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Sleep-Wake Disorders in Stroke—Increased Stroke Risk and Deteriorated Recovery? *An Evaluation on the Necessity for Prevention and Treatment*

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Abstract

Purpose of Review Sleep-wake disorders (SWD) are common not only in the general population but also in stroke patients, in whom SWD may be pre-existent or appear "de novo" as a consequence of brain damage. Despite increasing evidence of a negative impact of SWD on cardiocerebrovascular risk, cognitive functions, and quality of life, SWD are insufficiently considered in the prevention and management of patients with stroke. This narrative review aims at summarizing the current data on the bidirectional link between SWD and stroke.

Recent Findings Several studies have demonstrated that sleep-disordered breathing (SDB) is an independent risk factor for stroke and has a detrimental effect on stroke recovery. Short and long sleep duration and possibly other SWD (e.g., insomnia, circadian rhythm disorders) may also increase the risk of stroke and influence its outcome. Data on SDB treatment increasingly indicate a benefit on stroke risk and evolution while treatment of other SWD is still limited.

Summary A systematic search for SWD in stroke patients is justified due to their high frequency and their negative impact on stroke outcomes. Clinicians should actively consider available treatment options.

Keywords Stroke · Sleep-disordered breathing · Sleepiness · Insomnia · Sleep duration · Risk · Outcome

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This article is part of the Topical collection on *Stroke*

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Abbreviations

AHI	Apnea-hypopnea index
ASV	Adaptive servoventilation
BDNF	Brain-derived neurotropic factor
CBT	Cognitive-behavioral therapy
CBT-I	Cognitive-behavioral therapy for insomnia
CI	Confidence interval
CPAP	Continuous positive airway pressure
EDS	Excessive daytime sleepiness
HR	Hazard ratio
MSFsc	Mid-sleep on free days corrected for over-sleep on free days
NREM	Non-rapid eye movement
OR	Odds ratio
OSA	Obstructive sleep apnea
PLM	Periodic limb movements
RBD	REM sleep behavior disorder
RCTs	Randomized clinical trials

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REM	Rapid eye movement
RLS	Restless legs syndrome
SDB	Sleep-disordered breathing
SMD	Standardized mean difference
SRMD	Sleep related movement disorders
SWD	Sleep-wake disorders
TIA	Transient ischemic attack

Introduction

A good night's sleep is essential for physical and mental health and well-being. Although researchers and clinicians better understand the role of sleep for brain and body functions [1–3], sleep is still neglected in the prevention and management of neurological diseases.

Stroke, resulting from either thrombotic or embolic obstruction or hemorrhagic rupture of a supplying cerebral artery, is one of the most frequent neurological diseases affecting 2–3/1000 individuals a year [4]. Despite improved awareness of the relevant stroke risk factors, such as hypertension, dyslipidemia, glucose disorders, obesity, atherosclerosis as well as cardiovascular diseases, and the significant improvement of acute stroke management due to thrombolysis and thrombectomy, stroke is still the most frequent cause of long-term disability in adulthood (www.strokecenter.org). Hence, new preventive and therapeutic strategies to offer high-quality care to these vulnerable patients are of major importance.

Six main categories of sleep-wake disorders (SWD) are differentiated in the *International Classification of Sleep Disorders* (3rd Edition) [5]: (a) *Sleep-related breathing disorder* of obstructive or central origin is the most studied sleep disorder in stroke. Obstructive sleep apnea (OSA) syndrome affects up to 10% of men and about 2–5% of women in the general population [5, 6], whereas the prevalence of central sleep apnea syndrome varies with its underlying cause [6]. (b) *Insomnia disorder* is increasingly associated with adverse mental (e.g., depression) and physical (e.g., hypertension and metabolic disorders) health effects, and with a prevalence of 6–10%, it is the most frequent sleep disorder in the general population [7]. (c) *Central disorders of hypersomnolence* cause daytime sleepiness and/or prolonged sleep duration. Prevalence rates of excessive daytime sleepiness in the general population range between 4 and 26% depending on the method of assessment [7]. (d) *Circadian rhythm sleep-wake disorders*, in particular delayed and advanced sleep-wake phase disorder, affect about 0.17 and 1%, respectively, of the general population [8]. Phase delays are most prevalent in adolescents and young adults with a prevalence of 7–16% [5, 8]. (e) *Sleep-related movement disorders* include simple, repetitive movements during sleep. They are associated with daytime symptoms such as dysesthesia or urge to move the legs in restless legs syndrome (RLS), affecting about 5–10% of the European and North American population, but not in the case of periodic limb movements (PLM) [7]. The population prevalence of PLM with more than 15 events per hour is estimated at 7.6% in the 18- to 65-year-olds [5]. (f) *Parasomnias* include complex movements and actions during non-rapid eye movement sleep (NREM), rapid eye movement (REM), or both sleep stages. Prevalence rates in the general population largely vary with parasomnia subtype, age, and medical conditions. Prevalence of NREM parasomnias such as sleepwalking, sleep terrors, sleep-related eating disorder, and nightmare disorder is estimated at about 2–5% in adults and for REM parasomnias, i.e., REM sleep behavior disorder, at 0.5–2% with higher prevalence in males and adults over 50 years of age [5, 9].

SWD are frequently observed in stroke patients [10••, 11, 12•, 13]. They may either be a risk factor or a consequence of stroke [14, 15]. In addition to focal brain damage, medical, environmental, and psychological factors during the acute and the rehabilitation phases can contribute to their development, persistence, or aggravation. Increasing evidence suggests that disturbed sleep is associated with an increased cardiocerebrovascular morbidity and decreased stroke outcome [15]. Conversely, there is evidence that good sleep may have a neuroprotective effect and promote neuroplasticity as well as functional recovery after stroke [1, 3] (see Fig. 1).

This article reviews the interactions between sleep and SWD with stroke risk and stroke outcome.

Sleep-Disordered Breathing (SDB)

SDB as Risk Factor of Stroke

Several meta-analyses and population-based observational cohort studies have shown that obstructive sleep apnea (OSA), the most common form of sleep-disordered breathing, is a relevant risk factor for stroke. In the general population, OSA approximately doubles the risk for a stroke in untreated patients, with studies showing an odds ratio (OR) of 2.24 (95% confidence interval (CI), 1.57–3.19) or relative risk of 2.02 (95% CI, 1.40–2.90) [17–21]. In some studies, the risk was

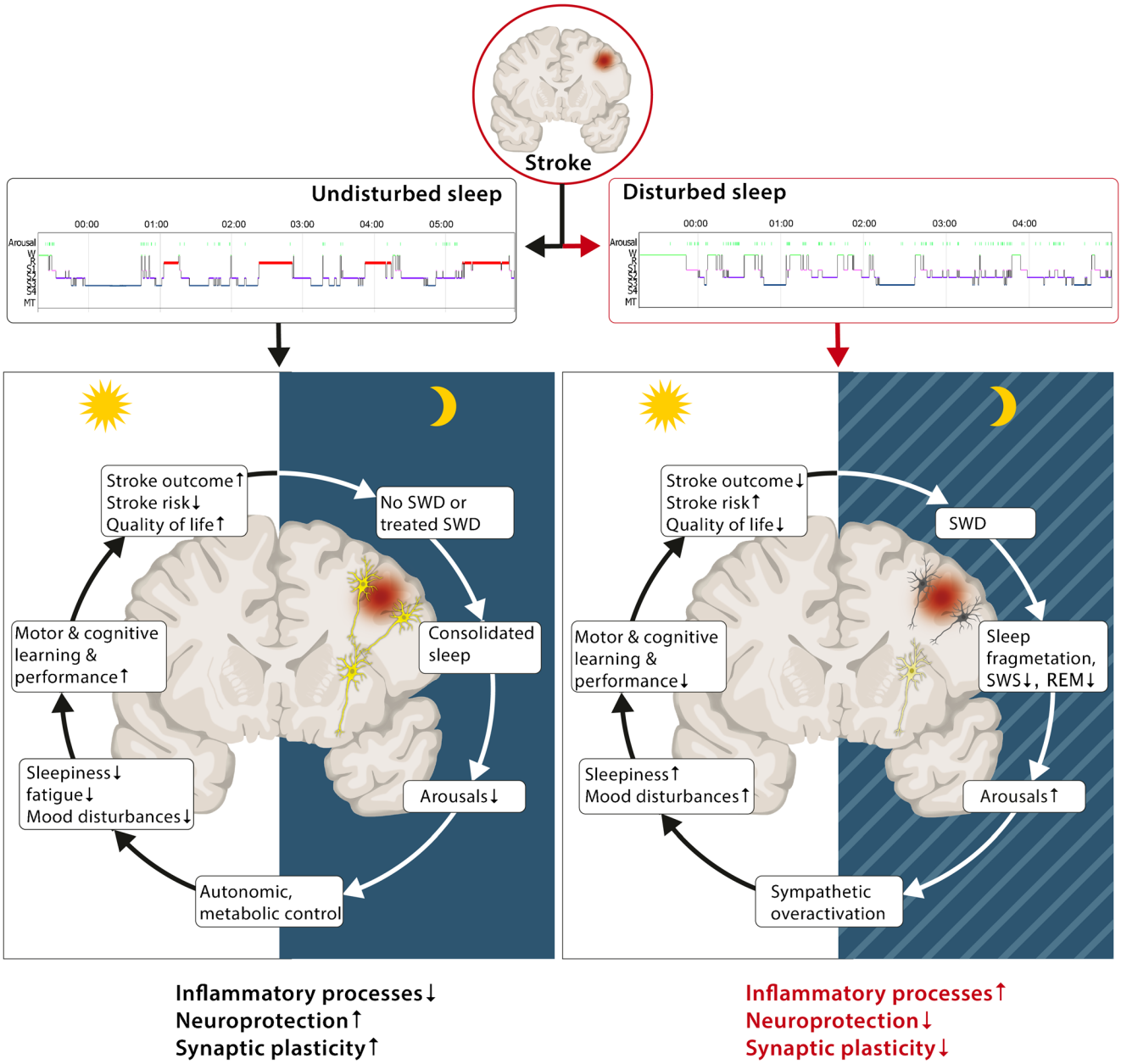

Fig. 1 Concept of impact of sleep-wake disorders and their treatment on stroke recovery. The two circles illustrate the impact of undisturbed sleep in stroke patients (absence of SWD or their effective treatment) and disturbed sleep due to the presence of SWD on neurological, physical, and psychological stroke recovery. Abbreviations: SWD, sleep-wake disorders; SWS, slow wave sleep; REM, rapid eye movement sleep. Adapted from Pincherle and colleagues [16]

highest in younger women and middle-aged OSA patients [22, 23]. In the Outcomes of Sleep Disorders in Men (MrOS) Study in 2872 community-dwelling men, the severity of nocturnal hypoxemia rather than the apnea-hypopnea index (AHI) bore a higher risk for a fatal stroke in elderly men [24]. There are also studies suggesting that OSA is an independent risk factor for the recurrence of stroke or transient ischemic attack (TIA) [25, 26].

SDB in Acute Stroke and Its Treatment

After stroke, the prevalence of SDB is high, with about 70% of stroke survivors presenting with an AHI of more than 5/h

and about 30% with an AHI of greater than 30/h [13, 27, 28]. As in the general population, OSA is also the predominant SDB type in patients with stroke or TIA. Central sleep apnea and hypoventilation syndromes are also seen, but overall less common.

The evolution of SDB after stroke is still uncertain. On the one hand, SDB and especially OSA has been described to be stable in severity in group comparisons [13, 27], which implies that it might be pre-existent or irreversibly caused by stroke. On the other hand, few longitudinal studies and clinical case observations [29] showed a decrease in SDB severity (and particularly in the central component) during recovery from stroke [30–33], supporting the hypothesis of de novo development of SDB with stroke or an acute aggravation of pre-existing SDB.

Stroke topography and etiology may have an influence on the type and severity of SDB. Infratentorial strokes were found to be associated with more severe and obstructive SDB [34], whereas supratentorial strokes affecting the central autonomic network [35] were associated with central SDB. In addition, wake-up strokes with right-to-left shunts and cardioembolic and macroangiopathic strokes were reported to be associated with SDB [33, 36, 37].

Several screening tools have been developed for SDB in the general population [38]. However, their validity has not been sufficiently tested in stroke patients. Home sleep apnea testing was shown to be feasible and financially affordable for the diagnosis of SDB in the acute stroke setting [13, 28, 34, 39–41]. The best timing to perform these studies remains, however, unclear [42].

Several studies have shown that OSA is associated with a higher mortality [43–46], worse stroke recovery, and longer hospital stays [47–49] after stroke. Data on central sleep apnea are conversely scarce.

Treatment of SDB is usually attempted first with continuous positive airway pressure (CPAP) and adaptive servoventilation (ASV). In a recent meta-analysis, Brill et al. could retrieve 10 randomized control trials performed between 1980 and 2016, which were performed in a total of 564 patients with stroke [50••]. The mean CPAP use across these trials was 4.53 h per night (95% CI, 3.97–5.08). Our group has shown before that ASV can be used also for CSA after stroke [51].

Impact of SDB Treatment on Stroke Risk and Stroke Outcome

Even though RCTs randomized clinical trials (RCTs) have not been able to demonstrate an overall primary risk reduction of stroke with CPAP in OSA patients in the general population, in the SAVE study [52], OSA patients who were adherent to CPAP (> 4 h/night) had a lower risk of stroke (hazard ratio (HR), 0.56; 95% CI, 0.32–1.00) and composite cerebral events (HR, 0.52; 95% CI, 0.30–0.90) in propensity score-matched analyses [53]. Nevertheless, CPAP treatment was associated with a higher rate of total hospital admissions for transient ischemic attack (TIA) (relative risk, 2.29; 95% CI, 1.05–4.99) [52]. A meta-analysis of cohort studies showed a lower incidence of stroke with CPAP treatment (relative risk, 0.27; 95% CI, 0.14–0.53) in adherent patients [54].

In stroke survivors, the initiation of CPAP can be challenging and requires a motivated multidisciplinary team. When feasible, CPAP may have a positive effect on sleepiness and depressive symptoms [50••, 55]. In a recent meta-analysis of 10 RCTs, Brill et al. found an overall functional improvement with CPAP (standardized mean difference (SMD), 0.5406; 95% CI, 0.0263–1.0548) but with a considerable heterogeneity (I^2 = 78.9%, p = 0.0394) across the studies [50••]. In one trial, long-term survival after stroke was improved with CPAP [50••, 56].

Two studies in our center currently assess the effects of SDB and other SWD on short- and long-term outcome in stroke/TIA patients (SAS-CARE study [57] clinicaltrials.gov NCT01097967, sleep disorders and stroke outcome study clinicaltrials.gov NCT02559739). In a third study, we assess the impact of early SDB treatment with adaptive servoventilation on the MRI evolution of stroke (eSATIS study, clinicaltrials.gov NCT02554487).

Insomnia

Insomnia is defined by the association of difficulties falling asleep and maintaining sleep or early awakenings with daytime symptoms such as fatigue, impaired concentration, irritability, or sleep-related concerns. Insomnia and short sleep duration can be associated but most commonly appear independently from each other. The current section focuses on insomnia as a factor for stroke risk. Sleep duration and adverse health outcomes are separately discussed in Box 1.

Box 1. Short and long sleep duration and stroke.

The U-shaped relationship between sleep duration and morbidity stating that too short (< 5-6h) and too long (> 8-9h) average sleep duration per night is associated with adverse health outcomes and mortality has been well established in prospective cohort studies. Looking at recently published meta-analyses, specifically investigating the association of sleep duration with stroke risk, the U-shaped relationship becomes less evident and favors a J-shaped relationship indicating that long sleep duration increases the risk for stroke and stroke mortality to a higher extent than short sleep duration [58, 59, 60].

Two out of three very recently published meta-analyses, all including prospective cohort studies only, report that both short and long sleep duration increase the risk for stroke outcomes [58, 59]. The third study however, concludes that predominantly long sleep duration increases the risk of stroke incidence [60]. Considering the pooled relative risks (RR) of the two former meta-analyses in more detail, long sleep duration seems to rise stroke risk by about 17 to 18 % per 1 hour of sleep duration increase (RR,1.17-1.18, 95% CI, 1.14-1.21) and short sleep duration by 5 to 7% per 1 hour reduction of sleep duration (RR, 1.05-1.07, 95% CI, 1.01-1.12) [58, 59].

Two systematic reviews from the same research group, investigating the association between short [61] and long [62] sleep duration with adverse health outcomes separately, using meta-regression, provide evidence for increased stroke risk in long (>7-8h/night) but not short (< 6 or <7h/night) sleepers compared to individuals with normal average sleep duration (>6-8h/night), whereas for hypertension the reverse association was found. However, at both ends of the spectrum, these studies report that short and long sleep duration was associated with increased risk for mortality, diabetes mellitus, cardiovascular diseases, coronary heart disease and obesity [61, 62]. Also Leng and colleagues conclude that mainly long-sleep duration increases the risk for fatal and non-fatal strokes [63].

Different mechanisms might lay behind the association of short- and long sleep duration with adverse cerebro-cardiovascular health outcomes. Short sleep duration might affect cerebro-cardiovascular morbidity and mortality via elevated blood pressure [64], the hormonal system (e.g., reduced leptin and elevated ghrelin levels [65]), and lifestyle factors and distress, since sleep curtailment is often influenced by professional and social pressure. Long sleep duration in contrary, might represent a symptom of an underlying disease or poor psycho-physiological health status [66].

The adverse effects of post-stroke sleep deprivation and fragmentation on the one side and the beneficial effects of post-stroke sleep enhancement on the other, were suggested by animal studies but still need to be assessed in humans [16, 67,68•, 69-71].

Insomnia as Risk Factor of Stroke

In a recent meta-analysis on 15 prospective cohort studies, difficulties initiating as well as maintaining sleep and non-restorative sleep increased the risk of future cardiocerebrovascular events [72]. However, only two included studies evaluated the relationship between insomnia symptoms and stroke risk. In the Augsburg cohort study [73], self-reported insomnia symptoms were not predictive for total, fatal, or non-fatal strokes for neither men nor women after adjusting for age, education, and relevant cerebrovascular risk factors. Similarly, Westerlund and colleagues [74] found that insomnia symptoms on their own were unrelated to the risk of overall cardiovascular events, including stroke, but participants with frequent insomnia symptoms together with short sleep duration (equal to or less than 5 h) had the highest risk of overall cardiovascular events (HR, 1.26–1.39). This is in line with a cross-sectional and retrospective cohort study suggesting that short-sleeping and chronic insomniacs are at greater risk for stroke [75, 76] and supports the view that insomnia

with objective short sleep duration seems to be the most morbid phenotype of the disorder [77].

Insomnia in Acute Stroke and Its Treatment

About 37 to 59% of the stroke patients report insomnia complaints within the first 3 months of stroke [78–82] and about 12–38% report insomnia complaints with daytime symptoms [10••, 11, 82, 83]. One study reported the de novo onset of insomnia symptoms in 18% of patients [78], suggesting that stroke may lead to insomnia. However, only in rare cases, specific brain lesions, such as thalamo-mesencephalic and tegmental pontine damage, can cause insomnia due to disruption of the neuronal circuits regulating sleep-wake states [14]. Environmental factors (e.g., noise, insufficient dark-light schedules), medication, stress, and post-stroke depression are stronger determinants of post-stroke insomnia [14].

Cognitive-behavioral therapy (CBT) is the recommended first-line treatment, especially for chronic insomnia and long-term management, and pharmacological treatments should be applied for short-term intervention only and in cases where CBT for insomnia (CBT-I) is not effective or available [84]. Despite CBT-I's effectiveness in different settings (face to face and online), only two studies have investigated its applicability and efficacy in patients suffering from post-stroke insomnia. In small samples of stroke patients suffering from fatigue and poor sleep ($n = 15$) or insomnia ($n = 5$), CBT-I reduced fatigue, depression scores, and dysfunctional sleep-related beliefs and enhanced sleep quality at least at short term [85, 86•]. Hence, cognitive behavioral approaches are applicable and even seem effective to reduce post-stroke insomnia. Nevertheless, long-term benefits on mental and physical health and secondary prevention of recurrent stroke need to be addressed in future studies with larger samples.

The same applies for pharmacological treatments of post-stroke insomnia. Zolpidem, one of the widest used GABAergic drugs against insomnia, might improve post-stroke functional recovery via neuroprotection [87] and enhancement of brain-derived neurotropic factor (BDNF) [88] in the acute phase of stroke. However, in a more chronic state of stroke, it might counteract sleep-dependent cortical plasticity as suggested by an animal study in cats in which zolpidem impaired sleep-dependent ocular dominance plasticity [89]. Moreover, it might even increase the risk for ischemic stroke especially with higher dosage [90]. One study by Palomäki and colleagues [91] suggests that mianserin—a sedative antidepressant—effectively treats post-stroke insomnia, but its impact on neurological stroke recovery was not evaluated.

Impact of Insomnia Treatment on Stroke Risk and Stroke Outcome

The impact of insomnia treatment on stroke risk and neurological recovery has not been investigated. A few correlational studies suggest that stroke patients with insomnia complaints and poor sleepers show worse stroke recovery measured by functional independence scores as well as scores assessing activities of daily living and health-related quality of life [78, 80]. Only in the past year, two prospective studies where published providing evidence for worse functional recovery, especially lower balance skills and greater dependence, of stroke patients with the additional burden of insomnia complaints [10••, 79]. If at all, these studies provide indirect evidence that post-stroke insomnia treatment could be beneficial for stroke recovery. However, treatment effects regarding secondary prevention and stroke recovery still need to be addressed.

Excessive Daytime Sleepiness (EDS) and Hypersomnia

Excessive daytime sleepiness (EDS), i.e., an irresistible diurnal sleep need or daytime lapses into sleep, and long sleep duration (i.e., > 10–11 h of sleep/day) can be associated but also appear independently from each other.

EDS and Hypersomnia as Risk Factors of Stroke

As also discussed in Box 1, meta-analyses show that short (< 5–6 h) and long (> 8–9 h) sleep duration increase the risk for stroke incidences with a tendency towards higher relative risks for long-sleeping individuals [58, 59]. In one meta-analysis, the authors conclude that predominantly long but not short sleep duration increases the risk of stroke incidence [60••]. Although all included studies control for several potential covariates such as demographical and medical factors, they did not assess whether the studied population also suffered from excessive daytime sleepiness.

In two large population-based studies, EDS was found to be an independent risk factor for stroke after controlling for medical comorbidities including self-reported symptoms or diagnoses of SDB [15, 92, 93].

EDS/Hypersomnia in Acute Stroke and Their Treatment

The frequency of EDS largely varies with its method of assessment (e.g., questionnaire-based assessment by the Epworth Sleepiness Scale or objective assessment by the multiple sleep latency tests) and with the location of the lesion [94]. Twenty-two percent of 100 consecutively recruited stroke patients reported a significantly enhanced Epworth sleepiness score (>

10) or an increased sleep need (defined by a 2-h increase of total sleep time compared to pre-stroke) [95].

Stroke topography can determine the presence of post-stroke EDS and hypersomnia. Patients with a paramedian thalamus often present severe hypersomnia and EDS [14, 15]. Besides stroke topography, comorbid SDB or depression or stroke risk factors such as obesity or diabetes mellitus may also be involved in post-stroke EDS and hypersomnia. Finally, reduced physical activity due to physical disability, in the sense of deconditioning, can also contribute (see ref. [94] for a comprehensive review).

Improvement of post-stroke hypersomnia and EDS is occasionally observed with modafinil, methylphenidate, with dopaminergic agents, and, in the case of comorbid depression, with a stimulating antidepressant [14, 15]. Experimental data suggest that these pharmacological interventions may also promote stroke recovery [96–98].

Impact of EDS/Hypersomnia Treatment on Stroke Risk and Stroke Outcome

The impact of excessive daytime sleepiness and prolonged sleep duration on physical and cognitive recovery independent of SDB has not been prospectively and systematically studied in stroke patients and thus also neither whether its treatment prevents recurrent stroke.

In patients with paramedian thalamic lesions, especially if unilateral, the post-stroke increase of sleep need declined to a large extent over the following 12 to 24 months [99]. However, frontal lobe functions such as attention, fluency, error control as well as learning and memory remained deficient, predominantly in left-sided and bilateral paramedian thalamic stroke patients [99]. Other findings suggest that sleepiness increases with stroke chronicity and is associated with reduced vitality in line with the deconditioning hypothesis [100]. Moreover, stroke patients classified as hypo-aroused and sleepy by nurses seem to present worse outcomes after acute rehabilitation assessed by independence scores in daily activities and admission rate to nursery homes [101]. Whether the impaired functional and cognitive outcomes are the result of the enhanced sleep need and daytime sleepiness in these patients or whether both phenotypes are the result of the same underlying brain lesion cannot be clearly differentiated (see also ref. [94] for a comprehensive framework of EDS in stroke survivors).

Circadian Rhythm Disorders

Circadian Rhythm Disorders as Risk Factor of Stroke

The consistency of circadian rhythms plays a significant role in the body's homeostasis and health. Shift work disorder as a frequently seen circadian rhythm abnormality has several consequences on health and increases the risk of arterial hypertension, diabetes mellitus, obesity, cardiovascular disease, and all-cause mortality [102–106]. The impact of shift work on stroke risk is, however, still unclear. A smaller cohort study did not find an association of shift work and incident stroke [107] while a large-scale cohort study on night shift in nurses showed that rotating night shift work was associated with a 4% increased risk of ischemic stroke for every 5 years of exposure, even after adjusting for standard vascular risk factors [108]. A systematic meta-analysis of 34 studies also revealed that shift work was associated with ischemic stroke (risk ratio, 1.05; 95% CI, 1.01 to 1.09) [109].

A Finnish study on 14,834 patients with ischemic stroke showed that the first days of daylight saving time transitions were associated with an increase in hospitalizations for ischemic stroke during the first 2 days (relative risk, 1.08; CI, 1.01–1.15; $p = 0.069$), with women and older people being more susceptible to this change [110].

Circadian Rhythm Disorders in Acute Stroke and Their Treatment

The frequency of circadian disturbances in acute stroke patients is unknown. In a study by Takekawa et al., acute stroke patients with disturbed consciousness and non-ambulatory patients showed an infradian rhythm of the body temperature [111]. Two studies with small sample sizes documented an altered timing in urinary melatonin as a marker of disturbed circadian rhythms in stroke patients [112]. One study assessed differences in phase of entrainment as a result of stroke by analyzing sleep timing in 35 first-ever stroke patients before and after stroke up to 3 months. The study revealed a significant change in chronotype, longer sleep durations on working days, and work-free days after stroke [113]. Patients with more severe strokes showed more severe changes in their sleep timing. In addition, there was a significant difference in mid-sleep on work-free days corrected for sleep deficit on workdays (MSFsc) changes between stroke locations. Strokes that occurred in the anterior circulation lead to delays of MSFsc, whereas strokes within the posterior circulation lead to advances of MSFsc [113].

An observational study of 46 stroke survivors indicates that early post-stroke alterations of sleep/wake circadian rhythms with decreases in sleep efficiency and increases in sleep fragmentation index are associated with a higher risk of post-stroke apathy at 3 months [114].

Interventions (e.g., with naturalistic light) to improve circadian functions after stroke are currently discussed [115] but, to our best knowledge, have never been tested.

Impact of Treatment of Circadian Rhythm Disorders on Stroke Risk and Stroke Outcome

This impact is unknown.

Circadian Variation of Stroke Onset

Contrary to circadian rhythm disorders, there have been extensive studies on the circadian variation of stroke onset. Ischemic stroke occurs most frequently in the morning hours, particularly after awakening. In a large meta-analysis, Elliott has found an almost 50% increase in stroke onset between 6 a.m. and 12 a.m. [116]. A cross-sectional observational study with 583 patients confirms the increased occurrence of stroke within this time span [117]. Circadian rhythm correlates also with stroke subtype. In a study with 1272 acute stroke patients, 31.6% of lacunar strokes were on awakening. Morning stroke occurrence (6–12 a.m.) was at most (30.5%) in cardioembolic strokes, followed by strokes of other/unknown mechanism (27.1%) and athero-thrombotic strokes (25.7%) [118]. Lago et al. [119] did not find any difference in the circadian occurrence of first-ever stroke and recurrent stroke. Atkinson et al. [120] suggest that the increased sympathetic activity, blood pressure surges, decreased endothelial function, and increased platelet aggregability explain the morning peak of stroke.

Stroke and Sleep-Related Movement Disorders (SRMD)

SRMD as a Risk Factor of Stroke

While some studies reported increased cerebrovascular risk in patients with restless legs syndrome (RLS) [121], and especially those suffering from other comorbidities [122], most studies failed to show a causative correlation [123–126]. There is only limited data on the prevalence of RLS prior to stroke. In a recent study, among 96 patients with acute ischemic stroke, 12% already suffered from RLS prior to stroke [127].

Periodic limb movements (PLM) occur during sleep and together with a sleep-related complaint requires polysomnography evidence for diagnosis. This has not yet been studied and, therefore, the prevalence of PLM prior to stroke and its role as risk factor for stroke remains unclear.

SRMD in Acute Stroke and Their Treatment

The data on the prevalence of RLS after stroke is also limited, and data sources were mainly small case series and small studies, some of them reporting also neuroimaging data. Lee et al. reported that 17 out 137 stroke patients fulfilled the criteria of new-onset RLS, suggesting a prevalence of 12% for new-onset post-stroke RLS [128]. In the same study and other reports, patients with infarction of the basal ganglia/corona radiata [128–130] and of the brainstem [128, 129] were more susceptible to developing RLS symptoms while infarcts of the thalamus [131] and of the internal capsule [128] and cortical strokes [128] were less associated to post-stroke RLS. Women were more likely to develop post-stroke RLS than men.

Similarly, some data suggested an increased prevalence of PLM in stroke patients compared to controls (77 vs 29%) [132, 133]. In several reports, the occurrence of post-stroke PLM was associated with infarctions in several different anatomical regions such as the corona radiata [132], the basal ganglia [132], the cortex [132], the thalamus [132], the pons [129, 134], and the cerebellum [135]. However, the results of a recent large prospective study from our group and a second smaller study in TIA patients reported that the prevalence of PLM was comparable between patients with stroke/TIA (either in the acute or in the chronic phase) and healthy controls [12, 136]. In other words, post-stroke RLS and PLM may be less common than first suggested and possibly related to a strategic localization of stroke [129].

Most studies referred to the beneficial effect of dopaminergic medication on post-stroke RLS and PLM [128, 131, 134], yet three patients only improved mildly [128, 130]. One patient with PLM did not respond at all [135], while in some cases, symptoms of RLS or PLM were transient and resolved totally without the need of a pharmacotherapy [129, 131].

Impact of Treatment of SRMDs on Stroke Risk and Outcome

RLS as stroke comorbidity is probable to have a crucial impact on the clinical stroke outcome. Currently, only one study assessed the relationship between post-stroke RLS and stroke outcome and reported a poorer functional recovery (measured with the Barthel index) in patients with RLS compared to those without RLS [127].

RLS or PLM symptoms appeared predominantly in the acute or the subacute post-stroke phase. Whether they affect recurrent strokes that frequently occur within the first month of an event has not been investigated.

The impact of RLS treatment on the cardiovascular and stroke risk remains unclear. A recent study [124] assessed clinical, socio-demographic, and RLS features in patients with primary RLS classified according to their cardiovascular disease and hypertension status. No relationship was found between cardiovascular disease and hypertension and treatment with dopaminergic agonists, alpha2/delta ligands, or the presence of RLS augmentation symptoms. However, prospective studies on the stroke risk or secondary prevention due to RLS treatment are lacking.

Parasomnias

Available data on the cross-sectional relationship between parasomnias and stroke is very limited and mostly refers to the REM sleep behavior disorder (RBD).

Parasomnias as a Risk Factor of Stroke

Ma et al. studied recently RBD preceding stroke in a community-based prospective study of over 12,000 adults and 159 documented incident stroke cases. Authors reported that subjects with probable RBD at baseline (no polysomnographic data were available) were approximately 1.5 times more likely to develop ischemic and especially hemorrhagic stroke even *after adjustment* for potential co-determinants, such as age, gender, obesity, hypertension, and smoking status [137]. Another multicenter case-control study including 318 subjects with idiopathic RBD and 318 matched controls reported that the presence of RBD was associated with significantly higher risk of developing a cardiovascular disease of any kind (OR, 1.6; 95% CI, 1.0–2.5) [138].

Data regarding the prevalence of RBD prior to stroke are lacking. There are also no large epidemiological studies on the prevalence of parasomnias after stroke. Data sources are mainly a limited number of case reports and the recently published study by Tang et al. In this study, among 119 stroke patients, 11% had probable RBD. The presence of RBD was significantly associated with lower volume of infarction mainly in the brainstem. In a multivariate analysis, brainstem infarcts were an independent predictor of RBD (OR, 3.686; $p = 0.032$) [139].

Parasomnias in Acute Stroke and Their Treatment

Post-stroke RBD can occur *secondary* to infarction in the brainstem [140–144]. These reports provided evidence that even small lesions in specific brain regions such as the pontine tegmentum at the lower/mid-pontine level [143], the rostral medial pons [141], the left upper pons, and the dorsomedial pons [142] are associated with human RBD.

Cases of post-stroke sleep-related hallucinatory phenomena (in patients with pontine tegmentum, midbrain or paramedical thalamus), dream-reality confusion, increased dreaming, or dreaming loss (in patients with lesions of the temporal, parietal, and occipital lobe) have been previously described [145–147]. However, to our knowledge, there are no reports on stroke-related parasomnias other than RBD.

The neuroanatomical correlates of parasomnias remain unclear. Therefore, functional and structural neuroimaging studies on secondary forms, such as post-stroke parasomnias, can provide valuable information on the pathophysiology of parasomnias.

The management of RBD include the symptomatic treatment to prevent injury and the prognostic counseling. Currently, there is no evidence that primary and secondary RBD should be treated differently. Clonazepam and melatonin can improve dream enactment and reduce the intensity and frequency of violent episodes. However, a solid evidence basis for pharmacotherapy in RBD is lacking. Clonazepam (0.25 mg) alleviated RBD symptoms in two cases of stroke-associated RBD. In another case of post-stroke RBD where cataplexy symptoms co-occurred, fluoxetine was also effective [141]. In the case from Peter et al., no treatment or RBD outcome was reported [140]. None of the cases reported follow-up or a conversion to synucleinopathy.

Impact of Parasomnia Treatment on Stroke Risk and Outcome

There are no available data regarding the impact of post-stroke parasomnias on stroke outcome.

New Insight from Animal Studies

Animal models of stroke enable pharmacological and physiological sleep manipulations, investigation of pre-stroke baseline sleep parameters, and induction of controlled infarcts, which is not possible in clinical studies. Animal research suggests an intricate relationship between sleep-wake processes and stroke. Rodents subjected to focal ischemic stroke show an increased amount of NREM sleep, and NREM sleep-promoting drugs improve functional recovery after stroke [67, 68•]. Experimental sleep deprivation performed prior to ischemic stroke results in post-stroke enhancement of NREM and REM sleep and has a neuroprotective effect [69, 70, 148]. Furthermore, the presence of periodic synchronized neuronal activity, resembling NREM sleep activity, within the perilesional brain area may play a favorable role in the post-stroke reorganizational processes [149]. In a recent translational study, Pace et al. suggested a relationship between (preserved) REM sleep and (better) outcome in both humans with stroke and rodent models of stroke [70, 150]. Conversely, sleep loss was shown experimentally to have a negative effect on stroke recovery [67, 71].

Animal models had been unique in elucidating the intricate mechanisms underlying sleep regulation and stroke pathophysiology, and rodent models for SWD such as obstructive sleep apnea, insomnia, narcolepsy, and restless legs syndrome have been described [151]. The classical model used to study sleep apnea oxygenation patterns is intermittent hypoxia (IH), where rodents are exposed to oxygen or nitrogen to induce oxyhemoglobin desaturation [152]. Studies showed that long-term exposure to IH induced proinflammatory responses in neurons and glia with injury diffuse to hippocampus, basal forebrain and pyramidal cortical, cerebellar, and wake-active neurons [153,

154]. Insomnia could be triggered in rodents through several exposures to stressful environment, or it could be induced either pharmacologically or genetically [155]. Using a cage-exchange stress-induced insomnia paradigm, Cano and colleagues showed simultaneous activation of arousal systems and sleep-active centers, suggesting that insomnia may result from a failure of coordination between neurons belonging to these two opposite sleep- and wake-promoting areas [156].

Restless legs syndrome may involve dopamine transmission abnormalities and iron deficiencies, but its pathophysiology has not been fully explained yet. Rodent models for the syndrome have been developed following the current theories of pathogenesis, such as dopamine D3 knockout mice and iron-deficient mice [157]. A recent study has shown that the cortico-spinal tract, rubrospinal tract, and A11 dopaminergic neurons are all contributing to the inhibition of motor activity during sleep in rats. Thus, the lesion of these pathways, together with their afferent sources, has been observed to lead to RLS-like movements, revealing the diffuse network involved in this syndrome [158].

Although basic research studies on understanding the pathophysiological mechanisms underlying sleep disorders have been numerous in the last years, the literature investigating the effect of specific sleep disturbances on ischemic stroke recovery has been limited. What has been clearly demonstrated is that sleep disruption following stroke exacerbates brain injury with negative impact on endogenous processes such as axonal sprouting, neurogenesis, synaptogenesis, and angiogenesis, thus interfering with long-term neurological and functional recovery [67, 71].

Conclusions and Take-Home Message

Clinicians should consider SDB and other SWD as potential risk factors for stroke and the possibility that SWD treatment may be beneficial for stroke prevention. In addition, clinicians should be aware of the high frequency of SWD in acute stroke patients and their negative impact on outcome and actively consider available (and potentially effective) treatment options.

Research on SDB and other SWD in stroke patients and animal models of stroke offers unique opportunities to expand our knowledge about how the brain controls sleep and wake functions. This knowledge can help to further optimize clinical care and the well-being of these vulnerable patients.

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Compliance with Ethical Standards

Conflict of Interest Simone B. Duss, Anne-Kathrin Brill, Panagiotis Bargiotas, Laura Facchin, Filip Alexiev, Mauro Manconi, and Claudio L. Bassetti declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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