Sleepiness

Causes, Consequences and Treatment

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Edited by

Michael J. Thorpy

Michel Billiard

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Foreword

Sleep research has made numerous discoveries that have enhanced the quality of human functioning across the 24-hour day. However, none compare to the potential impact of the insights that have been gained about Sleepiness as a biological drive state, and Excessive Sleepiness as an important symptom in public health and patient care. This volume assembles the research on normal and pathological sleepiness. Individual chapters address the measurement of sleepiness in the clinic, the "field" and the research laboratory. Other chapters address the various causes of sleepiness and the morbidity associated with excessive sleepiness. Finally, societal self-treatment for variants in normal sleepiness as well as medical treatment of excessive sleepiness in sleep disorder populations is addressed.

The term "sleepiness" is used to describe the normal biological drive for sleep. The ecological value of the sensation of sleepiness is to inform the individual that functioning is compromised and sleep is needed to correct this. Excessive sleepiness is used to describe 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, interfer with activities of daily living, and can be harmful to the individual.

Sleepiness is mediated by homeostatic drive variables including time since the last sleep period, as well as the duration and continuity of previous sleep and especially the last sleep period. Importantly, circadian processes modulate the timing of sleepiness across the 24-hour day. These two determinants are the major causes of sleepiness in the general population. Most people are sleepy because they do not sleep enough on a nightly basis, are severely sleep-deprived for a single night, or because they are trying to work late into the night (i.e. at a down phase in their circadian rhythm). In contrast, excessive sleepiness is caused by inadequate sleep at night, circadian rhythm disorders, drugs, as well as sleep, medical, and psychiatric disorders. Inadequate sleep at night is probably the most common cause of sleepiness. Among the general population, insufficient duration of sleep at night is thought to be the cause of excessive sleepiness. In contrast, among patients, and the elderly population, it is the fragmentation of sleep which leads to excessive sleepiness. Importantly, in clinical populations, a variety of pathologies as well as their treatments also give rise to excessive sleepiness. In this volume, individual chapters will address each of these causes of sleepiness and define how parametric variations in these factors impact the degree of sleepiness.

The pervasiveness of sleepiness in our society is evidenced by two societal indicators. These are oversleeping on weekends and caffeine consumption. Caffeine is the most widely used central nervous system (CNS) active drug in the world. In North America, 80–90% of adults regularly use caffeine. Caffeine is the only CNS drug that can be legally purchased by children. In a study of children and adolescents, it was found that 98% ingest caffeine at least once a week. Not only is caffeine widely used, but the brands of coffees with the highest caffeine content are the most widely consumed brands. In addition, there are numerous "energy drinks" (a variety of different beverages with high caffeine content) routinely advertised in national media and commonly consumed by adolescents. Oversleeping on weekends is another indicator of pervasiveness of sleepiness. According to polls conducted by the National Sleep Foundation, the average adult sleeps approximately 7 h per night on weekdays, but 8 h per night on weekends. Importantly, in several laboratory studies it was found that requiring subjects to stay in bed for 8 h a night for several nights increases their level of alertness as determined by the Multiple Sleep Latency Test (MSLT).

Another important consideration in understanding sleepiness relates to the concepts of masking and misattribution. Masking refers to the fact that there are many variables which make individuals

underestimate their level of sleepiness relative to their actual physiological state of sleepiness. Factors such as motivation, stress, and level of activity all mask our sleepiness. We have all had the experience of being engrossed in a task and it is not until we finish that we have a sense of overwhelming exhaustion or sleepiness. Similarly, when traveling on long journeys across multiple time zones you may not feel sleepy until you get into your room and see your bed. When these masking effects cease there is a sense of sleepiness often referred to as unmasking. What is interesting is that most individuals who deny sleepiness claim that a variety of situations make them sleepy. A group of sleep apnea patients who denied sleepiness reported that driving cars, watching television, going to church, and attending meetings all made them sleepy. We know that these factors do not cause sleepiness per se, but rather they unmask the sleepiness associated with their sleep apnea. In a National Sleep Foundation Poll, 90% of adult Americans reported that boredom makes them sleepy. Today we understand that there was a basal level of sleepiness in these individuals which was unmasked, not created, by the boring situation.

The existence of these masking phenomena raises an important clinical question. Namely, how does a clinician detect, evaluate severity of sleepiness and determine the effectiveness of treatment when patients are, at times, not aware of their own state of sleepiness? It is critical for the clinician, the employer and researcher to appreciate the importance of and the appropriate use of various measures of sleepiness. Historically, level of sleepiness has been assayed by introspection. The chapter on subjective sleepiness chronicles for the reader the evolution of subject-/patient-based scales. These have evolved from non-specific measures of mood to specific assays of subjective sleep propensity. In addition, laboratory studies have focused on the use of measuring various aspects of human performance as a measure of degree of sleepiness. These measures have been hypothesized to have the most direct application to industrial situations (e.g. transportation, shift work, health delivery systems). The seminal work of Carskadon and Dement in the development of the MSLT, often referred to as the gold standard measure of sleepiness, enabled research on sleepiness to dramatically expand. Since that initial description, variants of the MSLT and other physiological assays (e.g. evoked potentials) have advanced our ability to clinically identify and manage patients as well as to study sleepiness in the laboratory.

The importance of understanding sleepiness derives not only from its high prevalence, but also from the fact that it has significant associated morbidity. The early research on the effects of sleepiness focused on its effects on psychomotor performance in general and the frequency of lapses in performance specifically. There are seminal studies both in the USA and Europe that demonstrated that sleep-deprived subjects showed significant impairments. These effects were most clearly seen on long monotonous tasks (not different from driving) and the impairments seen were lapses. Lapses are short periods (less than a second) where people fail to respond to the environment. These lapses can have disastrous impact on behaviors such as highway driving, and other jobs that require sustained attention. Subsequent research has broadened the area of inquiry and demonstrated memory deficits, increased risk-taking behavior and impairments in executive function that are also associated with sleepiness. More recently, the focus has moved from the behavioral consequences of sleepiness to physiological consequences. Sleepiness has been shown to be associated with a variety of physiological functions including increased pain sensitivity and blunted arousal responses. These have significant implications. For example, in patients with sleep apnea, the degree of sleepiness correlates with the time to arousal and the resumption of breathing and hence with degree of hypoxemia.

As we look to the future, there are clear gaps in our knowledge which demand further research. An area of great need is in therapeutics. Historically, the pharmacological treatment of excessive sleepiness has consisted of medical treatment with dopaminergics and self-management with caffeine. In terms of medical management, modafinil was the first medication used for treating sleepiness which did not work primarily through dopamine. As we learn more about the neuropharmacology of sleep–wake systems, new therapeutic targets such as histamine and orexin need to be pursued. In terms of self-management, as higher-caffeine-containing substances become available and are used by larger segments of the population, we need to understand their abuse liability, severity and nature of withdrawal symptoms, effects on sleep, and the development of tolerance. Importantly in the area of patient management, there is a need to learn how to treat the underlying disorders, not simply excessive sleepiness as a symptom. Also, in terms of patient care, it is important to understand the causes of sleepiness.

What are the causes of refractory sleepiness in successfully treated obstructive sleep apnea (OSA) patients? Are there subgroups of patients with affective disorders who are truly sleepy, not simply reporting sleepiness? If they are truly sleepy, what mediates their sleepiness? Among shift workers, why do some shift workers report and exhibit sleepiness while others do not? Generally, as we try to understand chronic sleepiness, two questions are critical. What are the genes that differentiate individuals who show significant impairment from the various causes of sleepiness from those who do not? Also, are there adaptive mechanisms to decrease the accumulation of sleepiness? If so, what are they and how do they minimize the consequences of sleepiness across time?

One of the greatest needs in the sleep field is a reliable, valid, rapidly derived measure of sleepiness. The ability to rapidly and accurately determine alcohol concentration levels from the breath has facilitated research on the effects of alcohol, and produced regulations about driving and fitness for duty associated with alcohol consumption. Clearly, a biological assay for sleepiness would have profound effects on patient care and public safety.

Research is said to be a social enterprise in that the value of a research finding, in part, depends on the degree of its dissemination to the medical or general community. The greatest need in the area of sleepiness is education. The void in knowledge about sleepiness exists at all levels of our society. In terms of medical education, it is the view of most people in the sleep field that if a patient were to present to a clinician with sleepiness-related symptoms (e.g. tired, fatigued, can't get started), the most likely diagnosis would be depression and the most likely treatment would be an antidepressant medication. Before the awareness of sleep apnea by the general medical community, most apnea patients were diagnosed as depressed. Similarly, profound sleepiness was thought to be narcolepsy. In fact, in the medical literature one can find drugs that make people sleepy referred to as narcoleptogenic drugs. Clearly, sleepiness is a very common symptom in medicine and physicians need to have education on identifying and diagnosing the cause of the sleepiness, and treatment of that cause as well as symptomatic management of sleepiness. I can think of no medical intervention which improves patients' overall quality of life as much as treating daytime sleepiness. OSA, narcolepsy and other excessive sleepiness patients describe their treatment as a rebirth saying, "I am alive again."

Finally, the greatest need is for public education. Estimates suggest that 20% of the adult US population experience sleepiness at a level that puts them at risk for a car accident. The expanding degree of caffeine consumption, the number of sleepiness-related car accidents, and the frequency of oversleeping on weekends all attest to the need to educate the general population about sleepiness, its causes, dangers and appropriate coping skills. Children from primary school through high school learn about exercise and nutrition because of their importance for long-term health outcomes. On the other hand, an adolescent who is chronically sleep-deprived because of school start times, extracurricular activities, part-time jobs and the availability of the Internet receives no education about sleep, sleep need, changes in sleep need across the lifespan, consequences of insufficient sleep, the interaction of sleep loss and alcohol, and effective countermeasures for drowsy driving; this despite the fact that adolescents are at an increased risk of a car accident in the short term. How is a teenaged driver supposed to know that when he feels sleepy while driving, opening the window or raising the volume on the radio will be of no use, while taking a nap will help?

This volume contains information about what we know about causes, consequences, and treatments for sleepiness. This information is not only important to physicians, but also to all individuals to develop sleep practices which optimize the quality and duration of their lives.

Thomas Roth PhD
Detroit, MI, 2010

Preface

Sleepiness is a widespread condition in modern society, in part because sleep deprivation is so pervasive among adolescents and young adults, and increasing rates of obesity have led to sleep-related breathing disorders. However, many disorders that cause sleepiness are now recognized ranging from behavioral to medical, neurological and psychiatric causes. *Sleepiness: Causes, Consequences and Treatment* details the important pathophysiological and clinical features of most disorders of excessive sleepiness.

The understanding of sleepiness in modern times is punctuated by a series of clinical, laboratory and therapeutic landmarks. Clinically, one of the first and most well-known descriptions was of Joe – the fat, sleepy boy who snored loudly; described in *The Posthumous Papers of the Pickwick Club*, by Charles Dickens in 1836 [1]. The condition of a 47-year-old male with "an irresistible and incessant propensity to sleep" was referred to as narcolepsy by Gelineau in 1880 [2]. Then Kleine, in 1925, described a 13-year-old boy who abruptly became drowsy after a febrile illness and displayed cognitive peculiarities for a period of 3 weeks with a similar episode 14 days later [3]; a condition referred to in 1942 by Critchley and Hoffman as the Kleine–Levin syndrome [4]. In 1923, von Economo described excessive sleepiness in patients with encephalitis lethargica that was associated with lesions in the tegmentum and posterior hypothalamus [5]. In the 1950s, Roth described sleepiness, different from narcolepsy, that subsequently was called idiopathic hypersomnia [6]. In 1978, Guilleminault and Dement edited a book entitled *Sleep Apnea Syndromes*, disorders causing sleepiness involving at least 5% of the population [7], and the same year, Lugaresi and colleagues edited a book entitled *Hypersomnia with Periodic Apneas* [8].

Electrophysiological laboratory testing of excessive sleepiness began in 1978 when Carskadon and Dement introduced the multiple sleep latency test to quantify sleepiness [9]. It was some years later in 1991 when a widely useful questionnaire to evaluate the degree of subjective sleepiness, the Epworth sleepiness scale, was developed by Johns [10]. In the late 1990s, discoveries led to the finding that hypocretin, a neuropeptide, is reduced or absent in patients with narcolepsy and cataplexy.

Finally, active pharmacological treatments of sleepiness have evolved from early amphetamines, such as benzedrine [11], to more recently developed and approved agents for narcolepsy, such as gamma-hydroxybutyrate [12] and modafinil [13].

Today, after years of disdain, clinicians recognize the importance of the complaint of sleepiness and the impact on cognitive functions and quality of life. Governmental authorities are increasingly concerned about the role of sleepiness in industrial, road, rail, sea or air accidents, yet no book has ever been published which solely focuses on the causes, consequences and treatment of sleepiness.

Sleepiness: Causes, Consequences and Treatment accumulates the most recently available information on sleepiness and is written by top specialists in the field, including sleep disorders physicians and sleep researchers, from the USA, Europe, Canada and Japan. The chapters are arranged in four major sections: an introductory section, a primary sleep disorders section, a medical, psychiatric and neurological section, and a therapeutic section.

The Introductory section comprises chapters on the epidemiology, neurochemical and neuroimaging of sleepiness, clinical evaluation of the patient, objective and subjective tests of sleepiness, consequences, including the cognitive effects, motor vehicle driving risks and the medico-legal implications. The second section presents the primary disorders of sleepiness such as sleep deprivation, narcolepsy, other central nervous system hypersomnias, pediatric causes of sleepiness, sleep-related breathing disorders, and circadian rhythm disorders, including shift work and sleepiness in the military. The third

section details those medical, neurological, psychiatric, genetic, endocrine, toxic, and metabolic disorders that can cause sleepiness, as well as the effects of medications. The final and fourth section presents chapters on the medications used to treat sleepiness including the stimulants, modafinil, sodium oxybate, and newer alerting agents under investigation, as well as caffeine effects and behavioral treatments of sleepiness.

This volume is intended primarily for sleep disorders specialists and sleep researchers; however, it is suitable for neurologists, psychiatrists, and any researcher interested in the interdisciplinary field of sleep medicine. It will be of use for neurology and psychiatry residents and fellows, clinical psychologists, neuropsychologists, house officers, medical students and mental health and social workers who want to get an understanding of the importance and diagnostic features of excessive sleepiness. Also, this book is important for governmental agencies who are involved in public safety, particularly those in the transportation and occupational areas. In addition, military specialists concerned about fatigue will find this book of great interest along with the legal profession because of the medico-legal implications of excessive sleepiness.

We are greatly indebted to all the authors who have contributed to this book and we are appreciative of the help of the staff of Cambridge University Press in getting this publication in print so quickly so that the contents are up-to-date and current. As research into sleepiness is rapidly advancing, it is anticipated that future editions of this volume, *Sleepiness: Causes, Consequences and Treatment* will take these developments into account.

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Michel Billiard

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Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
AAS	ascending arousal system
ACGME	Accreditation Council for Graduate Medical Educations
ACh	acetylcholine
AD	adenosine
ADEM	acute disseminated encephalomyelitis
AHI	apnea–hypopnea index
ASL	arterial spin labeling
ASPD	advanced sleep phase disorder
Bas	Brodmann areas
BDI	Beck Depression Inventory
BF	basal forebrain
BiPAP	bilevel positive airway pressure
CAP	cyclic alternating pattern
CF	cystic fibrosis
CGI-C	Clinical Global Impression Scale of Change
CHD	coronary heart disease
CMT	Charcot–Marie–Tooth disease
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPT	continuous performance test
CSA	central sleep apnea
CSF	cerebrospinal fluid
CSR	chronic sleep restriction
DA	dopamine
DIMS	difficulty initiating or maintaining sleep
DLMO	dim light melatonin onset
DMD	Duchenne muscular dystrophy
DOPAC	dihydroxyphenylacetic acid
DS	Digit Span (test)
DSPD	delayed sleep phase disorder
DSPS	delayed sleep phase syndrome
DSST	digit symbol substitution task
EDS	excessive daytime sleepiness
EDSS	expanded disability status scale
EEG	electroencephalography
EMG	electromyogram
EOG	electrooculogram
ES	excessive sleepiness
ESS	Epworth sleepiness scale
FASPS	familial advanced sleep phase syndrome
FSS	Fatigue Severity Scale
GHB	γ-hydroxybutyrate
GPCR	G-protein-coupled receptor
HEEDNT	head, eyes, ears, nose, throat
HH	hypnagogic hallucinations
HLA	human leukocyte antigen
HMSN	hereditary motor and sensory polyneuropathies
HOMA	homeostasis model assessment
HOS	hours of service
HPA	hypothalamic–pituitary–adrenal
HRQoL	health-related quality of life
HTP	hypothalamo-pituitary–thyroid
HVA	homovanillic acid
ICC	intraclass correlation coefficients
ICSD	International Classification of Sleep Disorders
IGF BP	insulin-like growth factor binding protein
IH	idiopathic hypersomnia
IOM	Institute of Medicine
IPF	idiopathic pulmonary fibrosis
ISWT	irregular sleep–wake type
IVIg	intravenous immunoglobulin
KDS	Karolinska drowsiness score
KLS	Kleine–Levin syndrome
KSS	Karolinska sleepiness scale
LC	locus coeruleus
LHA	lateral hypothalamic area
MCH	melanin-concentrating hormone
MHAT	Mental Health Assessment Team
MHPG	3-methoxy-4-hydroxyphenylglycol
MIRS	muscular impairment rating scale
MMSE	mini mental status examination
MS	multiple sclerosis
MSL	mean sleep latency

List of abbreviations

MSLT	multiple sleep latency test
mTBI	mild traumatic brain injury
MWT	maintenance of wakefulness test
NAFLD	non-alcoholic fatty liver disease
NARP	neuronal activity-regulated pentraxin
NCL	neuronal ceroid lipofuscinosis
NCV	nerve conduction velocity
NE	norepinephrine
NHP	Nottingham Health Profile
NIAV	non-invasive assisted ventilation
NORD	National Organization of Rare Disorders
NREM	non-REM
OAD	obstructive airway disease
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
OSLeR	Oxford sleep resistance test
PAP	positive airway pressure
PASAT	Paced Auditory Serial Addition Task
PBC	primary biliary cirrhosis
PCS	post-concussion syndrome
PD	Parkinson's disease
PDSS	pediatric daytime sleepiness scale
PET	positron emission tomography
PFC	prefrontal cortex
PLMA	periodic leg movement arousal index
PLMI	periodic leg movement index
PLMS	periodic limb movements in sleep
PMDD	premenstrual dysphoric disorder
POMS	profile of mood states
PPN	pedunculopontine tegmental
PPT/LDT	pedunculopontine and laterodorsal tegmental nuclei
PRC	phase-response curve
PSD	partial sleep deprivation
PSG	polysomnography
PSQI	Pittsburg sleep quality index
PSQ-SS	pediatric sleep questionnaire, sleepiness scale
PST	pupillographic sleepiness test
PTT	pulse transit time
PUI	pupillary unrest index
PVT	psychomotor vigilance test
RAS	reticular activating system
RBD	REM sleep behavior disorder
rCBF	regional cerebral blood flow
RDI	respiratory disturbance index
REM	rapid eye movement
RES	residual excessive sleepiness
RLS	restless legs syndrome
SAFTE	sleep, activity, fatigue and task effectiveness
SBAR	situation background assessment recommendation
SCA	spinocerebellar ataxias
SCN	suprachiasmatic nucleus
SD	sleep deprivation
SDB	sleep-disordered breathing
SEM	slow eye movements
SLSJ	Saguenay–Lac-Saint-Jean
SMA	spinal muscular atrophies
SMS	Safety Management System
SO	sodium oxybate
SOL	sleep onset latency
SOREMP	sleep onset REM period
SPECT	single-photon emission computed tomography
SPMS	sleep/performance management system
SSRI	selective serotonin reuptake inhibitor
SSS	stanford sleepiness scale
SURT	surrogate reference task
SWA	slow-wave activity
SWD	Shift Work Disorder
SWE	slow-wave energy
SWMT	Sternberg Working Memory Task
SWP	sleep–wake predictor
SWS	slow-wave sleep
SXB	sodium oxybate
TBI	traumatic brain injury
TIB	time in bed
TMN	tuberomamillary nucleus
TMS	transcranial magnetic stimulation
TPM	the three process model of alertness
TSD	total sleep deprivation
TSH	thyroid-stimulating hormone
TST	total sleep time
UARS	upper airway resistance syndrome
VAS	visual analogue scale
VLPO	ventrolateral preoptic nucleus
VNS	vagus nerve stimulator
VNTR	variable number tandem repeat
vPAG	ventral periaqueductal gray matter
WASO	wake time after sleep onset
WRAIR	Walter Reed Army Institute of Research