LEADING ARTICLE

Excessive Sleepiness: Determinants, Outcomes, and Context

Marcella Oonk, BSc, Adrienne M Tucker, MS, Gregory Belenky, MD, and Hans PA Van Dongen, PhD

Sleep and Performance Research Center, Washington State University, Spokane, WA, USA

Sleepiness level is determined by two interacting neurobiological processes: the homeostatic balance between sleep and wakefulness, and the endogenous circadian rhythm. Disruptions of these two processes contribute to excessive sleepiness in a variety of sleep disorders (e.g. insomnia, shift-work disorder) and in operational settings involving extended hours and shift work. However, excessive sleepiness manifests itself in diverse ways depending upon which variables are measured and how. Broadly, sleepiness measures can be categorized as subjective, physiological, or cognitive performance-related. Aside from a variety of technical measurement issues, different demand characteristics and other context parameters contribute to discrepancies between these categories in measured sleepiness. Diagnosing excessive sleepiness is complicated by the context-dependent diversity in outcomes and by the intertwined contributions of the underlying neurobiological processes. Therefore, for successful diagnosis and treatment of excessive sleepiness it is essential to consider the metrics used to assess it, the underlying neurobiology, and the context. *Int J Sleep Wakefulness* 2008;**1**(4):141–7.

Neurobiological determinants of sleepiness

The International Classification of Sleep Disorders defines daytime sleepiness as "the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep" [1]. This will be adopted here as an operational definition of sleepiness, recognizing that there are gradations of sleepiness level and that sleepiness may occur both day and night. Other terminology is in use for the same general phenomenon, such as drowsiness and tiredness; the term fatigue is typically used in operational environments [2]. There is controversy about the precise interpretation of these concepts and what might differentiate them [3–5]. However, as will be explained, there are multiple dimensions of sleepiness and fatigue, which present more fundamental challenges than mere issues of definition. As such, we will bypass the definition debate, consider the alternative terms to be interchangeable in practice, and use only the term sleepiness here.

Sleepiness is regulated by two basic neurobiological processes: the homeostatic balance between sleep and wakefulness, and the endogenous circadian rhythm [6]. The balance between sleep and wakefulness results in pressure for sleep: the greater the amount of prior wakefulness and/or the smaller the amount of prior sleep, the greater the pressure for sleep. The circadian rhythm opposes the sleep pressure by providing a daytime pressure for wakefulness [7]. Driven by the endogenous biological clock, the wake pressure is greatest in the early evening and lowest in the early morning. During a normal day with daytime wakefulness and nighttime sleep, the two processes counteract each other in such a manner that a stable level of low sleepiness is maintained through most of the day, while a stable level of high sleepiness is maintained through most of the night. This results in alert daytime wakefulness and consolidated nighttime sleep [8].

Alterations in one or both of the two basic regulatory processes lead to increased sleepiness during periods of wakefulness. This can be observed under conditions of sleep deprivation, which disrupt the sleep–wake balance, enhancing the pressure for sleep and thereby the net sleepiness level. It may also be observed when the endogenous circadian rhythm is misaligned relative to the timing of wakefulness, e.g. as tends to occur in shift-work. In this case, the pressure for wakefulness from the circadian rhythm does not oppose the pressure for sleep in a timely fashion, resulting in greater sleepiness during wakefulness and less sleepiness during the sleep period. The latter effect may interfere with the consolidation of sleep, leading additionally to a disruption of the sleep–wake balance and thereby compounding the sleepiness problem.

Address for correspondence: Hans PA Van Dongen, Sleep and Performance Research Center, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495, USA. Email: hvd@wsu.edu

Sleepiness due to sleep disorders

Disruptions of the two basic neurobiological processes regulating sleepiness are involved in a variety of sleep disorders. These disruptions contribute to the excessive sleepiness that is associated with many of them. Therefore, sleep disorders associated with sleepiness can be categorized by the primary neurobiological disruption involved – the sleep–wake balance or the circadian rhythm.

Sleep disorders primarily entailing disruption of the sleep–wake balance include the insomnias, sleep-related movement disorders, and sleep-related breathing disorders. The insomnias are sleep disorders involving repeated difficulty initiating or maintaining sleep or poor quality sleep, usually in association with waking impairment [9]. Sleep-related movement disorders are associated with disturbed sleep and impaired waking function due to movements during sleep [1], in periodic limb movement disorder for instance. Sleep-related breathing disorders, such as obstructive sleep apnea, are characterized by disordered respiration during the sleep period [1], causing sleep disturbance. In these disorders the sleep–wake balance is disrupted in favor of excess wakefulness, causing chronically enhanced sleep pressure leading to sleepiness complaints. In the case of sleep-related breathing disorders, repeated exposure to hypoxia may contribute to waking impairment [10], but the disruption of the sleep–wake balance due to sleep fragmentation also plays a significant role [11].

Sleep disorders primarily entailing disruption of the circadian rhythm are known collectively as circadian rhythm sleep disorders. They are characterized by a misalignment between the timing of the endogenous circadian rhythm and the (desired) sleep time [1]. Examples include the advanced and delayed sleep phase syndromes, irregular sleep–wake rhythm, and shift-work disorder. The misalignment of the circadian rhythm results in improperly timed pressure for wakefulness, such that it is low during wakefulness resulting in enhanced sleepiness, and high during the sleep period resulting in sleep disturbance and disruption of the sleep–wake balance, which further enhances sleepiness.

Mitigating excessive sleepiness is an important goal in the treatment of many sleep disorders. Distinguishing which of the two basic neurobiological processes regulating sleepiness is the primary dysregulated factor is helpful for diagnosis and treatment. However, the causal pathways overlap, which is a problem when trying to differentiate the two processes on the basis of the observed sleepiness alone.

Sleepiness from occupational demands and lifestyle

Sleepiness is not just a symptom of sleep disorders; it is also a by-product of modern lifestyles and the 24/7 economy, which involve demands for wakefulness at all hours of the day and night in large segments of the population [12]. Extended work hours and long commutes leave little time for sleep [13], and shift work schedules interfere with sleeping at the appropriate circadian time [14]. The pathways leading to sleepiness are essentially the same as those described above for sleep disorders, namely disruption of the sleep–wake balance and disruption of the circadian rhythm.

In safety-critical settings sleepiness can have considerable consequences. Sleepiness has been implicated in errors and accidents in the work environment, including catastrophes like the Exxon Valdez grounding and the Chernobyl nuclear meltdown, resulting in monumental cost to society [15]. Conversely, decreasing work demands can help restore sleep–wake balance and circadian alignment, yielding reduced errors and improved work performance [16].

Measuring sleepiness

Sleepiness is expressed in various different ways [17], which can broadly be categorized as subjective, physiological, and cognitive performance related. The measurement of these aspects of sleepiness is discussed in an earlier article in this journal [18]. Here, we recapitulate some of the measurement issues as they relate to difficulties encountered in the diagnosis and treatment of excessive sleepiness.

Subjective sleepiness

The measurement of subjective sleepiness, i.e. the personal awareness of sleepiness, depends on introspection and self-report. Measures of subjective sleepiness include scales and questionnaires of either present feelings of sleepiness (present state) or present and past feelings of sleepiness (sometimes referred to as trait sleepiness [19]). Most subjective sleepiness measures, including the widely used Karolinska Sleepiness Scale [20], inquire about feelings (sensations) of sleepiness. Some measures have been developed to gauge sleepiness by self-report of subjects' behaviors (e.g. falling asleep while watching television), such as the Epworth Sleepiness Scale [21].

Measures of subjective sleepiness provide a convenient way of gathering information on sleepiness, but the sleepiness scores they yield are relative metrics. People vary in how they use subjective scales (e.g. some are more prone to using the extremes of a scale than others). In most cases subjective data can only be interpreted reliably as within-subject change scores, e.g. relative to a person's own baseline data [22]. Inter-individual comparisons are not likely to be meaningful unless averages over large groups are considered.

Furthermore, people may be biased in their personal evaluations of sleepiness and this bias may be affected by

sleepiness itself. The context (i.e. the conditions, circumstances, and social expectations) in which subjective ratings of sleepiness are recorded also affects the outcome [23]. Finally, there are issues of validity, reliability, and other psychometric considerations related to the construction [22] and administration [24] of self-report scales. Nonetheless, self-report measures of sleepiness are important because they aim to capture people's personal experience, which, more so perhaps than objective evidence, is what may prompt them to complain of excessive sleepiness.

Physiological sleepiness

Physiological sleepiness is commonly defined as increased sleep propensity, i.e. a greater tendency to fall asleep [25]. The most widely used measures of sleep propensity are the Multiple Sleep Latency Test (MSLT) [25] and the Maintenance of Wakefulness Test (MWT) [26]. Each of these involves multiple sessions in which a subject is sequestered in a sleep-conducive environment and the time to fall asleep is measured. In the MSLT the subject is asked to try and fall asleep, while in the MWT the instruction is to try and stay awake. The tests are based on the assumption that the more rapidly a person falls asleep, or the more difficult it is to stay awake, the more objectively sleepy he or she must be. The repeated test sessions are performed to help distinguish true physiological sleepiness from extraneous confounders resulting from, for example, motivation or anxiety.

Other physiological measures of sleepiness include the amounts of theta and alpha activity in the waking electroencephalogram (EEG), which are believed to be related to sleepiness [27], and event-related potential measurements derived from the EEG, which exhibit pattern changes in response to sleep deprivation in parallel with sleep propensity [28]. A range of oculomotor measures have been proposed to assess physiological sleepiness, including pupillometry, saccadic velocity, slow eye movements, blinking, and slow eyelid closures [29]. Furthermore, cardiovascular indices have been reported to co-vary with sleepiness [30]. These other physiological measures have been pioneered in operational settings, but are not frequently applied there and are seldom used in clinical practice.

The sleep–wake physiology underlying the various measures of physiological sleepiness is interwoven with other physiological and neurological systems, such as the sympathovagal balance (for EEG-based and cardiovascular measures) or the visual system (for ocular measures). This makes these measures susceptible to internal influences (e.g. mood states) and external influences (e.g. light exposure) that may be hard to control. An additional problem pertaining to the MSLT is that there appear to be people with high sleep ability, i.e. the ability to fall asleep rapidly, without being sleepy [31]. Despite these limitations and the fact that most physiological sleepiness tests are relatively invasive, time consuming, and/or expensive, they are considered useful as objective tools for measuring sleepiness. In fact, the MSLT is seen as the "gold standard" for assessing sleepiness in clinical settings [32].

Cognitive performance impairment

Sleepiness is associated with deficits in a variety of cognitive functions, including sustained attention, working memory, hand–eye coordination, memory retention, decision making, and planning [33]. Various performance tests, ranging from simple reaction-time tests like the widely used Psychomotor Vigilance Test (PVT) [34] to tests that require complex cognitive processing (e.g. the Tower of London test) [35], and even high-fidelity simulators for driving and other real-world tasks, are used to measure these deficits. Typical outcome variables include mean reaction times, number of delayed responses (lapses), number of correct responses, and number of errors.

Problems with performance measures of sleepiness include speed/accuracy trade-offs, practice effects, and vulnerability to internal and external influences, such as motivation, aptitude, environmental stimulation, and test characteristics [23]. Cognitive performance outcomes relying on executive functions – the cognitive abilities needed to set goals and flexibly direct behavior to achieve them – may be the most difficult to interpret. Although they are believed to be particularly affected by sleepiness [36], they are comprised of both simple and complex cognitive components that typically cannot be separated [37]. In addition, measures of complex cognitive performance may be confounded by uncontrollable variability in performance strategies and a variety of other psychometric issues [38].

Regardless of such methodological considerations, it could be argued that measures of cognitive performance deficits associated with sleepiness are valuable because they may have direct relevance to functioning in operational environments. Simple reaction-time tasks requiring sustained attention, including the PVT, have been found to be practical and sensitive performance assays of sleepiness in the laboratory as well as in the field [34,39].

Discrepancies among measures of sleepiness and the role of context

The scientific literature contains numerous reports concerning discrepancies among the various subjective, physiological, and performance-related measures of sleepiness [40–44]. Recent studies of inter-individual differences in the effects of sleep deprivation on sleepiness level have revealed that individuals ranking highest or lowest

on subjective measures of sleepiness do not necessarily rank the same way on physiological [45] or performance-based measures [46]. Within the same person the manifestations of sleepiness can be varied and the correlations among different types of sleepiness measures tend to be low (Fig. 1, top panels). Moreover, sleepiness outcomes are not mirrored in the physiology of sleep itself (Fig. 1, bottom panels), suggesting that sleep–wake neurobiological processes may not be the only determinants of sleepiness.

The discrepancies among measures of sleepiness can partly be explained by the demand characteristics associated with the different measurement tools. Each type of measure requires distinct actions from the individuals being tested. They may, for example, be asked to introspect, try to fall asleep, sit still for artifact-free EEG recording, sustain attention to perform a cognitive task, or drive a driving simulator. Thus, the demand characteristics associated with each measure – the context – constitute an influential differentiating factor. Therefore, what is being asked of people in order to measure their sleepiness co-determines what the outcome will be. Hence, it is important to consider which measure (or suite of measures) of sleepiness is the most relevant for any given situation.

Diagnosing excessive sleepiness

Excessive sleepiness may be defined as "inappropriate or undesired sleepiness that occurs when an individual would be expected to be awake and alert" [47]. Excessive sleepiness involves difficulty maintaining desired wakefulness and adversely affects functioning. Proper diagnosis [48] and treatment [49,50] of excessive sleepiness is challenging due to complexities associated with the basic neurobiological determinants of sleepiness and the different outcome measures of sleepiness (Fig. 2).

Diagnosing patients who report excessive sleepiness is complicated because the sleepiness may present itself in diverse ways, depending on the outcome variable. Rather than selecting one particular sleepiness measure and declaring it a (clinical) standard [1,32], it may be useful to consider the context that matters most to the patient. For instance, when a patient presents to a physician because of difficulty sustaining attention, performance tests assessing this ability could be employed to evaluate the sleepiness level. If a person's ability to drive safely is questioned, the MWT may be a reasonable method to assess excessive sleepiness as it requires staying awake in an environment with low levels of stimulation, which is a critical component of driving ability [51]. If the primary complaint is focused on the sensation of excessive sleepiness, then perhaps the diagnosis should be focused on that subjective concern.

In practice, it may not be possible to pinpoint one specific sleepiness concern and use of a suite of distinct sleepiness measures may be warranted. For instance, one could compose a battery of tests with an assessment of sustained attention (e.g. the PVT), a test of working memory (e.g. the Digit–Symbol Substitution Test [52]), a test of executive function (e.g. the Stroop Color and Word Test [53]), and a subjective measure of sleepiness (e.g. the Epworth Sleepiness Scale [21]). As discussed above, it is possible to obtain seemingly incongruent results from such a mixed test battery. However, when the findings are interpreted in their appropriate contexts, together they can help to determine specific sleepiness vulnerabilities. For example, if an individual were to exhibit considerable impairment only on the PVT this would indicate a sleepiness problem related primarily to sustained attention. It would suggest he or she is most at risk in circumstances highly dependent on sustaining attention, such as driving a car.

When diagnosing excessive sleepiness one should also differentiate which of the underlying neurobiological determinants is primarily involved, the sleep–wake balance or the circadian rhythm [54]. However, sleepiness reflects the influence of the neurobiological determinants in an irrevocably intertwined manner. To disentangle the two processes contextual information is needed, including a sleep–wake history and an assessment of the circadian rhythm [55].

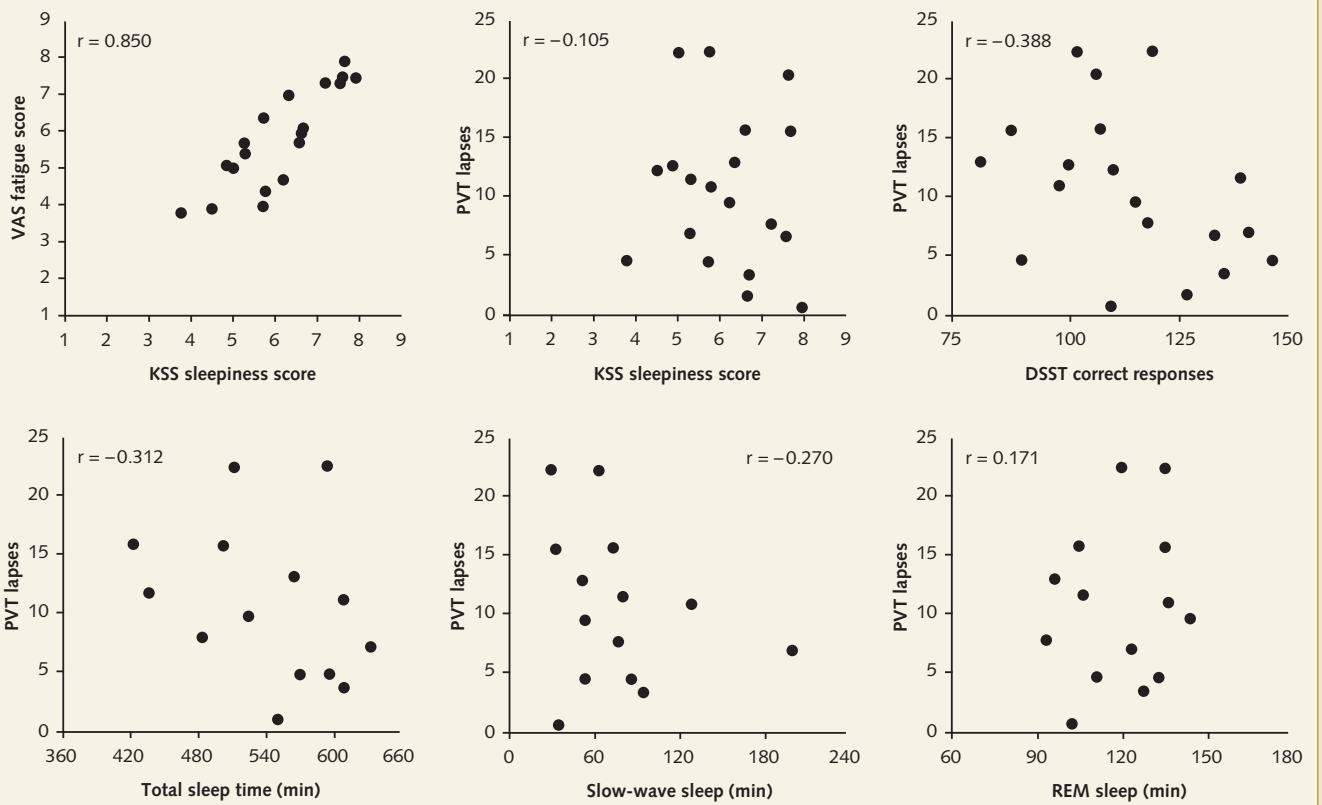
Treating excessive sleepiness

Prescriptive strategies have been established for the treatment of excessive sleepiness resulting from sleep disorders [1]. No such standardization has been implemented for sleepiness countermeasures in the work place and in daily life. However, effective treatment is possible [56]. For excessive sleepiness resulting from disruption of the circadian rhythm, treatment with melatonin or bright light may be useful [57]. For excessive sleepiness resulting primarily from disrupted sleep–wake balance, treatment with hypnotics to increase sleep duration [58] or with stimulants to counteract sleepiness during the waking period [59] may yield improvement. These approaches should typically be complemented with sleep hygiene education and a discussion of the specific sleepiness vulnerabilities and the contexts in which the patient may be at risk.

Treatment options for excessive sleepiness are discussed in the scientific literature [1,49,50,54]. To choose between options a consideration of the context may again be important. For example, the use of hypnotics is restricted in many round-the-clock operational settings because of the potential difficulty waking up to respond to an emergency. However, hypnotics may be useful to improve sleep–wake balance at home.

Excessive sleepiness is often combated by means of stimulants, with caffeine being the most widely used. Large inter-individual differences in sensitivity to caffeine limit the

Figure 1. Different manifestations of sleepiness in relation to each other and to baseline sleep physiology. Sleepiness was induced by keeping subjects awake for 36 h in a controlled laboratory environment [66]. Nineteen healthy adult subjects were twice subjected to this intervention. Their sleepiness levels were measured every 2 h by subjective assessments on the KSS [20] and a VAS of fatigue [46]; by lapses (reaction times ≥500 ms) on the PVT [34]; and by correct responses on a computerized DSST [46]. Data were averaged over the last 24 h of each 36-h sleep deprivation. In light of the trait-like nature of responses to sleep deprivation [46], the data were further reduced by averaging across the two sleep deprivations. The top panels show pair-wise relationships between the different sleepiness measures. For instance, the top left panel compares sleepiness scores on the KSS with those on the VAS; every dot represents a different subject. The correlation among these two variables – both being subjective measures of sleepiness – was high (see the r statistic in the upper left corner). However, as seen in the middle and right panels of this row, much lower correlations were found between the KSS and the PVT, and between the PVT and the DSST [46]. Thus, the overall expression of sleepiness varied considerably from one measure to another. This variability was not predicted by subjects' baseline sleep characteristics (recorded nocturnally at 12 h time in bed [66]), as illustrated in the bottom panels for the PVT (14 subjects).

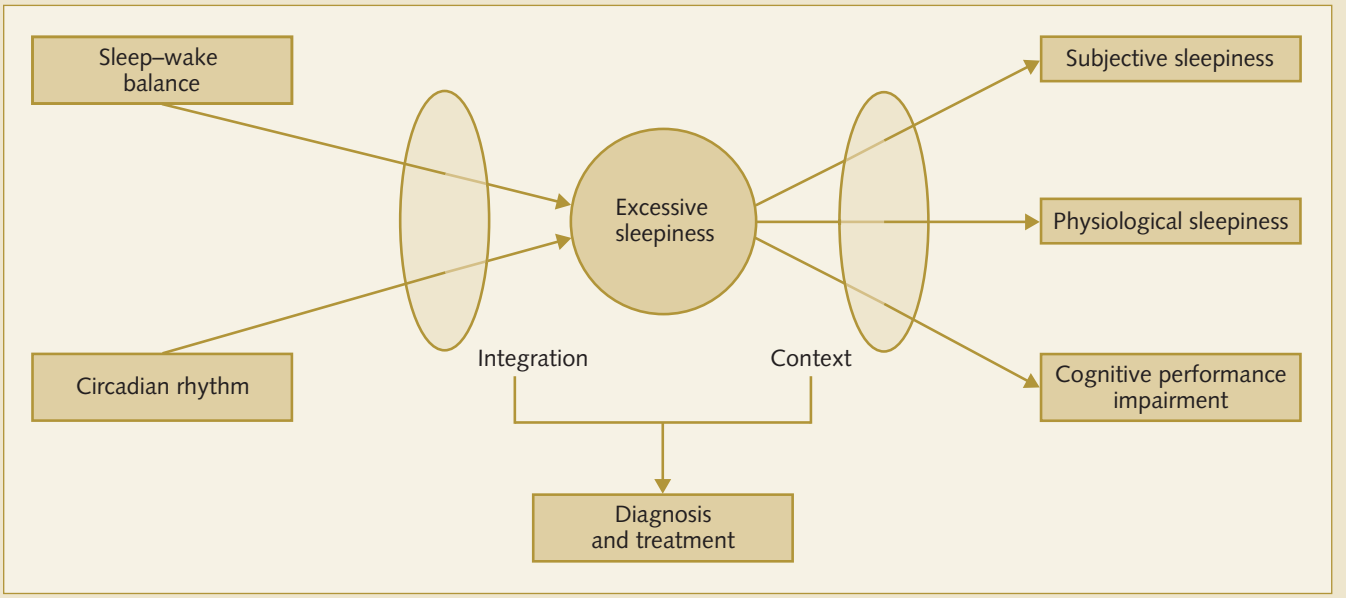


DSST: Digit–Symbol Substitution Task; KSS: Karolinska Sleepiness Scale; PVT: Psychomotor Vigilance Test; REM: rapid eye movement; VAS: Visual Analogue Scale.

usefulness of this countermeasure for some [60]. In addition, different stimulants may affect different aspects of sleepiness to varying degrees. While scientific knowledge in this area is incomplete, preliminary evidence suggests that stimulants may vary in the extent to which they can restore executive functions [61]. Furthermore, stimulants may or may not resolve any mood disturbances associated with excessive sleepiness. Future studies may yield more insight into the need to select specific stimulants depending on the nature of the sleepiness complaint.

To treat excessive sleepiness accompanying shift-work disorder the schedule IV drug modafinil may be prescribed [62]. An intriguing new approach to treating shift-work disorder is to try and improve daytime sleep using melatonin or melatonin analogues, which helps to restore sleep–wake balance and may consequently reduce sleepiness [63]. Recent discoveries regarding the genetics underlying specific vulnerabilities to sleepiness [64,65] will promote the development of more precisely targeted pharmacological countermeasures for different aspects of excessive sleepiness.

Figure 2. Conceptual framework for the underlying neurobiological pathways and the different manifestations of excessive sleepiness. Sleepiness is regulated by processes governing sleep–wake balance and circadian rhythm. Disruptions of these processes have an integrated effect, making it difficult to derive which process is the primary determinant of observed sleepiness. Furthermore, sleepiness manifests itself in different ways, as influenced in part by the context in which it is experienced or measured. These issues complicate the diagnosis and treatment of excessive sleepiness.



Conclusion

Considering excessive sleepiness and its manifestations in the proper context is important for accurate diagnosis and effective treatment. It is helpful to distinguish whether the sleepiness results primarily from disruption of the circadian rhythm or from disruption of the sleep–wake balance. Within a given individual, excessive sleepiness may be expressed to varying degrees depending on which aspect of sleepiness is considered (subjective, physiological, or performance-based). The way sleepiness is manifested depends on the context in which it is experienced, including how it is measured. Similarly, the success of a given treatment approach depends on the context in which it is experienced or evaluated. As such, diagnosis and treatment of excessive sleepiness are not to be seen as routine procedures, but as context-dependent processes requiring interaction with the affected individual, as well as access to a variety of diagnostic tools and treatment options.

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