafinil enhances DA efflux in dogs [21]), but these authors initially claimed that the DA-releasing action of modafinil was most likely to be secondary to its ability to reduce local GABAergic transmission. It should also be noted that a recent brain slice experiment by Dopheide et al. [31] reported that modafinil (100–300 μM) evoked [(3)H] overflow from rat striatal slices preloaded with [(3)H]dopamine in a concentration-dependent manner, although modafinil was less potent and efficacious than amphetamine. Furthermore, the DAT inhibitor nomifensine (10 μM) blocked modafinil-evoked [(3)H]overflow, suggesting that the DAT mediates modafinil's effect.

Korotkova et al. [36] recently evaluated modafinil action on dopaminergic and GABAergic neurons identified in the VTA and SN of rat brain slices and claimed that modafinil inhibits DA neurons (but not GABAergic neurons) through D2 receptors (but not alpha 1 receptors) on DA neurons, independent from DAT inhibition. This finding is interesting and may explain why pharmacological properties of modafinil are different from amphetamines and pure DA uptake inhibitors. However, the result is again paradoxical since modafinil had no significant binding affinity to D2 receptors. Furthermore, DAT plays significant functional roles at the DA terminals [37], and DAT is not enriched on VTA [38]. In addition, modafinil indeed increases DA efflux at the DA terminals [21, 28]. Therefore, it is questionable if the D2 receptor-mediated effects of modafinil observed in in vitro slices of the VTA play essential roles for the modes of action of wake-promoting effects of modafinil.

Not only is the exact molecular target of modafinil action uncertain, but also there is much debate regarding modafinil's neuroanatomical site of action. Anatomical studies coupled with functional markers of neuronal activity (i.e., the immediate early gene product, Fos) have been used to determine activation patterns induced by modafinil in comparison to other stimulants [39]. In cats, amphetamine and methylphenidate induce c-Fos throughout the cortex, striatum, and other brain regions. In contrast, modafinil induces a much more restricted pattern of neuronal activation, with marked expression of c-Fos in neurons of the anterior hypothalamus area and suprachiasmatic nuclei-brain regions implicated to regulate sleep and circadian cycle [39]. Modafinil also increases c-Fos expression in hypocretin cells [40, 41] and histaminergic cells of the tuberomammillary nucleus; these effects have been suggested to mediate the wake-promoting effects of modafinil. At higher doses, the striatum and cingulate cortex are also activated [41]. Of note, however, it is likely that the stimulation of hypocretin cells is not essential to induce wakefulness since both hypocretin receptor-2 mutated canine narcolepsy and hypocretin-ligand deficient human narcolepsy (90 % of narcolepsy–cataplexy patients) respond well to modafinil treatment. More likely, activation of these cell groups is secondary to the expression of increased wakefulness, as c-Fos expression in these cell groups increases in naturally occurring wakefulness. In anesthetized rats, it is also reported that modafinil (150 mf/kg) increases extracellular histamine concentrations by about 50 %, but the rise occurred 3–4 h after the injection—much later than the usual onset of wakefulness by modafinil [42].

Gallopin et al. recently reported that modafinil inhibits the sleep-active neurons of the ventrolateral preoptic nucleus (VLPO, a sleep-promoting network of neurons), by facilitating adrenergic neurotransmission [43]. In this study, modafinil potentiated the inhibitory effects of norepinephrine on VLPO neurons in a slice preparation.

Surprisingly, modafinil did not potentiate the inhibitory effects of dopamine or serotonin on VLPO neurons. Nisoxetine, a potent NET inhibitor with low affinity to DAT [13], had a similar effect and the responses to the two drugs were not additive, suggesting they might work through the same biochemical pathways.

Since modafinil does not bind to the NET in rats and dogs [13] and NE uptake inhibitors do not possess strong wake-promoting effects, modafinil may modulate norepinephrine/dopamine uptake mechanisms through novel mechanisms. In this case, modafinil may work on both the DA and NE system to promote wakefulness, and adrenergic/DAT interactions may be involved. Of note, however, very high modafinil concentrations (generally 200 μM, the maximum that can be dissolved) were used in this study in vitro. It may also be that at this very high dose, small effects on adrenergic uptake, undetectable with the usual radio receptor binding assays, could occur. It is uncertain if these small in vitro activities are indeed important for the wake-promoting effects of the compounds, but may contribute to some of the pharmacological properties of modafinil.

Interestingly, Madras et al. [44] recently reported by positron emission tomography imaging in rhesus monkey that modafinil (i.v.) occupied striatal DAT sites (5 mg/kg, 35 %; 8 mg/kg, 54 %). In the thalamus, modafinil occupied NET sites (5 mg/kg, 16 %; 8 mg/kg, 44 %). The authors also showed that modafinil inhibited [3H] dopamine (IC50 6.4 M) 5 times and 80 times more potent than [3H] norepinephrine (IC50 35.6 M) and [3H] serotonin (IC50 500 M) transport, respectively, via the human DAT, NET, and serotonin transporter expressed cell lines. The data provide compelling evidence that modafinil occupies the DAT in living brain of rhesus monkeys, consistent with the DAT hypothesis, but modafinil may also act on NET depending on the drug dose, brain structure, and other physiological conditions.

Furthermore, a recent human PET study in ten healthy humans with [11C] cocaine (DAT radioligand) and [11C] raclopride (D2/D3 radioligand sensitive to changes in endogenous dopamine) also demonstrated that modafinil (200 and 400 mg given orally) decreased [11C] cocaine binding potential in the caudate (53.8 %, $p<0.001$), putamen (47.2 %, $p<0.001$), and nucleus accumbens (39.3 %, $p=0.001$) [45], the results being consistent with the DAT hypothesis (Fig. 22.5). In addition, modafinil also reduced [11C] raclopride binding potential in the caudate (6.1 %, $p=0.02$), putamen (6.7 %, $p=0.002$), and nucleus accumbens (19.4 %, $p=0.02$) (Fig. 22.5), suggesting the increases in extracellular dopamine were caused by DAT blockades [45]. These results are highly consistent with the abovementioned results of the animal studies; modafinil's effects on alertness are entirely abolished in mice without the DAT protein [21] and in animals lacking D1 and D2 receptors [46].

Armodafinil, the *R*-enantiomer of racemic modafinil with longer half-life, was recently approved by the FDA for EDS associated with narcolepsy, as well as residual sleepiness in treated with nasal continuous positive airway pressure (nCPAP) and sleepiness in shift work sleep disorder. Importantly, the *R*-enantiomer of modafinil has a half-life of 10–15 h, which is longer than that of the *s*-enantiomer (3–4 h) [47]. The dual pharmacokinetic properties of the racemic mixture may explain why modafinil is often more potent when taken twice per day at the beginning of therapy, during the period of drug accumulation.

Other Wake-Promoting Compounds

This section describes the modes of action of less often used stimulants, mazinzol, bupropion, and caffeine, for the treatment of narcolepsy.

Mazindol is a weak releasing agent for DA that also blocks both DA and NE reuptake. Mazindol has a high affinity for the DA and NETs (see [13]), yet interestingly this compound has a low abuse potential. It is effective for the treatment of both EDS and cataplexy in humans [48] and in canine narcolepsy [49], possibly due to its dual dopaminergic and noradrenergic effects [13].

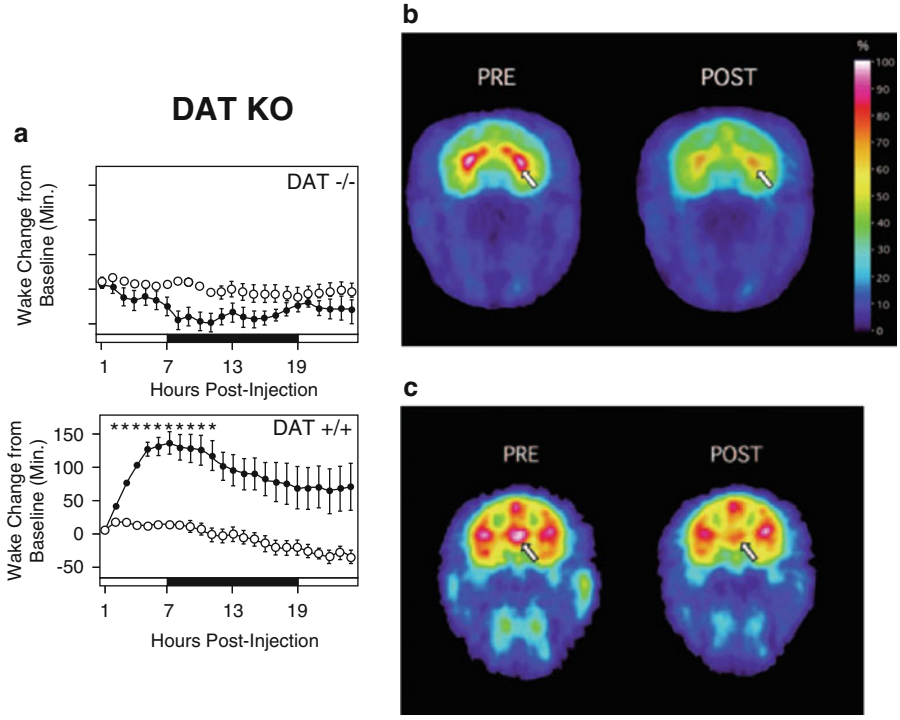

Fig. 22.5 (**a**) Wake-promoting effects of modafinil on dopamine transporter (DAT) KO mice and (**b**, **c**) PET imaging of the DAT and NET bindings in rhesus monkey before and after administrations of a wake-promoting dose of modafinil. (**a**) Wake-promoting effects of modafinil were completely abolished in DAT KO mice, suggesting that intact DAT function is required for the mediation of wake-promoting effects of modafinil. (**b**) Modafinil (8 mg/kg) occupancy by the DAT in the caudate and putamen, as detected by PET imaging of the DAT with [11C]CFT. *Left*, an adult rhesus monkey was injected with [11C]CFT and scanned over 60 min to develop baseline measures of DAT binding potential in the caudate and putamen. Images were color-transformed to display occupancy of the DAT with [11C]CFT, with highest levels detected in the caudate and putamen (*white–red*), as designated by the *arrow*, and lowest levels in *blue–purple*. Regions of interest are drawn over the caudate and putamen. *Right*, after decay of [11C]CFT radioactivity, modafinil was injected i.v., and [11C]CFT was injected again 1 h later. [11C]CFT accumulation was significantly lower compared with baseline levels of accumulation (left). (**c**) Modafinil (8 mg/kg) occupancy by the NET in the thalamus, as detected by PET imaging of the NET with [11C]MeNER. *Left*, an adult rhesus monkey was injected with [11C]MeNER and scanned over 60 min to develop baseline measures of NET binding potential in the thalamus. Images were color-transformed to display occupancy of the NET by [11C]MeNER, with high levels detected in the thalamus (*white–red*), as designated by the *arrow*, and lowest levels in *blue–purple*. Regions of interest are drawn over the thalamus. *Right*, after decay of [11C]MeNER radioactivity, modafinil was injected i.v., and 1 h later, [11C]MeNER was injected. [11C]MeNER accumulation was significantly lower compared with baseline levels of accumulation (Adapted from Wisor, J.P., et al., *Dopaminergic role in stimulant-induced wakefulness.* J Neurosci, 2001. **21**(5): p. 1787–1794 [21] with permission of the Society for Neuroscience, and from Madras, B.K., et al., *Modafinil occupies dopamine and norepinephrine transporters* in vivo *and modulates the transporters and trace amine activity* in vitro. J Pharmacol Exp Ther, 2006. **319**(2): p. 561–9 [44], with permission of ASPET)

Bupropion is classified as a monocyclic phenylbutylamine of the aminoketone group. It selectively blocks DA uptake and is six times more potent than imipramine and 19 times more potent than amitriptyline in blocking DA reuptake. The selectivity of bupropion for the dopamine transporter is not absolute. Bupropion is a weak competitive inhibitor of NE reuptake (65-fold less potent than imipramine), and very limited serotonergic effects are also observed (200-fold less potent than imipramine).

The mechanism of action of caffeine on wakefulness involves nonspecific adenosine receptor antagonism. Adenosine is an endogenous sleep-promoting substance with neuronal inhibitory effects. In animals, sleep can be induced after administration of metabolically stable adenosine analogs with adenosine A1 receptor's (A1R) or A2A receptor's (A2AR) agonistic properties, such as N6-L-(phenylisopropyl)-adenosine, adenosine-5′-*N*-ethylcarboxamide, and cyclohexyladenosine [50]. Adenosine content is increased in the basal forebrain after sleep deprivation. Adenosine has thus been proposed to be a sleep-inducing substance accumulating in the brain during prolonged wakefulness [51].

Most studies in the area of sleep and adenosinergic effects have focused on A1R-mediated effects. The rationale for this focus is that A1R is widely distributed in the CNS, whereas A2AR is discretely localized in the striatum, nucleus accumbens, and olfactory bulb. Interestingly, sleep/wake patterns and response to sleep deprivation were recently examined in adenosine receptor A1R knockout mice and found to be generally unaltered, suggesting that the constitutional lack of adenosine A1R does not prevent homeostatic regulation of sleep. In contrast, the sleep inhibitory effects of 8-cyclopentyltheophylline (a selective A1R antagonist) were abolished in these animals, indicating A1R mediation of stimulant effects with this compound.

Huang et al. [52] recently reported that wake-promoting effects of caffeine are abolished in A2AR KO mice, while the effects were not altered in A1R KO mice, suggesting a primary effect of caffeine through the A2AR, at least in this species. Interestingly, A2AR interacts strongly with dopaminergic transmission. A2AR forms a heterodimer with dopamine D2 receptors, and 2AR knockout mice have been shown to have reduced amphetamine-induced locomotor simulation and reward [53–55]. Recently, Lazarus et al. demonstrated the specific neurons on which caffeine acts to produce arousal using selective gene deletion strategies for A2ARs in animals [56]. The authors reported that A2ARs in the shell region of the nucleus accumbens (NAc) are responsible for the effect of caffeine on wakefulness. Caffeine-induced arousal was not affected in rats when A2ARs were focally removed from the NAc core or other A2AR-positive areas of the basal ganglia. The authors claim that caffeine promotes arousal by activating pathways that traditionally have been associated with motivational and motor responses in the brain.

Caffeine is metabolized into three active metabolites: paraxanthine, theobromine, and theophylline. A recent study demonstrated that paraxanthine significantly promoted wakefulness and proportionally reduced NREM and REM sleep in both control and narcoleptic mice [57]. The wake-promoting potency of paraxanthine (100 mg/kg p.o.) is greater than that of the parent compound, caffeine (92.8 mg/kg p.o.), and comparable to that of modafinil (200 mg/kg p.o.). High dose of caffeine and modafinil induced hypothermia and reduced locomotor activity, while paraxanthine did not [57]. In addition, behavioral test revealed that the compound possessed lesser anxiogenic effects than caffeine [57]. Although further evaluation in human should be needed, paraxanthine may be a better wake-promoting agent for normal individuals, as well as patients suffering hypersomnia associated with neurodegenerative diseases.

Mechanisms of Action of Tricyclic Anticataplectics

As discussed in the stimulant section, neuropharmacological understandings of cataplexy also have been greatly facilitated using the canine models [16]. Since cataplexy can be easily elicited by food or play and the severity of cataplexy can be quantified by a simple behavioral assay (i.e., food-elicited cataplexy test), these animals have been intensively used for evaluating anticataplectic effects of various compounds [16].

Although the mechanism for the induction of cataplexy is not identical to that for REM sleep, both likely share common physiological and pharmacological mechanisms, especially for the executive systems for muscle atonia. Thus, the understanding of the pharmacological control of

REM sleep is essential to the understanding of cataplexy.

The importance of increased cholinergic activity in triggering REM sleep or REM sleep atonia is well established (see Ref. [58]). Similarly, activation of the cholinergic systems using the acetylcholinesterase inhibitor physostigmine also greatly exacerbates cataplexy in canine narcolepsy, with various side effects [16]. This cholinergic effect is mediated via muscarinic receptors since muscarinic stimulation aggravates cataplexy while its blockade suppresses it, and nicotinic stimulation or blockade has no effect [16]. Application of muscarinic antagonists in human narcolepsy is, however, hampered by its peripheral side effects.

Monoaminergic transmission is also critical for the control of cataplexy. All therapeutic agents currently used to treat cataplexy (i.e., antidepressants or monoamine MAOIs) are known to act on these systems. Furthermore, whereas a subset of cholinergic neurons are activated during REM sleep, the firing rate of monoaminergic neurons in the brainstem (such as in the LC and the raphe magnus) is well known to be dramatically depressed during this sleep stage [59]. In contrast, dopaminergic neurons in the VTA and substantia nigra (SN) do not significantly change their activity during natural sleep cycles [59]. Using canine narcolepsy, it was recently demonstrated that adrenergic locus coeruleus (LC) activity is also reduced during cataplexy [60]. It is also shown that histaminergic tuberomammillary neurons reduce their firing during REM sleep, but not during cataplexy in the canine model [61].

Preferential Involvement of Adrenergic Neurotransmission in the Control of Canine Cataplexy

As mentioned above, tricyclic antidepressants have a complex pharmacological profile that includes monoamine reuptake inhibition, anticholinergic, alpha-1 adrenergic antagonistic, and antihistaminergic effects, making it difficult to conclude which one of these pharmacological properties is actually involved in their anticataplectic effects. Some of commonly used antidepressants are shown in Fig. 22.6.

In order to determine which property is most relevant, we studied the effects of a large number (a total of 17 compounds) of reuptake blockers/release enhancers specific for the adrenergic, serotonergic, or dopaminergic systems. Adrenergic

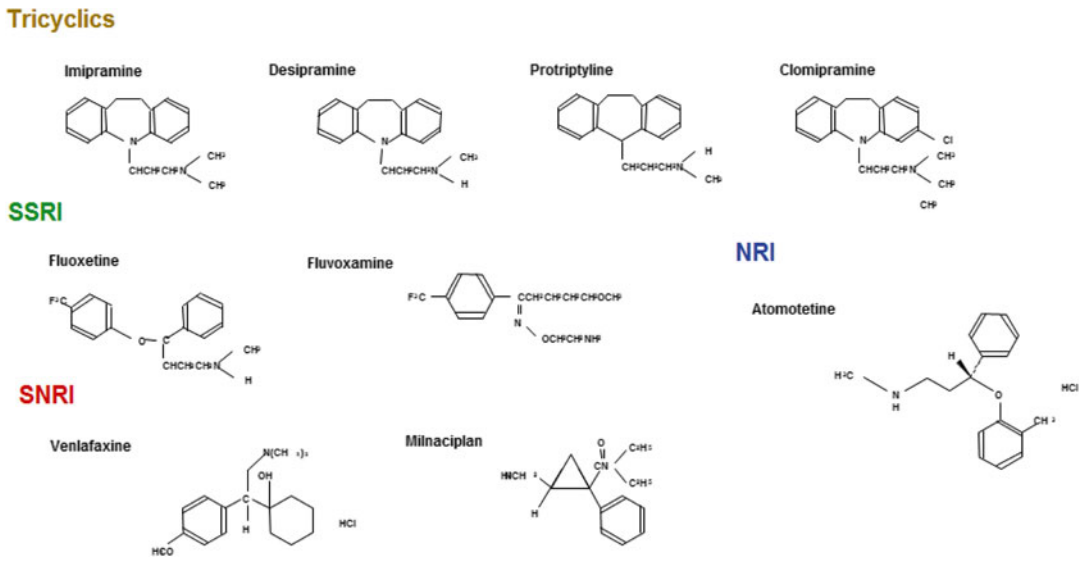

Fig. 22.6 Chemical structures for tricyclic, selective serotonin (SSRI), serotonin and norepinephrine (SNRI), and norepinephrine (NRI) antidepressants

Table 22.1 Effect of selective monoamine uptake inhibitors and release enhancers on canine cataplexy

Drugs	Dose range (μg/kg i.v.)	Effect on cataplexy	ED 50 (μg)
NE selective compounds			
1. NE uptake blockers			
Desipramine	2–500	0[1] ($p=0.002$)	20
Nisoxetine	1.58–100	0 ($p=0.004$)	18
Nortriptyline	2–500	0 ($p=0.004$)	28
Tomoxetine	16–1000	0 ($p=0.002$)	11
Viloxazine	8–2000	0 ($p=0.002$)	128
2. NE release enhancers			
Amphetamine*	2–128	0 ($p=0.02$)	37
5-HT selective compounds			
1. 5-HT uptake blockers			
Fluoxetine	62–4000	±[2] ($p=0.06$)	
Indalpine	62–4000	=[3] (ns)	
Zimelidine	62–4000	= (ns)	
2. 5-HT release enhancers			
Fenfluramine	62–4000	± ($p=0.05$)	
DA selective compounds			
1. DA uptake blockers			
Amineptine	62–4000	= (ns)	
Bupropion	16–1000	= (ns)	
GBR 12909	16–1000	= (ns)	
2. DA release enhancers			
Amfonelic acid	2–128	= (ns)	

*Also a dopamine and serotonin release enhancer

[1]0 means that for higher doses there was a total suppression of cataplexy in all dogs

[2]± means that there was a decreasing trend in cataplexy during the test, but without total suppression at the higher doses

[3]= means that there was no change during the test

reuptake inhibition was found to be the key property involved in the anticataplectic effect [62] (Table 22.1). Serotonergic reuptake blockers were only marginally effective at high doses and the dopaminergic reuptake blockers were completely ineffective. Interestingly, it was later found that these DA reuptake inhibitors had potent alerting effects in canine narcolepsy [16] (see also CNS stimulant section).

We also compared the effects of several antidepressants with those of their demethylated metabolites. Many antidepressants (most typically tertiary amine tricyclics) are known to be hepatically first-pass metabolized into their demethylated metabolites that have longer half-lives and higher affinities to adrenergic reuptake sites [63]. During chronic drug administration, these demethylated metabolites accumulate [63] and can thus be involved in the drug's therapeutic action. The effects of five available antidepressants (amitriptyline, imipramine, clomipramine, zimelidine, and fluoxetine) were compared with those of their respective demethylated metabolites (nortriptyline, desipramine, desmethylclomipramine, norzimelidine, and norfluoxetine) [64]. In all cases, the demethylated metabolites were found to be more active on cataplexy than were the parent compounds. We also found that the active dose of all anticataplectic compounds tested positively, correlating with the in vitro potency of each compound to the adrenergic transporter but not with that of the serotonergic transporter [64]. In fact, the anticataplectic effects were negatively correlated with the in vitro potency for serotonergic reuptake inhibition, but this may be biased since potent adrenergic reuptake inhibitors included in the study have a relatively low affinity to serotonergic reuptake sites. Although most of these results were obtained from inbred *hcrtr 2*-mutated narcoleptic Dobermans, similar findings (the preferential involvement of adrenergic system) have been also obtained in more diverse cases of sporadic canine narcolepsy, in various breeds donated to our colony (see Ref. [65]).

The fact that serotonergic reuptake blockers, also known to have inhibitory effects on REM sleep, have less or no effect on cataplexy is surprising. Like adrenergic cells of the LC, serotonergic cells of the raphe nuclei dramatically decrease their activity during REM sleep [58]. This discrepancy could be explained by a preferential effect of serotonergic projections on REM sleep features other than atonia, for example, in the control of eye movements. In this model, adrenergic projections may be more important than serotonergic transmission in the regulation of REM sleep atonia and thus cataplexy [62]. In favor of this hypothesis, a recent experiment

has shown that serotonergic activity does not decrease during cataplexy in narcoleptic canines [66]. In addition, recent case reports suggested that antidepressants act on not only serotonin but noradrenergic systems (i.e., selective norepinephrine and serotonin reuptake inhibitor like venlafaxine [67], duloxetine [68]) has powerful anticataplectic effects.

Receptor Subtypes Involved in the Control of Cataplexy

In order to dissect receptor subtypes that significantly modify cataplexy, more than 200 compounds with various pharmacological properties (cholinergics, adrenergics, dopaminergics, serotonergics, prostaglandins, opioids, benzodiazepines, GABAergics, and adenosinergics) have also been studied in the narcoleptic canine model (see Ref. [16] for details). Although many compounds (such as M2 antagonists, alpha-1 agonists, alpha-2 antagonists, dopaminergic D2/D3 antagonists, $5HT_{1A}$ agonists, TRH analogs, prostaglandin E2, and L-type Ca^{2+} channel blockers) reduce cataplexy, very few compounds significantly aggravate cataplexy (cataplexy-aggravating effects are assumed to be more specific, since cataplexy can be nonspecifically reduced by unpleasant drug side effects) [16]. Among the monoaminergic receptors, blockade of the postsynaptic adrenergic $alpha_{1B}$ receptors [33] and stimulation of presynaptic alpha-2 autoreceptors [69] were also found to aggravate cataplexy, a result consistent with a primary adrenergic control of cataplexy. We also found that small doses of DA D2/D3 agonists significantly aggravated cataplexy and induced significant sleepiness in these animals [70, 71]. The cataplexy-inducing effects of D2/D3 agonists are, however, difficult to reconcile considering the fact that dopaminergic reuptake blockers (in contrast to adrenergic reuptake inhibitors) have absolutely no effect on cataplexy [62] (see also CNS stimulant section). We also found that sulpiride (a D2/D3 antagonist) significantly suppresses cataplexy in the canine model but has no effect on REM sleep [72]. D2/D3 agonists are used clinically for the treatment of human periodic leg movements during sleep (PLMS). Incidence of PLMS is high in human narcolepsy, and it also occurs in the narcoleptic Doberman [73]. The dopaminergic system (i.e., D2/D3 receptor mechanisms) may thus be specifically involved in sleep-related motor control rather than REM sleep.

The sites of action of D2/D3 agonists were also investigated by local drug perfusion experiments, and a series of experiments identified acting sites for these compounds. These include dopaminergic nuclei or cell groups, such as the VTA [71], the substantia nigra [23], and A11 [74] (a diencephalic DA cell group that directly projects to the spinal ventral horn), suggesting a direct involvement of the DA cell groups and DA cell body autoreceptors in the regulation of cataplexy.

The mechanism for emotional triggering for cataplexy remains to be studied, but it is possible that multiple brain sites and multiple functional and anatomical systems are involved.

MAOIs

MAO inhibitors (MAOIs) are known to potently reduce REM sleep and are therefore candidate anticataplectic agents. This has led several investigators to use MAOIs for the treatment of narcolepsy [75, 76]. The extracellular effect of naturally released catecholamine is terminated by either reuptake or enzymatic degradation and either by MAO or catechol-*O*-methyl transferase. MAO is a flavin-containing dominating enzyme located in the outer membranes of neural and glial mitochondria (see Ref. [77]). It exists in two forms: MAO-A, blocked by clorgyline and having high affinity for noradrenaline and 5HT, and MAO-B, insensitive to clorgyline and having high affinity for phenylethylamine and dopamine (see Ref. [77]).

Even if these compounds are clearly active on narcolepsy [75, 76] and may be useful in cases refractory to more conventional treatment, the

first generation of MAOIs has been rarely used in clinical practice to date due to their poor safety profile (e.g., the "cheese effect") (see [78]). It is also dangerous to use other drugs with sympathomimetic effects (tricyclic antidepressants, amphetamine-like compounds, or simply catecholaminergic cardiac stimulants) in patients treated with MAOIs due to the existence of interactions (sometimes fatal) that are impossible to predict (see Ref. [77]). Other side effects include edema, impotence, weight gain, insomnia, long-term hypertension, and psychological disturbances (see Ref. [77]). Drug withdrawal may lead to REM sleep rebound with exacerbation of narcolepsy and the development of vivid nightmares [75]. In addition, the first generation of MAOI (irreversible MAOIs) has the unique property of binding covalently to the active site of the enzyme ("suicide substrate"), thus leading to long-term (up to several weeks) enzymatic inhibition even after a single dose (see Ref. [77]).

A safer generation of MAOIs is now becoming available. These include compounds with selective MAO-A or MAO-B inhibition and/or a reversible enzymatic inhibition profile. In contrast to irreversible MAOIs, reversible MAOIs are substrates for the MAOs and compete with the endogenous monoamines (see Ref. [77]). Some of these new reversible MAOIs (brofaromine, moclobemide) are now being used in clinical trials in Europe and seem to be effective and safe for the treatment of human narcolepsy without noticeable side effects [79]. These compounds can be used with minimal dietary precautions.

Selegiline is a potent irreversible MAO-B selective inhibitor used in the treatment of Parkinson's disease. This compound is essentially a methamphetamine derivative and is metabolized to a significant extent into amphetamine and methamphetamine (9–30 % and 20–60 % are found in urine respectively); the use of low doses of selegiline does not require dietary restriction. Ten milligrams of daily selegiline has no effect on the symptoms of narcolepsy, but 20–30 mg improves alertness and mood and reduces cataplexy somewhat. This effect is comparable to amphetamine at the same dose [80]. Indeed, an experiment in canines also suggests that the anticataplectic effects of selegiline are likely to be explained by its active metabolites, L-amphetamine and L-methylamphetamine [81].

GHB

GHB (also known as sodium oxybate), taken in the evening and once again during the night, reduces daytime sleepiness, cataplectic attacks, and other manifestations of REM sleep [82–87]. Although improvement in sleepiness occurs relatively quickly, anticataplectic effects appear 1–2 weeks after the initiation of the treatment.

GHB was originally synthesized as a γ-aminobutyric acid (GABA) analog that would readily cross the blood–brain barrier [88] and was later found to occur naturally in the brain [89] as a metabolite and, under certain conditions, as a precursor of GABA [90] (Fig. 22.7). Endogenous GHB has been suggested to act as a neurotransmitter/neuromodulator in a manner independent from that of the GABA systems [90]. GHB is believed to have its own high (and low) affinity binding sites in different species, including humans [90, 92, 93]. Its distribution and ontogeny differ from those of GABAA and GABAB receptors [90, 92]. Thus, GHB has multiple mechanisms of action in the brain.

Exogenously administered GHB induces a wide range of neuropharmacological actions, including sedation, memory impairment, an increase in sleep stages 3 and 4, seizures, dependence/abuse, and coma [91]. Experimentally, GHB-elicited absence seizures in the rat [91] are the best pharmacological model of human typical absence seizures [94]. It also has a limited use as an anesthetic [91] and for alcohol dependence/withdrawal [95]. By the use of potent and selective GABAB receptor antagonists, most of these actions of exogenous GHB have been shown to be mediated, either fully or in part, by GABAB receptors [90, 91, 96] (Fig. 22.7). Notwithstanding its endogenous presence in the brain, its few experimentally and clinically significant uses, and the toxicity resulting from its abuse/misuse or its pathological increase (e.g., in human GHB

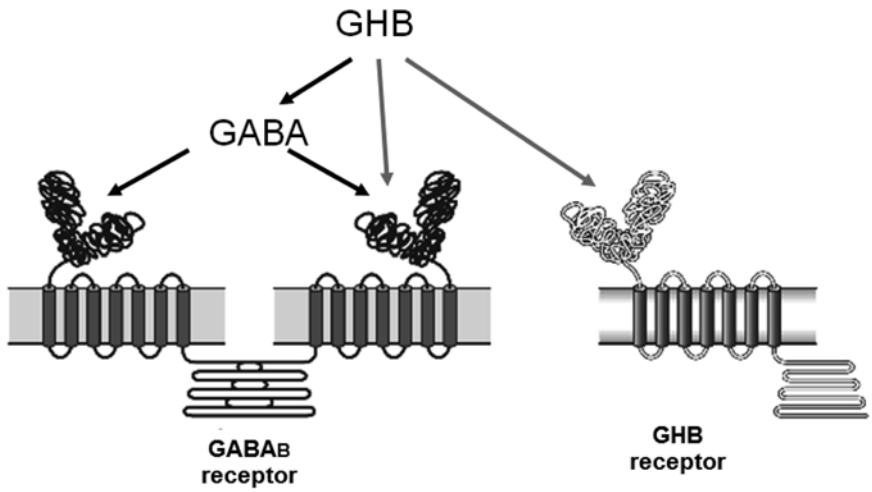

Fig. 22.7 g-Hydroxybutyric acid (GHB) has multiple mechanisms of action in the brain. Physiologically relevant concentrations (1–4 mM) of GHB activate at least two subtypes of the GHB receptor. In addition to binding to the GHB receptor, at supra-physiological concentrations (high micromolar to low millimolar), a sufficient quantity of GHB might be metabolized to GABA, which then activates the GABA receptors. At supra-physiological levels, GHB itself might also bind to the GABAB receptor (adapted from Wong, C.G., K.M. Gibson, and O.C. Snead, 3rd, *From the street to the brain: neurobiology of the recreational drug gamma-hydroxybutyric acid.* Trends Pharmacol Sci, 2004. **25**(1): p. 29–34 [91], with permission of Elsevier)

aciduria [91]), the physiological significance of a brain GHB signaling pathway and the detailed mechanisms of many actions of exogenous GHB remain unclear. In 2003, however, the cloning of a putative GHBR has been reported [97]. Using the high-affinity ligand NCS-400 (a GBH structural analog), a 512 amino acid protein (57 kDa) has been isolated that shows a predicted secondary structure indicative of seven-transmembrane-spanning regions [as for G-protein-coupled receptors (GPCRs)] and several phosphorylation sites. GHBR mRNA shows a brain distribution similar to that of native GHB binding sites, but with some differences, such as high density in the cerebellum where no or very few native GHB sites have been detected [90–92]. The pharmacological profile of the recombinant protein expressed in Chinese hamster ovarian cells is also similar to that of native GHB binding sites, but some discrepancies are also noted; it lacks NCS-382 (another putative GHB antagonist) binding and its link to a mixed cationic (Na^+/K^+) current (as opposed to a Ca^{2+} current in native brain GHB binding sites [98, 99]). These results and the presence of three mRNA bands are indicative of GHBR subtypes.

Despite of these new findings, the physiological significance of a brain GHB signaling pathway is still unknown, and there is an urgent need for a well-validated functional assay for GHBRs. Moreover, as GHB can also be metabolized to GABA, it remains to be seen whether the many GABAB receptor-mediated actions of GHB are caused by GHB itself acting directly on GABAB receptors or by a GHB-derived GABA pool (or both) (Fig. 22.7).

Conclusion

Over 90 % of diagnosed narcoleptic patients are reported to take medications to control symptoms [100], and better understanding on the pharmacology of therapeutic compounds for narcolepsy is essential in the clinical practice. Amphetamine-like stimulants have been used in the treatment of EDS in narcolepsy and various other conditions for decades, yet only recently has

the mode of action of these drugs on vigilance been characterized. In almost all cases, the effects on vigilance were found to be mediated via the effects on the DAT. This has generally led to the widely accepted hypothesis that wake-promoting effects will be impossible to differentiate from abuse potential effects of these compounds. Importantly however, the various medications available have differential effects and potency on the DAT and on monoamine storage/release. It thus appears more likely that complex properties (e.g., the ability to release DA rather than simply block reuptake, plus the combined effects on other monoamines [such as 5HT]) may be important to explain the characteristic of the wake-promoting effect of each compound.

The mode of action of the modafinil remains controversial and may involve dopaminergic and/or non-dopaminergic effects. Whatever its mode of action is, the compound is generally found to be safer and to have a lower abuse potential than amphetamine stimulants. Its favorable side effect profile has led to an increasing use outside the narcolepsy indication, most recently in the context of shift work disorder and residual sleepiness in treated sleep apnea patients, and the FDA approved these applications. This recent success exemplifies the need for developing novel and non-amphetamine wake-promoting compounds. A need for treating daytime sleepiness extends well beyond the relatively rare indication of narcolepsy–cataplexy.

Caffeine is a nonselective adenosine receptor antagonist, and wake-promoting effects of caffeine may be mediated by A1 and A2a receptors.

Cataplexy is currently treated with antidepressants, a class of compounds that enhance monoaminergic neurotransmission by inhibition of monoamine reuptake (NE, 5HT, DA). Most narcolepsy–cataplexy patients also take wake-promoting compounds, but these have little effect on cataplexy. Experiments in canine narcolepsy suggest a preferential involvement of NE rather than 5HT reuptake inhibition in the anticataplectic properties of the drugs. DA reuptake inhibition does not reduce cataplexy, but does significantly enhance wakefulness. In humans, compounds with NE reuptake inhibition also reduce cataplexy. SSRIs are also very commonly used as anticataplectics in the human. This is mostly due to their better side effect profiles, but the anticataplectic effects of these compounds are rather modest. Recently, selective NE and NE/5HT (SNRI) reuptake inhibitors were introduced, and one of the SNRIs, venlafaxine, has become the first line of anticataplectic medications.

Sodium oxybate (approved formula of GHB in the USA) given at night improves both EDS and cataplexy. Although improvement in sleepiness occurs relatively quickly, anticataplectic effects appeared 1–2 weeks after the initiation of the treatment. Central actions of GHB may be mediated by direct actions on GHB and/or GABAB receptors or though its metabolite, GABA, but modes of actions of GHB on EDS and cataplexy are by and large unknown.

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Modafinil/Armodafinil in the Treatment of Narcolepsy

23

Michael J. Thorpy

The Introduction of Modafinil/Armodafinil

Modafinil has been used for the treatment of narcolepsy in France since 1992 and had been studied in other disorders of excessive sleepiness in that country, as well as for depression and "vigilance enhancement" [1, 2].

Preclinical and phase I studies on pharmacokinetics and mechanism of action of modafinil [3–5] that supplemented previous French research were initiated in the USA in 1993 to compare the abuse liability of modafinil with that of central nervous system (CNS) stimulants. Clinical studies were performed in narcolepsy that led to the approval of the medication for the treatment of excessive sleepiness since narcolepsy in 1988. In 2007 approval was obtained to use modafinil in the treatment of excessive sleepiness associated with obstructive sleep apnea (OSA) syndrome and shift work sleep disorder (SWSD). By that time modafinil had been widely used off-label for the treatment of excessive sleepiness associated with other medical conditions such as Parkinson's disease, myotonic dystrophy, and multiple sclerosis. In 2007, a longer acting form of modafinil, armodafinil, the *r*-enantiomer, was approved for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and SWSD [6].

Treatment of Narcolepsy by Modafinil

Two double-blind, placebo-controlled studies of modafinil in narcolepsy evaluated both objective and subjective sleepiness, as well as overall clinical condition [7, 8]. Each trial (one conducted at 18 centers and one at 21 centers) used the Maintenance of Wakefulness Test (MWT), an objective measure of physiological excessive sleepiness, as a primary end point. To assess subjective improvements in clinical condition and response or lack of response to modafinil, the Clinical Global Impression of Change (CGI-C) was also used as a primary end point. The objective physiological measure, the Multiple Sleep Latency Test (MSLT), and the subjective questionnaire, the Epworth Sleepiness Scale (ESS), were used as secondary end points.

Each narcolepsy study was 9 weeks in duration, with clinic visits scheduled every 3 weeks (nocturnal polysomnography was performed the night before each clinic visit to assess sleep efficiency and changes in sleep architecture). The efficacy analyses used an intent-to-treat population (patients who received at least one dose of study

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drug and had at least one postbaseline assessment on both the MWT and CGI-C) [7, 8].

A total of 558 narcolepsy patients were randomized to placebo, modafinil 200 mg, or modafinil 400 mg. The majority of participants (81 % in both studies combined) had cataplexy. Patients who could not discontinue anticataplectic medications safely for the trial periods were excluded from participation. The maximum mean MSLT sleep latency was 3.3 min in any of the six treatment groups, well below the diagnostic criterion for narcolepsy, at that time of 5 min [9]. The mean ESS scores ranged from 17.1 to 18.3. All patients except one were at least mildly ill on the Clinical Global Impression of Severity (CGI-S), with about one third considered markedly to extremely ill.

The first study conducted, the 18-center study, used only a 1-day titration period for the 400-mg group (both groups received 200 mg on day 1). A higher percentage of patients in the 400-mg group withdrew due to adverse events compared with the 200-mg and placebo groups (12 % vs. 1 % and 0 %, respectively) [7]. Therefore, the subsequent 21-center study used a step-up protocol, giving each treatment group 100 mg of modafinil on days 1 through 7 and 200 mg on day 8. On day 9 those patients in the 400-mg group were moved to the higher dose. Only 1 % of patients in the 400-mg group withdrew due to adverse events; the lower incidence was likely (but not definitively) attributable to the longer titration schedule [8].

The 21-center study also included a 2-week discontinuation period to determine whether abrupt discontinuation of modafinil was associated with adverse events (especially those related to withdrawal from CNS stimulants, including fatigue, insomnia, increased appetite, and agitation). In this phase, those receiving placebo remained on placebo, while 80 % of those in the modafinil groups switched over to placebo at the end of week 9. The remaining 20 % continued on modafinil to serve as a comparator group [8].

The combined results of the two studies demonstrated a mean sleep latency on the MWT that increased by more than 2 min in each treatment group, compared with a decrease of 0.7 min in the placebo group ($p<0.001$, change from baseline vs. placebo for both doses) [7, 8]. A significantly higher percentage of modafinil patients showed improvement in overall clinical condition on the CGI-C (61–66 % vs. 37 % for placebo; $p<0.001$). Similar objective improvements were seen on the MSLT, and subjective improvements on the ESS [7, 8].

During the discontinuation period of the 21-center study, no symptoms consistent with tolerance or abrupt withdrawal were observed. However, improvements in wakefulness seen over the course of the study were lost on both subjective (ESS) and objective (MWT) measures in those who discontinued modafinil [8]. Polysomnographic recordings showed no significant changes in sleep efficiency (i.e., the time asleep as a percent of the total time in bed), time spent in REM sleep, or time spent in each non-REM sleep stage [7, 8].

The most common adverse event was headache (36–54 % of patients), the majority of which occurred in the first month of treatment and resolved within a few days. Modafinil was considered generally well tolerated in these studies. There was no difference in treatment response among those with or without cataplexy. The incidence of cataplexy as an adverse event ranged from 1 to 4 %, with no difference between the treatment and placebo groups. Because those who could not discontinue anticataplectic medications were excluded from the studies, however, it is likely that patients with severe cataplexy were underrepresented (a potential limitation of these studies).

Although the absolute changes from baseline on the MWT and MSLT may appear small, small increases in sleep latency (e.g., 1–2 min) can represent clinically significant improvements in wakefulness [10]. However, modafinil did not completely resolve sleepiness in these narcolepsy patients; the mean sleep latency, although significantly improved, was still considered to be in the mild to moderate range [7, 8].

A randomized, double-blind, placebo-controlled, 6-week trial that consisted of three 2-week crossover phases also showed significant improvements on the MWT and ESS. In this

study, modafinil 200-mg and 400-mg doses were given twice daily in the morning and at noon [11].

The discontinuation results in the 21-center US trial were also supported by similar results from a 16-week open-label extension of the Canadian study, which ended with a 2-week, double-blind, abrupt discontinuation period [12]. Together, the US and Canadian studies formed the basis for recommending modafinil as a standard of care in a 2000 update to the American Academy of Sleep Medicine (AASM) guidelines for narcolepsy treatment and again in the recent 2007 AASM guidelines [13, 14]. The standard-of-care designation reflected the favorable risk/benefit profile of modafinil in these three studies, as well as several supporting studies conducted in the USA and France [15, 16]. Modafinil has now become the "first-line" treatment for excessive sleepiness in most patients newly diagnosed with narcolepsy.

Several US studies have focused on determining optimal dosing protocols for modafinil in narcolepsy patients, including the use of doses higher than the recommended dose of 200 mg, as well as split dosing to achieve improvements in evening wakefulness. While no dose–response effect was seen for the 400-mg dose compared with 200 mg in the placebo-controlled clinical studies, the first MWT nap opportunity was generally performed an hour after dosing of modafinil, too early for the agent to reach peak plasma concentrations. A study employing a modified version of the MWT that included evening test sessions demonstrated an improved response to the 400-mg dose compared with 200 mg, whether it was given as a single morning dose or a split dose in the morning and at noon. The greatest improvements in evening wakefulness were seen with the split-dose regimen [17]. A 600-mg split-dose regimen (400 mg in the morning and 200 mg in the early afternoon) was found to achieve more consistent wakefulness throughout the day (morning, afternoon, and evening) compared with 200- or 400-mg qAM or a 400-mg split-dose regimen [18]. Anecdotally, in clinical practice some physicians have reported increased favorable responses with doses up to 1200 mg/day. This contrasts with research studies on fatigue, where significant improvements have not been seen consistently with doses higher than 200 mg/day [19].

Dosing studies have also addressed considerations involved in switching from CNS stimulants to modafinil. A recent study of 151 patients showed that modafinil can improve daytime wakefulness in patients who have used previous CNS stimulant therapy [20]. Additional data have shown that patients may be safely switched from methylphenidate both with or without a short washout or dose titration period [21]. European data, however, have shown greater difficulty in switching from amphetamine, with some cases of failure to withdraw [22].

Armodafinil

Armodafinil is the *r*-enantiomer of modafinil and has a half-life of 10–14 h, whereas the *s*-enantiomer has a half-life of 3–4 h [3, 23]. Modafinil has equal amounts of *r*- and *s*-enantiomers; however the *s*-enantiomer is eliminated three times faster than the *r*-enantiomer and therefore most of the circulating compound is armodafinil. Armodafinil is well absorbed and peak levels are obtained after 2 h [24]. Armodafinil and modafinil both have a mean single-dose terminal elimination half-life of approximately 13 h, with similar mean maximum plasma drug concentration [*C*(max)] and median time to *C*(max) values [25]. After reaching *C*(max), plasma concentrations decline in a monophasic manner with armodafinil but in a biphasic manner with modafinil due to the initial rapid elimination of its *S*-isomer. As a result, mean areas under the plasma drug concentration values are 33 % and 40 % higher, respectively, with armodafinil compared with modafinil on a milligram-to-milligram basis. Therefore despite similar half-lives, plasma concentrations following armodafinil are higher late in the day than those following modafinil administration on a milligram-to-milligram basis. The pharmacokinetic profile of armodafinil may result in improved wakefulness throughout the day in patients with EDS compared with modafinil.

Food will delay the peak concentration by 2–4 h. Metabolism is predominantly hepatic and therefore severe hepatic disease will cause elevated concentrations of armodafinil. The main pathway for metabolism is by amide hydrolysis, which is a non-CYP pathway [3, 23]. There is a small tendency for CYP inhibition and induction, but the only clinical interaction is predominantly CYP3A4/5 induction and CYP2C19 inhibition [23, 26].

Efficacy of Armodafinil in Narcolepsy

Studies in healthy sleep-deprived individuals compared armodafinil with modafinil and placebo [27]. These studies showed longer MWT latencies and fewer PVT lapses during 6 to approximately 14 h compared with modafinil. From these studies and other modeling studies, it was determined that the bioequivalent dose of 200-mg modafinil was 150-mg armodafinil, and the 400-mg modafinil was bioequivalent to 250-mg armodafinil. Subsequently these doses were used in the clinical placebo-controlled studies of disorders of excessive sleepiness.

Studies in 196 patients with narcolepsy compared 150 and 250 mg of armodafinil with placebo [28]. The MWT was the main end point and the test was extended later into the day (09:00–15:00 h) to assess the longer duration of effect. Other tests included the ESS, the Brief Fatigue Inventory (BFI), and a Cognitive Drug Research (CDR) computerized battery of tests to assess attention and memory.

The MWT mean sleep latency was significantly increased compared with placebo. The mean sleep latencies increased over baseline at final visit were 1.3 min for 150-mg armodafinil, 2.6 for 250-mg armodafinil, and 1.9 min for combined groups of armodafinil, whereas placebo gave a decrease of 1.9 min ($p<0.01$ for all comparisons). Significant improvements were seen at all time points for the 150-mg dose but statistical significance was not reached at 8 and 12 weeks for the 200-mg dose.

The clinical global impression scale was improved at final visit for all groups, with proportions of 69, 73, and 71 % for the 150 mg, 250 mg, and combined armodafinil groups compared with 33 % for placebo. The CDR and BFI showed statistically significant improvements in memory, attention, and fatigue ($p<0.05$).

A 12-month, open-label, flexible-dose study with an extension period evaluated the efficacy of armodafinil (100–250 mg) in adult patients with excessive sleepiness associated with treated OSA, shift work disorder (SWD), and narcolepsy. At the final visit, 84 % (72.7, 94.8) of patients with narcolepsy were rated on the CGI-I as at least minimally improved with regard to overall clinical condition. Armodafinil improved ESS total scores in patients with narcolepsy (−4.7 [6.0] [−7.41, −1.93]). Armodafinil administered for 12 months or more was generally well tolerated and improved wakefulness and the overall clinical condition in patients with narcolepsy [29].

In summary, armodafinil showed improvements in wakefulness over the day and improvements in overall clinical condition, memory, and attention compared with placebo. Comparisons with modafinil were not made.

Mode of Action of Modafinil/Armodafinil

There are no known receptors that modafinil/armodafinil binds to or inhibits [24, 30]. Evidence exists that modafinil in vitro binds to the dopamine transporter (DAT) and inhibits dopamine reuptake [30]. DAT knockout mice are unresponsive to modafinil [30]. PET studies have shown armodafinil occupying the DAT in striatum and changes in extracellular dopamine in human subjects at different times after drug administration [31]. However, modafinil has activity that differs from other compounds that have presynaptic dopaminergic activity. Modafinil does not induce stereotypy at high doses and dopaminergic blockers do not affect modafinil's locomotor activity.

Although there has been the suggestion that modafinil interacts with adrenergic alpha-1 systems, studies in canine narcolepsy and hypertension suggest otherwise. Adrenergic alpha-1 stimulation exacerbates hypertension and inhibits cataplexy in canine narcolepsy, but modafinil does neither. Clinical evidence suggests that modafinil does not have adrenergic activity.

Modafinil increases serotonin 5HT metabolism in the striatum and reduces GABA flow to the cortex, but these effects may be indirect and it is unlikely that these activities are involved in the action of modafinil [32].

Modafinil increases C-fos activity in the anterior hypothalamus, suprachiasmatic nucleus, hypocretin neurons, and tuberomammillary nucleus and at higher doses the striatum and cingulated cortex [4, 33, 34]. It is likely that activation of these cell groups is secondary to increased wakefulness as C-fos expression occurs in these areas in normal wakefulness.

Modafinil may modulate norepinephrine uptake mechanisms to promote wakefulness, as modafinil inhibits the sleep-inducing nucleus, the ventrolateral preoptic nucleus (VLPO) [35]. However, VLPO-lesioned rodents show the same degree of alertness as seen in intact rodents suggesting that it acts other than through the VLPO [36]. Modafinil works in a manner similar to nisoxetine, a potent norepinephrine transporter (NET) inhibitor [37]. So, modafinil may act on both DAT and NET enhancing norepinephrine/dopamine systems.

Safety and Adverse Event Data with Modafinil/Armodafinil

Substantial safety data on the use of modafinil has been compiled through a number of sources, including adverse event monitoring in the clinical trials, postmarketing adverse event reporting, preclinical studies on drug interactions, studies on abuse and dependence potential, and active postmarketing surveillance programs. Overall, modafinil ,exhibited a favorable adverse event profile in placebo-controlled studies [1, 7, 8, 38]. The most common adverse event was headache; most were mild or moderate in severity, appeared in the early stages of therapy, and resolved within several days. A dose–response relationship was seen with headache and anxiety.

Armodafinil has been studied in over 1000 patients and exhibits a similar safety profile to modafinil [24]. The most common side effects are headache (17 %), nausea (7 %), dizziness (5 %), and insomnia (5 %). There have been some slight changes with armodafinil in the hepatic enzymes, gamma glutamyltransferase (GGT) and alkaline phosphatase (AP), compared with placebo. An open-label study of armodafinil (50–250 mg per day) in 743 patients with narcolepsy OSA and shift work showed mild to moderate side effects with headache [25 % (180/731)], nasopharyngitis [17 % (123/731)], and insomnia [14 % (99/731)] being the most common [39]. Modest increases were observed in vital sign measurements [blood pressure (3.6/2.3 mmHg), heart rate (6.7 beats per min)] across all patient groups.

Neither long-term, open-label studies nor postmarketing adverse event reporting for modafinil has revealed patterns of adverse events that differ from those in the double-blind, placebo-controlled studies. Patients in the narcolepsy studies were enrolled in an open-label extension study using flexible doses of 200- to 400-mg modafinil; results through 136 weeks have demonstrated continued improvement in wakefulness on the ESS and expected treatment-emergent adverse events including headache, nervousness, and nausea [1, 40]. A total of 28.7 % of patients discontinued treatment, for reasons that included "insufficient efficacy" (11.5 %) and adverse events (9 %).

In clinical trials of modafinil, the incidence of rash resulting in discontinuation of modafinil was approximately 0.8 % (13/1585) in pediatric patients (age < 17 years); these rashes included one case of possible Stevens–Johnson syndrome (SJS) and one case of apparent multi-organ hypersensitivity reaction. No serious skin rashes have been reported in adult clinical trials (0/4264) of modafinil [41].

Rare cases of serious or life-threatening rash, i,ncluding SJS, toxic epidermal necrolysis (TEN),

and drug rash with eosinophilia and systemic symptoms (DRESS), have been reported in adults and children in worldwide postmarketing experience. The reporting rate of TEN and SJS associated with modafinil use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate. Estimates of the background incidence rate for these serious skin reactions in the general population range between 1 and 2 cases per million-person years.

Most cases of serious rash associated with modafinil occurred within 1–5 weeks after treatment initiation and there are no factors that are known to predict the risk of occurrence or the severity of rash. As it is not possible to reliably predict which rashes will prove to be serious, modafinil should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related.

One serious case of angioedema and one case of hypersensitivity (with rash, dysphagia, and bronchospasm) were observed among 1595 patients treated with armodafinil. No such cases were observed in modafinil clinical trials. However, angioedema has been reported in postmarketing experience with modafinil. Patients should be advised to discontinue therapy and immediately report to their physician any signs or symptoms suggesting angioedema or anaphylaxis (e.g., swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).

Multi-organ hypersensitivity reactions, including at least one fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days: range 4–33) to the initiation of modafinil. If a multi-organ hypersensitivity reaction is suspected, modafinil should be discontinued. Although there are no case reports to indicate cross-sensitivity with other drugs that produce this syndrome, the experience with drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

Modafinil has been tested with a number of drugs that are metabolized by the hepatic cytochrome P450 enzyme system, including oral contraceptives, warfarin, and triazolam [26, 42]. In patients who are CYP2D6 deficient, an elevation of clomipramine levels can occur. Blood levels of fluoxetine may be increased slightly by modafinil. Among the notable interactions was a decrease in the peak plasma concentrations of ethinylestradiol. As a result, the prescribing information contains a precaution advising women to seek alternative or additional methods of contraceptive while taking modafinil and for 1 month following discontinuation. Armodafinil, is a moderate inducer of CYP3A4 and a moderate inhibitor of CYP2C19 in healthy subjects, and therefore dosage adjustments may be required for drugs that are substrates of CYP3A4 (e.g., cyclosporine, triazolam) and CYP2C19 enzymes (e.g., diazepam, phenytoin) when administered with armodafinil [23].

There are no drug interactions with medications taken concurrently for cataplexy. The anticataplectic medication, sodium oxybate, has been shown to provide additional benefit to daytime alertness when given with modafinil [43].

Modafinil and armodafinil are both Schedule IV medications of the Controlled Substances Act. Abuse potential is relatively low and may lead to limited physical or psychological dependence. Postmarketing surveillance of modafinil has not detected generalized interest in modafinil as a drug of abuse. However, there have been isolated cases of modafinil abuse reported through these methods of surveillance [44]. In addition, clinical studies in persons experienced with drugs of abuse have demonstrated the modafinil can produce mild psychoactive and euphoric effects consistent with those of CNS stimulants [41, 45].

In studies of OSA syndrome, while mean systolic or diastolic blood pressure did not rise significantly in patients treated with modafinil, more patients taking modafinil in the placebo-controlled clinical studies required either an increase in dose or an additional prescription for an antihypertensive agent [38, 46]. Small but consistent changes in systolic and diastolic blo,od pressures have been seen in clinical trials with armodafinil. Analyses of electrocardiographic features such as QTc intervals have not revealed any evidence of detrimental effects. In clinical

studies of modafinil, signs and symptoms including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse (MVP) or left ventricular hypertrophy [24]. It is recommended that modafinil and armodafinil not be used in patients with left ventricular hypertrophy or in patients with MVP who have experienced the MVP syndrome with other CNS stimulants. Modafinil and armodafinil have not been studied in patients with recent myocardial infarction or angina and it is recommended that caution should be exercised in such patients. The overall cardiovascular profile of modafinil and armodafinil is favorable compared with that of the stimulants.

Psychiatric adverse experiences associated with the use of modafinil have included mania, delusions, hallucinations, and suicidal ideation, some resulting in hospitalization. Many patients had a prior psychiatric history. In the adult modafinil controlled trial database, psychiatric symptoms resulting in treatment discontinuation were anxiety (1 %), nervousness (1 %), insomnia (<1 %), confusion (<1 %), agitation (<1 %), and depression (<1 %). In the controlled trial armodafinil database, anxiety, agitation, nervousness, and irritability were reasons for treatment discontinuation more often in patients on armodafinil compared to placebo (armodafinil 1.2 % and placebo 0.3 %). In the armodafinil-controlled studies, depression was also a reason for treatment disco,ntinuation more often in patients on armodafinil compared to placebo (armodafinil 0.6 % and placebo 0.2 %) [24]. Caution should be exercised when modafinil/armodafinil is given to patients with a history of psychosis, depression, or mania. The medication should be stopped if there is the emergence or exacerbation of psychiatric symptoms.

Modafinil and armodafinil are category C for pregnancy. The general recommendation is for patients to avoid taking modafinil or armodafinil during pregnancy unless the risk/benefit ratio suggests otherwise.

Studies in the elderly (>65 years of age) have shown that steady-state AUC(τ) and *C*(max) armodafinil values are approximately 15 % greater in elderly subjects compared with young subjects [47]. Although the increase in plasma armodafinil concentration did not result in more adverse events compared with young subjects, consideration should be given to lower dosages of armodafinil in the elderly.

Summary

Modafinil is regarded as a first-line medication for the treatment of excessive sleepiness in narcolepsy. Although not the only medication recommended as a standard of treatment for the excessive sleepiness of narcolepsy by the AASM (sodium oxybate is also regarded as a standard of treatment), it is the most widely used medication. Despite there being common side effects of nausea and headache, these are usually self-limited and are only mild in severity. Since approval, modafinil has been found to have some serious adverse effects such as hypersensitivity reactions and skin rashes; however these are rare but the clinician needs to be aware that they might happen and, if so, stop the medication. In general, modafinil is safe and well tolerated by most patients. Modafinil is recommend as a single daily dose although many patients may require twice a day dosing to provide coverage in the late afternoon.

Armodafinil, the isomeric form of modafinil, is an effective medication for excessive sleepiness that is the isomeric form of modafinil. It has a longer duration of effect and has some of the same adverse effects as modafinil. As with modafinil the adverse effects are only mild and the medication is well tolerated. The dose of armodafinil required is less in terms of milligrams than for modafinil (250 mg vs. 400 mg, respectively). Armodafinil has a longer half-life and is useful for those patients who need additional control of sleepiness in the late afternoon or early evening. When combined with sodium oxybate for cataplexy, modafinil or armodafinil can produce some of the biggest improvements in daytime sleepiness in patients with narcolepsy [48].

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Sodium Oxybate in the Treatment of Narcolepsy

24

Geert Mayer

Conservative Treatment of Narcoleptic Symptoms

Since 1934 medication has been available for the treatment of narcoleptic symptoms. With the full-blown symptomatology, patients had to be treated with two or three different substances: (1) excessive daytime sleepiness (EDS) with stimulants, (2) cataplexies with antidepressants, and (3) fragmented nighttime sleep with hypnotics.

The majority of stimulants are amphetamines, which act as dopaminergic agonists that can cause central stimulation, inhibition of sleepiness, improvement of cognition, concentration, and learning capacity, improvement of attention, reduction of appetite and thirst, increase of body temperature and blood pressure, vascular resistance, and energy metabolism of the brain. Because some of these substances have been on the market for 60 years, the available therapeutic studies often do not meet the criteria of modern evidence-based medicine. The available studies often have low evidence levels, even though their clinical effects are beyond doubt. Modafinil introduced into the therapeutic spectrum in the 1980s was the first non-amphetamine-like stimulant. Its mode of action has not been sufficiently understood until nowadays. However, it is the only stimulant that does not act via dopamine receptors but via GABA (reduction of extracellular concentrations) [1]. It is a postsynaptic α_1-receptor agonist. Its few side effects are quite different from that of the amphetamines [2]. It has no potential for addiction.

Cataplexies have been successfully treated for more than 60 years with tricyclic antidepressants. In the recent years, a growing number of selective and nonselective serotonin, noradrenaline, and catecholamine reuptake inhibitors have been efficacious in studies with small patient numbers. However, the most potent anticataplectic medication is that with the highest noradrenaline reuptake inhibition.

Studies on the treatment of fragmented nighttime sleep are extremely scarce and comprise only very small patient numbers.

Gamma-Hydroxybutyrate (GHB)/ Sodium Oxybate (SO)

In the 1960s, shortly after its discovery, GHB was used for the treatment of narcolepsy. The rationale was that it evokes sleep that resembles physiological sleep but comprises a higher amount of slow-wave sleep and consolidates

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REM sleep. Initial studies documented the improvement in sleep quality and a reduction of cataplexies [3–6]; for overview see [7].

Pharmacology

GHB is an endogenous fatty acid produced within the brain that is found in many other tissues [8]. It has specific receptors (GHB, $GABA_B$) that are located within the central nervous system and to which it has a different affinity. There are no high-affinity GHB receptors in the peripheral tissues. GHB receptors seem to mediate the signaling of endogenous GHB, whereas $GABA_B$ receptors mediate the action of GHB and the GHB precursor gamma-butyrolactone (GBL). Application of GHB and GBL $GABA_B$ receptor-deficient mice could not induce a dose-dependent behavior (hypothermia and hypolocomotion) or physiological changes like the induction of slow-wave activity in the electroencephalogram and increase of striatal dopamine synthesis, seen in GHB-non-deficient mice [9]. The binding to the $GABA_B$ receptor seems to be responsible for sleep induction. However, recent studies in GHB_B receptor-deficient mice indicate that GBL induced slow-wave activity results in a dose-dependent sub-anesthetic to anesthetic state with behavioral wakefulness [10]. Therefore, the concept of "slow-wave sleep" caused by SO does not correspond to behavioral sleep. The concept of "sleep induction" has been depending on the methodology of early studies [11] that defined sleep as the time between application of GHB and the restoration of the righting reflex. GHB applied in physiological doses has a modulating effect on GABAergic, dopaminergic, noradrenergic, and serotonergic neurons [12].

GHB may partly be exerting its actions on state and motor control by acutely mediated strong inhibition of serotonergic dorsal raphe (DR) neurons and a more modest inhibitory action on a smaller proportion of laterodorsal tegmentum (LDT) cholinergic neurons [13]. The impact on these sleep–wake regulating nuclei is consistent with the promotion of sleep. Differences in GHB-mediated calcium suggest differential regulation of calcium-dependent processes, which may also contribute to functioning of the LDT and DR in state and motor control and the therapeutic pharmacologic actions of GHB, which develop following chronic administration.

GHB is synthesized and stored in cerebral neurons. Neuronal depolarization releases GHB into the extracellular space in a calcium-dependent manner. After its metabolization, it is not reverted into GABA. In vivo GHB acts as an inhibitor of dopamine release. In patients with high levels of calcium, it stimulates dopamine. Stimulation of $GABA_B$ receptors causes hypothermia with the respective behavioral changes [14]. This finding fits core body reduction on falling asleep. In sleep-deprived subjects, SO counteracts the expected alertness deficits by increased slow-wave activity, thus reducing the homeostatic response to sleep loss [15]. The mechanisms by which GHB enhances wakefulness over the daytime remain unclear. It is assumed that it shifts the relation of sleep–wake neurotransmission toward wakefulness by acting on the noradrenergic locus coeruleus.

Pharmacokinetics

SO is rapidly absorbed after oral intake. Peak plasma concentrations are measured after 0.5–1.25 h. The half-life is 40–60 min. GHB dehydrogenase metabolizes SO into succinic semialdehyde which is converted into succinic acid that enters the Krebs cycle where it is converted to CO_2 and water [16]. Five percent are eliminated unchanged in the urine. There is no induction of cytochrome P450 isoenzymes by SO [17, 18].

SO is a liquid. Due to its pharmacokinetics, it should be administered in two equal doses directly prior to going to bed and 2.5–4 h later [19]. Plasma concentrations increase disproportionally with dose [20].

Since food can reduce absorption of SO to quite an extent, it is recommended to administer the fluid at least 2 h after last meals [21]. Due to enzyme saturation, plasma levels are increased after the second intake. The rationale for the

twice nightly administration is the effect on sleep duration taken from the older pharmacological studies [2, 4–6]. Whether SO is efficacious after intake of one dose—which some patients would prefer—has not been studied. In some patients SO-induced sleep duration is shortened to 1.5 h or less from the first intake on. These patients often split the total amount of SO into three doses. The amount of SO per dose depends on the time they want to stay in bed. Some patients even go to sleep without taking SO, because they fall asleep easily for the first 1–2 h. They start taking SO after the first awakening.

Efficacy of SO in Treating Symptoms of Narcolepsy

Cataplexy

Safety and efficacy of SO were established in two double-blind, randomized, placebo-controlled studies and in one open-label extension study. In the first study, 136 patients who were allowed to maintain their stimulants were randomly exposed to 3, 6, or 9 g of SO in two equal doses per night, respectively. A significant dose-dependent reduction of cataplexies was found in 52 % of patients treated with 6 g and 62 % treated with 9 g [22]. The results were confirmed in a group of 228 patients [23, 24]. In a 12-month study, the initial dose of 6 g was up- or down-titrated every 2 weeks according to a defined protocol [25]. The most significant reductions in cataplexies were found after 4 weeks. The 90 % reduction of cataplexies remained stable until the 12th month.

An open-label study in 55 patients with a treatment duration of 7–44 months (3–9 g) confirmed the results and showed a gradual return of cataplexies after withdrawal of SO [26]. In a retrospective analysis of Swiss patients, cataplectic attacks were reduced from a mean of 20 to 1 per week [27]. A meta-analysis [28] found that 9 g/night was superior to placebo for reducing mean weekly cataplexy attacks.

None of the studies evidenced tolerance. After withdrawal of SO, none of the patients reported rebound cataplexies.

Excessive Daytime Sleepiness

Most of the studies for the investigation of cataplexies comprised an evaluation of daytime sleepiness by using the Maintenance of Wakefulness Test (MWT) and the Epworth Sleepiness Scale (ESS) [23, 44]. In an 8-week double-blind, placebo-controlled study, 228 patients who under controlled conditions had been withdrawn from their antidepressants and maintained their stable doses of stimulants were randomly exposed to 4.5, 6, or 9 g of SO. Patients receiving 9 g had a significant reduction of the median ESS score from 17 to 12 points compared to placebo. The median changes for 4.5 and 6 g were 1 and 2 points, respectively. In the 9 g group, sleep latencies in the MWT increased significantly by 10 min, and median inadvertent naps decreased significantly in the 6 and 9 g group. A detailed analysis attributed the changes to SO as additional effect to the concurrent stimulant treatment [23].

In the 12-month study, all doses of SO showed a significant improvement after 2 months when compared with placebo.

In an 8-week randomized, placebo-controlled, double-blind, double-dummy, controlled four-arm study (placebo, placebo plus modafinil, placebo plus SO, SO plus modafinil, 228 patients), switching the patients from modafinil to SO did not result in any change of sleep latencies in the MWT. The combination of SO plus modafinil caused an increased extension of NREM sleep and reduction of nocturnal wake periods as compared to SO alone as well as a significant increase in sleep latency (plus 2.7 min) compared to placebo. Apparently modafinil enhances the pharmacological effects of SO [29].

Sleep

It has been known for more than 20 years that GHB increases theta and delta activities in EEG recordings [2]. In all GHB studies polysomnographies showed an increase of stages NREM 3 and NREM 4 as well as of delta power [30].

SO consolidated sleep by significant reduction of nocturnal wake episodes in the 6 and 9 g group when compared to placebo. Total sleep time was extended significantly with 9 g [23]. In the MWT, sleep latency was significantly increased in the 9 g group. The number of inadvertent naps during daytime was significantly reduced in the 6 and 9 g group from 18 to 12 and 14 to 8, respectively. Retrospective analysis of Swiss patients treated with SO showed an increase in sleep latency in the MWT from initially 5.5–17.5 min [27]. In the same study, improvement of sleep quality/efficiency could be documented by actigraphy with a significant increase in sleep/rest efficiency over 24 h.

Ancillary Symptoms

Sleep Paralysis and Hallucinations

SO studies show conflicting results. A class I evidence study [22] did not show any effect on sleep paralysis and hallucinations, whereas a study with 21 patients treated with doses up to 9 g/night showed a decrease in the number of reported episodes of sleep paralysis and hallucinations [31]. Similar results were reported in a Swiss cohort [27]. Sleep paralysis disappeared in 8 of 8 NC patients and hallucinations in 8 of 10 NC patients.

RLS

RLS has a prevalence of about 14.6 % in narcolepsy patients. One case report showed that RLS was reversible under SO treatment [32]. In the Zurich experience, there was no significant increase in PLMS, which is frequent in NC patients and which is associated with RLS [27]. It remains unclear if this effect of SO is dose dependent.

Depression

Early GHB studies indicated some effect on depression [33], but so far no specific evaluation for efficacy of SO on depression in NC patients has been performed.

REM Sleep Behavior Disorder (RBD)

RBD has been reported in 45–61 % of NC patients and could be confirmed in 36–43 % by PSG [34–37]. According to preliminary findings, a dose-dependent effect of SO on RBD in narcolepsy patients can be expected [33].

Weight

Mean weight loss of 3.4 kg (30.9 kg maximum) has been reported in a retrospective study in 54 NC patients who were taking a mean dose of 6.9 g SO [38]. In a postmarketing surveillance from 2002 to March 2008, weight loss was the ninth most frequent side effect (reported by 0.7 % out of 26,000 patients) [39]. Recently a study of the effect of SO on growth hormone [40] found a consistent increase in nocturnal GH secretion. These results suggest that SO may alter somatotropic tone which could explain body weight reduction.

Clinical Use in Children

Unfortunately there are no guidelines on how to treat children with narcolepsy. Worldwide prescription for narcolepsy medication for children is "off-label." A group of European pediatric researchers studied 26 children (age 6–16 years) who were treated with SO [41] (mean dose 5.9 ± 1.6 g) over a period of 4.1 ± 2.1 years. Thirty-five percent of the patients were taking SO in monotherapy and 52 % in combination with modafinil, 9 % in combination with venlafaxine and modafinil, or 4 % in combination with venlafaxine only. Despite adverse events similar to those in adults [weight loss, headache, nausea, disturbed nocturnal sleep, irritability, parasomnias (sleepwalking, sleep talking, enuresis, episodes of sleep drunkenness)], the efficacy outweighed the adverse events. Only four patients had to be taken off medication due to severe nausea and sleep loss. Few children even reported spontaneous improvement of school performance. An earlier retrospective study [over 11.4 months (mean)] in eight children reported

significant improvement of cataplexies and sleepiness as measured by ESS [42] under 3–7 g. Insomnia occurred in 25 %, and three children stopped intake due to various reasons.

Experts recommend SO for children with severe forms of narcolepsy with cataplexy and sleep disorders. Apparently children need the same mean dose of SO as adults. In contrast to adults, insomnia seems to be a severe side effect that needs to be considered.

Pregnancy

Studies in pregnant rats at doses up to 1000 mg/kg (about equal to maximum recommended human daily dose) and in pregnant rabbits up to 1200 mg/kg (approximately three times the maximum recommended human daily dose on a mg/m^2 basis) revealed no evidence of teratogenicity [43]. There is no human data available; therefore, SO is not recommended during pregnancy. The US prescribing information classifies SO as Pregnancy Category B and states that "Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." Effects on later growth, development, and maturation in humans are unknown.

So far no teratogenic effects in humans are known. SO rather has neuroprotective properties. Pregnant narcoleptic women need to decide whether they go on with medication throughout the pregnancy to protect themselves from severe cataplexies or severe insomnia or if they stop SO.

Quality of Life

In a 10-week open-label, dose-escalating study, patients reported changes of symptoms by a questionnaire: improvement of cataplectic attacks (86 %), hypnagogic hallucinations (76 %), sleep paralysis (76 %), daytime sleep attacks (76 %), nighttime awakenings (57 %) and daytime sleepiness (76 %), nighttime sleep quality (81 %), ability to concentrate (67 %), and overall condition (81 %) [31].

In a 6-month study with 140 narcoleptic patients, a statistically significant improvement ($p < 0.05$) was seen in 7 of the 8 domains measured by the SF-36 questionnaire, namely physical functioning, limitations due to physical functioning, general health, vitality, social functioning, limitations due to emotional problems, and mental health [44].

The analysis of quality of life in one of the multicenter studies showed that SO 9 g produced a dose-related improvement in four out of five subscales of the FOSQ, with two subscales (activity and social outcome level) improving at the lower 6 g dose. No improvements were observed with SO 4.5 g [45].

Adverse Events

In the multicenter international SO studies, the overall incidence of adverse events was 5 %.

The "Safety Overview of Postmarketing and Clinical Experience of Sodium Oxybate" [39] included 26,000 patients who received SO between 2002 and 2008. The 20 most frequently reported adverse events are given in Table 24.1.

Most frequent adverse events were dizziness, nausea, headache, somnolence, enuresis, vomiting, and sleep walking. Sweating was one of the major problems. Dizziness and somnolence were experienced when patients were getting up and walking around in the active phase of SO or as "hangover" in the morning within the first days after intake. Nocturnal enuresis occurred in 7.9 %, namely, in elderly and pharmaco-sensitive patients. Psychosis only occurred in one patient who had a history of psychiatric disorder unknown to the investigators. In the long-term studies, side effects were similar to the 8-week studies.

Thirty deaths were reported worldwide. In six cases the deaths were not considered to be related to SO by the prescribing physicians: three cases were due to drug overdose and one from lung cancer, suicide, drowning, renal failure, and cardiac arrest. Death also occurred in patients who had been treated with multiple other drugs not known to the investigators. In the clinical trials, 10 % of patients discontinued because of adverse

Table 24.1 Twenty most frequently reported adverse events in postmarketing use through March 2008 (Wang et al.)

Events (MedDRA preferred term)	Number of reports (Incidence)
Nausea	578 (2.2 %)
Insomnia	365 (1.4 %)
Headache	362 (1.4 %)
Dizziness	339 (1.3 %)
Vomiting	264 (1.0 %)
Somnolence	234 (0.9 %)
Initial insomnia	207 (0.8 %)
Feeling abnormal	195 (0.8 %)
Weight decreased	169 (0.7 %)
Confusional state	166 (0.6 %)
Tremor	164 (0.6 %)
Anxiety	162 (0.6 %)
Depression	158 (0.6 %)
Fatigue	149 (0.6 %)
Diarrhea	111 (0.4 %)
Dyspnea	110 (0.4 %)
Hyperhidrosis	100 (0.4 %)
Blood pressure increased	99 (0.4 %)
Paresthesias	99 (0.4 %)
Sleep walking	94 (0.4 %)

1. Cited from Wang et al. (2008). With friendly permission of the American Academy of Sleep

events. The most frequent reasons for discontinuation (>1 %) were nausea (2 %), dizziness (2 %), and vomiting (1 %).

0.2 % of the 26,000 patients reported ≥1 of the events studied, 0.039 % met DSM-IV abuse criteria, 0.016 % dependence criteria, 0.031 % withdrawal symptoms after discontinuation of SO, two confirmed cases (0.008 %) of sodium oxybate-facilitated sexual assault, 0.031 % overdose with suicidal intent, 21 deaths (0.08 %) in patients receiving SO treatment with 1 death known to be related to SO, and three cases (0.01 %) of traffic accidents. Postmarketing surveillance in the USA, Australia, and Europe has shown a decline of abuse, intoxication, and overdose of SO [46]. The misuse is lower than in cannabis, analgesics, and hypnotics. Sexual assault was only reported in two patients.

SO has the potential to induce respiratory depression. Apneas and respiratory depression have been observed in a fasting healthy subject after a single intake of 4.5 g at once (twice the recommended starting dose = 2 × 2.25 g). The potential effects of SO on respiratory measures during sleep was assessed as a secondary end point in a 10-week, open-label, multicenter trial (4.5, 6, 7.5, and 9 g SO per night) on overnight polysomnographic measures. SO was not associated with a dose effect on sleep-disordered breathing or a decrease in mean oxygen saturation in patients in this study, including six patients with obstructive sleep apnea [47, 48]. Respiratory depression has been noted in some patients and was addressed in an extra study in an open-label multicenter trial, which showed neither change in respiration nor in oxygen saturation in PSGs [28]. An Italian study with 51 narcolepsy patients with cataplexy and sleep apnea who were treated with nCPAP showed a worsening of respiration in 21.6 % and development of catathrenia in 13.7 % [49]. A recent publication reported central sleep apnea after intake of SO [50]. Two recent meta-analyses of the efficacy and side effects of SO confirmed that most adverse events were mild and moderate in severity [28, 51]. However, patients should be asked and watched for signs of CNS or respiratory depression, and special monitoring should be warranted.

On rare occasions the combination of SO with modafinil has led to severe depression [52].

In one patient rhythmic movement was observed under SO [53].

Contraindications

SO treatment is not indicated for patients with sensitivity to one of its components, those with succinic semialdehyde dehydrogenase deficiency (a very rare disorder), patients treated with barbiturates or opioids, and pregnant or lactating women. Treatment of patients with sleep-disordered breathing should only be performed under control of nocturnal breathing parameters. Patients consuming alcohol have to be instructed to skip the intake of SO which may potentiate its CNS effects. Infrequent psychiatric side effects (0.1–1 %) are instability of affect, crying, emotional disorder, euphoric mood, fear, auditory

hallucinations, hypnagogic hallucination, initial insomnia, altered mood, increased libido, middle insomnia, panic disorder, paranoia, restlessness, sleep attacks, and stress symptoms. SO prescription for patients with a history of psychiatric disorders should therefore be closely monitored (authors' remark).

Experts do not recommend SO in patients who are on night duty and who have to attend to newborns or young children, in elderly patients (due to the risk of falling when on SO) or patients living alone, and in patients with known heart failure, hypertension, or compromised renal function.

Off-Label Treatment in other Hypersomnolences

Practical experience has shown that some patients with hypersomnolence with long sleep may benefit from SO which allows some of them to wake up spontaneously in time in the morning (authors experience).

Treatment Recommendations

In 2006 the European Federation of Neurological Societies (EFNS) published guidelines on the management of narcolepsy. For EDS, first-line treatment is modafinil (100–400 mg/day) at two doses, rarely 600 mg; second-line treatment is methylphenidate 10–60 mg; and third-line treatment is SO (evidence level 1). For cataplexy first-line treatment is SO and second-line is antidepressants, specifically clomipramine (10–75 mg). A combination with behavioral treatment (evidence level 2) is recommended [54].

In 2007 the American Association of Sleep Medicine (AASM) published practice parameters for the treatment of narcolepsy [55] stating that several large randomized, placebo-controlled studies indicate that modafinil and sodium oxybate are effective for treatment of hypersomnia associated with narcolepsy (evidence level 1): "The traditional stimulants [amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (evidence level 2)] which are available in generic form and are less expensive, have a long history of use in clinical practice, but have limited high-level evidence from published studies." None of the guidelines address the treatment of narcolepsy without cataplexy. Since both types of narcolepsy respond to stimulants and patients without cataplexies often suffer disturbed nocturnal sleep and ancillary (REM associated) symptoms, it seems clear that SO should work in them as well as in those with cataplexies.

For the treatment of cataplexies, "The recommendation for use of antidepressants (evidence level 2) for cataplexy is based largely on clinical experience and lower-evidence level clinical trials. Randomized controlled trials of these agents, particularly with comparison to sodium oxybate (evidence level 1), a more expensive medication that has high-level evidence of efficacy, are needed to assist the clinician in medication selection." SO is indicated for the treatment of EDS, cataplexy, and disrupted sleep due to narcolepsy (evidence level 1). In children not responding well to stimulants and anticataplectic medication, SO can be very efficacious. Parents and pediatricians however should carefully monitor for controlled intake and adverse events, especially insomnia.

Patients should be thoroughly instructed not to ingest hypnotics and sedatives that can augment the hypnogenic effect of SO. Those with hypertension should regularly look for their sodium in order to prevent increase of blood pressure (the sodium amount increases dose dependently). Nocturnal hunger spells in between the first and second doses can occur and can be managed by providing an easy digestible, light snack. Patients suffering from sleep apnea (treated or untreated) should be controlled for deterioration of snoring and apneas. There is no data what SO does to children with ronchopathies. SO might cause apneas in these children which could lead to decrease in cognitive and physical performance.

In patients with severe weight loss, doses may need to be reduced until weight normalizes again which happens after about 8–10 weeks (authors' experience).

SO improves comorbid NREM and REM parasomnias as well as RLS in many patients, but some patients may develop these sleep disorders newly under SO treatment. This can happen at low dose and sometimes the disorders improve at higher doses. However, dosage has to be adjusted individually according to the side effects. Patients with nausea may also take doses that are too low to make them fall asleep fast to overcome the nausea that many patients experience shortly after intake. They should try an increase of dose to shorten this unpleasant sensation. They should, however, be taken off SO if nausea persists. The instruction to take SO in bed to prevent falling asleep to fast is an experience which narcoleptic patients generally do not share. Even when fasting they do not experience extremely short sleep latencies as healthy persons. Patients report that SO is still effective as usual when they take a snack immediately prior to the intake of the first or second dose.

In very few patients tolerance may develop over time. These patients may be recommended to make a "drug holiday" for several days. Normally they can go back to their initial SO dose and sleep as good as an initial SO treatment. For patients who suffer from severe insomnia without SO, hypnotics like non-benzodiazepine receptor agonists may be helpful during the "drug holiday" only. Even when SO is not causing sufficient sleep length and quality, a combination with hypnotics is absolutely contraindicated. The patient information warns patients about consuming alcohol which can augment the hypnogenic effect of SO. Most patients skip one or two doses of nocturnal SO after alcohol intake. Due to the absence of rebound phenomena, they take into account a night of bad sleep or sleep loss.

Conclusion

SO is a well-tolerated, new compound for the treatment of the important narcoleptic symptoms such as EDS, cataplexy, and fragmented nighttime sleep which does not cause symptom rebound after withdrawal.

SO has few side effects and shows little interaction with other drugs: it should be considered for treatment in patients who do not respond well to conservative drugs or those who display a combination of symptoms for which SO is efficacious. Due to its indication for a rare disease and its special application, SO should be administered by sleep specialists.

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Pregnancy and Anesthesia in Narcolepsy

25

Michael J. Thorpy

Narcolepsy persists throughout pregnancy; however, whether the symptoms of narcolepsy change during pregnancy will vary from patient to patient. Sleep quality in healthy women may be impaired during both the first and the second trimester in part due to high levels of progesterone in women. During the third trimester, sleep disturbance and sleepiness usually increase due to discomfort, nocturia, leg cramps, restless legs, heartburn, sleep-related breathing disorders, and fetal activity [1]. The nocturnal sleep and daytime sleepiness symptoms in narcolepsy women have not been well characterized during pregnancy, but they appear to follow the pattern seen in healthy women but with greater variability. Recent animal studies have suggested that the neuropeptide, hypocretin, may be an important neuropeptide involved in pregnancy [2]. Patients with type 1 narcolepsy have reduced number of hypocretin neurons, but the significance of this in human pregnancy is not known [3].

The management of narcolepsy during pregnancy has been discussed in several recent publications [4–8]. A recent retrospective review of 249 female narcolepsy patients with and without cataplexy indicated that minor complications were more common in patients with narcolepsy at the time of delivery, and those with cataplexy had caesarian section more frequently [6].

Therapy for narcolepsy usually involves modafinil for daytime sleepiness, antidepressants for cataplexy, and gamma-hydroxybutyrate for both symptoms [8, 9]. Most patients are advised by the treating clinician not to take narcolepsy medication during pregnancy to limit any possible risk. However, if the benefits of treating outweigh the risks of adverse effects or fetal medication-induced abnormalities, then some clinicians would treat.

Teratogenic Effects of Medications for Narcolepsy

The risk of teratogenic effects from most clinically used medications in therapeutic doses is essentially nonexistent [10]. Approximately 4 % (1 in 28) of babies are born each year with a major birth defect or congenital malformation [11]. Of the major defects, 25 % are of genetic origin (genetically inherited diseases, new mutations, and chromosomal abnormalities), 65 % are of unknown etiology (multifactorial, polygenic, spontaneous errors of development, and synergistic interactions of teratogens), and only 2–3 % of malformations are thought to be associated with medication treatment.

Most of the medications used to treat narcolepsy (modafinil, armodafinil, gamma-hydroxybutyrate, amphetamine and methylphenidate, venlafaxine,

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clomipramine, fluoxetine, and selegiline) have shown some teratogenic risks in animal studies [US Federal Drug Administration (FDA) category C rating]; however, no controlled studies exist in humans (Tables 25.1 and 25.2A).

The European Medicines Agency (EMA) does not have a rating scale for medications but allows for acceptable statements for use in the pregnancy section of a product monograph (Tables 25.1 and 25.2B).

Many of the medications used to treat narcolepsy are those that have a high abuse potential. The available information on pregnancy and lactation with these medications includes use in medication abusers and patients who may be taking additional drugs and medications often in unknown doses. The alerting medications are often used for conditions other than narcolepsy such as attention deficit disorder, obstructive sleep apnea, and shift work disorder. Animal and human data have shown no evidence for increased teratogenicity or malformations with modafinil, gamma-hydroxybutyrate, methylphenidate, or amphetamines. Intrauterine growth retardation has been reported with use of modafinil, amphetamines, and methylphenidate although the clinical relevance is unclear [12–18].

In clinical trials of sodium oxybate for the treatment of fibromyalgia, out of six pregnancies, there were three cases of spontaneous abortions. One of the patients had had a prior spontaneous abortion. The spontaneous abortions were not believed to be due to the medication, and the rate in the general population is between 10 and 15 % [19].

Case reports of narcoleptic women taking antidepressant anticataplectic medication during pregnancy, such as a selective serotonin reuptake inhibitor, have not indicated a bad outcome [20, 21].

The European Medical Agency (EMA) has a data pregnancy registry with modafinil information on 14 clinical studies, 72 spontaneous cases, and 1 healthy child reported in the literature [22]. Even without any details or references on the data, the registry reported 87 healthy births, 9 congenital abnormalities, 18 spontaneous abortions, 1 still birth, 11 premature labors, and 1 abnormal labor. Both the EMA and FDA believe that there is limited data available to establish or exclude an association between human pregnancy exposure to modafinil and congenital malformations, spontaneous abortions, or other birth complications.

The Management of Narcolepsy Related to the Trimester of Pregnancy

The timing of fetal medication exposure during pregnancy is a critical issue as teratogenicity depends upon developmental stage [23]. The embryonic period, from 18 to 60 days after conception when organogenesis occurs, is the period of maximum sensitivity to teratogenicity since tissues are differentiating rapidly and structural damage may become irreparable. However, during the fetal phase, teratogen exposure will affect fetal growth and the size or function of an organ, rather than cause gross structural anomalies.

Pregnancy Course in Patients with Narcolepsy

A recent retrospective cohort study reported 54 pregnant women with narcolepsy [7]. Except for one patient, none were treated with medications during pregnancy. The patients were divided into two groups: those with narcolepsy symptom onset occurring before pregnancy and those who developed narcolepsy symptoms after pregnancy. No significant differences were found between groups in terms of age of mothers at delivery, history of spontaneous abortion, alcohol and nicotine consumption, complications during pregnancy, symptoms of narcolepsy, weight gain during pregnancy, length of pregnancy and delivery, complications during delivery, and weight and length of the newborn. However, women with narcolepsy symptom onset before pregnancy tended to have higher impaired glucose tolerance or type 2 diabetes compared to the asymptomatic group, but there was no control group.

Table 25.1 FDA and EMA pregnancy categories

Medication	FDA pregnancy category	EMA SPC pregnancy and lactation statements
Modafinil/armodafinil	C	Modafinil should not be used during pregnancy and lactation
Sodium oxybate	C	GHB is not to be recommended during pregnancy or breastfeeding
Methylphenidate	C	Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy. A risk to the suckling child cannot be excluded
Dextroamphetamine	C	Dextroamphetamine is contraindicated during pregnancy. Dexedrine passes into breast milk
Selegiline	C	It is preferable to avoid the use of selegiline in pregnancy. Selegiline should not be used during breastfeeding
Venlafaxine	C	Venlafaxine must only be administered to pregnant women if the expected benefits outweigh any possible risk. A risk to the suckling child cannot be excluded
Atomoxetine	C	Atomoxetine should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Atomoxetine should be avoided during breastfeeding
Clomipramine	C	No information available
Fluoxetine	C	Not recommended during pregnancy and lactation
Protriptyline	C	No information available

FDA Federal Drug Administration, *EMA* European Medicines Agency, *SPC* Summary of product characteristics

Risk During Delivery and Anesthesia

The question of whether the narcolepsy patient is at greater risk of complications with vaginal delivery, or with general anesthesia during caesarian section, has been addressed in the literature [7, 20, 21, 24]. Rarely, some patients can have cataplexy that interferes with delivery but caesarian section is infrequently required [7]. In 37 pregnancies in narcolepsy women, five had caesarian due to failed induction of labor, premature birth of twins, prolonged labor, transverse position of the baby, and "syncope" in one [7]. A narcolepsy woman attempted vaginal delivery and experienced cataplectic attacks consisting of limb weakness and lack of verbal responsiveness for a few minutes following each uterine contraction and required a cesarean delivery [24]. Another woman with narcolepsy, cataplexy, and glutaric aciduria type II had increasingly frequent cataplectic attacks as she approached 37 weeks gestation and also underwent elective cesarean delivery [21]. There were no increased epidural or general anesthetic or surgical risks in these narcolepsy women. A case series of the results of general, non-pregnancy-related, perioperative events (time for extubation, duration of stay in the postanesthesia care unit, and duration of stay in the hospital) in 37 narcolepsy patients, including 10 who were pharmacologically treated, showed no evidence of increased risk for complications compared to non-narcolepsy patients [25]. One non-narcoleptic patient who was an abuser of GHB had mild respiratory depression following combined spinal–epidural analgesia for labor [26].

Breastfeeding

Breastfeeding raises the question of whether medications taken for narcolepsy are present in breast milk and are safe for the infant. Sleep disturbance is greatest in the postpartum period and can be exacerbated by postpartum depression. In narcolepsy, postpartum mood lability may precipitate cataplexy, and there may be a greater need for narcolepsy medications at this time. Little is known regarding the risk to the baby from narcolepsy medications in breast milk after delivery.

Table 25.2 (A) FDA pregnancy category definitions. (B) EMA acceptable statements

A. FDA pregnancy category definitions
Pregnancy category A rating
Controlled studies show no risk: Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy
Pregnancy category B rating
No evidence of risk in humans: Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals, *or* in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility
Pregnancy category C rating
Risk cannot be ruled out: Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk
Pregnancy category D rating
Positive evidence of risk: Studies in humans, or investigational or postmarketing data, have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective
Pregnancy category X rating
Contraindicated in pregnancy: Studies in animals or humans, or investigational or postmarketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient
B. EMA acceptable statements
1. Based on human experience (specify), Drug X is suspected to cause congenital malformation (specify) when administered during pregnancy
2. Drug X should not be used during pregnancy (specify trimester) unless the clinical condition of the woman requires treatment with Drug X
3. A moderate amount of data on pregnant women (between 300 and 1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity for Drug X
4. No effects during pregnancy are anticipated, since systemic exposure to Drug X is negligible

Treatment During Breastfeeding

Almost all psychotropic medications (modafinil, armodafinil, amphetamine, methylphenidate, venlafaxine, clomipramine, fluoxetine) are excreted in milk at varying concentrations. A relative infant to maternal weight-adjusted dose of greater than 10 % is believed to be of concern for medications that are regarded as nontoxic [27]. However, the medication dose consumed by the infant depends on several factors such as molecular weight and lipid solubility of the medication, production and characteristics of milk, and pharmacokinetics of medication excretion in milk [28]. Medications with a molecular weight less than 200 pass more readily into breast milk [29].

There is very little information about stimulant medications and breast milk. The current literature indicates that breastfeeding while taking newer antidepressants at therapeutic doses is safe and usually beneficial to the patient [30]. Both the American Academy of Pediatrics and the National Institutes of Health-based database (LactMed) consider SSRIs–SNRIs compatible with breastfeeding. The numerous nutritional and immunologic advantages of breastfeeding are believed to outweigh any theoretic risk of antidepressants during breastfeeding. However, the benefit risk ratio of the use of SSRIs–SNRIs during the breastfeeding in patients with narcolepsy is not known. The risk of serious complications caused by neonatal exposure to psychotropic medications appears to be very low, although there are no controlled studies of their safety. The effects of even minuscule amounts of such medications on the developing brain are mostly unknown, and therefore, psychotropic medication is usually not recommended for nursing mothers.

Conclusion

The perceived risks of narcolepsy medication during pregnancy to the mother and fetus are usually overestimated, as the risk of teratogenic effects from narcolepsy medications in therapeutic doses is very low and based on current data may be essentially nonexistent. In addition, most narcolepsy patients have vaginal delivery without complications. Rare patients may have cataplexy that interferes with delivery, but if caesarian is required, there appear to be no increased anesthetic or surgical risks.

Based on the current data available, medications for narcolepsy should be discontinued during the time of conception, during pregnancy, and during lactation in narcolepsy. Most patients are able to be managed unmedicated with appropriate advice regarding work and activities, which should be given before conception in order to be prepared for medication withdrawal. For medication-free women, safety precautions during pregnancy and after delivery are indicated to ensure safety for the mother, fetus, and newborn. However, the information available suggests that the risk from narcolepsy medications in therapeutic doses to the mother, fetus, and newborn during breastfeeding is low, and if the mother requires medication at these times, she can be reassured that there is little evidence for harm.

But, the decision to continue or withhold medications for narcolepsy during pregnancy should be made on an individual basis—by an informed patient—weighing the risks and benefits as outlined. In the context of severe symptoms with risk of frequent daytime sleepiness and cataplexy, and the inability to manage for family or work if not treated, patients could stay on their medication, preferably in reduced dosage. Recommendations should be done on an individual basis to an informed patient taking into consideration the preferences, symptoms, and lifestyle of the patient.

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Emerging Treatments for Narcolepsy

26

Meredith Broderick and Christian Guilleminault

Introduction

Treatment for narcolepsy is currently aimed at reducing the two symptoms associated with the most impairment in daytime functioning. In the case of narcolepsy–cataplexy, those symptoms are excessive sleepiness (ES) and cataplexy. In contrast, emerging therapies for narcolepsy are being driven by uncovering the pathophysiology and neurobiology of the neurological deficits involved such that the underlying cause of symptoms is targeted. The shift in approach has been fueled by the discovery of the relationship between decreased activities of hypocretin-producing neurons and narcolepsy–cataplexy. Emerging therapies also include modifications of currently used therapies with the intention of fine-tuning effectiveness, combinations of currently used medications, novel pharmacological agents developed in conjunction with discovery of pathophysiological mechanisms, or applications of treatment modalities used for other diseases which are hypothesized as having an application to narcolepsy. Although important advances have been made in narcolepsy research in the past few decades, optimal treatment remains a challenge. This is reflected in standard guidelines utilizing a 60 % reduction in sleep latency as an outcome measure [1]. Since current treatment for narcolepsy is based on symptomatic treatment of excessive sleepiness (ES), cataplexy, and fragmented sleep, an ideal treatment would be effective in treating all of these symptoms with minimal side effects.

Future treatment categories can be roughly divided into five categories. Those five categories include hypocretin-based treatments, immunotherapy, thyrotrophin (TRH) analogues and promoters, histamine (H3) antagonists, and combinations or variations of currently used therapies. Each category has theoretical mechanisms of actions based on our current understanding of the pathophysiology of narcolepsy, each with a unique set of limitations and barriers. These five categories will be reviewed and discussed in this chapter. A summary of these therapies is listed in Table 26.1.

Hypocretin-Based Treatments

Mignot and Nishino speculated that one day the gold standard treatment for narcolepsy will be hypocretin replacement therapy [2]. Their statement reflects the important discoveries made in the past two decades describing the pathophysiology of

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Table 26.1 Categories of future treatments for narcolepsy

Hypocretin-based treatments	Intranasal hypocretin Hypocretin cell transplantation Hypocretin gene therapy Stem cell transplantation
Immunotherapies	Corticosteroids Plasmapheresis Intravenous immunoglobulins (IVIG)
Thyrotropin (TRH) analogues	TRH Metallopeptidase inhibitors
Histamine (H3) antagonists	Histamine stimulation
Combinations or variations of existing treatments	Duloxetine, reboxetine, atomoxetine, armodafinil, sodium oxybate, baclofen

narcolepsy. In 1999 Lin et al. published a study demonstrating a mutation of the hypocretin-2 (Hcrtr2) gene is responsible for canine narcolepsy [3]. The appearance of narcolepsy–cataplexy in hypocretin knockout mice was demonstrated by Chemelli et al. [4]. In humans, low or undetectable levels of hypocretin 1 have been reported in 95 % of patients with narcolepsy and cataplexy [5, 6]. Hypocretin neurons have widespread projections to the areas of the brainstem linked to motor inhibition including the locus coeruleus, raphe nuclei, laterodorsal tegmental nuclei, and ventral tegmental neurons [7]. Hypocretin-1 and hypocretin-2 are synthesized in the lateral hypothalamus after being cleaved from a single precursor, preprohypocretin. They are both medium-sized peptides important in the regulation of arousal, appetite, sleep architecture, neuroendocrine, and autonomic control. In the blood and cerebrospinal fluid (CSF), hypocretin-1 is more stable than hypocretin-2 so that it has been applied more readily in pharmacological studies. Both peptides bind to two known seven-transmembrane G protein-coupled receptors named hypocretin receptor 1 (hcrtr1) and hypocretin receptor 2 (hcrtr2). Despite the fact that both peptides come from a single precursor, each has slightly different properties. Hypocretin-1 binds to hcrtr1 with two to three times greater affinity than hypocretin-2. Hypocretin-1 is a key modulator in the arousal state and locomotor activity through its actions on the locus coeruleus [8]. Table 26.2 contains a comparison of the two ligands.

Table 26.2 Comparison of hypocretin 1 to hypocretin 2

Hypocretin-1	Hypocretin-2
33 amino acids	29 amino acids
More stable in vivo	Less stable in vivo
Higher binding affinity to hcrtr1	Higher binding affinity for hcrtr2
Longer half-life	Shorter half-life
Prefrontal, infralimbic, hippocampus, amygdala, bed nucleus of stria terminalis, paraventricular thalamic nucleus, anterior hypothalamus, dorsal raphe, ventral tegmental area, and laterodorsal tegmental nucleus, pedunculopontine nucleus	Amygdala, bed nucleus of the stria terminalis, paraventricular thalamic nucleus, dorsal raphe, ventral tegmental area, laterodorsal tegmental nucleus, pedunculopontine nucleus, arcuate nucleus, tuberomamillary nucleus, dorsomedial hypothalamic nucleus, paraventricular nucleus, lateral hypothalamic area, cornu ammonis 3 in hippocampus, medial septal nucleus
BBB permeability low	BBB permeability none

Researchers are using animal models of narcolepsy to investigate the potential of hypocretin supplementation as a treatment modality for narcolepsy–cataplexy. John et al. published a study showing systemic administration of hypocretin-1 produces increases in activity levels and wake times, reduces sleep fragmentation, and has a dose-dependent reduction in cataplexy in canines with narcolepsy [9]. Lee et al. conducted a study in rats showing discharge of hypocretin neurons correlates with the wake state including muscle tone and locomotion, contrasting with an absence of discharges during sleep [10]. Important studies looking at the potential of hypocretin-1 and hypocretin-2 replacement as an effective treatment for narcolepsy have yielded important implications.

In order to reach the central nervous system, hypocretin-1 must cross the blood–brain barrier (BBB) by diffusion. Hypocretin-1 has low permeability through the BBB, limiting its bioavailability to the central nervous system when injected peripherally [11]. Hypocretin-2 does not pass through the BBB intact [11, 12]. Therefore, very high doses of hypocretin-1 would be required to yield a therapeutic effect. Increasing

systemic concentrations raises the chances of peripheral side effects. Also, very high doses of hypocretin would be limited by supply and cost. With this in mind, therapies exploring alternate modalities of drug delivery are becoming more of interest. The other potential possibilities for hypocretin replacement include intracerebroventricular hypocretin replacement, intranasal hypocretin administration, hypocretin cell transplantation, hypocretin gene therapy, and hypocretin stem cell transplantation.

Intracerebroventricular (ICV) replacement of hypocretin-1 has been studied and observed as being effective in narcoleptic mice, but not in hcrtr2-mutated dobermans [12].

The presence of several neuropeptides in the cerebrospinal fluid after intranasal administration has been demonstrated suggesting intranasal delivery of hypocretin may be an effective method of treatment [13]. Intranasal delivery of hypocretin bypasses the blood–brain barrier with the added benefits of onset of action within minutes and fewer peripheral side effects. Intranasal delivery works because of the connections between the central nervous system to the outside environment through the olfactory and trigeminal nerves. The mechanism of action is extracellular so there is no dependence on receptors or axonal transport for drug delivery. Studies have shown the presence of diurnal fluctuations in hypocretin secretion, suggesting integration with a circadian pacemaker. Therefore, to achieve optimal results, successful therapy may require timed administration [14].

Seeking to overcome the low permeability of hypocretin-1 through the blood–brain barrier, scientists developed hypocretin peptide analogues. Ideally, novel peptide analogues would possess greater stability in the blood and greater CNS penetration. An effective peptide analogue would act as a hypocretin agonist by selectively targeting hcrtr1 or hcrtr2 [6]. Asahi et al. experimented with amino acid substitution in hypocretin-2 as a means of successfully increasing the selectivity for hcrtr2 [15]. In this process, they made an important discovery. They found that the entire hypocretin protein is not necessary for biological activity and selectivity for the corresponding receptors [16]. Instead it is the C-terminus of hypocretin-1 and hypocretin-2 that are critical for these properties. Lang et al. took this one step further and determined the minimal sequences needed for receptor activation by synthesizing different combinations of C-terminus and N-terminus truncated peptides in addition to fragments of central sequences of hypocretin-1 and hypocretin-2. In their study, only full sequences of hypocretin-1 activated receptors, while with hypocretin-2, fragments containing the C-terminus remained active as long as greater than 19 amino acids were active. They also reported several analogues that selectively activated hcrtr1. These analogues hold great potential in the development of hypocretin agonists for the treatment of narcolepsy. Asahi et al.'s and Lang et al.'s findings constitute a foundation for fine-tuning peptide analogues to selectively activate hcrtr1 or hcrtr2. One of the barriers in developing these drugs is finding a peptide analogue with the right combination of selective activation while minimizing peripheral side effects and then prescribing it to the right patient. It is unknown whether hypocretin agonists would only be effective when used in patients with absent or low hypocretin 1 levels, that is, narcolepsy–cataplexy, or if it would also be effective in treating narcolepsy patients without cataplexy. Exploration to determine whether sensitivity to these peptides or peptide analogues persists for a long time or if there is a limited time window to begin treatment due to disappearance and remodeling of a receptor if it is not stimulated for a long time should also be conducted.

Hypocretin Gene Therapy

Another approach to hypocretin replacement is through gene therapy. Gene therapy aimed at stimulating the production of hypocretin could theoretically address the deficiency of hypocretin in narcolepsy–cataplexy. Mieda et al. conducted a study examining the possibility of genetic rescue in mice with ablated hypocretin neurons [17]. They produced mice with overexpression of a preprohypocretin transgene with a beta-actin/cytomegalovirus hybrid promoter and found that

ectopic transgenic expression of hypocretin prevents cataplexy even in the setting of hypocretin neuron ablation. This study suggests that deficiency or absence of hypocretin-1 does not confer a permanent loss of function. Their study highlights hypocretin gene therapy with viral vectors as a potential future treatment for narcolepsy–cataplexy. In 2008, Liu et al. reported successful hypocretin gene delivery into the lateral hypothalamus of mice utilizing a replication-defective herpes simplex virus-1 amplicon-based vector [18]. The results of the study were promising, reporting a 60 % reduction in narcoleptic behavior and normalization of nighttime REM sleep levels. Later, in 2011, a study utilizing recombinant adeno-associated viral vectors (rAAV) successfully facilitated insertion of the hypocretin gene into the zona incerta of transgenic mice. The results showed improvement in cataplexy without impacting levels of sleep-wake [19]. Improvement in sleepiness of mice with narcolepsy has also been demonstrated after successful hypocretin gene therapy [20].

Additional evidence examining the molecular genetics of narcolepsy has suggested a potential relationship between monoaminergic genes and immune-related genes which could serve as another target for gene therapy [21]. These combinations of genes could provide the clinician with useful predictive value in predetermining patients who would be responsive or unresponsive to specific or combinations of treatments.

Hypocretin Cell Transplants

Hypocretin cell transplantation is another potential treatment of narcolepsy. If the ligands themselves cannot be supplemented, then the cells producing the ligands may be substituted. There are an estimated 70,000 hypocretin neurons in normal humans. In narcolepsy–cataplexy, an estimated loss of 85–95 % of hypocretin neurons is thought to produce symptoms, corresponding to a CSF hypocretin-1 level of less than 30 % of normal. Therefore, it is postulated that a minimum of 10 % of the hypocretin-producing cells would need to be replaced to obtain therapeutic effects [6, 22]. Transplantation techniques, such as those used in Parkinson's disease for dopaminergic neurons, could be applied, although graft survival and immune reactions are current limiting factors [7]. To examine the survivability of grafted hypocretin neurons, Arias-Carrion et al. examined the survival of hypocretin-containing rat neurons to the pontine reticular formation [23]. Initial trials of transplantation were unsuccessful, but with enriched transplant medium, survival was extended to 36 days. Transplant of hypocretin grafts is limited by available supplies of hypocretin neurons and graft reactions. The current barrier in graft survivability confers the additional limit of cost-effectiveness because the transplants need to be done on a continuous basis at various intervals.

Stem Cell Transplantation

The barrier of graft survivability, graft reactions, and cost barriers could be reduced if genetically engineered cells or stem cell techniques were used instead. Further investigation is required to determine the possibility of these therapies but they remain a theoretical possibility.

Hypocretin Receptor Agonists

The current concept of narcolepsy as destruction to the hypocretin neurons may evolve with increasing research such as known genetic mutations that could be screened for, identified, and targeted. If this is the case, then hypocretin receptor agonists may be an obvious target for pharmacotherapy. Evidence showing that the entire hypocretin sequence is not required for agonist activity raises the possibility of abbreviated hypocretin peptide analogues that may be useful for drug treatment if they could be targeted to hcrtr1 and hcrtr2, thus serving as hypocretin receptor agonists [15].

Animal models of narcolepsy differ from the human model in that rather than destruction of hypocretin-producing neurons, some are hypocretin receptor 2 deficient (hctr2). To investigate the polymorphisms of the hypocretin receptors in humans, Peyron et al. screened over 500 patients

HLA-DQ1B*0602-negative patients and found 14 genetic polymorphisms in the hcrtr gene in a total of 192 patients (74 Caucasian and 118 ethnically matched controls) [24]. Even though the majority of patients in their study did not show a connection between these genetic polymorphisms and narcolepsy, they did report one patient with a point mutation in the hcrtr associated with narcolepsy–cataplexy at 6 months of age. Various genotypes and phenotypes of narcolepsy may exist, similar to what is observed in animal models. Hcrtr2 deficiency is responsible for the canine model of narcolepsy and hcrtr knockout mice [4, 24]. These findings allude to the possibility of narcolepsy as a heterogeneous disease, with variations in symptoms depending on the basic defect, and in turn a need to tailor treatment based on these factors insofar as they impact disease severity, characteristics, and responsiveness to treatment. Another study comparing HLA predispositions demonstrated the heterogeneity of narcolepsy in two different ethnic populations [25].

Immunotherapy

An autoimmune process has been speculated as one of the possible pathophysiological mechanisms for destruction of the hypocretin neurons in narcolepsy. A major reason for this hypothesis has to do with the association of narcolepsy–cataplexy with human leukocyte antigen HLA-DQB1*0602, the sporadic nature of the disease, and low concordance in homozygotic twins [16, 24].

The hypothesis of an autoimmune etiology led some investigators to explore immunotherapy as a treatment for narcolepsy including corticosteroids, plasmapheresis, and intravenous immunoglobulin (IVIG) based on application in the treatment of other autoimmune disorders. The results are mixed suggesting immunotherapy may not be effective at all, only effective in certain clinical scenarios, or only with very specific treatment regimens.

A study in narcoleptic canines treated from birth with a combination of methylprednisolone, methotrexate, and azathioprine showed an initial delay in onset of symptoms with a 90 % reduction in cataplexy [26]. Interestingly, they also found that canines treated later in life have a lesser response to therapy, suggesting immunotherapy must be instituted early in the disease course. In humans there is a case report of an 8-year-old boy who presented with a 2-month history of daytime sleepiness, undetectable levels of hypocretin, and was HLADQ1B*0602 positive treated with prednisone [27]. Treatment with prednisone did not have a noticeable benefit on the symptoms. Chen et al. reported a 60-year-old woman with a 2-month history of cataplexy treated with plasmapheresis [28]. She experienced a temporary benefit from plasmapheresis but further treatments became limited by a severe catheter infection. This patient was then treated with azathioprine but developed hepatitis and it had to be discontinued. She was then treated with IVIG which was also ineffective. Lecendreux et al. reported a 10-year-old boy with cataplexy and excessive daytime sleepiness diagnosed with narcolepsy. He was treated with IVIG 1 g/kg for 2 days, followed by 1.3 mg/kg of prednisolone for 3 weeks within 2 months of symptomatic onset [29]. Three days after treatment was instituted, an improvement was noted. He had no daytime sleepiness or cataplexy after 3 weeks. After 3 weeks, prednisolone was weaned to half the dose and symptoms remained improved. However, side effects such as weight gain and acne led to the eventual discontinuation of treatment. Dauvilliers et al. reported four cases of hypocretin deficient narcolepsy; three were treated with IVIG 1 g/kg within months of symptom onset for 2 days and repeated three times at 4-week intervals [30]. They found a lasting reduction in cataplexy, hypnagogic hallucinations, and sleep paralysis up to 7 months after treatment. After IVIG therapy, there was no change in the finding of low or undetectable levels of hypocretin. Knudsen et al. reported two cases of narcolepsy–cataplexy, both of whom received IVIG 1 g/kg/day in 2 days/month, 5 times, at 3 and 6 months [31]. They reported an improvement in cataplexy in both patients, but only sustained in one case. They also concluded that IVIG treatment initiated before 9 months disease duration has clinical efficiency. The postulated mechanism of action for high doses of IVIG in narcolepsy involves downregulation of patho-

logical T-cell functions and cytokine production which may lead to a reduction or reversal in the destruction of hypocretin-producing neurons.

To summarize, the case studies reported limited success and reduction of symptoms, suggesting that if a therapeutic benefit is obtained, it may be limited by timing treatment to the onset of disease. Some postulate that the hypocretin deficiency that occurs in narcolepsy–cataplexy is due to an irreversible destruction of neurons, in which case it would be imperative that immunotherapy be given at the onset of disease. Others postulate that the destruction is reversible and the hypocretin-producing cells are only inactivated or that immunotherapy works through abatement of symptoms. In these cases, immunotherapy may have applications throughout the course of the disease. One of the important failures of the current report is that no long-term follow-up is available, and when short-term follow-up is reported, there is no clear persistence of initial improvement and the important side effects of treatment lead to discontinuation. From analyses of these studies, one may conclude that immunosuppressants are not always effective, and effective therapy may be directly related to the timing of treatment, with only specific immunomodulating agents, or specifically outlined and studied dosing regimens being effective treatments, similar to what has been found in treatment of multiple sclerosis. For example, in multiple sclerosis, prednisone given orally is not effective in treating exacerbations while methylprednisolone intravenously is.

Thyrotrophin-Releasing Hormone Agonists

Thyrotrophin-releasing hormone (TRH) is a tripeptidic hormone (L-pyroglutamyl-L-histidyl-l-prolineamide) distributed throughout the central nervous system. TRH functions to stimulate the release of thyroid-stimulating hormone and prolactin. TRH receptor-1 is found predominantly in the hypothalamus, while TRH receptor-2 is more widespread and located in the reticular nucleus of the thalamus [32]. Evidence has also demonstrated that TRH may have stimulant, antidepressant, and neurotrophic effects, thus making it a possible treatment modality for narcolepsy [33].

Nishino et al. tested three TRH analogues for effectiveness in treating excessive sleepiness and narcolepsy in the setting of canine narcolepsy [34]. All three compounds had a significant impact on the frequency of cataplexy, whereas only two of the three had benefit in excessive sleepiness. Free T3 and T4 levels were not altered and no significant side effects were noted. The most potent of these compounds, CG-3703, was further investigated in canine narcolepsy [33]. CG-3703 orally was active and at 2 weeks reduced cataplexy and sleepiness in a dose-dependent manner. Most cataplexy was suppressed with maximum of 16 mg lasting 3–6 h at a time. The anticataplectic potency was described as being equal to doses of desipramine and clomipramine, while the effective dose in producing wakefulness was similar to a reasonable dose of D-amphetamine. With prolonged exposure, there was a trend toward requiring increasing doses of CG-3703 to elicit the same therapeutic benefit. The researches concluded that the anticataplectic effects of CG-3703 may be due to enhancement of norepinephrine (NE) release and postsynaptic alpha-1 stimulation, while the alerting effect is due to enhancement of dopaminergic effects. In any case, their findings suggest that with fine tuning and further research, a potential application of TRH agonists exists in the treatment of humans with narcolepsy. Another potential approach to using TRH agonists is through inhibition of the breakdown of TRH, by blocking the TRH-degrading enzyme, described by Schomburg et al. [35].

Histamine 3-Receptor (H3) Antagonists

Numerous studies have demonstrated the importance of histamine in sleep regulation. Histaminergic neurons project from the tuberomammillary nucleus in the hypothalamus diffusely to the cortex, playing a key role in facilitating wakefulness. The sedative effects of H1-receptor blockers are one example of the properties of histaminergic neurons. Studies have

also demonstrated decreased histamine levels in the CSF of patients with narcolepsy [2]. This background knowledge facilitated interest into the theoretical possibilities of treatments involving histamine transmission for future therapies in narcolepsy–cataplexy.

There are four types of histamine receptors, all of which are G protein-coupled receptors. The H3 receptor is an autoreceptor with the highest density in the striatum, substantia nigra, and cortex. The H3 receptor helps regulate neurotransmitters such as glutamate, histamine, norepinephrine, and acetylcholine, and H3 receptor antagonists increase the release of these neurotransmitters. Histaminergic activation leads to wakefulness whereas decreased activity leads to sleepiness and therefore H3 receptor antagonists activate histaminergic neurons, increasing histamine and producing wakefulness [36]. Application of H3 antagonists or H3 inverse agonists may be useful in the treatment of narcolepsy.

Barbier et al. tested JNJ-5207852, a diamine-based H3 antagonist in rodents with demonstrated potency and selectivity for H3 receptors which was also shown to have clear wake-promoting properties [37]. It was also shown to increase wakefulness without rebound hypersomnolence or increasing locomotor activity, similar to the actions of modafinil. Similar findings have been demonstrated in other H3 receptor antagonists such as thioperamide, carboperamide, and ciproxifan in rats, mice, canines, and cats [36, 38–42]. Parmentier et al. conducted a study with two H3 receptor antagonists, thioperamide and ciproxifan, and both demonstrated an increase in wakefulness and cortical EEG fast activity without an increase in sleep rebound [41]. In cats, thioperamide has been studied which revealed a dose-dependent enhancement in wakefulness [36]. H3 receptors antagonists are thought to exert their effect by increasing histamine release and thereby increasing H1 activation.

In rats, BF2.649, another H3R inverse agonist/antagonist, has been found to increase levels of dopamine, histamine, and acetylcholine in the prefrontal cortices of rats [43]. The first clinical trial with an H3 inverse agonist was conducted in

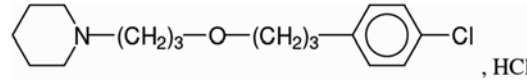

Fig. 26.1 Chemical structure of pitolisant. Reproduced from Schwartz [44], with permission of the author

BF2.649. This phase II study showed tiprolisant has an improvement on ES compared to placebo. The dose studied was 40 mg orally and the most frequent side effects were headache, nausea, insomnia, and a fainting sensation. This study did not examine the effect of tiprolisant on other symptoms of narcolepsy such as cataplexy. In studies with healthy human volunteers given doses up to 120 mg, no cardiovascular or biological adverse events were noted [44]. Since those initial studies, BF2.649 has since been renamed pitolisant and is currently in phase III clinical trials [45]. The chemical structure of pitolisant is illustrated in Fig. 26.1.

In 2012, a case series of four teenagers with narcolepsy–cataplexy was published demonstrating some positive data for off-label use of pitolisant [46]. The four subjects selected were refractory to other available treatments such as modafinil, methylphenidate, mazindol, sodium oxybate, and D-amphetamine). Pitolisant doses were increased from 10 to 40 mg. The authors noted a reduction in Epworth Sleepiness Scale (ESS), an increase in mean sleep latency on Maintenance of Wakefulness Test (MWT), and a reduction in severity and frequency of cataplexy. Adverse effects such as insomnia, headache, hot flushes, leg pain, and hallucinations were noted but largely temporary. The benefit was sustained over 13 months.

A study to assess the safety and efficacy of pitolisant in patients with narcolepsy in a double-blind, randomized, parallel-group controlled trial was published in 2013. Patients were given treatment for 8 weeks at doses of pitolisant 10, 20, or 40 mg versus modafinil 100, 200, or 400 mg. The results showed doses of pitolistant up to 40 mg were efficacious on reducing excessive daytime sleepiness as measured by a reduction in the Epworth Sleepiness Scale (ESS). Pitolisant was also well tolerated compared with modafinil [47]. Researchers have also looked at the abuse

potential of pitolisant in vivo and in primate models and no evidence of potential drug abuse liability was identified [48].

Modified Current Medical Therapies

Modafinil is a first-line non-amphetamine alerting agent used in the treatment of narcolepsy. Although it is extremely effective in treating ES, it has a short half-life and in often must be taken twice daily. Derived from modafinil, armodafinil is an improved version. While modafinil contains a racemic mixture of 10 % of the *R*-enantiomers and the 90 % of the *S*-enantiomers, armodafinil is solely the *R*-enantiomer. The chemical names of armodafinil are 2-[(*R*)-(diphenylmethyl)sulfinyl] acetamide and 2-(*R*-benzhydrylsulfinyl)acetamide [49]. Cephalon obtained FDA approval for armodafinil in 2007 for the treatment of narcolepsy, obstructive sleep apnea, and shift work sleep disorder (SWD). The *R*-enantiomer of modafinil has a half-life of 10–14 h versus a half-life of 3–4 h for the *S*-enantiomer. The elimination half-life of the *S*-enantiomer is three times faster than the *R*-enantiomer and therefore armodafinil is a longer acting medication than modafinil [50]. Armodafinil has two metabolites, acid and sulfone, neither of which appear to have wake-promoting activity. Typical oral doses of armodafinil range from 50 to 400 mg. After 7 days of dosing, steady-state concentrations are 1.8 times what is measured after a single dose [50]. In addition, peak plasma concentrations are reached approximately 2 h after administration if taken in a fasting state. Even though the bioavailability is not affected by food intake, the absorption can be delayed by up to 2–4 h if taken with food. Table 26.3 compares the characteristics of modafinil and armodafinil.

Dinges et al. compared the effects of a single doses of armodafinil (100, 150, 200, or 300 mg) to modafinil (200 mg) and placebo in 107 men using the Maintenance of Wakefulness Test (MWT) as the primary outcome measure [49]. Armodafinil was associated with longer MWT latencies and higher plasma concentrations 6–14 h after administration. It was generally well tolerated and the most commonly reported side effects were abdominal pain, headache, and nausea. In a multicenter double-blind study, 196 subjects were randomized to receive oral armodafinil 150 mg, armodafinil 200 mg, or placebo once daily for 12 weeks [51]. The primary outcome measure was the MWT. In this study, both doses of armodafinil increased the MWT mean sleep latency compared to placebo. Both doses also showed an improvement in memory, attention, and fatigue. Adverse events reported in this study were headache, dizziness, and nausea. Armodafinil is a moderate inducer of CYP3A4 and a moderate inhibitor of CYP2C19, and therefore, dosing adjustments are needed in the setting of coadministration of triazolam, diazepam, or phenytoin [52]. The mechanism of actions of modafinil and armodafinil is most likely through dopamine reuptake [2].

Table 26.3 Comparison of modafinil to armodafinil

	Modafinil	Armodafinil
Chemical composition	Racemic mixture	*E*-enantiomer
Elimination half-life	*S*-enantiomer 10–14 h *R*-enantiomer 3–4 h	*R*-enantiomer 3–4 h
Therapeutic dose	200 mg	150 mg
Time to peak in serum	2–4 h	2–4 h
Side effects	Headache, nausea, dry mouth	Abdominal pain, headache, nausea

Armodafinil is generally well tolerated. Headache (17 %) is the most commonly reported side effect, followed by nausea (7 %), dizziness (5 %), and insomnia (5 %) [50]. There have not been reports of Steven's Johnson syndrome or multiorgan hypersensitivity reactions in armodafinil, but two cases have been reported with use of modafinil. Since there is a close connection between the two drugs, prescribing physicians should instruct supervision for development of a rash. Steroid-based contraceptives may have reduced effectiveness for up to 1 month after discontinuation of modafinil or armodafinil.

Phase 1 clinical trials on JZP-386, a deuterium containing analogue of Xyrem (sodium oxybate), are currently underway in Europe.

Combination Therapies

Antidepressants are well known to improve cataplexy through their properties of adrenergic, serotoninergic, and dopaminergic reuptake inhibition. However, not all antidepressants have a therapeutic effect on cataplexy and may only be useful in the treatment of ES. These variable effects depend on the selective receptor reuptake or combination of selective reuptake receptors for each antidepressant. Novel therapies are being developed to block two or even three neurotransmitters to capitalize on this feature of antidepressants. DOV 216,303 is an antidepressant that blocks norepinephrine, serotonin, and dopamine. Beer et al. tested DOV 216,303 in seven subjects demonstrating safety and tolerability in doses up to 100 mg per day for 10 days [53]. The observation that venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), improves cataplexy has led some investigators to develop and test other drugs with SNRI activity. Duloxetine, a novel SNRI, was examined in a pilot study by Izzi et al. [54]. In this study, three patients with narcolepsy–cataplexy were identified. One patient was successfully treated with a dose of duloxetine 60 mg by mouth each morning in conjunction with modafinil 200 mg by mouth twice daily. The two remaining patients were successfully treated with duloxetine monotherapy. Polysomnography and multiple sleep latency tests were conducted and showed REM sleep suppression, increase in REM latencies, and improvement in ES. The studies of duloxetine in the treatment of depression also showed an increase in stage 3 sleep [55]. No tolerance or adverse events were observed in a 1-year follow-up period [54]. Another SNRI, reboxetine 10 mg by mouth was given to 12 patients in a pilot study [56]. After 2 weeks, a measurable improvement in ES as determined by the Epworth Sleepiness Scale (ESS) and MSLT was observed. There was also a measurable decrease in the frequency of cataplexy. The same rationale was employed in a case reported by Niederhofer et al. when they administered atomoxetine, an SNRI to a patient with newly diagnosed narcolepsy [57]. Atomoxetine 40 mg by mouth three times daily was given for 4 weeks. Improvement in ES and cataplexy was observed starting on day 6. Development of dual or triple monoamine uptake inhibitors may allow treatment of ES and cataplexy with one agent, therefore improving compliance, side effects, and costs in the treatment of narcolepsy.

Others

Although disturbed nocturnal sleep is not typically included in the tetrad of symptoms describing narcolepsy, it is nonetheless an important and disabling aspect of the condition. Studies in orexin knockout mice have demonstrated that even though amounts of total sleep times are comparable to wild-type mice, the sleep is more fragmented. Sleep fragmentation is postulated as one possible cause of ES in narcolepsy such that hypnotics to consolidate sleep may improve ES [58]. Currently, sodium oxybate (GHB) is used successfully in the treatment of narcolepsy–cataplexy. Part of its effectiveness may be due to its ability to consolidate sleep and increase slow wave sleep. Its mode of action is thought to be related to effects on GABA-B and possibly GHB receptors [59]. GHB has also been shown to increase slow wave sleep, delta power, daytime sleep latency and to decrease nocturnal awakenings [60]. This overall improvement in sleep architecture translates into improvement in daytime functioning. However, GHB has a short half-life requiring dosing in the middle of the night, which is inconvenient and may decrease compliance with using it. GHB has also been implicated as being used for nonmedical purposes necessitating strict prescribing, regulation, and distribution of the drug. The limitations of GHB call for the development of novel GABAergic agents with similar effects, but distinct modes of actions. Current studies includes other GABAergic hypnotics that increase slow wave sleep such as gaboxadol [61] and tiagabine [62]. A double-blind, placebo-controlled, multicenter study was conducted in Europe to evaluate the efficacy of ritanserin, a 5HT2-antagonist in improving sleep in narcoleptics [63]. One hundred thirty-four patients with narcolepsy were randomized to receive ritanserin 5 mg, ritanserin 10 mg, or

placebo for 28 days. Both doses of ritanserin resulted in an increase in the quantities of slow wave sleep with a reduction in NREM stage 1 sleep. Landholt et al. studied SR 46349B, another 5-HT2 antagonist administered 3 h prior to bedtime. At a dose of 1 mg by mouth, SR 46349B increased the amount of slow wave sleep while reducing the amount of stage 2 sleep [64]. These studies suggest that there is potential for use of hypnotics as supplemental therapy in narcolepsy patients with poor quality of sleep that have not responded to GHB.

Studies in mice utilizing the GABA-B agonist properties of R-baclofen (R-BAC) were studied in two mouse models of narcolepsy [65]. In both models, positive results were shown with increases in NREM sleep and decreased cataplexy. The results after treatment with R-BAC were superior to GHB. These results suggest that R-BAC may have an application in treatment of narcolepsy.

A study conducted in drug-naive teenagers with narcolepsy comparing GHB, baclofen, and baclofen with modafinil compared the effect of baclofen in treatment of narcolepsy. Baclofen has a longer half-life than GHB which is advantageous so as to negate the need for twice nightly dosing. In 10/13 subjects, baclofen 10 mg was found to improve nocturnal total sleep time and increased delta wave sleep with no effect on excessive sleepiness or cataplexy [66]. That baclofen had no effect on excessive sleepiness or cataplexy prompted the authors to conclude that GHB has a mechanism distinct from GABA-B.

JZP-110 is a new and experimental drug currently being tested for treatment of excessive daytime sleepiness and narcolepsy by Jazz Pharmaceuticals. A phase 2b double-blind, placebo-controlled, parallel-group, multicenter, randomized 12-week study of 93 individuals with narcolepsy showed a promising effect in the reduction of excessive sleepiness with a mechanism of action not the result of dopamine or norepinephrine [67].

Conclusions

While investigating future directions for narcolepsy treatment, one must keep several factors in mind. Responses to pharmacological agents can be variable based on individual differences. Factors such as sex, age, BMI, ethnic background, and more specific genetic factors play a role in drug metabolism.

Other potential targets for reducing ES in narcolepsy may involve targeting novel neuropeptides and proteins such as circadian clock proteins, ion channels, prokineticin [68], or neuropeptide S [69]. One must also not forget about the role of non-pharmacological treatments in the treatment of narcolepsy. Education and support groups play a role in assisting patients to maintain good sleep hygiene, encourage scheduled naps, and to provide social support to patients with narcolepsy. With the growth of behavioral sleep medicine, a structured program designed to address the unique challenges for patients with narcolepsy could play a role in therapy for narcolepsy, especially since some of the emerging pharmacological agents could depend heavily on circadian factors for optimal efficacy. This could include behavioral techniques aimed at regulating the sleep-wake cycle, reinforcing sleep hygiene, light therapy, and scheduled naps. Advances in basic science, neurobiology, and neurogenetics are leading to an increase in knowledge that will guide and facilitate both a better understanding of narcolepsy and more effective treatment modalities.

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27 Behavioral and Non-pharmacological Management of Narcolepsy

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Introduction

Narcolepsy is a lifelong condition mainly characterized by excessive daytime sleepiness (EDS) and sleep attacks that affects about 1 in 2000 people [1]. Onset of narcolepsy can begin as young as 2 years old [2] with bimodal peaks that occur at ages 15 and 35 [3]. The recognized symptoms of narcolepsy include EDS, cataplexy, sleep paralyses, hypnagogic hallucinations, and nighttime sleep disruption [4]. However, the consequences of narcolepsy extend beyond the effects of these symptoms and the impact on quality of life has been well documented [5–11]. Patients with narcolepsy have more educational problems and behavioral problems, show higher rates of depression and anxiety, experience more challenges at work, and are more prone to driving accidents [5–14].

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Currently, there is no cure for narcolepsy and thus the goal of treatment is symptomatic control, generally achieved with pharmacotherapy [4, 15, 16]. While pharmacological approaches are used as a first line of treatment, there are significant limitations to their use. Medications alone may not provide sufficient symptomatic relief and may involve side effects that can have marked impact on adherence, and some medication may not be appropriate due to other medical conditions (i.e., hypertension) [17, 18]. For example, sodium oxybate at higher doses, which is sometimes necessary to improve EDS [4], may cause gastrointestinal symptoms, morning sluggishness, dizziness, and enuresis [19]. The use of stimulant medications has been controversial. Guilleminault [20] reported that 80 % of a group of patients taking ≥60 mg of amphetamines per day reported significant psychological effects such as aggressive behavior, unpleasant cognitive processes, as well as agitation. Long-term use of stimulants has also been associated with medical complications such as liver dysfunction and hypertension. While rare, there have also been reports of psychosis and some of these medications may involve the risk of tolerance or addiction [4, 20]. Additionally, the compliance with pharmacotherapy in this patient population is extremely poor with only 36–51 % of the patients using the medications as prescribed [21, 22]. Due in part to these negative outcomes, less than 15 % of patients rely on medications alone and most patient incorporate other non-pharmacological techniques [17].

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Non-pharmacological approaches for the management of narcolepsy may include behavioral and lifestyle techniques such as scheduled naps, sleep hygiene, dietary manipulations, and physical activity. In fact, such approaches are commonly recommended by practitioners as an adjunct to medication or as an alternative treatment, and up to 54 % of patient rely exclusively on such approaches [7, 10, 11, 23]. In a survey study of patients with narcolepsy, non-pharmacological strategies were identified for managing EDS, sleep attacks, cataplexy, and sleep paralysis. Patients reported using a variety of approaches for naps, sleep, rest, exercise, diet, environmental manipulations (e.g., avoid hot rooms, keep room cool, seek fresh air), engagement or disengagement in activities (e.g., be active in conversations, avoid "boring" events, restrict evening events), and different physical (e.g., pinch self, clench teeth) and emotional techniques (e.g., avoid emotions, excitement) [23]. Patient's behavior can have a significant impact on the experience of symptoms, and a study by Volk and colleagues [24] demonstrated the impact of behavior on daytime sleep in narcolepsy. In their study, seven patients were instructed to stay in bed throughout the day and another seven patients were asked to sit by a table. While patients in both conditions were free to nap as they wished, those who stayed in bed slept 2–3 times more during the day compared to those sitting at a desk. This highlights the importance of behavior and that while sleepiness is inherent in narcolepsy, patients' behavior may have a significant and direct influence on its experience and impact.

The goal of this chapter is to synthesize and evaluate the available research on non-pharmacological strategies for the management of narcolepsy. Our first aim is to conduct a systematic review of the empirical evidence for non-pharmacological interventions that are commonly recommended by clinicians or reported by narcolepsy patients. Our second aim is to critically evaluate the evidence base to identify clinical targets and any unmet needs for patients with narcolepsy for consideration of future directions to maximize the impact of non-pharmacological treatments.

Literature Search

We conducted a review of two major electronic bibliographical databases: MEDLINE and PsycINFO. Our desire was to use comprehensive research terms to identify studies that evaluated the efficacy or effectiveness of non-pharmacological strategies with patients with narcolepsy. Therefore, no temporal limits were utilized and we did not restrict the search to major topic terms (e.g., "MeSH" terms in MEDLINE). We utilized a simple strategy for both MEDLINE and PsycInfo that uses the term "narcolepsy" as the main indicator combining by "AND" the following search terms: "behavioral therapy," "behavioral management," "non pharmacological," "cognitive therapy," "coping," "naps," "exercise," and "diet." To ensure a comprehensive review, references were reviewed throughout the process for any additional studies that may have been missed using these research terms. We included studies that assessed the use of any non-pharmacological approach for the management of narcolepsy symptoms. We also included studies that provided evidence for/against a specific strategy even if these were not systematic studies designed for assessing the specific technique (e.g., case studies). Studies were excluded if they were clinical opinions, animal studies, pharmacological studies, or not in English or did not provide data on the effectiveness of the non-pharmacological approach.

A total of 218 unique studies were extracted by this research strategy. Of these studies only 13 were included in this systematic review. An additional 10 studies that were not identified by our search strategy were identified post hoc during the review. This review identified nine studies that assessed daytime naps (Table 27.1), nine that assessed self-regulatory approaches (i.e., extended nighttime sleep, diet, light therapy, and temperature manipulation) (Table 27.2), and five case studies.

All of the studies identified evaluated for EDS using either objective or subjective measures even when EDS was not the target of intervention. Nocturnal sleep was rarely the target of intervention but was evaluated in 10 studies,

Table 27.1 Summary of studies evaluating napping approaches

Author	Year	*N*	Conditions/intervention/design	Timing of naps	Duration of intervention prior to testing	Outcome measures	Medication control	Main findings
Billiard [25]	1976	*N* = 18 Group 1 = 8 Group 2 = 10	Group 1: allowed to sleep ad libitum on day 1 and were tested after they woke up. On day 2, patients were allowed to sleep at any time but were awakened after 10 min of sleep and tested Group 2: was on a fixed testing schedule throughout both days (9 A.M., 11:45 A.M., 2 P.M., 4:15 P.M., and 6:30 P.M.). The testing session included two 30-min test periods with a 15-min break in between	9:30 A.M., 12:15 P.M., 2:30 P.M., 4:45 P.M., 7 P.M.	Same day	SSS, WAT, and 24 h polygraphic monitoring	All patient were withdrawn from all narcolepsy medication and were medication-free for 2 weeks prior to testing	1. When allowed 10 min of sleep patients napped more frequently 2. Subjective ratings were improved on the day with shorter naps (group 1) 3. Subjective rating of sleepiness improved on a day with naps versus a day without naps 4. No significant performance differences on the WAT between the days in either group
Roehrs et al. [26]	1986	45 (15 per condition)	All patients had 4-nap MSLT and were allowed 15 min of sleep on naps 1–3. Manipulation was on nap 4 time in bed and duration of time to nap 5: Group (1) allowed 15 min in bed at nap 4 and nap 5 was 15 min after Group (2) allowed 30 min in bed at nap 4 and nap 5 was 15 min after Group (3) allowed 15 min in bed at nap 4 and nap 5 was 30 min later	10 A.M., 12 P.M., 2 P.M., 4 P.M., and either 15 or 30 min after the fourth nap	Same day	SOL on MSLT nap 5	Not reported	1. 15 min and 30 min naps increase SOL when tested 15 min after the nap 2. 30 min nap did not have significant benefit over the 15 min nap 3. Gains achieved from naps were lost when testing 2 h later
Godbout and Montplaisir [27]	1986	10	Assessed performance (reaction time) on days with naps (MSLT naps) and days with no naps	10 A.M., 12 P.M., 2 P.M., 4 P.M., 6 P.M.	Same day	MSLT, 4-choice reaction time test	Never treated	1. Napping improved performance on task 2. Patients did not score significantly different from controls when naps were implemented
Rogers and Aldrich [28]	1993	16	Patients were assessed before, during, and after maintaining a daily 3-nap schedule (each nap 15 min) for 1 month	Individually scheduled	1 month	Sleep logs, MWT, NSSQ	All patients were on stimulant medications	1. SOL on MWT significantly increased after the 1 month 2. No changes in reported sleep attacks or symptom severity 3. Less alert patients experience more benefit from naps

(continued)

Table 27.1 (continued)

Author	Year	*N*	Conditions/intervention/design	Timing of naps	Duration of intervention prior to testing	Outcome measures	Medication control	Main findings
Mullington and Broughton [29, 30]	1993 and 1994	Eight patients tested in all conditions	Three conditions: (1) single long nap, (2) multiple short naps, (3) no nap. TST per 24 h was constant	The long nap was placed 180° out of phase with nocturnal mid-sleep time. Short naps were spaced equidistantly. Sleep time per 24 h was held constant	Each condition was followed for 2 days (testing was on the 2nd day)	Performance tests, 24-h ambulatory EEG	All patients were withdrawn from stimulant medications	1. Long nap improved performance over no-nap condition 2. Unintended naps did not differ across conditions 3. Trend toward less unscheduled naps and less minutes of unscheduled naps in the long nap condition 4. Napping results in sleep inertia 5. Morning short naps and midday long nap produce minimal sleep inertia compared to afternoon short naps
Guilleminault, Stoohs and Clerk [31]	1993	8	Patients were tested with and without 2 15-min scheduled naps	12:30 P.M. 5 P.M.	One week	MWT	Medication-free	1. Significant increases on MWT
Helmus et al. [32]	1997	Eleven patients tested in both conditions	Two conditions: 1. One nap of 15 min allowed time in bed 2. One nap of 120 min allowed time in bed All participants received an additional 1-h nap opportunity at 3 P.M.	In both conditions the nap was terminated at 12 P.M.	Same day	Modified MSLT from 12:15–1:55 P.M.	Medication-free	1. Longer SOL were found for the 120 min nap compared to the 15 min nap 2. Alerting effects gained from the 120 min nap were lost when tested 3 h later
Rogers, Aldrich, and Lin [22]	2001	*N* = 29 Group 1 = 10 Group 2 = 10 Group 3 = 9	Three conditions: 1. Two 15-min naps per day 2. Regular schedule of nighttime sleep 3. Combination of scheduled naps and regular bedtimes	Patients encouraged to take 1st nap in the morning and 2nd nap in the afternoon	Two weeks	NSSQ, 24-h ambulatory PSG	All patients were on stimulant medications	3. Only the combination of regular nighttime schedule and 2 daytime naps reduces both subjective symptom severity and duration of unintended sleep 4. Those with more severe EDS benefited from the addition of scheduled sleep periods while those with moderate EDS did not

MSLT Multiple Sleep Latency Test, *MWT* Maintenance of Wakefulness Test, *SOL* sleep onset latency, *EDS* excessive daytime sleepiness, *TST* total sleep time, *EEG* electroencephalogram, *NSSQ* Narcolepsy Symptoms Severity Questionnaire, *SSS* Stanford Sleepiness Scale, *WAT* Wilkinson Addition Test

Table 27.2 Summary of studies evaluating self-regulatory approaches

Author	Year	*N*	Aims/intervention/design	Type of intervention	Duration of intervention prior to testing	Outcome measures	Medication control	Main findings
Mouret et al. [33]	1988	8	Evaluated the effect of L-tyrosine intake on symptoms of narcolepsy	L-tyrosine supplement	Patients were assessed pre- and post-6 months of treatment	Sleep diary of cataplectic attacks and nocturnal sleep	Not reported	1. After the 6 months all patients were free of narcolepsy symptoms
Hajek et al. [34]	1989	7	Evaluated the effect of bright light therapy	Light therapy (5000 LUX) two times per day between 7–9 A.M. and 6–8 P.M.	Ten days	MSLT, actigraphy, vigilance test, and subjective reports of mood, anxiety, cataplexy, and sleepiness	Medication-free	1. There were no effects found on either subjective or objective measures
Pollak and Green [35]	1990	6	Evaluated the relationship between meals, sleep, and sleepiness while patients were in a time-isolation laboratory for 8–22 consecutive days. Patients were either allowed to eat when they wished ("free-running") or were on a strict meal schedule	Scheduled versus free-running meal schedule	"Free-running" condition was maintained for 8–14 days; strict meal schedule was maintained for 6 days	Continuous polygraphic recording throughout the study Subjective rating of sleepiness	Drug-free for more than 2 weeks prior to the study	1. There was a period of 1.5–2 h preceding the meal of subjective improvement in alertness and decreased napping 2. After the meal there was a period (40–50 min) of decrease subjective alertness and increased napping
Guilleminault et al. [31]	1993	NR	Attempted to replicate the study by Mouret et al. and evaluate the effect of L-tyrosine intake on symptoms of narcolepsy	L-tyrosine supplement	3 months	Polygraphic monitoring and MSLT	Medication-free	1. Were not able to replicate the findings by Mouret et al. or find any differences on MSLT
Uchiyama et al. [36]	1994	10	Evaluated extended nighttime sleep on sleepiness	Eight versus twelve hours of nighttime sleep	Up to 2 weeks	PSG, MSLT	Medication-free	1. Patients fell asleep on fewer naps when having extended nighttime sleep opportunity

(continued)

Table 27.2 (continued)

Author	Year	*N*	Aims/intervention/design	Type of intervention	Duration of intervention prior to testing	Outcome measures	Medication control	Main findings
Bruck et al. [37]	1994	12	A placebo-controlled, cross-over study that evaluated the effect of high carbohydrate intake on sleepiness and sleep variables in narcolepsy	Adding a 50-g glucose drink to lunch	Same day	EEG measures from a 60-min WAVT; sleep variable from a 45-min nap opportunity; the SSS	Patients were withdrawn from stimulant medications for a minimum of 24 h	1. In the narcolepsy group, adding the glucose drink resulted in increase sleep stage shifts during the WAVT and had shorter latency to stage II sleep 2. In the narcolepsy group, adding glucose resulted in increase REM sleep during the nap and higher polygraphic sleepiness score from the nap 3. Adding glucose had no effect on subjective ratings of sleepiness
Husain et al. [38]	2004	9	Evaluate the effect of a low-carbohydrate diet on daytime sleepiness in narcolepsy. Patients were instructed to reduce carbohydrate intake to <20 g per day for 8 weeks	Low-carbohydrate, ketogenic diet	Eight-week intervention with follow-up visits at weeks 2, 4, and 8	NSSQ; ESS; SSS	All patients maintained their stimulant schedules	1. After the 8-week intervention, patients reported improvements on the NSSQ 2. No improvements were found on the ESS or SSS 3. Patients lost significant weight over the 8-week study (from 99.3 kg to 92.2)
Fronczek et al. [39, 40]	2008	8	Evaluated the effect of manipulating core-body and skin (distal and proximal) temperatures on nocturnal sleep, sleepiness, and performance during a constant routine protocol	Different combinations of temperature regulations were achieved with a thermosuit (skin) and cold/hot drink (core body)	Same day	PVT, MWT, PSG	Medication-free	1. Cooling distal skin results in improved sleepiness compared to distal skin warming 2. There were no effects on sleepiness with manipulating core body temperature 3. Core body warming improved performance 4. Proximal skin warming improves nighttime sleep while distal skin warming worsened nighttime sleep

WAVT Wilkinson Auditory Vigilance Task, *NSSQ* Narcolepsy Symptoms Severity Questionnaire, *ESS* Epworth Sleepiness Scale, *SSS* Stanford Sleepiness Scale, *EEG* electroencephalogram, *REM* rapid eye movement, *MSLT* Multiple Sleep latency Test, *NR* not reported, *PSG* polysomnography, *PVT* Psychomotor Vigilance Test, *MWT* Maintenance of Wakefulness Test

Table 27.3 Subjective (S) and objective (O) evaluations of narcolepsy symptoms by study

Study	EDS	Sleep attacks	Cataplexy	Hallucination/ vivid dreams	Sleep paralysis	Nocturnal sleep	Performance	Psychiatric symptoms
Billiard [25]	S						O	
Roehrs et al. [26]	O							
Godbout and Montplaisir [27]	O						O	
Rogers and Aldrich [28]	O, S	S	S	S	S	S		
Mullington and Broughton [29, 30]	O	O				O	O	
Guilleminault, Stoohs, and Clerk [31]	O							
Helmus et al. [32]	O					O		
Rogers et al. [22]	O, S	O, S	S	S	S	O		
Mouret et al. [33]	S		S			S		
Pollak and Green [35]	O, S					O		
Guilleminault et al. [31]	O		S			S		
Bruck et al. [37]	O, S							
Husain et al. [38]	S	S	S	S	S			
Uchiyama et al. [36]	O					O		
Fronczek et al. [39, 40]	O					O	O	
Hajek et al. [34]	O, S		S			O	O	S

Note: No studies examined quality of life as an outcome measure

cataplexy was subjectively assessed in six studies, performance (e.g., reaction time, logical reasoning test) was objectively assessed in five studies, sleep attacks were subjectively assessed in four studies, and hallucinations and sleep paralysis were subjectively assessed within a single measure by three studies. Only one study assessed for psychiatric symptoms and no studies evaluated quality of life. Summary of types of symptoms evaluated by study is provided in Table 27.3.

Daytime Naps

Effect of Naps on Alertness and EDS

The most common behavioral recommendation for coping with EDS is scheduled daytime naps, whereby the clinician establishes a structure of predetermined, intentional nap periods during the day with the intent of improved alertness and functioning. Several studies evaluated the effect of naps on alertness and EDS in patients with narcolepsy (see Table 27.1). In a review paper, Guilleminault and colleagues [31] reported on an unpublished study of eight patients with narcolepsy who were evaluated for EDS with and without two short naps (15 min each) scheduled at 12:30 P.M. and 5:00 P.M. Their results showed that sleep onset latency (SOL) on a Maintenance of Wakefulness Test (MWT) significantly improved (from 4.5 to 9 min) following this 2-nap schedule. Similar findings were reported by Rogers and Aldrich [28] who assessed the impact of three, individually tailored, 15-min naps on alertness. Mean SOL on the MWT significantly increased after one month of maintaining the napping schedule (from 7.4 to 10 min) suggesting improved alertness. However, there was no decrease in the number of nap trials on which

patients did not fall asleep and the frequency of subjectively reported sleep attacks did not change. The authors also reported that SOL for the more alert patients at baseline ($n=2$) did not change posttreatment but that for patients who were less alert at baseline ($n=14$), mean SOL significantly increased from 5.8 to 8.5 min. This finding suggests that naps may only benefit patients with more profound EDS despite the use of stimulant medications.

Decreases in degree of sleepiness were also reported in a study by Roehrs et al. [26] who demonstrated that both 15-min and 30-min naps resulted in increased SOL on a nap test that was conducted 15 min after the end of the therapeutic nap. However, their results suggested that alerting effect of naps (of any length) is not sustained over a 2-h period. Similarly, Helmus et al. [32] showed that the alerting effect of a 120-min nap was lost when tested 3 h later. Finally, Billiard [25] reported that subjective ratings on the Stanford Sleepiness Scale (SSS) improved on a day with naps versus a day without naps (mean score decreased from 3.5 to 2.9 on the day with naps).

Effect of Naps on Performance

Effects of napping on performance tasks were also evaluated. Godbout and Montplaisir [27] showed that compared to controls, patients with narcolepsy performed significantly worse on a reaction time test on a day without naps. However, when including five short naps during the day, there were no significant differences between patient and control groups. They concluded that any performance differences seen between narcolepsy patients and controls are due to EDS and difficulty to maintain alertness rather than to a cognitive deficit. When comparing narcolepsy patients on a day with versus without naps or on days with long versus short naps, Billiard [25] found no difference in performance. Nonetheless, positive effects of napping on performance were reported by Mullington and Broughton [29] in patients taking a single long nap compared to patients taking no naps but there were no differences in performance between the short- and long-nap conditions.

Nap Duration

Nap duration was also a question that received some attention with studies evaluating the difference between short and long naps. Roehrs et al. [26] investigated the alerting effects of a 15-min versus a 30-min nap. While both nap lengths improved SOL on Multiple Sleep Latency Test (MSLT), the 30-min nap did not provide increased benefit above that achieved by the 15-min nap. Helmus et al. [32] assessed the effects of a short (15-min) versus a long (120-min) nap. Their results suggested improved EDS after a single long nap compared to a short nap. Finally, in the study by Billiard [25] eight patients were tested on 2 consecutive days. On day 1 they were allowed to sleep as they wished, and on day 2, patients were allowed to sleep as they wished but were awakened after 10 min of sleep. Their results showed that on day 2 patients took significantly more naps during the day (3.6 naps on day 1 vs. 6.4 naps on day 2) and ratings of sleepiness improved at day 2.

Napping Schedules

A couple of studies evaluated different napping schedules in patients with narcolepsy. Mullington and Broughton [29] evaluated three conditions, a single long nap, multiple short naps, or no nap while total sleep time per 24 h was held constant for all conditions. In the napping conditions, 75 % of their total sleep time during 24 h was given at night and 25 % was provided for naps during the day. The timing of the single long nap was given at 180° out of phase with the nocturnal mid-sleep time. Average duration of the single long nap was 129 min. In the short-nap condition, each nap was assigned 5 % of total sleep time per 24 h (average length of 26 min) and the naps were scheduled equidistantly throughout the day. There were no differences between the conditions in the number of unscheduled sleep episodes during the day. However, patients in the long-nap condition showed a trend for fewer unscheduled naps (long nap = 4.3, multiple short naps = 6.5, and no naps = 7.1) and shorter unscheduled naps (long nap = 17.4 min, multiple short naps = 33.0 min, and no naps = 31.3 min).

Patients in the short-nap condition had better nighttime sleep efficiency (93.8 %) compared to those in the long-nap condition (91.8 %) or no-nap condition (89.8 %) as patients tended to have less wakefulness during the night in the short-nap condition (long nap = 4.8%, multiple short naps = 2.9%, and no naps = 5.5 % of active wakefulness during the scheduled nocturnal sleep). This study suggested two periods during the day with highest likelihood of unscheduled naps: the first between 150 and 170° out of phase with the nocturnal mid-sleep time and the second between 250 and 270°. The work by Mullington and Broughton [30] also assessed sleep inertia following the naps. Their findings suggest that sleep inertia, as assessed by a descending subtraction test, chosen for its sensitivity to sleep inertia, is evident in patients with narcolepsy following naps throughout the day. Sleep inertia was minimal after the first morning nap, which contained highest amount of REM sleep, and was most pronounced after slow-wave sleep arousals that were more common in the afternoon short naps. However, there were no sleep inertia effects on a four-choice reaction time test that followed the single long nap. The study by Billiard [25] showed that rating of sleepiness after a 15-min nap opportunity at 12:15 P.M. and 2:30 P.M. was similar to sleepiness ratings reported by normal controls at baseline. Interestingly, the afternoon naps (at 4:45 P.M. and 7 P.M.) resulted in higher sleepiness rating levels compared to that of normal controls at the same times.

Rogers et al. [22] compared three sleep schedules: (1) two 15-min naps during the day, (2) maintaining a consistent nocturnal sleep schedule, (3) a combination of the two naps and a consistent nocturnal sleep schedule. Their findings suggested that including two short naps does not reduce the number of unintentional naps during the day and does not improve self-reported sleepiness. Maintaining consistent nocturnal sleep schedule resulted in improved self-reported sleepiness but did not reduce number of unintentional naps. The combination of both naps and consistent nighttime schedule had an impact on both number of unintentional sleep during the day and improved subjective sleepiness. Similar to their earlier findings [28], they noted that the benefit from naps was a function of degree of sleepiness and that patients who presented with more severe sleepiness at baseline despite stimulant use were more likely to benefit from scheduling naps and consistent nighttime sleep benefited.

Clinical Considerations

These studies provide a great deal of information and have been the basis for professional clinical recommendations to date. Taken together, the research to date suggests that naps may be effective in improving alertness and can be an appropriate strategy to manage EDS [22, 25, 26, 28–32]. However, benefits achieved by naps may be transient [26, 32], and patients who are sleepier at baseline may experience more benefits from napping compared to more alert patients [22, 28]. These studies also suggest that the poor performance evidenced in narcolepsy is a result of sleepiness and improves post naps rather than a true disease-related cognitive impairment [27, 29, 30].

Based on the available studies, specific guidelines for number, timing, and duration of naps are difficult to ascertain. There is some variability in these studies regarding the appropriate length of naps. One study [26] suggested no significant difference between short (15 min) and long (30 min) naps; one study reported a trend for a single long nap [29, 30] similar to a different study that reported increased benefit for a long nap (2 h) compared to a short nap (15 min) [32]. However, one study suggested improved subjective alertness after short naps (10 min) compared to long naps (average nap length of 67 min) [25]. The reported benefits from a long nap (these were always given around midday) may be due in part to the finding that sleep inertia is least pronounced after short naps in the morning and after a single long nap in approximately midday [30]. Timing and number of naps are also difficult to ascertain based on these studies. There is some evidence to suggest that naps scheduled around midday and late afternoon may have more impact

[25, 29, 31]. Nonetheless, multiple short naps throughout the day appear to result both in performance improvement and increase in alertness [27–29].

This conclusion is consistent with the practice parameters published by the American Academy of Sleep Medicine [41] which found that scheduled naps were a "guideline treatment," denoting a moderate degree of clinical certainty but did not comment on specific recommendations for the timing, duration, or frequency of naps.

Nocturnal Sleep Consolidation

Behavioral strategies for regulating sleep schedules have been used to consolidate nocturnal sleep and to optimize time in bed. A study by Uchiyama, Mayer, and Meier-Ewert [36] evaluated the effect of extended sleep opportunity on daytime sleepiness (see Table 27.2). Patients were given a sleep opportunity of 8 and 12 h that resulted in average total sleep time of 7 and 9.9 h of sleep. Following the longer sleep opportunity, patients fell asleep on fewer naps within 10 min and mean SOL on the MSLT increased (from 4.1 min after an 8 h in bed to 8.2 min after 12 h in bed) suggesting decreased sleepiness. The authors concluded that this study provides support for increasing nighttime sleep to reduce EDS. The study by Rogers et al. [22] (reviewed earlier) assessed the effectiveness of a consistent nighttime sleep schedule on EDS and reported subjective but not objective improvement of EDS. However, when combining consistent nighttime schedule and naps, improvement was noted on both objective and subjective measures [22].

Clinical Considerations

The relationships between nighttime sleep and narcolepsy symptoms have been a topic of significant interest. Studies have demonstrated that nocturnal sleep is commonly fragmented [42, 43] and attempts to consolidate sleep using pharmacological approaches have been effective in improving cataplexy but not EDS [43–45]. Such findings suggest that EDS experienced in narcolepsy is independent of any nighttime sleep fragmentation that may occur. The study by Uchiyama et al. [36] suggests that increasing nighttime sleep may improve EDS. However, the improvements in EDS were marginal and not clinically significant (mean SOL on MSLT was <10 min). The study by Rogers et al. [22] (reviewed earlier) assessed the effectiveness of a consistent nighttime sleep schedule on EDS and reported subjective but not objective improvement of EDS. However, when combining consistent nighttime schedule and naps, improvement was noted on both objective and subjective measures [22]. There is sufficient evidence to suggest that pharmacologically consolidating nighttime sleep is beneficial especially for improving cataplexy [43–45]. Future studies should assess the impact of behavioral sleep consolidation on cataplexy. Additional studies are necessary to assess the impact of increasing time in bed, as this method has been shown detrimental in other sleep disorder populations (i.e., insomnia) and recommending this approach is contradictory to the use of stimulus control therapy suggested by others [46] for improving nighttime sleep in patients with insomnia.

Dietary Approaches and Alternative Supplements

Several studies have evaluated the use of different dietary supplements and diets and their impact on narcolepsy symptoms (Table 27.2). The effect of carbohydrates on EDS was evaluated by a couple of studies. A placebo-controlled study by Bruck, Amstrong, and Coleman [37] assessed the impact of adding a 50-g glucose drink to lunch. The finding confirmed the authors' hypothesis that high carbohydrate intake would exacerbate sleepiness in patients with narcolepsy as measured objectively but not subjectively. A study by Husain et al. [38] evaluated the effect of a low-carbohydrate, ketogenic diet (i.e., Atkins' diet) on subjective sleepiness. They found significant improvement in sleepiness rating (total scores decreased by 18 %) at posttreatment on only one of three of the subjective measures (Table 27.2). Patients experienced a marked decrease in weight during the 8-week study, and

therefore, it is hard to ascertain whether the improvements in sleepiness were due to the indirect effects resulting from weight loss or the direct effects of the diet itself despite patients' reported benefits prior to experiencing substantial weight loss.

A study by Mouret et al. [33] evaluated the effect of L-tyrosine, an amino acid precursor to dopamine and norepinephrine, on unintended sleep attacks, cataplectic attacks, and nocturnal sleep. They reported that within 6 months of treatment, all patients were completely free of daytime sleep attacks and from cataplexy as recorded in self-reported daily diary logs. Mouret et al. also reported that based on these findings, they treated an additional 23 patients with L-TYROSINE and found similar findings. However, Guilleminault and his colleagues [31] reported that they have attempted to replicate this study using similar methods to that which were reported by Mouret et al. [33] but could not replicate the findings and did not find any improvements on objective measures of sleepiness.

We are aware of only one study that systematically evaluated eating patterns in patients with narcolepsy. Pollak and Green [35] evaluated the relationship between sleep, eating, and subjective alertness in six patients with narcolepsy and seven controls while in a time-isolation laboratory. When the subjects were on a set meal schedule, patients exhibited changes in sleepiness associated with meals. Patients had a period of 1.5–2 h preceding the meal of subjective increase in alertness and decreased napping, which peaked at the start of the meal. For narcolepsy patients, the meal followed by a period (40–50 min) of decreased subjective alertness and increased napping to below pre-meal baseline while for controls the increase in alertness pre-meal was maintained for more than an hour post-meal. The size of the meal did not appear to have an effect on alertness. Thus, the authors did not attribute the deactivation post-meal to the metabolic effects of the meal but rather evidence for a relationship between naps and meals and the importance of accounting for timing of meals in non-pharmacological approaches.

Clinical Considerations

Based on the studies identified, there is insufficient data to support any given strategy. It appears that increase in carbohydrates (i.e., 50 g glucose drink at lunch) exacerbates EDS [37], and a low-carbohydrate, ketogenic diet resulted in subjective symptom improvement but this result is possibly confounded by the indirect effects of weight loss [38]. L-tyrosine was reported to improve both EDS and cataplexy [33] but others [31] could not replicate these results. Nonetheless, meals appear to be related to postprandial sleepiness or decrease alertness post-meals, which is important data when attempting to structure consistent patterns and schedules of meals and naps [35].

While there are insufficient studies to support any single dietary approach, diet and weight are significant concerns for patients with narcolepsy. There is a debate in the literature about whether patients with narcolepsy tend to eat more than controls or have increased prevalence of eating disorders [47]. Obesity has been reported to be common in patients with narcolepsy [48] and studies have demonstrated higher body mass index (BMI) in patients with narcolepsy compared to the general population [49–51], to matched controls [52], and to patients with idiopathic hypersomnia [53]. Increased BMI in this patient population is thought to be a consequence of disease-associated neuroendocrine abnormalities such as hypocretin/orexin deficiency [53–55]. One study [56] reported increased frequency of type II diabetes among patients with narcolepsy and a more recent study [55] suggested that patients with narcolepsy tended to be overweight and have lower basal metabolism. From this review, it appears that diet and weight management should receive more research attention, and, if further positive results are found, these should be given consideration as a component of a comprehensive non-pharmacological approach designed for narcolepsy.

Temperature Manipulation

Patients report the use of temperature manipulation to manage EDS such as maintaining cold room temperatures and avoidance of hot environments

[23]. Although no studies have directly investigated this in patients with narcolepsy, parallels can be drawn from research by Eus van Someren and his colleagues [39, 40] who evaluated the effect of manipulating core body and skin temperature on nocturnal sleep, EDS, and vigilance (see Table 27.2). Their results showed that cooling distal skin resulted in significant decreases in SOL compared to distal skin warming. Additionally, their findings indicated that core body warming improves performance. Finally, their study showed that proximal skin warming decreases wake during nocturnal sleep and enhances slow-wave sleep while distal skin warming enhanced wakefulness, increased stage I sleep, and decreased REM and slow-wave sleep. Due to the experimental nature of these studies, further research is needed on patients with narcolepsy before clinical recommendation or considerations can be provided.

Light Therapy

There has been one study [34] that assessed the use of bright light therapy in seven patients with narcolepsy (see Table 27.2). The authors did not find any subjective or objective benefit of 4 h of bright light therapy (5000 LUX) given twice daily for 10 days and concluded that bright light therapy is not an appropriate treatment for narcolepsy.

Case Studies of Other Behavioral Interventions

There has been one case study that reported improved EDS and cataplexy symptoms after providing progressive muscle relaxation and initiating multiple behavioral strategies for maintaining alertness (e.g., snapping a rubber band, fluid restriction) [57]. A different case study reported on the implementation of a "broad-spectrum" approach in an 18-year-old female with narcolepsy that included self-monitoring, sleep scheduling, a nap, performance of activities to increase arousal, and reinforcement strategies. Over a 22-week period, the patient reported a decrease in sleep attacks that occurred during classes (from 6.75 at a 4-week baseline period to 1.52 sleep attacks posttreatment). This patient reported that several strategies (e.g., consistent nighttime sleep, naps each afternoon, 10 min of a brisk walk before classes, sitting in front row, increase participation, sipping ice water, or nibbling on a snack during class) were more successful than other strategies (e.g., use of rubber band, asking a friend for a nudge, or taking a walk when feeling very sleepy) in reducing sleep attacks in the classroom. However, no systematic studies were identified that assessed such methods that were utilized in these case studies (e.g., progressive muscle relaxation, sipping cold water, using a rubber band, or exercise) [58].

There have been a few case studies that suggested that hypnotherapy might result in improved EDS, cataplexy, and sleep paralysis [59–61]. However, our review did not find any systematic studies that assessed such methods.

Summary and Conclusions

The overall body of literature on non-pharmacological treatments for narcolepsy is still at a nascent stage with areas of promise but also with many mixed findings. The most evaluated and targeted symptom of narcolepsy was EDS (see Table 27.3). This is not surprising as EDS is the most debilitating symptom reported by patients with narcolepsy [10, 11, 17, 23]. Nocturnal sleep and to a lesser extent cataplexy and performance also received attention. However, few studies evaluated sleep attacks, hallucinations, and sleep paralysis. Most surprisingly, psychiatric symptoms were assessed in only one study and no study evaluated quality of life. We also found no study of cognitive strategies to improve management and coping with the disease and no study that utilized multiple approaches and their impact on symptoms as well as on quality of life. This is in direct contradiction with the clinical need of such studies as difficulties in managing and coping with the symptoms of narcolepsy result in such devastating outcomes for these patients.

The measurement of EDS was heterogeneous across studies, making it challenging to draw conclusions about the impact of behavioral treatments on EDS. Studies used either a MSLT [27, 34, 36], a modified version of the MSLT [26, 32], the MWT [28, 31], continuous 24-h recordings [22, 25, 29, 30, 35], EEG measures [37], and/or subjective measures [22, 25, 28, 33, 35, 37, 38]. There are important theoretical differences between these assessment tools (see Arand et al. [62] for a review). For example, MSLT is a test of sleep pressure and the ability to fall asleep, and the MWT more closely assesses the ability to sustain wakefulness. MSLT is recommended to help establish the diagnosis of narcolepsy, but the research question should be carefully considered when determining the selection of the MSLT versus MWT as an outcome measure.

Another methodological concern is the management of narcolepsy medications in conjunction with these behavioral interventions. Some studies evaluated medication-free patients [25, 27, 29–31, 34–37, 39, 40], while other studies assessed patients while on their regular pharmacological management schedule [22, 28, 38]. As non-pharmacological strategies, on their own, are not likely to result in complete amelioration of symptoms, allowing patients to use their prescribed medications has more clinical relevance. However, in such cases, some control must be in place as impact of non-pharmacological approaches may be dependent on type/dose of the medication.

Studies also differed in the length of time in which the therapeutic approach was established prior to testing intervention effect. This begs a legitimate and important theoretical concern of appropriate therapy duration prior to assessing for therapeutic effects. For example, establishing a nap schedule prior to testing an effect varied in studies from a single day [29, 30, 37] to 1- [28], 3- [31], and 6- [33] month duration. Compliance is an additional concern and is a difficult variable to monitor. In a study assessing three scheduled naps per day, 9 of 16 patients (56 %) reported poor adherence to the prescribed schedule napping, on average, less than twice per day [28]. Finally, most of these studies involve small sample sizes, which appear to reflect early stages of testing rather than definitive randomized clinical trials.

In evaluating the non-pharmacological treatment literature collectively, the current state of the literature resembles a collection of pilot studies. The small sample sizes, use of different outcome measures, and testing of different "doses" of naps (i.e., timing and duration of naps) or self-regulatory approaches (i.e., amount of carbohydrate intake) are characteristic of pilot studies conducted during treatment development [63]. Although several studies used randomization and control groups as elements of the study design [22, 25, 27, 32, 35], few studies established a priori outcome measures or a global index of clinical significance, such as quality of life, that are key components of modern clinical trials.

Future Directions

Most studies reviewed were published more than 10 years ago, suggesting little recent activity in this area. It would appear that advances in the understanding of narcolepsy, advances in health psychology related to coping and behavior change, and the emergence of behavioral sleep medicine as a subspecialty would open on many avenues for further clinical research on non-pharmacological approaches for narcolepsy. For example, cognitive techniques could be used to help patients cope with chronic sleepiness and regulate mood and anxiety. Also, identification of treatment moderators, such as baseline levels of sleepiness, could help identify which patients are most likely to benefit from which non-pharmacological intervention. As such, future studies may consider developing and assessing a comprehensive treatment and assess its impact on symptom management. Development of a cognitive-behavior therapy for narcolepsy could also provide a standardized treatment package that could be tested in a clinical trial, therefore, improving our understanding about the effectiveness and mechanisms behind these strategies. Ultimately, these efforts could help to establish more specific recommendations for the use of non-pharmacological strategies for narcolepsy.

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Part V

Health Care Delivery and Medico-Legal Considerations

Narcolepsy and Developmental Disability

28

William Ted Brown and Meeta Goswami

Is Narcolepsy Considered a Developmental Disability?

The short answer is that it depends.

The New York State Office for People with Developmental Disabilities (OPWDD) coordinates and provides services for people with developmental disabilities and their families and conducts research into the causes and prevention of developmental disabilities. Some services provided through OPWDD include family support, case management, housing, supported employment, recreation, skills development, training, long-term habilitative services, nursing and psychiatric services, and respite (short-term caregiver relief). Services for eligible persons in NYS are provided through a network of public and nonprofit service providers, all of whom work collaboratively to assure that high-quality care is provided.

In New York State, for anyone to be eligible for state-supported services, the person must be determined to have a developmental disability and to meet the established criteria for eligibility. There are four general requirements for determination of eligibility. These four conditions are based on the definition of developmental disability that is found in the New York State Mental Hygiene Law 1.03(part 22) (http://codes.lp.findlaw.com/nycode/MHY/A/1/1.03).

The person must have a developmental disability that (1) is attributable to mental retardation, cerebral palsy, epilepsy, neurological impairment, familial dysautonomia, and autism, or (a) is attributable to any other condition of a person found to be closely related to mental retardation because such condition results in similar impairment of general intellectual functioning or adaptive behavior to that of mentally retarded persons or requires treatment and services similar to those required for such person, or (b) is attributable to dyslexia resulting from a disability described in subparagraph (1) or (2) of this paragraph, (2) originates before such person attains the age of 22, (3) has continued or can be expected to continue indefinitely, and (4) constitutes a substantial handicap to such person's ability to function normally in society.

It is not necessary for someone to have an intellectual disability in addition to another one of the "qualifying conditions" in order to be found eligible. For the nonintellectual disability (ID) qualifying conditions, what is needed is clear and adequate diagnostic documentation of the condition and evidence of its

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creating/resulting in a substantial impairment in adaptive behavior functioning. "Substantial handicap" is defined by most professional associations and agencies that are concerned with developmental disabilities—as evidence of adaptive functioning at or below a level that is two standard deviations below the mean established for a comprehensive, structured, nationally normed assessment instrument. For the current adaptive behavior assessment instruments with a mean of 100 and SD of 15, that would be a resulting score of 70 or below. Thus, "a diagnosis does not always mean a disability." There has to be significant impairment in adaptive functioning, and not all types among or degrees of the disorders or syndromes will affect individuals to the same degree of severity.

One of the qualifying conditions is "neurological impairment." Neurological impairment is defined as any disorder/disease/injury/malformation or malfunction originating in or ultimately affecting the central nervous system. Thus, while a genetic metabolic disorder in and of itself may not clearly be a "developmental disability," its mechanism may negatively affect or prevent CNS development or functioning to a significant degree. The disorder itself is then considered to be "the named condition" or diagnosis that falls within the mental health law developmental disability classification of "neurological impairment."

In the case of narcolepsy, there should be:

1. Clear differential diagnostic evidence that narcolepsy is the identified condition and that it is linked to the development or functioning of the CNS.
2. The onset of narcolepsy must occur prior to age 22; documentation should be made available to establish the age of onset.
3. The condition must be expected and documented to be permanent or to continue indefinitely.
4. Evidence from structured assessment(s) of adaptive behavior functioning that establishes "substantial handicap" (i.e., the general composite score or the majority of domain scores falling within the range of $\leq$70).

If the type of narcolepsy that a person has is treatable, it would not necessarily impair a person's functioning to the degree that intellectual disability, autism, or a significant brain injury would. The diagnostic work-up and documentation should make it clear that other possible causes for excessive daytime sleepiness have been ruled out and that adherence to available non-pharmacologic and/or pharmacologic treatment regimens has not been effective.

Functional Limitations and Substantial Handicap

Functional limitations are generally considered to constitute a substantial handicap when they prohibit a person from being able to engage in self-care or exercise self-direction independently or when the development of self-care and self-direction skills are significantly below an age-appropriate level. Such limitations may also seriously disrupt age-appropriate social and interpersonal relationships. The clinical determination of when a condition constitutes a substantial handicap is complex and involves numerous factors.

Functional limitations constituting a substantial handicap are defined as significant limitations in adaptive functioning that are determined from the findings of assessment by using a nationally normed and validated, comprehensive, individual measure of adaptive behavior, administered by a qualified practitioner. Onset of significant limitations in adaptive behavior constituting substantial handicap, as defined below, must be before the person attains age 22 in order to satisfy the requirements of MHL 1.03(part 22)(b). Onset must be verified as entailing occurrence of significant limitations in adaptive behavior prior to age 22.

Frameworks for Adaptive Behavior

The two sets of domains below each include areas of practical abilities, social competence, and performance in everyday life. These domains

constitute two possible frameworks for describing adaptive behaviors. People may be fairly judged within the context of these elements. The federal definition of developmental disability promulgated by the federal Administration on Developmental Disabilities mentions seven domains of life activity: language, learning, mobility, self-care, capacity for independent living, self-direction, and economic self-sufficiency. This framework applies to services funded through federal Developmental Disabilities Planning Council funds. The Fifth Edition of the American Psychiatric Association's Diagnostic and Statistical Manual [1] includes additional aspects of life activity as domains, including communication, social participation, and independent living across multiple environments, such as home, school, work, and community.

This framework corresponds to the domains set forth by the American Association on Intellectual and Developmental Disability (aaidd.org). They define adaptive behavior is the collection of conceptual, social, and practical skills that are learned and performed by people in their everyday lives:

- Conceptual skills—language and literacy; money, time, and number concepts; and self-direction
- Social skills—interpersonal skills, social responsibility, self-esteem, gullibility, naïveté (i.e., wariness), social problem solving, and the ability to follow rules/obey laws and to avoid being victimized.
- Practical skills—activities of daily living (personal care), occupational skills, healthcare, travel/transportation, schedules/routines, safety, use of money, use of the telephone.

Clinicians are advised to use a framework in characterizing adaptive behavior that is comprehensive, that adequately reflects personal and social skills, and that is relevant throughout a person's life span. Generally, adaptive behavior scales are based on these kinds of frameworks. However, New York State law or regulation does not require that either of the groupings of domains above be used for assessing adaptive behavior.

Using Scores on Adaptive Behavior Measures to Establish Functional Limitations

For adaptive behavior measures that provide an overall composite or summary index score, the criterion of significance for defining substantial handicap is an overall composite or summary index score that is 2.0 or more standard deviations below the mean for the appropriate norming sample or that is within the range of adaptive behavior associated with an intellectual level consistent with mild to profound mental retardation in instrument norms (the latter may be used if the adaptive behavior instrument does not present information on the means and standard deviations of the norming sample).

For adaptive behavior measures that provide factor or multiple scale summary scores, another criterion of significance is that the majority of these factor or multiple scale summary scores lie 2.0 or more standard deviations below the mean for the appropriate norming sample or lie within the range of adaptive behavior associated with an intellectual level consistent with mild to profound mental retardation, as indicated by the instrument norms. Significance may also be demonstrated if the majority of factor or multiple scale summary scores from an adaptive behavior measure lie at 2.0 or more standard deviations below the mean, as qualified above, and the composite score is less than 2.0 standard deviations below the mean (i.e., a person can qualify for services when the majority of subtest scores fall at −2.0 SD or more below the mean, even when the composite score does not).

Adaptive behavior measures that provide neither overall summary index scores nor factor or summary scores, as described above, are unacceptable as a means for determining the presence of functional limitations constituting substantial handicap. For adaptive behavior measures that permit assessment of both adaptive and maladaptive behavior, the presence of clinically significant maladaptive behaviors in the absence of significant limitations in adaptive behavior, as defined here, does not meet the criterion of significant limitations in adaptive functioning.

Assessing Intellectual Functioning and Adaptive Functioning

Significant limitations in general intellectual functioning and limitations in adaptive functioning should be determined by different kinds of tests or measures. Significant limitations in general intellectual functioning are determined from the findings of assessment by using a nationally normed and validated, and comprehensive, individual measure of intelligence that is administered in a standardized format, in its entirety in accordance with standardization, and interpreted by a qualified practitioner. In exceptional circumstances, when standardized formats have been determined to be inappropriate by a qualified practitioner, non-standardized testing formats should be used, provided that this is documented and an appropriate rationale is clearly stated.

Significant limitations in adaptive functioning are determined from the findings of assessment by using a nationally normed and validated, comprehensive, individual measure of adaptive behavior and may not be stipulated based upon a comprehensive, individual measure of intellectual functioning. Similarly, presence of significant limitations in adaptive behavior does not constitute a basis upon which presence of significantly subaverage intellectual functioning may be stipulated.

The completion of an adaptive behavior measure should be required by the assessing center in all instances where initial determinations of eligibility are made or when application is made on behalf of a person previously receiving family or individual support services for additional services that may entail different or further eligibility criteria. An exception can be made in cases where a professional psychological examination using a comprehensive, individual, nationally normed intelligence scale results in a full-scale (overall or summary) IQ of 70 or lower (based on a scale with a mean of 100 and a standard deviation of 15). The presence of significant adaptive behavior limitations may be assessed and confirmed through clinical observation or interview in such cases. Based on findings from professional assessments, as indicated above, and review of historical and contemporary clinical records, a determination should be made, based on available evidence and clinical judgment, that significant functional limitations are not due to a current acute or severe phase of a psychiatric disorder, that they are not a consequence of psychiatric disorder, alcoholism, or alcohol or substance abuse disorders, and that these disorders did not result in a condition similar to mental retardation (as specified in MHL 1.03(part 22)) before the age of 22. The determination should also be made that significant functional limitations are associated with, attendant to, or result from, a particular developmental disorder or combination of such disorders. For the purposes of eligibility determination, developmental disorders are defined as conditions that meet the criteria set forth in the Mental Hygiene Law for developmental disability and that involve injury, dysfunction, disorder, or impairment of the central nervous system, i.e., brain or spinal cord.

Which Standardized Assessment Measures Are Appropriate?

Standardized assessment measures that are appropriate as sources of information to be used in eligibility determination have several key characteristics:

- Their reliability and validity are suitably verified by peer-reviewed research.
- Their reliability, validity, indicated uses, and performance parameters are adequately presented in the relevant technical manuals and test manuals.
- They are normed or criterion referenced and their performance has been ascertained, on a representative suitably structured population sample of sufficient size to permit stability of scores and score patterns.
- They are normed on suitably sized and reasonably contemporary representative population samples (i.e., the norms are not outdated, e.g., established within the past 10 years).
- They are standardized in their mode and parameters (process) of administration and

administered in conformance with those parameters.
- They are suitably structured and comprehensive or targeted for their respective purposes, such as assessing intellectual, behavioral, social and personality, or academic functioning.

Examples of appropriate intellectual measures include:

- Kaufman Assessment Battery for Children
- Leiter International Performance Scale
- The Stanford-Binet Scales
- The Wechsler series of Intelligence Scales

Brief or partial administration of comprehensive intellectual measures may be utilized only in circumstances where standardized administration is impossible due to sensory disability (e.g., deafness, blindness) or profound and generalized impairment of activity and in conformance with ERA/APA/NCME [2] standards for use and interpretation of individual test results.

Examples of standardized measures that are not considered to be comprehensive in nature:

- The Peabody Picture Vocabulary Test
- The Quick Test
- Slosson Intelligence Test-R (revised) or Slosson Full-Range Intelligence Test
- Testing formats that project unadministered subtest scores from those that are administered
- Tests that do not include both high-verbal and low-verbal format items

Examples of appropriate comprehensive measures of adaptive behavior:

- AAMR Adaptive Behavior Scale
- Adaptive Behavior Assessment System
- Comprehensive Test of Adaptive Behavior
- Scales of Independent Behavior
- Vineland Adaptive Behavior Scales

A more complete description of the process for determining eligibility in New York State can be found online at http://www.opwdd.ny.gov/opwdd_services_supports/eligibility.

Consideration of Narcolepsy as a Developmental Disability

Narcolepsy, a sleep disorder of neurological origin, is characterized by loss of hypothalamic hypocretin (orexin) neurons [3] but not in patients who have narcolepsy without cataplexy [4]. The typical age at onset is 12–16 years. It is strongly associated with the HLA-DQB1*06:02 genotype and has been thought of as an immune-mediated disease [5].

Narcolepsy is characterized by uncontrollable *excessive daytime sleepiness* (EDS) episodes at inappropriate moments and cataplexy, a sudden loss of muscular control brought on by deep emotions, especially joy or laughter. Cataplexy is unique to narcolepsy. It can be partial or complete, during which the individual may fall to the ground. Other symptoms include hypnagogic hallucinations (vivid dreams or images during transition from wakefulness to sleep and often mistaken for reality) and sleep paralysis (inability to move upon transition from sleep to wake state or immediately upon awakening). Another associated symptom is automatic behavior, the performance of simple or routine tasks while remaining largely unaware of the activity. Examples include talking, writing, and putting away things while resisting drowsiness. Patients also complain of overwhelming fatigue and problems with memory and concentration. Patients report that EDS, cataplexy if present, and fatigue are the most bothersome features of narcolepsy and have devastating effects on their activities of daily living, socialization, education, and work. Following is how one patient described the effect of EDS on his life:

"I feel completely useless, like my life is in slow motion—my mind and body are separate. I feel dead, void—my thoughts come slowly, my body reacts (responds) slowly—I am the walking dead. I yawn sometimes, I sweat profusely. I say, do bizarre things. Drowsiness—I'm fighting drowsiness from a few minutes to sometimes over an hour. I probably spend 15–20 % of my life redoing what I already did while I was falling asleep. This page is an example; here is 2 h of time."

The symptoms of narcolepsy, when severe, compromise the individual's ability to function adequately, forcing many to drop out of school or the work force and go on disability insurance. Some of the patients at the Narcolepsy Institute with severe symptoms were eligible for support services provided by the Office of People with Developmental Disabilities (OPWDD).

Presented below are case reports of two individuals who were approved for OPWDD-funded support services and one individual who was denied access to such services. All names are fictitious to maintain the privacy of the patients. The diagnosis of narcolepsy was established by all-night polysomnogram and the multiple sleep latency test.

1. Sharon came to the Narcolepsy Institute in July 1991 with a chief complaint of EDS. She had never gone to a doctor for this problem, although she developed the symptoms at the age of nine. We referred her to a Sleep Center in New York where narcolepsy was confirmed. EDS developed at age 11, cataplexy (CPX) at 12, and sep paralysis (SP) at 15. EDS was the most bothersome feature. She would fall asleep while reading, listening, watching television, and traveling and would be sleepy within half an hour of waking up in the morning. She scored 22/24 on the Epworth Sleepiness Scale (ESS), indicating severe sleepiness. She took long afternoon naps and was drowsy most of the day. Her nocturnal sleep was disrupted by a couple awakenings, restlessness, and vivid dreams. During these awakenings, she would go to the bathroom and eat/drink. Sleep comorbidities include sleep apnea and symptoms of RBD (REM behavior disorder).

Sharon had difficulty completing some of her daily activities due to a lack of self-direction, poor planning, inefficient time management, and delayed reaction to stimuli. Although she was independent in routine self-care, she had accidents at home when she would drop things or burn herself while cooking due to episodes of EDS and automatic behavior. She described an incident when she fell asleep while ironing and burnt her hand and a few clothes. She was upset and embarrassed by this accident. Due to EDS and fatigue, she had difficulty being punctual and holding onto a job.

Results of vineland adaptive behavior scale (VABS). Age at evaluation: 36 years

	Standard score	Age equivalent
Communication	48	9–8
Daily living skills	58	9–0
Socialization	48	6–9
Adaptive behavior composite	47	

The VABS indicated that, despite normal intellectual ability, her adaptive functioning was two to three standard deviations below the expected norm due mainly to her narcolepsy. The report revealed: "Her difficulties in sustaining concentration have resulted in an inability to consistently use written forms of communication effectively, to engage in routine activities around the house, and to sustain employment and manage money effectively."

She was eligible to receive the support services offered by OPWDD, by programs funded by OPWDD, and by the Narcolepsy Institute (funded by OPWDD), including counseling, case management, and participation in recreational programs.

Sharon had severe depression and saw a therapist for this condition in the past. These symptoms improved after attending our individual counseling sessions, support groups, and recreational program. A similar beneficial effect is observed on her reported feelings of loneliness and tendency to feel guilty and blame herself for not accomplishing tasks as expected. She no longer feels embarrassed about her symptoms of narcolepsy.

Over the years, with appropriate medications (Provigil) and with support and information on non-pharmacological management of narcolepsy provided by the Narcolepsy Institute, she has learned to live with her narcolepsy and appreciates the help she receives from members of the support group. She has improved her communication skills, socializes with friends, reports no depressive symptoms, and has improved her confidence and self-esteem. She continues to engage actively in her medical care and in support group meetings at the Narcolepsy Institute.

2. Derrick was in sixth grade when he was diagnosed with narcolepsy and as "mentally disabled" by the Board of Education when he was in seventh grade. He attended special education classes until tenth grade, when he dropped out of school. He later tried working for a GED but could not complete the program.

He was diagnosed with narcolepsy at a sleep disorder center in New York. He presented symptoms of excessive daytime sleepiness (EDS), hypnagogic hallucinations (HH), cataplexy (CPX), sleep paralysis (SP), and automatic behavior (Aut B). According to his mother, he was very sleepy despite taking his medications. He was prescribed Ritalin and then Xyrem for narcolepsy and was treated for obstructive sleep apnea with a continuous positive airway pressure machine (CPAP).

Other medical/psychiatric problems: Patient is obese. He weighs 334 lbs. and his height is 6 ft.

VABS score age at evaluation: 26 years

Domain	Standard score
Communication	60
Daily living skills	52
Socialization	59
Adaptive behavior composite	56

Percentile rank in all domains was ‹1 and adaptive level was "low."

He was eligible for all OPWDD-funded services. He availed himself of several services from OPWDD-funded programs, such as supported work; individual, family, and group counseling services; advocacy; and appropriate housing. He continues to attend the support groups at the Narcolepsy Institute. Derrick has improved his communication skills, interacts positively with the group members, and engages in a responsible manner in self-care, work, and socialization with family members.

Case Report of an Individual Who Was Not Eligible for OPWDD Services

Remy came to the Narcolepsy Institute in 1992 with a chief complaint of excessive daytime sleepiness (EDS), hypnagogic hallucinations (HH), and cataplexy (CPX). Remy was told by her mother that she had EDS since infancy, CPX began at the age of 10, and HH at the age of 30. She did not have automatic behavior or sleep paralysis. She reported disturbed nocturnal sleep, waking up four to five times a night. At the age of 21, she was diagnosed clinically as having narcolepsy by a psychiatrist. We referred her to a sleep center in New York for a diagnostic work-up. Narcolepsy and sleep apnea were confirmed, and she was prescribed Ritalin for narcolepsy and a CPAP for sleep apnea.

Presently, Remy does not use the CPAP because "it is awkward." Her HH are visual and tactile and are very frightening and anxiety-provoking. Cataplexy occurs with any strong emotion; her knees may buckle or she may fall over. Over the years, she has adapted to this situation by "just not feeling too much." Cataplexy causes embarrassment and fear of having accidents.

When Remy worked, she found that EDS profoundly reduced her productivity. She worked as a clerk but soon had to go on disability insurance and receives Supplemental Security Income (SSI).

Results of VABS: age at evaluation: 50 years

	Standard score	Age equivalent
Communication	57	10–4
Daily living skills	100	18–6
Socialization	63	11–6
Adaptive behavior composite	68	13–5

Adaptive level was "low" in communication and socialization domains but "adequate" in daily living skills, so although the adaptive behavior composite was 68 and below the established eligibility level of 70, Remy was deemed ineligible for OPWDD-funded services.

Many people with narcolepsy who are disabled because of the effect of the symptoms on education, work, and socialization may not be eligible for these support services because their disability level is not severe enough to meet the eligibility criteria of OPWDD. Others who receive these services claim their beneficial effects on the quality of their lives.

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Succeeding in School and in the Workplace with Narcolepsy

29

Julie Flygare

Introduction

Living with narcolepsy can be challenging. People with narcolepsy manage symptoms, medications, side effects, and other complications. In addition, they often face misunderstanding at school, in the workplace, and at home.

While great strides in narcolepsy awareness have been made, challenges remain. According to the AWAKEN survey, only 70 % of adults in the USA have heard of narcolepsy, and 50 % believe that the disorder can severely impact overall health [1]. Misperceptions may lead to exaggerated concern or lack of concern, while the true nature of narcolepsy may remain invisible to peers and authority figures.

Given low public awareness and misperceptions, people with narcolepsy face an uphill battle to gain accommodations in school and in the workplace. Learning about the legal protections that may be available to people with narcolepsy will empower doctors, patients, and caregivers to work together to help maximize patients' skills and talents.

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Patients and caregivers must educate themselves on narcolepsy and find tools to communicate effectively. Physicians and health-care professionals play a vital role in helping patient advocates locate resources and navigate this journey.

There are three main factors to impart upon authority figures in any accommodations discussion, including basic information about narcolepsy, how narcolepsy affects the individual, and accommodation suggestions.

It is important to note that a narcolepsy diagnosis does not, by itself, qualify any individual as "disabled" under the law. The determination is always an individualized process taking into consideration the patient's particular circumstances. Generally speaking, the nature and severity of an individual's symptoms and how the symptoms disrupt major life functions will be considered in the decision process.

Likewise, qualifying as "disabled" in one area of law is not a blanket determination applicable to all other rights and regulations. Each area of legal protection may consider different factors and thus may reach different conclusions.

Moreover, no two people with narcolepsy are exactly the same. Some patients may experience great improvements with proper diagnosis and treatment, while others struggle to find adequate therapies to manage symptoms, side effects, and other complexities. Some individuals may find short naps restful while others do not. Cognitive functioning, brain fog, and memory issues severely

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affect some patients [2]. Thus, it's important that individuals' specific circumstances be considered closely in identifying the accommodations that will help each patient succeed.

The following chapter will focus on two areas of legal protection—educational and employment accommodations. While both involve the Americans with Disabilities Act of 1990 (ADA) and some overlapping terminology, different factors, processes, and protections are in play [3]. In addition to outlining the key legal factors and procedures, this chapter will highlight the medical professional's opportunities to help patients. Lastly, this chapter will provide specific accommodation ideas for people with narcolepsy in school and in the workplace.

School Accommodations for Narcolepsy

Adjusting to narcolepsy as a student may significantly disrupt one's education. All too often, narcolepsy diagnosis is delayed. Before diagnosis, a student's grades and relationships of trust with teachers and administrators may have suffered. Once diagnosed, school authority figures may not be knowledgeable about narcolepsy and may not know how to help this student. Educating school administrators and teachers will greatly improve a student's ability to manage their condition and succeed in school.

Understanding 504 Plans for Narcolepsy

What Is Section 504?

Section 504 of the Rehabilitation Act of 1973 (Section 504) is anti-discrimination, civil rights act prohibiting discrimination based on disability [4]. Section 504 requires public school districts and other institutions of higher education receiving federal financial assistance to provide a "free appropriate public education" (FAPE) to each qualified student with a disability [4]. Title II of the Americans with Disabilities Act of 1990 (Title II) extends this prohibition against discrimination to a wide range of additional state and local government services, programs, and activities (including public schools) regardless of whether they receive any federal financial assistance [3].

What Is Covered by Section 504?

A free appropriate public education (FAPE) for qualified students with disability may include education in the regular classroom, education in the regular classroom with supplemental services, and/or special education and related services [4]. It cannot cost the child's family any extra money and must be designed to meet the student's individual educational needs to the same extent as the needs of nondisabled students are met.

Who Is Covered by Section 504?

Section 504 covers students who are "qualified" (which is generally between ages 3 and 22, depending on the program, and must have a disability). Federal law defines "An individual with a disability means any person who: (i) has a mental or physical impairment that substantially limits one or more major life activity, (ii) has a record of such an impairment; or (iii) is regarded as having such an impairment" [4].

Determining if a student has a physical or mental impairment that substantially limits a major life activity under Section 504 is an individualized evaluation made on a case-by-case basis [4].

A "physical or mental impairment" is defined as any physiological disorder or condition, cosmetic disfigurement, or anatomical loss affecting one or more of the following body systems—neurological; musculoskeletal; special sense organs; respiratory, including speech organs; cardiovascular; reproductive; digestive; genitourinary; hemic and lymphatic; skin; and endocrine—or any mental or psychological disorder, such as mental retardation, organic brain syndrome, emotional or mental illness, and specific learning disabilities [4]. The definition is open-ended to allow for interpretation.

Interestingly, "substantially limits" are not defined in Section 504, but the Amendments Act of 2008 (Amendments Act) provided guidance stating that the determination "is intended to afford a broad scope or protection to eligible persons" [5].

What Are Major Life Activities Under Section 504?

This physical or mental impairment must substantially limit one or more major life activities. "Major life activities," as defined in Section 504, include functions such as caring for one's self, performing manual tasks, walking, seeing, hearing, speaking, breathing, learning, and working [4]. In the Amendments Act, additional examples of major life activities were added including eating, sleeping, standing lifting, bending, reading, concentrating, thinking, and communicating [5].

While narcolepsy affects many aspects of life, the inclusion of sleeping as a major life activity is helpful for students with narcolepsy and other sleep disorders to gain a favorable Section 504 determination toward receiving accommodations.

Furthermore, the Amendments Act states that, in determining whether a student has a physical or mental impairment that substantially limits that student in a major life activity, the school district cannot consider the ameliorating effects of any mitigating measures that the student may be using, such as medication, medical supplies, assistive technology, or accommodations as part of the determination [5]. This is especially helpful for students with narcolepsy, as narcolepsy's effects on quality of life are often underappreciated by outsiders; the fact that ameliorating factors like medication will no longer be considered in the determination is helpful.

The Office of Civil Rights has also acknowledged that some students have "hidden disabilities" that are not readily apparent to others [6]. Invisible disabilities may not be obvious, but if they substantially limit that child's ability to receive an appropriate education as defined by Section 504, the student may be considered to have an "impairment" under Section 504 [6]. These students, regardless of their intelligence, may be unable to fully demonstrate their ability or attain educational benefits equal to that of non-disabled students. Examples of hidden conditions include certain learning disabilities, diabetes, epilepsy, and allergies. Narcolepsy may also be considered a hidden disability.

How Does the Section 504 Process Begin?

At the elementary and secondary school level, the process to determine if a child qualifies as disabled under Section 504 begins with an evaluation conducted by the school's Section 504 committee [3].

Who Initiates the Section 504 Process for Accommodations?

Anyone can refer a child for consideration for evaluation under Section 504, including a doctor, parent, teacher, or school nurse. If a child is experiencing chronic problems at school and interventions are proving unsuccessful, and a disability is suspected, the school has an obligation to refer the child for an evaluation. However, parents must always receive notice before their child is evaluated and/or given accommodations under Section 504 [3].

If a parent or doctor refers a student for evaluation, the school district must also have reason to believe that the child is in need of services under Section 504 [3]. Thus, a school district does not have to evaluate a student under Section 504 solely upon the demand of a doctor or parent. The key to a referral is whether the school district staff suspects that a child is suffering from a mental or physical impairment that substantially limits a major life activity and is in need of services.

If a parent initiates a request for evaluation and the school district denies the request, the school district must provide the parent with notice of their procedural rights under Section 504, so that parents can file a complaint with the school district Section 504 coordinator or with the appropriate regional Office for Civil Rights (OCR) [3].

Who Determines If a Student Qualifies Under Section 504?

According to federal regulations, "placement decisions are to be made by a group of persons who are knowledgeable about the child, the meaning of the evaluation data, placement options, least restrictive environment requirements, and capable facilities" [4]. Without a definitive "list" of qualifying conditions, school administrators and teachers must use their collective, professional judgment to make the determination.

Section 504, unlike Special Education Regulations, does not demand or even mention parents as being part of the decision-making committee. The decision to include parents on the committee is a determination made by each school district and should be explained in each school district's procedural documents for implementing Section 504. Parents should at least be asked and encouraged to contribute information that they may have (including doctor reports, outside testing reports, etc.) that would be helpful to the Section 504 committee in making their determination of what the child may need. Schools are expected to make sound educational decisions as to what the child needs in order to receive an appropriate education.

What Information Is Used in Conducting a Section 504 Evaluation?

Schools must consider a variety of sources. One source of information, like a doctor's letter, cannot be the sole information considered [4]. Schools must be certain that all information is documented and analyzed by the Section 504 committee.

Schools often receive a doctor's letter stating that a student has a disability and requires certain services. While the school considers the recommendations of medical doctors and other professionals knowledgeable about the child, it remains the committee's responsibility to review multiple sources of information to determine eligibility and to implement any services for the student.

The committee will look at grades over the past couple years, teachers' reports, information from parents and medical providers, standardized test scores, discipline reports, and attendance records [4]. No formalized testing is required under Section 504.

How Is a 504 Plan Developed?

If a student is determined to have a disability under Section 504, the committee will make an individualized determination of the educational needs and a Section 504 plan will be developed [4]. The plan should also identify the individual(s) responsible for implementing these services [4].

What Type of Accommodations Will a Student Receive Under Section 504?

There is no list of approved accommodations. Generally, the student eligible under 504 (and not Special Education) will remain in the regular classroom. The Section 504 committee determines the student's needs on a case-by-case basis, in accordance with the nature of the condition and what that child needs to have an equal opportunity compared to nondisabled students of the same age [4].

The 504 committee should review the 504 plan and eligibility status annually; however, there is no specific time requirement. At a minimum, the 504 plan should be reevaluated once every 3 years or whenever there is going to be a "significant change in placement." In addition, accommodation plans can be revised at any time during the school year if necessary.

What Accommodations Would Best Help a Student with Narcolepsy Succeed?

Accommodations should be tailored to meet each individual's needs. Some possible accommodation ideas include scheduled nap breaks, designated nap location, recording devices such as a "smart pen," shared notes from teacher or classmates, extended time on tests and homework assignments, breaks during tests, and excused absenteeism (see Table 29.1).

Table 29.1 Educational accommodation ideas for students with narcolepsy

This list was compiled directly from students with narcolepsy at all grade levels including elementary school, secondary school, college, and graduate school. Every student with narcolepsy is different. Every school is different. What works best for each student may be a creative combination of these ideas
Managing EDS: nap accommodations – Providing a designated area for scheduled nap time – Going to the nurse when a nap is needed – Walking out of class for fresh air whenever necessary – Staying in the classroom at break times to sleep – Designating a reserved cubicle in the library basement to nap anytime – Leaving the classroom if a sleep attack is coming or for any other reason – A study hall period to nap daily – Midday study hall for a nap time
Note-taking – Allowed to choose to anonymously assign a classmate to take notes and use their notes as well in order to grasp concepts better – Allowed to take notes and teachers also provide copies of their notes – Using a "smart pen" that records audio with writing
Day to day in classroom – Snacking in class if stomach is upset from medication – Providing tutors who understand if student is late—knowledgeable about difficulties with sleep and EDS – Ability to participate in extracurricular activities such as volleyball and cross-country running – Opportunities to revise material at a time that suits child better
Absenteeism – Permitted (if needed) to have 4 excused days if I'm just too tired to make it to class – Allowed to be late if sleep is an issue – Absences excused – Providing one doctor's note for the semester or year, especially if the child is newly diagnosed and trying new medications—the child may be having cataplexy attacks or unable to wake up in the morning and unable to make it to school but won't be running to the doctor's office to get a note each time
Homework – For younger kids, flexibility with homework. Sometimes barely able to make it through the day, let alone finish homework – Extra time to make up homework
Class schedule – Rearranging four block classes a day so the two boring ones are while medication is still strong – In a block schedule system, the ability to come in second period – Priority scheduling—first period study hall for those with trouble waking up or midday study hall for nap time. Taking the most difficult classes at the most alert time of day
Alternatives to standard classroom – Virtual school programs – Online classes to make up credits to graduate – Summer classes/summer online classes
Testing/final papers – Extra time on tests, breaks during tests (every 45 min or so as needed), mark in book only, no answer sheet to bubble, separate room if needed – Air conditioning – Tests and quizzes first thing in the morning – During exams, the ability to take a break every half an hour to get fresh air, seat placement next to a window for natural light, and extra time – Standing while taking tests – Limiting testing to only 3 h of testing a day, at most – Extensions for all final papers – Extra time on all deadlines – For ACT, accommodations for one test per day instead of all of them back to back

How Can a Doctor Best Help a Student with Narcolepsy with This Process?

For a doctor treating a student with narcolepsy, it's important to discuss how narcolepsy is affecting their school performance. Soon after diagnosis, it may be challenging for students to clearly articulate exactly how their symptoms and medications affect their performance.

As the student adjusts to symptoms and new treatments, it may take time to find a good schedule and accommodations that best meet the student's needs. This may be an evolving process and should be discussed during each doctor's visit. Yet, it is never too early to start discussing a student's education and brainstorming practical accommodation ideas.

In reviewing possible accommodation ideas, doctors can help students find practical ways to improve their patient's ability to succeed in school. Some questions to ask may include:

- Are short naps helpful?
- Does the student have trouble waking up in the morning?
- Is cataplexy an issue at school?
- Does the student have trouble retaining information from classroom lectures?
- Are there behavioral issues?

What If a Student Resists Identifying with the Term "Disability"?

It may take some time for a student to adjust to narcolepsy and open up to a discussion about accommodations. Students may fear that accepting accommodations is a sign of weakness—"letting narcolepsy win" or "giving up on themselves."

These feelings are natural. Students should be reminded that making adjustments for narcolepsy doesn't mean you are disabled or a failure, it means you are being smart and strategic, working with your narcolepsy to live your most successful life.

Nonetheless, for a doctor, starting the discussion around accommodations is a good idea to ensure the student is aware of the possibilities and can inquire more.

What Is the Appropriate Role of the Health-Care Provider in the Section 504 Process?

A doctor's report is an important part of the Section 504 review documentation, especially for students with narcolepsy, as school personnel may know little about narcolepsy. A student struggling with the basic symptoms may be misunderstood as lazy, depressed, hyperactive, moody, clumsy, untruthful, or forgetful.

A doctor's letter can educate the Section 504 committee on the symptoms of narcolepsy, current treatment options, and effects on quality of life. Furthermore, the doctor's letter can highlight the individual's unique struggles and suggest specific accommodations to best meet the student's individual needs. Helpful accommodations for students with narcolepsy may include a creative combination of suggestions from Table 29.1.

Do Accommodations Extend to Extracurricular Activities?

School districts must provide equal opportunity in areas such as counseling, physical education and/or athletics, transportation, health services, recreational activities, specific interest groups, and clubs.

What About College and Graduate School?

Unlike elementary and secondary school, postsecondary schools have a different definition of disability. At the postsecondary level, a qualified student with a disability is a student with a disability who meets the academic and technical standards required for admission or participation in the institution's educational program or activity [7].

If the student meets the qualifying standards, the school must provide students with the appropriate academic adjustments and auxiliary aids and services that are necessary to afford an individual with a disability an equal opportunity to participate in a school's program [7]. However, the postsecondary school is not required to make adjustments or provide aids or services that

would result in a fundamental alternation of a school's program or impose an undue burden [7].

Although college and graduate school may sound intimidating, postsecondary education may provide greater scheduling flexibility for students with narcolepsy. Students may elect classes that stimulate their personal interests and find styles of learning that work best for them—choosing interactive discussion-based classes as opposed to lecture-based classes or choosing classes with final exams versus final papers.

In addition, college may offer a wide variety of clubs and interest groups along with alternative housing accommodations. While a student with narcolepsy may feel isolated in an elementary and secondary school environment, a college environment may offer more diversity that may be empowering and help to improve overall quality of life.

Do Accommodations Extend to Standardized Testing Like ACT or SAT?

As students with narcolepsy start high school, it's important to begin considering accommodations for standardized tests including the American College Testing (ACT), Scholastic Aptitude Test (SAT), and Advanced Placement (AP) exams. Students should begin this process early, in case initial requests are denied. Receiving Section 504 accommodations or Special Education IEP accommodations at school will not guarantee accommodations for standardized tests, but it can be helpful in the determination process. Providing detailed diagnosis documentation, explaining functional impairments, and making requests for specific accommodations are key factors. ACT and the College Board (for SAT) have different requirements. Check the ACT and College Board website for detailed information.

What Is the Difference Between Special Education (IEP Plans) and Section 504 Plans?

Individualized Education Program (IEP) plans are geared toward special education and placement outside of the regular classroom, whereas Section 504 accommodations are geared toward accommodations within the general education classroom. While every student is different and severity of symptoms should be considered, Section 504 accommodations may generally be the appropriate option for students with narcolepsy.

The Office of Civil Rights oversees both Section 504 and Title II. Both Section 504 and Title II are anti-discrimination laws and do not provide any funding. The Office of Civil Rights also administers the Individuals with Disabilities Education Act (IDEA), which is a grant statute funding Special Education programs for students with IEP plans requiring specialized education and placement outside of the classroom.

Tips for Success

1. Address concerns in advance of problems arising.
2. Put everything in writing when interacting with school district.
3. Secure a full report from doctor, not just parents' input on child's illness.

Additional Resources

Disability.gov
Children's Law Center
College Board and ACT websites
US Department of Education, Office of Civil Rights

Succeeding in the Workplace with Narcolepsy

Successfully managing narcolepsy in the workplace is an individualized process depending on the circumstances. Many employers are obligated to make reasonable accommodations for a disability under the Americans with Disabilities Act (ADA) to help employees meet their essential job duties. Reasonable accommodations for a disability may help a person with narcolepsy succeed in his or her career.

In order to successfully secure accommodations, the patient and his/her physician should clearly explain to the employer what the patient's specific limitations are and how with a clearly defined reasonable accommodation the patient

will be able to be a valuable employee performing the essential job duties.

What Is a Disability Under the Americans with Disabilities Act (ADA)?

Under the ADA, a disability is defined as having one of the following: a physical or mental impairment that "substantially limits" one or more "major life activities" a record of such an impairment, or being regarded as having such an impairment [3].

While not everything that restricts activities qualifies as an impairment, the Amendments Act states that the definition of disability must be construed in favor of broad coverage to the maximum extent permitted [5].

A physical impairment is any medical disorder, condition, disfigurement, or loss affecting one of the body systems, such as neurological, musculoskeletal, special sense organs, respiratory (including speech organs), cardiovascular, reproductive, digestive, genitourinary, immune, circulatory, hemic, lymphatic, skin, and endocrine. A mental impairment is any mental or psychological disorder, such as intellectual disability (formerly termed mental retardation), organic brain syndrome, emotional or mental illness, and specific learning disabilities.

What Is a Substantial Limit on a Major Life Activity?

In order to have a disability under the ADA, a physical or mental impairment (or a record of it or a perception of it) must "substantially limit" one or more "major life activities" [3].

Major life activities consist of functions such as caring for yourself (including bathing, dressing, shaving, preparing a meal, and going to the restroom), performing manual tasks, eating, sleeping, standing, walking, lifting, reaching, bending seeing, hearing, speaking, breathing, learning, reading, concentrating, thinking, communicating, interacting with others, and working [5].

Major life activities do not include the following: caring for others, driving, ability to have a relationship, and grocery shopping. An impairment does not need to entirely prevent or severely or significantly restrict a major life activity to be considered "substantially limiting." The question of whether an impairment is substantially limiting requires an individualized assessment, but does not require an extensive analysis. In other words, the determination whether an impairment substantially limits a major life activity does not usually require scientific, medical, or statistical evidence. However, this evidence may be used if appropriate.

What About Medications or Other Mitigating Measures?

The good or positive effects of use of any corrective or mitigating measures must be ignored in determining if a person meets the definition of disability. Instead, the determination of disability must focus on whether the individual would be substantially limited in performing a major life activity without the mitigating measure [5].

Examples of mitigating measures include: medication, medical equipment and devices, prosthetic limbs, low vision devices that magnify an image, hearing aids, mobility devices, oxygen therapy equipment, use of assistive technology, reasonable accommodations, psychotherapy, behavioral therapy, and physical therapy.

Furthermore, some mitigating measures, such as medications, have negative side effects. If an individual experiences negative effects, this may be included in the disability determination [5].

Could Narcolepsy Be Considered a Disability by These Standards?

Before 2009, people with narcolepsy and other sleep disorders faced difficulties securing reasonable accommodations from their employers (flexible scheduling, nap breaks, etc.) because they could not prove their condition was a "disability" under the ADA.

Courts were split as to whether or not "sleep" constituted a major life activity (like hearing, seeing, eating, breathing, etc.). As a result, many cases involving sleep disorders like narcolepsy were dismissed by the courts. In examining these cases, they often included tepid letters from the employee's doctor. These letters frequently emphasized the patient's successes under medication rather than their ongoing limitations.

Fortunately, the Amendments Act clearly sets the precedent that sleep is a "major life function." Also, the issue of disability is now evaluated in the patient's unmedicated state [5].

With these changes, sleep disorder disability cases may more easily overcome the burden of proof to reach a more in-depth discussion of the individual's circumstances. Within this new legal framework, it is now more favorable to persons with narcolepsy and other sleep disorders to receive reasonable accommodations due to a disability.

What Is a Reasonable Accommodation?

A reasonable accommodation is a change or adjustment to a job or a workplace that allows a person with a disability to apply for a job or to perform the essential duties of a job. The "essential duties of a job" include more than one function—the duties and skills that are necessary to perform the job.

Examples of reasonable accommodations may include changing the employee's work schedule; assigning nonessential functions of the job to other employees; providing the employee with special equipment, devices, or software; restructuring the employee's job; providing the employee with additional training; and providing the employee with paid or unpaid leave needed due to the disability.

What Would Be an Unreasonable Accommodation?

Unreasonable accommodations would be those that would not help an employee perform the essential functions of the job or would pose a significant financial hardship on the employer.

For example, a school bus driver could not reasonably expect an employer to provide an accommodation that he only be required to work after 6 p.m. The nature of the job is such that it can only be performed during hours when transportation to and from schools is needed, i.e., in the morning and early afternoon. The ability to work at these times is therefore an essential function of the job.

In addition, it would be unreasonable for a paralegal for a small law firm to expect a reasonable accommodation that her employer hire a full time assistant to do those things that she cannot do because of her disability. This would pose an undue financial hardship on the employer.

When Should an Employee Disclose to an Employer?

There is no hard and fast rule about when to disclose one's narcolepsy to an employer. Potential employers cannot make disability inquiries until after a conditional offer is made. Drug tests and medical exams should only be conducted after the offer of employment is made as well. There are rules about confidentiality.

It's a good idea to discuss narcolepsy with an employer before problems arise. For example, many employers may be able to accommodate an employee taking afternoon nap or arranging a more flexible schedule arrangement. However, if narcolepsy affects a person's performance before disclosure, an employer may misinterpret symptoms as laziness, inattentiveness, or poor performance. Individuals may be reprimanded for actions related to narcolepsy, like falling asleep on the job, while the employer is unaware of the disability. Misperceptions and poor performance will hurt the trust and mutual respect between the employer and employee.

When requesting reasonable accommodations due to disability, a patient will have to disclose what his or her disability is exactly and patients should be prepared to provide specific examples of the reasonable accommodations that he or she would like (see Table 29.2). Also, a physician's letter providing basic narcolepsy information and detailing the patient's symptoms and treatment will be helpful for securing accommodations.

Table 29.2 Accommodation ideas in the workplace

This list is compiled directly from people with narcolepsy in the workplace. Work situations and job requirements vary greatly. This list offers a starting point to brainstorm ideas for work accommodations with patients
Taking nap breaks – A nap during lunch – Additional breaks to take medication – An early lunch (10:30 a.m.) to take a nap – A nap daily for 20–30 min – A 15-min nap every 3–4 h during 9-h day
Providing space to nap – Providing a nap area – Creating a "nap room" for naps – Providing the new mothers' nursing room as a nap space with sofa and locked door for naps – Allowing naps in the general quiet room with couches – Provided a key to various first aid rooms to use as crash room for sleep attacks – Allowing naps in the workplace's clinic if needed
Flexible scheduling – Flexibility in arrival time – Not scheduling clients back to back – Flexible working hours to avoid peak traffic hours – Allowed to be up to 5 min late for shift regularly, given difficulty waking up – Flexible working arrangements
Working from home – Working from home office once or twice a week – Working from home with broadband Internet to still be involved in web meetings – Option of telecommuting from home on days when brain fog is strong – Provided a laptop and allowed to work from home
Working environment – Not working in "high noise level" area of the workplace since it triggers EDS and cataplexy – Providing a more comfortable desk and moved to an area that has a window that gets plenty of natural light – Permission to stand or take breaks during meetings – When traveling longer than 2 h for a business trip, permission to stay overnight at a hotel – Bringing a service dog into the workplace
Consistent scheduling – Moved to the morning shift to allow for routine sleep schedule – Not required to do "clopening" shifts—closing shift one night and then opening the next morning – Not put on the 8 a.m. shift after working late the night before – Changed shifts to afternoons because unable to wake up consistently with alarm in the morning
Addressing cognitive issues – Providing dictation software or "smart pen" to record meetings – Reviewing and writing down tasks with supervisor in case of brain fog

Patients may feel anxious about discussing narcolepsy with employers. Yet, many employers are obligated to make reasonable accommodations under the ADA to help employees meet their essential job duties. In some settings, an informal disclosure may be appropriate. After establishing good rapport with an employer, an honest discussion about narcolepsy may be a good idea for some patients.

What Is the Proper Role for a Medical Professional in Helping Patients Secure Workplace Accommodations?

A doctor's report is an essential part of the formal disclosure process for workplace accommodations. In disclosing a disability, the employer will likely ask for documentation from a doctor. A doctor's report may confirm diagnosis, discuss

the symptoms of narcolepsy generally, and suggest ways in which the individual is affected and suggest accommodations.

Tips for Success

1. Foster teamwork with coworkers.
2. Improve communications with management.
3. Get advice when needed.

Additional Resources

Social Security Administration
State Disability Law Centers
Human resources department

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Medicolegal Aspects of Disability in Narcolepsy

30

Francesca Ingravallo and Giuseppe Plazzi

Introduction

Narcolepsy is a severe, chronic, disabling disease affecting almost all personal and social activities. Pioneer studies [1–4] clearly disclosed the psychosocial impact of narcolepsy; the disorder affects all aspects of everyday life: family, school, work, interpersonal relationships, and social activities. Broughton et al. [2, 5] suggested that this is "an integral part of the disease or of the human reactions to it."

More recent SF-36 questionnaire-based studies describing the health-related quality of life in people with narcolepsy corroborate this hypothesis: a comparable quality of life impairment that can be improved, but not restored, by medical treatments, was found in the USA [6], the UK [7, 8], Italy [9, 10], Norway [11], Germany [12], New Zealand [13], Portugal [14], and Japan [15]. This quality of life impairment is extensive and similar to other chronic neurological diseases like Parkinson's disease and multiple sclerosis [12].

Sleep disorder specialists deal with the disabling burden of narcolepsy since their first approach to the patient. Diagnosis of narcolepsy is often established after many years of unrecognized evolution, misdiagnosis, and inappropriate treatments. Although the delay in diagnosis seems to have been reduced in more recent decades [16], even a short diagnostic gap may represent an excessive delay in diagnosis because of the negative consequences for untreated patient [17]. The disease continues to be a burden throughout the patient's life as pharmacological and behavioral treatments only seldom control the variety of symptoms.

Since people with narcolepsy experience a wide range of occupational problems, both clinicians and researchers are interested in how to help their patients to hold down a job, return to work, and, if necessary, receive benefits for work disability.

This chapter considers the medicolegal aspects of work disability in narcolepsy, summarizing essential issues clinicians and researchers have to address in providing medical information to assist disability determination in people with narcolepsy.

Disability and Work Disability

Research over the past several decades has clearly shown that "disability" is defined and conceptualized differently from one society to the next [18].

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Different conceptual models of disability have influenced the definition of disability and hence the identification of persons with disability. The medical model views disability as a characteristic or attribute of the person, whereas the social model views disability as a socially created problem.

The 1980 World Health Organization (WHO) International Classification of Impairments, Disabilities, and Handicaps [19] made distinctions for *impairment*, as loss or abnormality of psychological, physiological, or anatomical structure or function; *disability*, as any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal; and*handicap* as a disadvantage for a given individual, resulting from an impairment or a disability, that prevents the fulfillment of a role that is considered normal (depending on age, sex, and social and cultural factors) for that individual.

In 2001, WHO published a major revision of its disability classification: the International Classification of Functioning, Disability and Health (ICF) [20]. Based on a biopsychosocial model, the ICF uses disability as an umbrella term for impairments, activity limitations, and participation restrictions. Impairments are "problems in body function or structure such as significant deviation or loss"; activity limitations are "difficulties an individual may have in executing activities"; and participation restrictions are "problems an individual may experience in involvement in life situations" [20]. The ICF construes disability and functioning as outcomes of interactions between health conditions (diseases, disorders, and injuries) and contextual factors; among contextual factors are external environmental factors (e.g., social attitudes, architectural characteristics, legal and social structures, as well as climate, terrain, and so forth) and internal personal factors, which include gender, age, coping styles, social background, education, profession, past and current experience, overall behavior pattern, and character and other factors that influence how disability is experienced by the individual [21].

A first Comprehensive ICF Core Set for Sleep Disorders (120 categories) and a Brief ICF Core Set for Sleep Disorders (15 categories) have been developed through a formal consensus process on behalf of WHO and WASM (World Association of Sleep Medicine) in 2009 [22]. These Core Sets should be considered a first step toward the development of a "worldwide, acceptable and standardized tool for the assessment of functional impairment in patients with sleep disorders" [23]. Even if the selected Core Set categories need further validation, and a Core Set or a subset for narcolepsy is still lacking, some interesting insights emerged from the preparatory studies to the consensus process. Gradinger et al. [24, 25], exploring the patient perspective, disclosed that family environment, colleagues and supervisors, and healthcare professionals can be perceived as a facilitator or a barrier in the life of persons with sleep disorders. Regarding the group of patients with narcolepsy, they seemed to be overtly challenged to develop distinct strategies of coping with a disorder that is not directly visible in the interaction with the environment, but more evident through performance-related problems than other sleep disorders [24]. Typological behaviors in social encounter and in disclosing or hiding the disorder were also recognizable [24].

The ICF framework was adopted by the Sixth Edition of the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment, in which impairment is defined as "a significant deviation, loss, or loss of use of any body structure or body function in an individual with health condition, disorder, or disease" [26].

However, the medical impairment is only one of the several determinants of work disability, whose definition and medicolegal determination vary according to each social security program. The latter, in turn, may vary substantially in the type of economic (invalidity pension, lump-sum benefit, occupational benefits, etc.) and other (medical care, occupational or social rehabilitation, home help, etc.) disability benefits and in conditions governing eligibility. In addition, also the complementary or supplementary schemes of protections against work disability have discrete rules.

For our purposes, we can define work disability as the "inability to meet the demands of

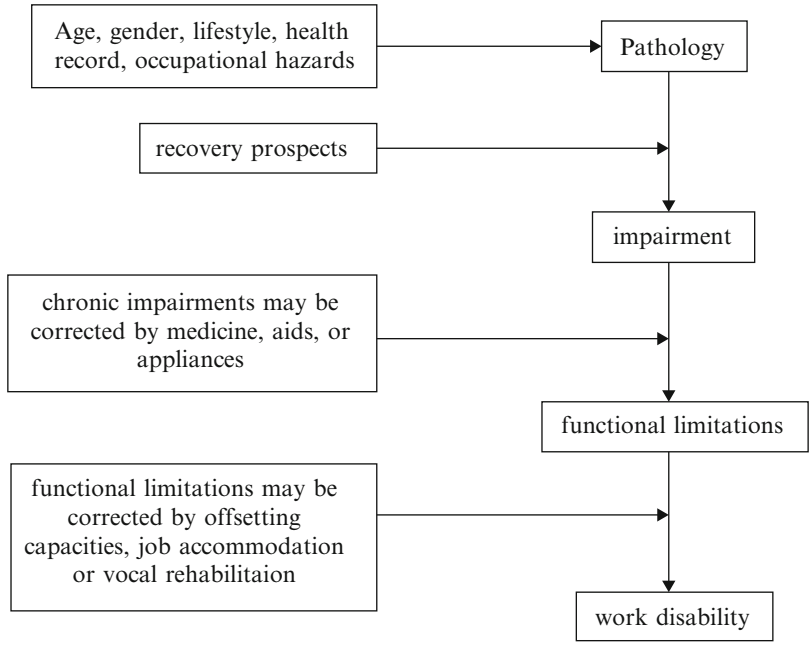

Fig. 30.1 Etiology of work disability [de Jong, P.R. (2003)]. Disability and disability insurance (In: Prinz, C. (Ed.) European disability pension policies (pp. 77–106). Aldershot, United Kingdom: Ashgate [27], with permission of the author)

gainful activity, due to functional limitations, caused by impairment" [27]. Figure 30.1 summarizes the causal chain leading from pathology to disability, taking a medical vocational point of view that coincides with the definition of disability under a disability insurance scheme [27]. According to this scheme, the role of the sleep expert in the complex medicolegal process of work disability determination is to describe both the impairment due to narcolepsy and the patient's functional limitations remaining after therapy and rehabilitation efforts.

Work Limitations in Narcolepsy

The disorder-related work problems reported by people with narcolepsy included inability to use their qualifications, low productivity, reduced job performance, loss of promotion, decreased earnings, and fear of losing their job [2, 7, 8, 28, 29]. Several studies that collected data on patients' professional career disclosed that the disease burdens the patients' working life across the countries. The rate of patients who reported to have lost or left a job because of the disease ranged from 37 [7] to 52 % [8] in the UK, while Dodel et al. [12] reported that 43 % of the 75 German patients surveyed cited narcolepsy as the main reason for their unemployment. Ozaki et al. [15] found that 36 and 25 % of Japanese patients with Type 1 ($n=83$) and Type 2 ($n=48$) narcolepsy were forced to relocate or leave their job due to the presence of symptoms. Consistently, in a cohort of 100 Italian patients with Type 1 narcolepsy, we found that among the 84 who were currently or had been previously working, 31 % had changed their job due to the disease (58 % of these patients changed job type, 31 % lost or left their jobs without finding another one, and 11 % changed their job schedule) [30]. Finally, Frausher et al. [31] disclosed that 50 % of 92 Austrian patients with Type 1 ($n=82$) and Type 2 ($n=10$) narcolepsy had difficulties at work and 21 (46 %) of these patients selected or switched their job in order to cope with the disease.

On the other hand, inconsistencies across different studies exist regarding patients' rate of unemployment or early retirement.

Indeed, higher rates of unemployment were reported in Germany (59 %) [12] than in the USA (16 %) [32], Japan (0 %) [15], Italy (8 %) [30], and Austria (13 %) [31]. Similarly, high indirect costs due to early retirement were reported in Germany [33], but not in Denmark [34, 35], and other studies did not disclose a remarkable rate of early retirement related to the disease [15, 30]. The above contrasting findings may stem from national differences in both work habits and social security systems across the countries or may reflect variations in study designs, sampling population, and measures used [30].

Two large database studies recently provided important objective data on the occupational burden related to narcolepsy.

Jennum et al. [35], using records from the Danish National Patient Registry, identified 816 patients with narcolepsy and their partners and compared them with 3254 controls matched for age, gender, geographic area, and civil status. They found that, in comparison to controls, patients had lower employment rates, lower income if employed, and received welfare payments significantly more often. Interestingly, both patients' employment and income were affected years before the diagnosis and worsened further once the diagnosis was established. The authors outlined that this was the same pattern described in other chronic and progressive disorders, such as multiple sclerosis, Parkinsonism, and sleep-disordered breathing [35].

The US BOND study [36] performed a subanalysis of the productivity outcomes between 600 subjects with narcolepsy and 2279 matched controls for short-term disability days, accidents, and disability costs and between 728 patients and 2648 controls for workers' compensation. The study revealed that narcolepsy patients had a higher degree of absence due to short-term disability and were more than twice as likely to experience short-term disability accidents and disability days compared with controls, with higher economic costs. On the contrary, there were no significant differences between the two groups in workers' compensation claims.

Finally, some less recent studies from the USA reported that between 8.3 [4] and 15 % [28] of people with narcolepsy had a work disability status, and 62 % of patients older than 47 years from one sleep center had applied for Social Security disability benefits [37].

The only study that explored associations between age at diagnosis and patients' job career [30] found that a diagnosis at a young age (before the age of 30) improves patients' occupational prognosis, protecting them from forced work modifications and early dropout, suggesting that an early diagnosis allows patients to look for a job that better matches their individual needs. These findings stress the need for better public and professional education to diagnose and treat people with narcolepsy at an early age to prevent some of the negative consequences of narcolepsy [38]. Furthermore, since both indirect and direct costs due to narcolepsy were affected several years before the diagnosis, early disease identification could be effective also in reducing the consequences of the disease, especially among younger patients [35].

People with narcolepsy attributed their job difficulties mainly to excessive daytime sleepiness (EDS), sleep attacks, and inability to concentrate [1, 4, 39], and most patients reported falling asleep at work [3, 8].

Patients' reports were confirmed by several studies. Sleep attacks and irresistible sleepiness appeared to be associated with indirect costs due to narcolepsy in two studies [30, 33], and irresistible sleepiness was directly associated with loss of working days in one study [30]. On the other hand, in both studies, cataplexy was not associated with costs or absenteeism. Furthermore, the BOND study [36] did not reveal differences in short-term disability days, accidents, and associated costs between patients with cataplexy and those without cataplexy. More generally, presence or absence of cataplexy was not found to alter the pattern of economic burden due to the disease [36].

However, Overeem et al. [40] recently provided a detailed description of cataplexy in a cohort of 109 patients with hypocretin deficiency, disclosing that while 65 % of patients reported from none to moderate limitation in

education or employment due to cataplexy, 35 % of them had strong or very strong limitation due to cataplexy. This is in line with the rate of patients with uncontrolled cataplexy despite medications found in other studies [30]. Furthermore, in the study by Overeem et al. [40], almost half of patients have sustained some form of injury due to cataplexy during life. We speculate that in this group of patients, cataplexy may be a very disabling symptom with regard to work. Consistently, cataplexy severity correlated with the disability rating of narcolepsy performed by Italian Medical Commissions deputed to assess work disability [41].

While the detrimental effect of narcolepsy on patients' working lives could be severe and long-lasting, it should be emphasized that a substantial part of patients do not report problems at work. This is because narcolepsy causes different levels of impairment that, according to the extent of patients' adaptation as well as to several nonmedical determinants, leads to different degrees of work disability.

Impairment Variability

The impact of narcolepsy may vary widely with respect to work disability: not all narcoleptic patients have a work disability, and those that do may only have a partial disability. Consistently, people with narcolepsy showed a high interindividual difference in driving simulator performance [42, 43], and Vignatelli et al. [9] found a variance in health-related quality of life, noting a subgroup of patients without specific drug treatment and a satisfactory health-related quality of life among their cohort of 108 patients.

As mentioned earlier, this variability is mainly attributable to the different impairment due to narcolepsy according to the broad clinical spectrum of both narcolepsy Type 1 and Type 2 (i.e., not all patients showed all symptoms) and to the major interpersonal (and sometimes intrapersonal) variations of symptom severity.

For instance, recently Frausher et al. [31] have well described the broad clinical spectrum of narcolepsy in their cohort of patients: 36/100 patients had all four cardinal symptoms of narcolepsy, 28/100 patients had three cardinal symptoms, 29/100 had two cardinal symptoms, and 7 had only EDS. Furthermore, symptom severity also varied.

Indeed, EDS in narcolepsy is generally characterized by brief repeated episodes of daytime naps or lapses into sleep, often associated with dream mentation. However, EDS may manifest itself as a persistent feeling of being sleepy, or as an urgent need to sleep, only in boring or monotonous conditions or even in very active situations (such as walking or talking), and daytime naps may recur only at characteristic times (midmorning or after lunch) or every 2–3 h or do not occur at all during work time.

Cataplexy also shows a similar broad spectrum of severity, pattern, and frequency: the loss of muscle tone ranges from a mild sensation of weakness to a complete loss of muscular tone and may be limited to some facial muscles or generalized. Cataplexy may occur rarely in a month or many times during a day, and even the inducing stimuli vary widely from patient to patient. As mentioned earlier, Overeem et al. [40] recently provided a detailed description of the large phenotypical diversity of cataplexy, disclosing also that cataplexy affects variably different aspects of daily life. Consistently, in the cohort by Frausher et al. [31], cataplexy severity ranged from patients with daily severe cataplectic attacks, which have led to serious injuries in the past, to patients with very mild attacks without any relevant subjective complaint.

Associated symptoms, such as sleep paralysis, hypnagogic hallucinations, nocturnal sleep disruption, and automatic behaviors also vary in occurrence and severity. In addition, the efficacy and acceptance of medical and behavioral therapy vary and will also have an impact on narcolepsy-associated symptoms.

The variety of narcolepsy impairment is also due to the different extent to which patients adjust to this disorder, which mainly depends on coping strategies the person employs to manage and counterbalance the negative effects of the disease.

Thus, the impairment assessment must address both disease severity, as modified by therapies, and the efficacy of a patient's coping strategies in managing narcolepsy symptoms.

Furthermore, it should be considered that narcolepsy restricts the range of adequate occupations. According to Guilleminault and Abad [44], patients should avoid jobs that involve shift work, on-call schedules, professional driving, or any job that is monotonous and requires continued attention for long hours without breaks. Consistently, Alaia [28] outlined that several people reporting the highest levels of job satisfaction indicated that they had found jobs in which they were physically active, could take short naps, or arrange their schedules to coincide with their more alert periods of the day. In this regard, potential approaches that may ensure job opportunities and continued employment have been proposed (see Chap. 4).

The Lack of a Severity Scale

The assessment of impairment due to narcolepsy is further hampered by the lack of a worldwide-accepted severity scale.

Indeed, the impairment rating of narcolepsy, and more generally of sleep disorders, has been paid relatively little attention so far. An impairment classification of "Sleep and arousal disorders" is present in the AMA Guides to the evaluation of permanent impairment [26], but this classification is only a generic reference, because it is not specific for narcolepsy. Criteria for rating the degree of disability in narcolepsy have been suggested [45–48], but they still need to be validated.

Furthermore, the severity criteria provided by the 2001 International Classification of Sleep Disorders (ICSD-R) [49], including those for narcolepsy, have been discarded from the second edition (ICSD-2) because "such criteria could not uniformly be applied in different areas of the world" [50]. Indeed, Ohayon et al. [51] have emphasized that ICSD-R criteria for "mild severity" appeared like a catchall category that cannot be used in epidemiology because it would overestimate the prevalence of the disease.

Above all, even if some data suggest that the patient self-assessment of symptoms is reliable with regard to disability assessment [41], there is the greater problem of a lack of validated and consistent tools to quantify narcolepsy symptoms, especially EDS. Indeed, simulation and dissimulation may occur in disability determination so that the procedure must be based on methods which are as objective as possible.

An overview of sleepiness measures is beyond the scope of this chapter, but it should be emphasized that at present, no validated tools or direct biologic measures are appropriate for an objective measure of EDS severity in narcolepsy. The Multiple Sleep Latency Test is indicated only to confirm the diagnosis [52], while the Maintenance of Wakefulness Test could serve as an adjunct to clinical judgment in determining the improvement following treatments [53], but more data are needed to establish its value as a measure of EDS severity.

Finally, there is some evidence that EDS is a complex phenomenon in relation to work disability and no single scale or technique is currently appropriate to assess the disabling burden of sleepiness in narcolepsy and other hypersomnias [41].

The Contribution of Sleep Experts to Work Disability Determination

Lacking objective tools to rate the impairment due to narcolepsy, the clinician's contribution to work disability determination is pivotal.

Ideally, clinical assessment should include: (1) diagnosis, (2) information on the clinical severity of narcolepsy, and (3) a description of the patient's functional limitations.

EDS seems to be the main symptom associated with work disability in narcolepsy. Ideally, it should be therefore carefully described specifying:

- The patient's sleep propensity in active and passive situations
- The number of daytime naps the patient needs and the personal daytime sleep schedule
- Whether sleep attacks occur and if they are sudden and without warning
- Quality of sleep during the night
- The occurrence of automatic behaviors and their frequency

Additional information could be given enclosing a copy of questionnaires (not just the final score) filled in by the patient and the Maintenance of Wakeful Test results, if available.

The pattern, frequency, and severity (how protracted the attacks are and whether the patient falls down) of cataplexy should be described. The most inducing stimuli also have to be reported, along with strategies adopted by the patient to avoid or control cataplexy and their efficacy.

Hypnagogic hallucinations, sleep paralysis, and REM behavior disorder should be reported, specifying their influence on the patient's life, especially when they cause psychological problems and risk of accidents.

The clinician should also detail medication efficacy and side effects, behavioral recommendations (i.e., naps, sleep hygiene), and significant comorbidities.

Then, the functional limitations in a patient's activities should be described, including those related to drug intake schedule (e.g., sodium oxybate twice per night), as well as driving issues. The major areas of everyday activities to be considered are self-care, home care, family care, mobility (moving away from home alone on foot or by car), and physical and social activities, specifying whether the person has difficulties in living independently.

Finally, a description of a patient's work problems (or difficulties in finding and holding down a job) and of the risk of accidents and near accidents is also very important.

Conclusions

It is notoriously difficult, in practice, to determine what constitutes disability and work incapacity and to distinguish those who are able to work from those who are not [54]. Work disability determination remains a difficult process, irrespective of how disability is defined and how national procedures are implemented, and inclusion and exclusion errors are common [55]: a 35 % average of unemployed disabled persons is excluded from disability benefits, whereas 33 % of disability beneficiaries report being without disabilities [27].

Empirical data showed that from one fourth to half of people with narcolepsy are forced to modify or leave a job due to the disease, which may also cause higher absenteeism due to disability and accidents, as well as being more subjected to unemployment and early retirement with high social and economic costs. EDS seems to be the main symptom associated with work disability, but cataplexy may be even more disabling in cases with many cataplectic attacks.

Work disability assessment in narcolepsy is complicated by the lack of both objective tools to quantify EDS and standardized criteria to rate the medical impairment due to the disease. In addition, various symptoms are in part paroxysmal and modulated by circumstances and emotions, so that most people suffering from narcolepsy could experience a kind of "intermittent disability," often with an individual time schedule of daytime sleep [41].

Two further aspects should be considered in assessing work disability in narcolepsy [41]. Firstly, narcolepsy characteristically not only limits patients' working capacity but also restricts their range of occupations to jobs which do not entail periods of physical inactivity or boredom or risk of sleep-related accidents. Secondly, people with narcolepsy are probably unfit for current "standard" work, consisting of an office job that is not appropriate for people with EDS, and they are still not aided by the new technologies that may play a major role in integrating other disabled workers.

Since the spectrum of narcolepsy symptoms is broad in terms of pattern, frequency, and severity, the disability assessment should be always highly tailored to the individual patient given the variability in patients' adjustment to the disease.

Further efforts are needed to devise and validate tools for the assessment of narcolepsy severity and disability.

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The Affordable Care Act and the Future of Sleep Medicine

31

Dennis Hwang and Burton N. Melius

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act (PPACA) or commonly called the Affordable Care Act (ACA). This was a historic event. While there were widely differing opinions regarding the wisdom of this legislature, no one doubted the impact this law would have on virtually all who live in the United States, whether directly or indirectly and whether a health-care provider or a patient. But the ACA was not conceived as an idea that "came from nowhere." Rather it can be described as the product of a costly and suboptimally effective health-care system that desperately needed to evolve to emphasize outcomes and cost-effective care. While these elements were already being implemented into our health-care system and naturally coalesced as foundational components of the ACA, the ACA is also directly impacting the future structure of health care in the United States. Sleep medicine likewise has undergone several years of significant stress to our standard model of care which has historically emphasized testing services and diagnosis. For sleep medicine to thrive, it is important for us to understand the future health-care model and embrace the elements that drove the formation of the ACA. In this chapter, we will discuss the current state of our health-care system, the ACA, and the future of health care and how this may shape the future of sleep medicine.

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Overview of US Health Care

The US health-care system is unique when comparing it to health-care systems in other developed countries around the world [1]. The United States tends to lean toward private, employer-provided health care, while other countries in the developed world have national insurance programs which are typically run by the government and financed through general taxes and provide coverage to the majority of their citizens [1]. In the United States, the majority of people (64.2 %) are covered by private health insurance (see Fig. 31.1), of which most (53.9 %) is employer provided and the remaining (11 %) is direct purchase. An additional 34.3 % are covered by government health insurance (17.3 % on Medicaid and 15.6 % on Medicare). The final 13.4 % do not have health insurance coverage, which equates to 43 million people without coverage.

The total percentage is greater than 100 % due to people changing coverage midyear, having multiple coverage through a spouse or second job, or not having coverage for the full year [2].

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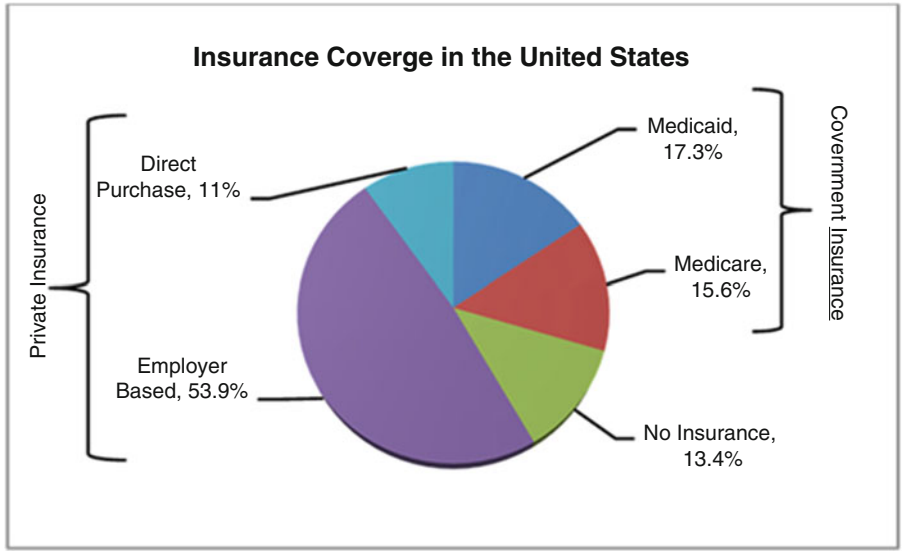

Fig. 31.1 Insurance coverage in the United States

History of the US Health-Care System

So how did the United States end up with this type of system? Prior to the 1800s, medicine was considered a "family affair" also called "domestic medicine." It was typically practiced at home and based on the ancient Greek principle of the "four humors." These were blood, phlegm, black, and yellow bile, and it was thought that the balance between the four was the key to health. To balance these, hot, cold, dry, and wet preparations were used along with a variety of plants and herbs [3]. During this period, those who became sick or injured and had the ability to pay stayed at home for treatment. It was only those who couldn't pay that went to the hospital, and often, the hospital was just a separate area of the jail or poorhouse [4].

It wasn't until the late 1700s that the first medical college opened, the first medical society was incorporated to license physicians, and the first few communities opened community owned or voluntary hospitals. These medical schools were often opened by physicians who wanted to improve the quality of American medicine. With this training, physicians would become more authoritative and begin to open small practices where they would charge a fee for their services [3].

The 1800s began to see more change in US health care, particularly in the areas of medical training, the creation of dispensaries, which gave medicine to the poor and offered free physician services, the development of departments of public health by many city governments, and the building of hospitals. With the development of these hospitals in the mid-1800s, physicians who had gained authority and power began to stop traveling and treat their patients in one location. In 1846, the American Medical Association (AMA) was established, but it wouldn't be until the early part of the 1900s when they would become stronger and begin to hold more influence (see Fig. 31.2). Medical sciences achieved great victories in the late 1800s by practically eliminating the great diseases—tuberculosis, yellow fever, cholera, and others [3]. It was during this period that many workers began to have access to company doctors in "industrial clinics" or union-operated infirmaries, at least those who worked in the more dangerous jobs like mining, steel, railroads, and lumber. As unions were becoming more powerful during this period, they began to develop their own sickness protections as well. The most likely to see this type of coverage were tradesmen and factory workers, although fraternal organizations and "mutual

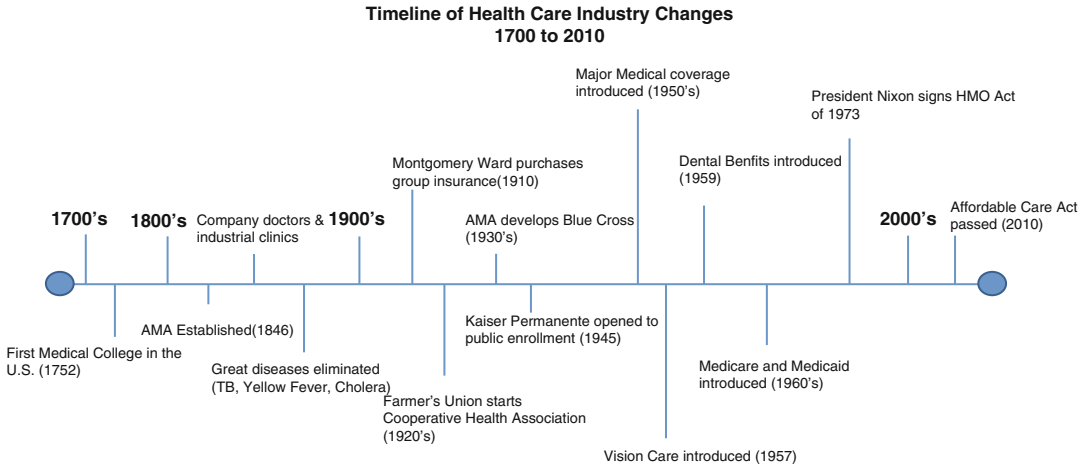

Fig. 31.2 Timeline of health-care industry changes (1700–2010)

protection societies" also began to offer limited coverage [5]. At this time, many European nations were providing national health insurance, although this quickly became associated with socialism and therefore was unpopular, paving the way for private health insurance to cover the cost of medical care [3].

The first modern group insurance can be traced to retailer Montgomery Ward, who had a health insurance policy through London Guarantee and Accident Co. in 1910. It paid an annual benefit to sick or injured employees and functioned as a plan that focused on covering disability. However, there was still no cohesive health-care system, and most care was still taking place at home, including some primitive surgeries [5].

It was the Great Depression which caused a dramatic change in the way health care was paid for and paved the way for the first medical insurance company. As patients stayed away from hospitals and hospital receipts decreased, the AMA developed the Blue Cross concept to assure stable revenues. Blue Cross plans guaranteed payment of hospital costs but were paid directly to patients. Even at this time, the AMA feared third-party payers might eventually play a part in determining medical treatment and would require medical decisions to be based on their interests rather than the patient's interest. Under increasing pressure from politicians and state medical societies, they approved plans called Blue Shield. These plans allowed their members to pay both the costs of hospitalization and treatment by physicians. This type of payment system was called "fee for service [3, 4]. Several years later, during World War II, Henry J Kaiser began offering a medical plan that was based on the premise of prepayment that would pave the way for health maintenance organizations (HMOs) [3]. Voluntary premiums were deducted from paychecks, and these premiums were sent to an insurer, who then sent the money to an on-site physician who treated the injured. Everyone from the insurer to the doctor was paid in advance, and the program began to be replicated at construction sites on the West Coast [5].

The post-World War II era saw advancements in medical science and care, expansions in the workforce, and rising health-care costs. This was also a time of widening roles for nurses and increasing specialization among physicians. Additionally, the roles of non-physicians became more professionalized, including respiratory therapists, physical therapists, and x-ray technicians which contributed to escalating the cost of health care. Around this time, government programs were established, including the National Institutes for Health (NIH) and the Centers for Disease Control and Prevention (CDC) and then Medicare (medical care for the aged) and Medicaid (medical care for the poor) during the 1960s. At this time, most physicians were still

paid through the fee-for-service model, although the AMA and other organizations were fighting off the attempts to create a national or universal coverage system [3].

During World War II, the Congress passed the 1942 Stabilization Act, which was meant to combat inflation, but in effect, limited wage increases during wartime. The overall effect was that employers who needed to recruit workers began to offer more generous health benefits, during a time when the majority of able workers were overseas. An additional effect was that any premiums deducted by employers didn't count as income, so there were no income or payroll taxes. This resulted in employers being incentivized to make health insurance arrangements, and thus, insurers began to add new types of coverage such as major medical (1950s), vision care (1957), and dental (1959) benefits. The postwar boom in employees came hand in hand with a rise in employer-based health insurance. This soon became the cornerstone of our system, but this association between health care and employment left out those who were unable to work or worked in low-paying jobs and those who were beyond working age [5].

Development of Health Maintenance Organizations

While there were various forays into the world of HMOs, it wasn't until the late 1950s that there began to be some advocacy for this model. In the late 1920s in Oklahoma, the Farmers Union started the Cooperative Health Association using a pooled financing structure. Around the same time, two physicians in Los Angeles started a prepaid group health delivery plan with comprehensive services. Dr. Sidney Garfield began a fee-for-service hospital in the Mojave Desert in 1933 to provide care for the Metropolitan Water District of Southern California whose workers were building an aqueduct to bring water from the Colorado River to Los Angeles. Because insurance companies were slow to pay and nonpayment was also an issue, he made an arrangement with Industrial Indemnity Exchange, the largest insurer on the project, to prepay for hospital services at a rate of a nickel a day per worker. The prepaid plan was an immediate success and would eventually lead to Dr. Garfield's partnership with Henry Kaiser to provide care at the Kaiser Shipyards in 1942 [6].

Just prior to Henry Kaiser and Sidney Garfield's venture into prepaid health care, the AMA had adopted a strong position against prepaid group practices, instead favoring indemnity insurance which protected the policy holder from expenses by reimbursement. The AMA took this stance even though there were only a few prepaid group practices in existence at this time, and a recommendation had come out in 1932 by the Committee on the Cost of Medical Care that the expansion of group practice was an "efficient health care delivery system" [7].

In December 1973, President Richard Nixon signed the Health Maintenance Organization Act of 1973, which had been sponsored by Sen. Edward Kennedy. The HMO Act provided grants and loans to start or expand an HMO, removed certain restrictions, and required employers with 25 or more employees to offer a federally qualified HMO plan if they offered traditional health insurance [8, 9]. Doctors seemed to miss the growth of HMOs which had begun to dominate how health care was organized and reimbursement for physicians by the mid-1980s. HMOs were revolutionizing how health care was organized and provoked much controversy with patients and providers as well. Fee for service was replaced with capitation (a system that pays doctors a set fee to take care of all their patient's needs) as physicians found themselves working for corporations who focused on preventive health care, restricted services, and attempts to reduce health-care costs to allow for profits from prepaid health care [3].

In parallel to the growth of HMOs, there were developments in the indemnity insurance arena. Case management was adopted to coordinate services for patients that required expensive medical care, patients were encouraged to obtain second opinions before undergoing elective surgeries, and work site wellness programs became more prevalent, leading to programs like screenings for hypertension or diabetes, exercise promotion, stress reduction, classes, and mental health counseling [7].

Challenges of the Fee-for-Service Model

By the 1970s, there were sharp increases in medical costs which led to various types of legislation aimed at slowing health-care inflation. From 1940 to 1970, health-care inflation had ranged from 1 to 8.0 %, with an average hovering around 4 %. By 1975, it had jumped to 12 % (see reference [10]—Parameters to be entered: From "1940"; To "1975"; Check "include annual averages"). Despite various measures to contain health-care costs, they continued to increase. When President Jimmy Carter took office in 1977, he viewed health-care cost containment as a first step and proposed legislation to restrain health-care inflation. Even with the perceived mandate to implement a national health insurance program, Carter's legislation became bogged down in the Congress, and the Congress had become entangled in a debate over competition versus regulation, which would continue until President Reagan was elected in 1980.

Reagan's belief in deregulation and free markets led him to attempt to shift responsibility away from the federal government and onto the markets. Washington eliminated the federal aid that helped to support the nonprofit operations of nearly all the HMOs. In response, many converted to for-profit entities. However, market-based care wasn't able to provide the results they were looking for. By 1982, health-care inflation was back at its previous high of 12 % [11].

There are several different types of HMOs that should be differentiated. The first is the typical HMO, where the HMO serves as the middleman between the doctor and the patient. As the middleman, the HMO adds an additional layer and subsequent burden to costs as they need to turn a profit to stay in business. This is in comparison with a fully integrated HMO, like Kaiser Permanente, who provides the health insurance and the clinics and hospitals that provide services and has an exclusive relationship with a Permanente Medical Group (the Permanente Medical Group in Northern California, the Southern California Permanente Medical Group in Southern California, etc.).

In the early 1990s, health-care reform was once again at center stage. The Task Force on National Health Care Reform led by Hillary Rodham-Clinton was established, and a comprehensive plan to provide universal health care for all Americans was introduced. The Health Security Act failed to gather enough support, and health-care costs continued to rise particularly during the early 2000s when the economy went into recession. Once again, employers looked for ways to reduce rising premiums and began to look at benefit restructuring, mainly in the form of greater employee cost sharing rather than an expansion of managed care [11].

Our learning from all of this is that the health-care landscape in the United States is constantly evolving and changing. Additionally, new models of health care take many years to have an impact [12].

Health-Care System Challenges That Paved the Way for the Affordable Care Act

As previously mentioned, the majority of Americans receive their health care through an employer plan. This is a good thing, right? Well, it's a good thing for covered employees. However, by its very nature, there are segments of the population who don't have coverage or who don't have adequate coverage. Examples include retirees under the age of 65, people who are not currently employed, individuals who work for a business that does not provide medical coverage, independent contractors, or employees who may opt out of employer-provided coverage because they cannot or chose not to pay their portion of the costs [13].

While the employer-based system remains the foundation of modern health care in the United States, it's facing many challenges and may have reached its peak in 2000 when 66.8 % of the population had employer-based coverage. Earlier in the chapter, it was discussed that more and more cost sharing, in the form of rising deductibles or higher premiums, has been one way employers have attempted to reign in costs. Some firms are

going a step further and only offering employee coverage and eliminating dependent coverage. Most drastic of all, some firms have opted for cost shifting approaches rather than sharing the costs, either cutting wages to offset health-care costs or eliminating health care from their benefit package. The two groups that have been most impacted negatively are retirees and working adults. In 1990, a ruling by the Financial Accounting Standards Board (FASB) stated that as of 1992, firms that provided health benefits to their retirees would have to include their future retiree health-care expenses in their current financials. The immediate effect was a devaluation of these firms on Wall Street and a reduction by almost 50 % of firms that offered health care to retirees. The second group, working-age adults, saw a near 27 % drop in employer-based coverage, between 2000 and 2004. This group is also the least likely to find government programs to help them when they do lose employer coverage [11].

Around this same time, the Institute of Medicine published two reports: the first in 1999, titled *To Err Is Human: Building a Safer Health System*, and in 2001, *Crossing the Quality Chasm: A New Health System for the 21st Century. To Err is Human* focused on quality concerns that fell in the category of medical errors. There were a variety of reasons for the focus on medical errors, but one of these reasons was the sizable body of knowledge and successful experiences of other industries to draw on. The committee looked at two large studies, one in Colorado and Utah and the second in New York. They found that adverse events occurred in 2.9 and 3.7 % of hospitalizations, respectively. Adverse events led to death in 6.6 % of cases in Colorado and Utah and 13.6 % of cases in New York. If this were to be extrapolated to all the admissions to hospitals in the United States during this time period (1997), it would equate to at least 44,000 Americans dying each year from medical errors up to a high of 98,000 based on the New York study results. This would be the equivalent of a 737 crashing every day for a year [14].

The second report, *Crossing the Quality Chasm*, concluded that the US health-care system does not provide "consistent, high-quality medical care to all people." It went on to say "health care harms patients too frequently and routinely fails to deliver its potential benefits." The report goes on to detail the failings in the health-care delivery system, including poor organization to meet challenges, overly complex and uncoordinated care, and numerous patient handoffs that slow down care and decrease safety. The report concludes that making incremental improvements will not suffice and that a fundamental, sweeping redesign of the entire health system would be required to bring high-quality, safe, modern health care to all Americans [15].

Components of the ACA

- The Patient Protection and Affordable Care Act (PPACA or ACA) was enacted with the goals of increasing the quality and affordability of health insurance, lowering the rate of the uninsured, and reducing the costs of health care for both individuals and the government [16]. There are many parts to the ACA, and they come into effect over a period of time. The essential components of reform include quality, affordable health care, by eliminating lifetime and unreasonable annual benefits, prohibiting rescissions of policies, requiring coverage of preventive services, extension of dependent coverage to age 26, and developing uniform coverage documents for apples-to-apples comparisons.
- Strengthening and expanding of public programs.
- Improving the quality and efficiency of health care, including linking payments to quality outcomes, improving payment accuracy, and the development of new patient care models.
- Prevention of chronic disease and improving public health by increasing access to preventive services, creating healthier communities through grants for pilot programs, and funding for research.
- Ensuring a vibrant and competent health-care workforce through the encouragement of innovations in health-care training, recruitment, and retention.

- Providing transparency and program integrity though physician disclosures, compliance, and ethics programs for nursing homes; establishment of a private, nonprofit entity for patient-centered outcomes research; and integrity provisions across existing suppliers and programs.
- Improving access to innovative medical therapies through new FDA licensing processes and expansion of drug discounts to inpatient drugs and certain children's hospitals, cancer hospitals, and other critical access hospitals.
- Establishment of a national voluntary insurance program for community living assistance services and support.
- Revenue provisions including tax on high-cost employer-sponsored plans, limiting contributions to health-care savings accounts, and an annual flat fee on the pharmaceutical manufacturing sector, the medical device sector, and the health insurance sector.
- Strengthening quality and affordable care by requiring coverage improvements from employers, improvements in the role of public programs, improvements to the Indian healthcare system, and improvements to Medicare beneficiary services [17].

As part of improving the quality and efficiency health care, the ACA includes provisions for pilot programs that would allow providers to test an idea on a smaller scale that, if it proves successful, could be expanded across the entire country. Many of these pilots could be considered cost control experiments. One cost control experiment that Medicare is trying is a bundled payment system. In this pilot, a hospital is paid a lump sum, and then it's up to the hospital to provide the care through the entire episode. This means the hospital would need to have a team that can manage the patient across the entire episode and not just the hospitalization portion. Normally, the hospital would only be concerned with the time the patient is in the hospital. Now, an argument could be made that this type of system would cause the hospital to want to discharge the patient as soon as possible to maximize the amount of money left after the cost of the hospitalization. However, when this is coupled with another pilot program which aims to reduce hospital readmissions within 30 days, it becomes apparent that the hospital and care team will need to find the right balance between keeping the patient hospitalized as long as necessary to get the highest-quality outcome and discharging as soon as it is appropriate to have some dollars left over for investment and expansion back into their system.

One additional pilot program worth mentioning is the use of accountable care organizations (ACOs). In an ACO, a group of health-care professionals deliver team-based care to patients, similar to what would happen in the bundled payment pilot. Each ACO that signs up will have to take all patients, regardless of health condition. What is different about the ACO approach from the bundled payment approach is that each member of the health-care team is paid on a fee-for-service basis. However, bonuses would be paid out when care delivered is below a predetermined threshold (which hasn't been determined yet). The idea is to provide an incentive for team members to provide quality care and be interdependent with other team members, thus helping to drive down costs [18].

Impact of the ACA on the US Health-Care System

There has been much written about the cost of health care in America as well as the rate at which it increases each year. Health-care spending is projected to increase from 17.2 % of gross domestic product (GDP) in 2011 [19] to 19.9 % in 2022 [20]. With health-care spending projected to increase and Medicare reimbursements set to decrease as part of the ACA, this will put immense pressure on the current system. According to an estimate by the Institute of Medicine, approximately 30 % of health-care dollars ($2.5 trillion) spent in 2009 did nothing to help patients become healthier. This 30 % equates to $760 billion and was mainly due to unnecessary tests and surgeries, inefficiency in how care is provided, missed opportunities to identify and treat diseases, pricing issues, overhead, and fraud [21].

As components of the ACA continue to be implemented, we would expect to see continued reduction of payments to providers, an increase in the number of patients covered by the system to be upward of 30 million by 2022 [20], and increases in the quality of care provided through the use of pilots (e.g., readmissions, ACOs, bundled payments). The health-care system, however, will have to adjust or correct itself to balance these opposing forces. With $760 billion in waste and inefficiency in the system, there is room for this correction to occur.

According to the website www.healthaffairs.org, since January 2013, nearly 200 new public and private ACOs have been formed across the country. This brings the total number of ACOs to 606, some who had been in existence before and some who were part of the 2012 Pioneer ACO Model pilot [22]. An advantage of the ACO type model is that it allows care to be provided in less expensive settings. The CareerBuilder website states "the U.S. health care system has a new business model—one that is transforming the delivery system from hospital-centric sick care to a super outpatient model that will emphasize community-based care." The era of mergers and acquisitions is beginning again, this time in health care. There are an increasing number of acquisitions, both horizontal and vertical, with hospitals now becoming health systems by buying physician practices, surgery centers, medical equipment, and other types of health-care providers [23]. As they become more vertically integrated, they have the ability to shift more care to other settings. In conjunction with this, many consumers are finding their share of the cost of health care is increasing, and they are driving a shift away from higher cost settings [24].

There are several other trends that are growing and that will continue to grow, which will help with the movement toward less costly settings and increasing efficiency while lowering the cost of health care. Those trends are an increasing use of technology to deliver care and connect patients to their provider, the use of alternate providers that are less expensive than physicians but who have training and often licensure of their own, and, finally, the use of telemedicine, allowing a general practitioner to manage a patient with backup, support, and consultation from a specialist located elsewhere physically.

In terms of technology, one only has to look at the burgeoning business of medical and health-care-related applications for mobile phones. Mobile apps are allowing consumers to direct more control over their health care, allow for the exchange or transfer of information, reduce in-person visits, and even improve adherence to a treatment plan. Meanwhile, the capabilities that apps have are increasing exponentially particularly with the addition of sensors. They are now able to remotely monitor conditions, capture patient data, and monitor and help manage chronic conditions. With high rates of consumer acquisition, projected to be near 215 million devices in 2016, close to 70 % of the US population could have access to health-care information and be able to communicate with their provider by mobile technology. This mobile technology offers convenience and flexibility, real-time monitoring of conditions, and additional tools for compliance [25].

The next trend that we've already seen and that will continue to grow is the use of non-physician providers. These may come in the form of nursing practitioners (NPs), midwives (CNM), or other types of allied health professionals that are licensed and/or certified. According to research at RAND Health in Boston, it's predicted that the number of full-time NPs will increase from 128,000 in 2008 to 244,000 in 2025, with a range of 227,000 on the low end up to 268,000 on the high end. This also aligns with the current forecasts of a physician shortage that ranges to a high of 90,000 physicians over the next 10 years [26].

Alongside this rising usage of alternate providers is the idea of "practicing at the top of license." Typically, many larger organizations will begin to silo providers and narrowly define their roles, often allowing a higher-level provider a broader role. This is in contrast to the current training many allied health-care professionals receive, which allows them to provide care along a broader spectrum. Many professional organizations for allied health professionals have been

lobbying for a broader scope of services. According to the Advisory Board, "many primary care staff members are under-utilized compared to what their licensure and personal potential should permit them to do. The challenge for medical homes is to enhance staff skills and roles to do more complex, meaningful and hands-on-work. Doing this at each licensure level allows less-complex work to be offloaded from the level above- up to and including the physician, NP or PA provider" [27].

One final trend that needs to be mentioned is that of telemedicine. Something as simple as a skin rash could be looked at by a provider remotely as long as there is a location with a camera. This technology would also allow an emergency room physician to consult with a specialist allowing for local treatment rather than needing to transport a patient to another location, incurring ambulance costs as well as additional treatment costs at the subsequent location. Between 2007 and 2012, just this piece of the telemedicine market focused on patient monitoring grew 237 %, from $4.2 billion to more than $10 billion [28]. There are new state-of-the-art robots that often come with a "head" which allows the patient and/or provider to see and hear the remote physician. Similarly, the remote physician can hear what is going on with the patient, including listening to the lungs and heart of the patient or zooming in and checking pupil dilation, skin tone, or other physical information needed. By using this technology, Lincoln Hospital in Spokane Washington was able to reduce the number of patients needing to be transferred out of its emergency department to another hospital in Spokane by 21 % between 2010 and 2011. This helps increase capacity in the system by keeping patients in a level of care that is adequate for their clinical needs, allowing for a high-quality outcome without overburdening the system [29].

We've taken this journey through the history of our health-care system which has evolved toward an emphasis on outcomes and along with this optimizing the cost-effectiveness of medical care. In attempting to achieve this goal, we have highlighted the following directions of our health-care system: (1) changes in health-care finances that are based on outcomes rather than services, (2) promotion of team-based disease management which includes utilizing allied health providers to their appropriate potential, and (3) leveraging the use of technologies, including implementation of telemedicine. In the next section, we will discuss how each of these elements specifically impact sleep medicine and explore how it may shape the future of sleep medicine. To envision the future, however, it is necessary for us to understand our history to realize how we got to where we are today.

History of Sleep Medicine

In 1929, a German psychiatrist named Berger first recorded human brain activity, giving birth to electroencephalogram (EEG) and subsequently described differences between sleep and wake states [30]. Loomis and Kleitman not only further differentiated non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, but they also introduced the recording of additional physiologic parameters such as respirations, heart rate, and movement which subsequently formed the foundational components of polysomnography which would become central to the birth of sleep medicine and its growth as a field [31, 32].

Initially, sleep studies were utilized only for research and largely focused on investigating patterns of normal sleep, characterizing normal sleep architecture with a pattern of NREM sleep punctuated by periodic cycles of REM sleep starting about 90 min after sleep onset [33]. In the 1950s, sleep-onset REM was seen in a patient with narcolepsy, and REM sleep was also captured occurring in conjunction with a sleep attack [34, 35]. This discovery heralded the use of polysomnography for the study of sleep pathologies and eventual evolution into a field of medicine. It was William Dement who formed the first sleep disorders clinic at Stanford University, initially managing patients with narcolepsy and quickly expanding to include the treatment of insomnia. Obesity hypoventilation syndrome and obstructive sleep apnea were also described in the 1950s with polysomnographic findings of airflow cessation associated

with discontinuous sleep, while restless leg syndrome was found to be associated with periodic limb movements [36, 37]. Although the field of sleep medicine was clearly developing and polysomnography was recognized as a useful clinical tool, it was not until 1975 that insurance payers began to reimburse for sleep studies, which removed a significant barrier to the utilization of polysomnography leading to growth of sleep medicine as a field. It is evident that sleep medicine was historically founded upon polysomnography. Thus, it is not surprising that it has functioned as the primary driver for the expansion of this specialty, but our overreliance on it may now ironically be a function as a source of weakness.

Current Challenges to Sleep Medicine

The field of sleep medicine has grown substantially over the past few decades, from the original Stanford clinic to now 2575 sleep centers accredited by the American Academy of Sleep Medicine (AASM). The growth of sleep medicine is supported by the high prevalence of sleep disorders, particularly obstructive sleep apnea and insomnia which together may affect 40 % or more of the general population [38, 39]. There is also the increased recognition that these disorders may impact comorbidities such as hypertension and other cardiovascular diseases that significantly affect overall health and well-being. The AAA Foundation for Traffic Safety recently concluded that up to 21 % of crashes during the 4 years prior to 2013 likely involved a drowsy driver [40]. Highly publicized disasters such as the Exxon Valdez accident have been linked to sleepiness, and the frequency of sleep-related articles in the mainstream media is now a regular occurrence. While sleep medicine has been thriving due to a high prevalence of the disease and increasing public awareness of sleep disorders, the field is also currently under significant pressures related to changes in the health-care environment emphasizing the importance of cost-effective care, highlighted by (1) overreliance of testing and (2) insufficient number of sleep specialists to effectively manage the full population of sleep disorders.

Polysomnography (PSG) remains central to sleep medicine care for its ability to comprehensively characterize sleep pathologies in the management of sleep disorders. But reimbursement for PSG was also the primary vehicle by which sleep specialists were able to generate an income, and this further increased our reliance on this tool even beyond its medical usefulness. However, reimbursement rates for PSGs have been declining, and this has coincided with a push toward home sleep testing which is arguably thought to be more cost-effective. In 2009, one of the most prominent sleep laboratory networks, Sleep HealthCenters, filed for bankruptcy after major insurance payers forced the transition to home sleep testing and limited the use of in-laboratory PSG to patients with more complex disease. It is now common place, particularly in the Northeastern United States, to require preauthorization before performing PSG. Currently about 70 % of sleep centers perform out-of-center testing although most perform less than 20 % of their overall sleep studies in the home [41]. Eventually, home testing will likely become the dominant testing modality, and in our center, which is part of a capitated health-care system, the rate of home sleep testing exceeds 90 % of studies performed.

The field of sleep medicine is also facing a shortage of sleep specialists to effectively provide care for the population, even beyond the shortage of physicians that was described in the previous section regarding the health system in general. Not only is there already an insufficient capacity to meet the demands for diagnostic testing, the demands for services will continue to rise with increasing emphasis on providing effective follow-up care. As the health system emphasizes optimal outcomes, follow-up management with streamlined ability to report outcomes is essential to the future sleep specialist. While the availability of sleep specialists is well established in metropolitan areas, access remains problematic in many parts of the United States, especially the more rural areas. The overall shortage and uneven distribution of sleep providers creates a barrier to patient access, and specialists such as pulmonologists and primary care physicians are now increasingly performing sleep testing and

managing obstructive sleep apnea (OSA). The optimal relationship with nonformally sleep-trained specialists is an area of significant debate and requires further evaluation. Sleep testing and management of sleep disorders has historically been the domain of the sleep specialists, but the field must now answer several critical questions relevant to shaping the future of sleep medicine: (1) What is the appropriate and optimal use of home sleep testing? (2) How do we improve the cost-effectiveness of our care delivery? (3) How do we address the short of sleep specialists? In this next section, we will explore how the specific components of the evolving health-care system described earlier in the chapter will function to impact the future of sleep medicine. It seems clear that we are currently at a critical evolutionary juncture.

Impact of Affordable Care Act and Current Health-Care Trends on the Future of Sleep Medicine

Health-care-related costs in the United States currently account for about 17 % of the national gross domestic product and continue to escalate. This is double that of comparable countries, yet outcomes are inferior when measured by life expectancy [42, 43]. The country recognized the need to contain health-care costs which required a change in focus to achieving optimal outcomes rather than providing services. It is no longer adequate to consider the goal of medicine to provide effective care, but rather it is now crucial to promote and incentivize care that is cost-effective. Earlier in the chapter, we discussed health-care system changes that are occurring aimed at trying to achieve this goal: (1) changes in reimbursement practices, (2) team-based disease management, and (3) technology. We will address how these factors are specifically relevant to sleep medicine in our mission to improve the cost-effectiveness of sleep disorder care. It should be emphasized that many of these components are still evolving and their actual impact largely remains to be determined.

Changes in the Reimbursement Paradigm

The Healthcare Effectiveness Data and Information Set (HEDIS) is a set of performance metrics used by the Centers for Medicare and Medicaid Services (CMS) that determines reimbursement rates for a given health system. A health system is rewarded if it is able to achieve an extensive set of performance metrics for the control of disorders such as hypertension and diabetes and appropriate drug utilization, while a financial penalty is imposed if the HEDIS measures are not achieved. HEDIS is relevant to the sleep specialist in several ways. First, one criterion mandates a yearly limit in prescriptions of high-risk medications in those at least 65 years of age, and this includes non-benzodiazepine sleep medications. As a result, the availability of a robust insomnia cognitive behavioral therapy (CBT) program is critical. However, these programs are currently structured primarily as multiple individual sessions that may be effective for the individual but not for the health system population with insomnia. Further investigation regarding cost-effective mechanisms for delivery of CBT is required, such as considering group and single-session programs, as well as promoting Internet-based programs. While obstructive sleep apnea is not directly represented as a HEDIS measurement, it impacts optimal control of hypertension and diabetes which are HEDIS criteria. Eventually, OSA outcomes are likely to become a reportable metric. For these reasons, the importance of utilizing non-continuous positive airway pressure (non-CPAP) therapies increases to provide more complete therapy penetrance for the population of patients with OSA.

Additional changes in reimbursement paradigms include the use of bundled payments as previously discussed. For example, a fixed amount would be reimbursed to the sleep physician to diagnose and manage a patient with obstructive sleep apnea, and the amount left over after cost of care is the net revenue for the sleep specialist. This incentivizes the sleep provider to utilize lower-cost mechanisms for care, and thus, the sleep specialist will likely be forced to embrace home sleep testing.

Team-Based Care

Physicians comprise an expensive component of health care, and the use of lower-cost allied health professionals as extenders may potentially reduce costs while also enhancing the volume of patients that can be under the care of a single physician. A randomized controlled study was performed in Australia comparing obstructive sleep apnea care of the sleep physician and care provided by primary care registered nurses, who were given basic sleep medicine education and a care protocol to follow. The authors concluded that nurse-based care was not inferior to that of a sleep physician specialist. While the conclusion is likely limited to patients already prediagnosed with obstructive sleep apnea, and there is uncertainty regarding the generalizability to actual real-world clinical sleep practices, it nevertheless promotes the potential benefits of utilizing physician extenders. In our own system, we have used respiratory therapists to provide protocolized care of obstructive sleep apnea with evidence they can provide effective care and improve overall patient engagement. When we utilized a respiratory therapist to provide CPAP follow-up, CPAP adherence doubled at 3 months even without direct physician contact. In addition to the usual technologist-related skills of testing setup and scoring sleep studies, the care manager can be effective at performing broader responsibilities that include components of clinical management traditionally reserved for physicians such as limited triaging, CPAP troubleshooting, and other aspects of follow-up care, all of which require some degree of clinical judgment. In order for this paradigm to be successful, it requires well-established predefined clinical pathway protocols and a robust infrastructure of care manager supervision. The physician's role in the future is one that expands from primarily providing direct patient care to that balanced with providing leadership for a team of extended providers.

The use of care managers can also be very effective in the care of specific diagnoses that are more limited in volume but more complex in management. For example, the Stanford Sleep Disorders Center has a dedicated narcolepsy case manager that coordinates care including patient communication and medication management. Just as care managers are often utilized in caring for patients with chronic obstructive pulmonary disease (COPD), care managers can be very effective at coordinating care for patients with hypoventilation syndromes that require assisted ventilation in the sleep center. These patients often require frequent follow-up, near-immediate telephone access to a provider, and coordination of multiple medical tests at regular intervals. These responsibilities are often more appropriate for a case manager and is typically difficult for physicians to provide that level of interaction. While the level of responsibility and ratio of care managers to physicians will differ depending on specialty and diagnosis, implementing some form of team-based care is a crucial consideration for success in the future health-care environment.

Telehealth

Sleep medicine has been ahead of the curve in regard to the use of remote technology to provide care, given the critical role of digital recording. For example, remote viewing of polysomnography studies in real time and as a store-and-forward mechanism has long been available. Several home sleep testing platforms have the ability to upload and view studies from an Internet cloud server; there is even the capability of having a home sleep testing vendor automatically send devices to a patient's home and provide setup assistance, automatic data upload via a cellular network, and remote processing and interpretation of the study. As technology continues to improve, telemedicine video visits (and other forms of communicating such as text messaging) are being recognized as being potentially effective at improving access to health care, especially in more rural areas which lack proximity to sleep specialists. Medicare reimburses for video visits to care for patients in rural areas if specific criteria are met, and the American Academy of Sleep Medicine (AASM) has convened a task

force to specifically address telemedicine video visits relevant to the care of sleep disorders. Video encounters may be particularly useful in caring for sleep disorders considering many patients may experience excessive sleepiness that can potentially render them higher driving risk. Furthermore, video assessments may be particularly useful in addressing mask fit among other equipment-related issues. Whether utilizing center-to-center or center-to-home video visits, it is likely that the sleep practitioner of the near future will have to embrace video encounters as a core part of his or her practice.

While remote video encounters have the ability to improve quality of care by improving access to care, its impact on efficiency is likely limited as it still requires dedicated provider time to manually deliver care. A randomized controlled study demonstrated near doubling of 3-month CPAP usage in a cohort of patients that had daily review of their CPAP usage compared to a cohort with usual punctuated follow-up care [44]. While this study proved that remote care is effective, the personnel resources to provide that level of manual care is excessively labor intensive. This example highlights the importance of utilizing automated care processes:

1. Automated education such as web-based educational programs. This type of education can provide more consistent and reviewable education, and data suggests that it improves patient engagement by improving show rates by 30 % to sleep center OSA evaluation appointments [45].
2. Automated follow-up mechanisms. Some CPAP vendors have platforms that automatically process CPAP usage data that is remotely uploaded. The algorithms are able to provide feedback messages to the patient as a mechanism to improve patient engagement with therapy. Furthermore, they are able to identify a list of patients with suboptimal CPAP usage for the sleep specialist, prioritizing patients that require intervention, rather than having to manually follow up with every patient.
3. Self-directed care mechanisms. Mobile applications are now available that allow patients to track their own CPAP use and educate on specific issues such as mask fitting in patients with a high leak. Internet-based cognitive behavioral therapy programs are self-directed programs proven to be effective and likely necessary to effectively treat the population given the high prevalence of insomnia. This provides not only automated and continuous care, but it also allows patients to take more ownership over their disease management and increase their level of engagement.
4. Integration. To maximize impact of telehealth on efficiency, telehealth must be able to comprehensively and efficiently connect patient to provider. This requires extensive integration between sleep technologies and electronic health records, including the integration of sleep diagnostic and therapy technologies and the ability to send questionnaire and other messages automatically linked to appointments and connect wearable sensors and other end-user devices.

Telehealth has the potential to improve patient engagement and to provide continuous rather than punctuated disease management. Health-related technologies have proliferated in recent years yet remain in its infancy. But once the field of technologies coalesces into an organized system of integrated technologies, it holds great potential to improve access, quality, and cost-effectiveness of care.

Impact of Specific Affordable Care Act Components on Sleep Medicine

It is increasingly recognized that the primary components of the health-care system (medical providers, hospitals, and payers) cannot continue to function independently in this emerging era of outcomes-based medicine. As previously discussed, this has led toward the formation of accountable care organizations (ACOs) in which providers and other health-care components group together to provide coordinated care with reimbursement tied to quality metrics. The Affordable Care Act applies further pressure to

consolidate these care components, and this is reflected on the high percentage (up to 60 %) of ACA plans on the health-care exchange that are constructed as narrow network plans [46]. Narrow networks are organized so that payers are in contract with a limited set of providers to care for a given population of patients at a fee structure aimed at limiting cost. This limits the flexibility of patients to seek sleep medicine or other specialty care outside of this network. While the effect of ACOs and narrow networks on the sleep medicine field remains uncertain, it seems prudent for the sleep practitioner to explore whether it is advantageous in the practitioner's local area to integrate services with these entities by considering factors such as referral patterns.

An additional challenge of caring for the patient with an ACA health plan is that many of these patients subscribe to plans that have very high deductibles and many have limited or no durable medical equipment (DME) coverage. In a field such as sleep medicine that involves a high degree of DME-related equipment use, this can significantly impact the acceptance of therapy especially in managing sleep-disordered breathing. A well-defined process of referring patients to lower-cost DME providers is helpful when paying out of pocket, but there is also the disincentive for patients to replace CPAP accessories such as masks on a regular basis which can impact effectiveness of therapy. The group of patients this most affects are those with complex breathing disorders such as hypoventilation that require assisted ventilation often with additional oxygen supplementation. In these situations, the cost of the DME equipment can be exorbitant and can be a barrier to optimal care.

Currently written into the ACA is the inclusion of a medical device tax. Historically, medical devices such as sleep diagnostic and therapy equipment are exempt from being taxed, but on January 1, 2013, a tax of 2.3 % went into effect (the rate was negotiated down from 4.6 %) There is disagreement regarding the effect of this tax on health-care economy and employment, but it does likely impact sleep centers which are inherently heavy utilizers of medical equipment and heavy prescribers of medical therapy equipment. This tax is a matter of political debate, and it is possible that it may be repealed in the near future. If the tax remains, it is likely that this cost will ultimately be passed downstream to the patient potentially adding further impact on patient acceptance of therapy, although the degree of impact is unclear.

The ACA emphasizes prevention and wellness initiatives, especially for women and children, which includes no-cost preventative services and screening for core medical conditions. While sleep disorders are not included as mandated preventative conditions, sleep medicine is indirectly relevant given its inherent role in wellness and its relationship with conditions targeted for prevention such as obesity and cardiovascular diseases. It is an enviable position in that we can enhance the value of our services by promoting the relationship of sleep disorders with these targeted conditions. Population screening mechanisms, such as utilizing diagnosis codes, demographic information, pharmacy utilization, and other discreet information available within health records, can be utilized to identify a cohort of patients at high risk for OSA as a function within electronic health record systems. Another strategy that has been explored involves presenting municipalities or companies with sleep wellness initiatives aimed at improving workforce productivity and overall health. Streamlining standardized mechanisms to identify at-risk patients in a given population can be potentially advantageous toward the work for the sleep specialist and a benefit for the health system as a whole.

The Future of Sleep Medicine

As this chapter has discussed, sleep medicine is facing a number of challenges from an evolving health-care system. Cost-effectiveness initiatives are forcing the shift from in-laboratory polysomnography to out-of-center testing and balancing the focus on testing to a greater emphasis on follow-up care. While these changes are already making a major impact on the way that sleep medicine care is delivered, the future of sleep

medicine is likely to undergo a much greater evolutionary shift. In this section, we will explore key areas in which the care of sleep disorders is likely to further develop.

Comprehensive End-to-End Care

The current health-care system paradigm currently emphasizes the diagnostic process, therapy initiation, and immediate follow-up. However, significant care gaps are present, specifically a lack of infrastructure to provide effective population preventative care and effective continuous disease management; thus the pattern of care is typically punctuated and reliant on acute illnesses, physician visits, and other periodic events that inconsistently and temporarily enhance patient engagement. Sleep medicine providers are reliant on primary care physicians to appropriately recognize the risk of obstructive sleep apnea, but there is clearly a deficiency in this nonsystematic way of risk identification since it is estimated that 80 % of OSA remains undiagnosed [47]. After initiating CPAP therapy, follow-up is emphasized during the first 3 months, but extended follow-up beyond that period is dependent on patients taking the initiative to contact their provider. These gaps need to be addressed if preventative care is to be truly effective and follow-up care is to be continuous rather than punctuated and driven by acute or subacute changes in health.

Automated Population and Disease Management

We have previously discussed the use of electronic health record data, automated disease management platforms, and self-directed care mechanisms as critical functions within the future health-care system. This includes our discussion on automated population management in regard to screening, while automated population management may also impact follow-up care. For example, remote data transfer from CPAP units into cloud platform can allow for continuous algorithmic processing of the data to provide a list of patients that are identified to be having trouble with therapy. Instead of having to request a face-to-face follow-up encounter for an entire population of patients on CPAP therapy, the effort can be focused on the limited group of patients identified to be having problems. Eventually, this data could potentially be used to provide disease management for patients with other comorbid conditions. For example, patients with congestive heart failure on positive airway pressure therapy can be assessed for imminent acute exacerbation by evaluating periodic breathing parameters. Finally, it is possible that several technologies can be combined for more comprehensive disease management. Mobile applications may be able to remind patients with congestive heart failure to daily measure their weight with a wireless scale. That information along with CPAP breathing parameters and data from other wearable sensors can be compiled together for risk assessment and provides a window to intervene before the patient ends up in the hospital.

Integration and Technology

In order to provide remote care and utilize automated population and disease management processes, technology integration and utilizing advanced capabilities within electronic health records are necessary. The US Department of Health and Human Services (Office of the National Coordinator for Health Information Technology) released a 5-year strategic plan from 2015 to 2020 "encouraging health-care providers to adopt new technology." One of the objectives is to "identify, prioritize, and advance technical standards to support secure and interoperable health information" [48]. For the technologies to be truly effective, they need to be interoperable and have the ability to exchange information. Ultimately, end-user devices require integration with electronic health records which acts as the hub for information exchange, and the data collected can be organized and utilized for population and disease management. Successful integration is a critical component in achieving the goal of enhancing the connection between patient and provider.

In addition to technology integration, workflow integration is critical especially with the increasing emphasis on team-based care. Provider-to-provider team-based communication needs to be streamlined especially with disease management processes now including team members of other specialties. For example, the future sleep center likely requires the inclusion of a behavioral sleep medicine specialist and perhaps on-site dentists to manage oral appliance therapy for OSA. Perioperative programs may require close communication between the surgeon screening for risk of OSA, sleep specialist making a diagnosis and initiating therapy, anesthesiologist utilizing specific OSA precautions, hospitalist and nursing staff managing postoperative CPAP therapy, and then finally transition back to the sleep specialist for long-term follow-up. Automated patient-provider communication mechanisms are likely to play an important role in workflow efficiency. Questionnaires can be electronically sent to the patient linked to scheduled appointments or scheduled at specific time frames after CPAP is ordered.

Identity of Sleep Medicine and the Future

In 2013, a series of editorials in the Journal of Clinical Sleep Medicine highlighted the urgency in which the field of sleep medicine needed to respond to its challenges [49]. This was heralded by the abrupt closing of Sleep HealthCenters in the Northeastern United States which the authors presented as evidence that "the old paradigm will no longer work." Strategies that were highlighted included that the need to change is essential and urgent, and "the vision for our field should be a quality outcomes-based chronic disease management discipline for all sleep disorders, not just for sleep apnea" [50]. It is clear that a field that "has focused on the testing and diagnosis of patients with obstructive sleep apnea" needs to radically change [51]. These changes have been discussed in the previous sections of this chapter as reflective of the evolving health-care system in the United States.

While obstructive sleep apnea management is likely to remain the largest portion of work for the sleep specialist, the field needs to further explore methods of increasing the relevance of sleep apnea care. We have discussed expanding care to address the end-to-end spectrum so that the care is continuous and less punctuated while also promoting self-directed mechanisms. But further collaboration with other medical specialties including expansion of sleep apnea management into the inpatient setting is necessary to improve its relevance by associating this condition with tangible measurable outcomes, particularly cardiovascular, perioperative, and utilization outcomes. Kauta et al. demonstrated reduced hospital readmission rates in hospitalized cardiac patients that had underwent portable monitoring and initiation of positive airway pressure therapy in those with sleep-disordered breathing [52]. However, for sleep medicine to thrive, the field must expand beyond the focus of a singular diagnosis [53]. Epidemics of certain diseases such as obesity, diabetes, coronary artery disease, and obstructive sleep apnea can be viewed as fundamental drivers of subspecialty practices of bariatric surgery, endocrinology, and cardiology. For sleep medicine, the field needs to invest in new areas of emphasis for this specialty to continue to grow. A few immediate areas to consider include the management of neonatal sleep-disordered breathing conditions such as prematurity-related apnea and bronchopulmonary dysplasia, whose disease findings are often present or most prominent during sleep and perhaps could be related to risk of sudden infant death syndrome. Traditionally shared conditions such as chronic hypercapnic respiratory failure between pulmonary and sleep medicine should be considered as a primarily sleep medicine condition since therapy typically requires polysomnographic testing and nocturnal ventilation. Likewise, neurologic-related conditions such as narcolepsy and restless leg syndrome should be considered the primary jurisdiction of the sleep specialist rather than a neurologist. Finally, it is critical that we continue our investment into basic science and translational research in order to answer fundamental questions regarding the purpose of sleep, the

effect of our modern technology-oriented "24-h society" on overall health, and innovative techniques of sleep/wake cycle manipulations to improve overall wellness [54]. It is our quest in answering these questions that hold the potential of transforming this field.

Conclusion

In conclusion, challenges within the current health-care environment are forcing the field of sleep medicine to evolve. While change, as is often the case, has proven to be difficult, the field is also positioned in an enviable situation given the high prevalence of sleep disorders, the inherent emphasis on use of technology, and the importance of sleep on wellness and other emphases of the future health-care system. But the most exciting aspect regarding the future of sleep medicine is actually realizing how little we know about sleep. It remains a deep and intriguing mystery as we even do not fully grasp its purpose and understand the role of dreaming. But it is this mystery that renders this field ripe for unlocking new paradigms that allows us to reimagine our field. It is our ability to reimagine our future that will not only allow the field to grow but to achieve our greater goal of being able to radically transform lives.

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